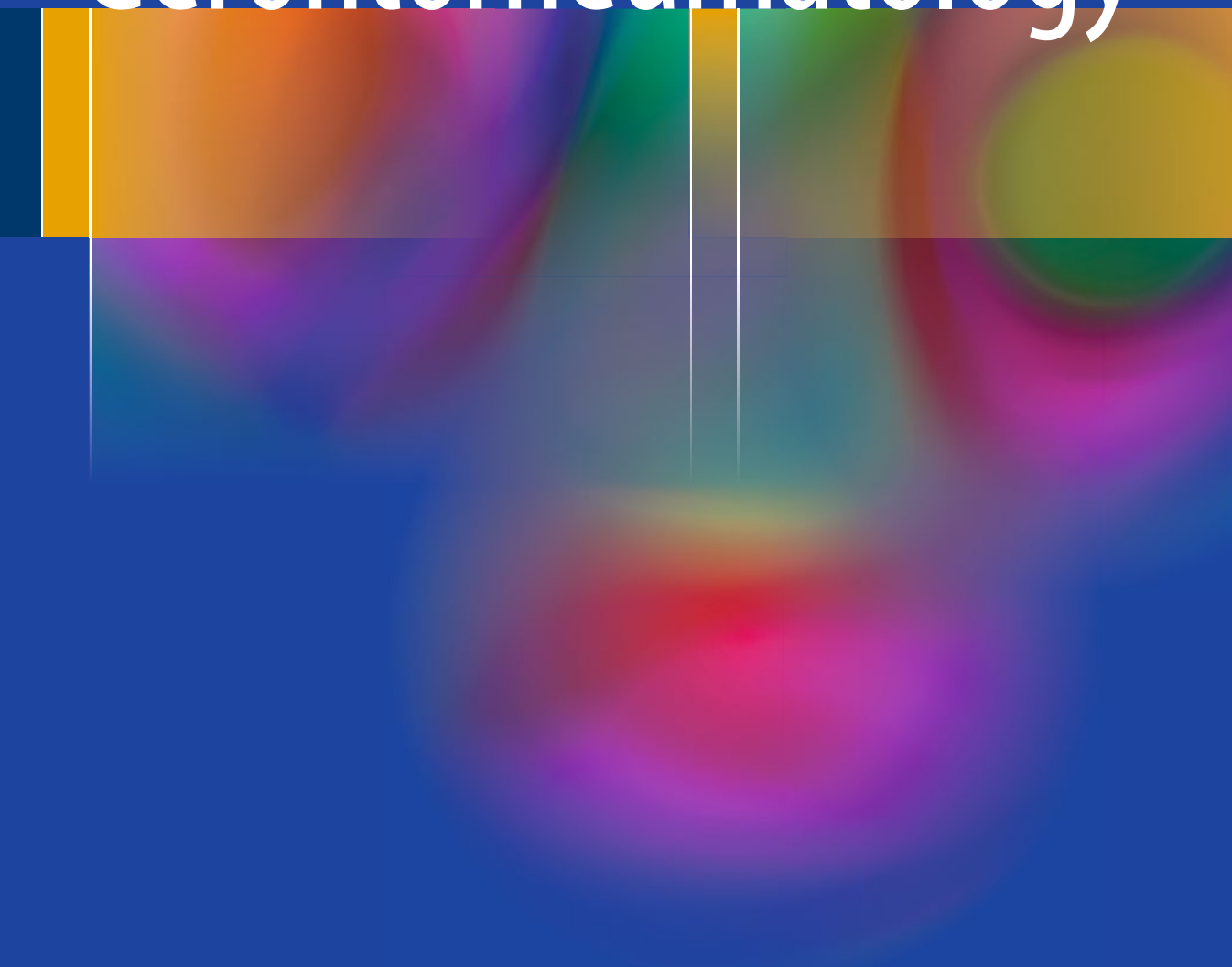
Jozef Rovenský
Editor

Gerontorheumatology



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National Institute of Rheumatic Diseases
Piešťany
Slovakia

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To my Czech and Slovak teachers

Jozef Rovenský

Preface

The publication of prominent Czech and Slovak authors led by Prof. Jozef Rovenský, MD, DSc, from the National Institute of Rheumatic Diseases in Piešťany, Slovakia, has the ambition to become the standard monograph of gerontorheumatology, a specialized field that deals with movement disorders associated with aging and old age.

In individual patients, the musculoskeletal diseases have their characteristic features, different etiology, and different course and require more attention to diagnosis and treatment. In patients at older age, it is also necessary to be aware of comorbidities, which may lead to doubts in accurate diagnostics.

The entire publication clearly describes the basic rheumatic diseases with emphasis on pathogenesis, diagnosis, prevention, and therapy. It is designed to the rheumatologists and internists, but especially to the general practitioners who usually meet elderly patients with movement disorders as the first in their offices.

Piešťany, Slovakia — Jozef Rovenský

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Contents

1 Pathogenesis, Clinical Syndromology and Treatment of Rheumatoid Arthritis 1
Jozef Rovenský, Miroslav Ferenčík†, and Richard Imrich

2 Osteoporosis in Rheumatoid Arthritis in Relation to Age 23
Juraj Payer, Zuzana Kužmová, Zdenko Killinger, and Jozef Rovenský

3 Biological Therapy for Rheumatoid Arthritis 27
Jozef Rovenský, Dagmar Mičeková, and Vanda Mlynáriková

4 Systemic Lupus Erythematosus 33
Alena Tuchyňová and Jozef Rovenský

5 Sjögren's Syndrome 39
Jozef Rovenský, Dagmar Mičeková, and Vanda Mlynáriková

6 Systemic Scleroderma 45
Radim Bečvář

7 Vasculitides 49
Radim Bečvář and Jozef Rovenský

8 Polymyalgia Rheumatica and Giant Cell Arteritis 61
Jozef Rovenský, Alena Tuchyňová, Viera Štvrtinová, and Svetoslav Štvrtina†

9 Aortic Aneurysm as a Cause of Death in Giant Cell Arteritis 75
Svetoslav Štvrtina†, Jozef Rovenský, and Štefan Galbavý

10 Relapsing Polychondritis 83
Jozef Rovenský and Marie Sedláčková

11 RS3PE: A Disease or a Syndrome? 91
Jozef Rovenský

12 Clinical and Laboratory Manifestations of Paraneoplastic Rheumatic Syndromes 99
Jozef Rovenský and Ľubica Švancárová

13 Osteoarthritis. 111
Jozef Rovenský, Helena Tauchmannová, Mária Stančíková, Jana Sedláková, and Mária Krátka

14 Haemochromatosis Arthropathy 139
Tomáš Dallos, Jochen Zwerina, and László Kovács

15 Diabetic Charcot Neurogenic Osteoarthropathy 151
Renáta Palmajová and Juraj Palmaj

16 Changes of the Musculoskeletal System in the Metabolic Syndrome 191
Juraj Palmaj and Renáta Palmajová

17 Clinical Syndromology of Gouty Arthritis 215
Jozef Rovenský, Marián Kovalančík, Karol Bošmanský, Emília Rovenská, and Jana Sedláková

18 Radiology and Ultrasonography Findings in Chondrocalcinosis. 223
Mária Krátka and Jozef Rovenský

19 Alkaptonuria and Ochronosis 233
Jozef Rovenský, Richard Imrich, Tibor Urbánek, and Vladimir Bošák

20 Metabolic Osteopathy in Late-Onset Celiac Disease 245
Hana Ciferská, Pavel Horák, and Martin Tichý

21 Coeliac Disease in Elderly Patients 255
Petr Fojtík, Martin Kliment, and Pavel Novosad

22 Bone and Joint Involvement in Celiac Disease. 261
Lenka Franeková and Marie Sedláčková

23 Diffuse Idiopathic Skeletal Hyperostosis 269
Andrea Pavelková

24 Senile Osteoporosis 275
Petr Broulík

25 Nutrition and Osteoporosis 281
Petr Fojtík, Martin Kliment, and Pavel Novosad

26 Neck and Shoulder Pain 285
Marie Sedláčková

27 Vertebrogenic Disorders. 293
Ivan Buran

28 Pain. 301
Ľubomír Lisý

29 Pharmacological Treatment of Rheumatic Diseases 307
Marta Olejárová

30 Drug-Induced Rheumatic Syndromes. 315
Jozef Holjenčík Jr., Jozef Rovenský, and Milan Kriška

31 Rehabilitation in Rheumatic Diseases. 321
Helena Tauchmannová and Zuzana Popracová

32 Surgical Treatment of Sequelae of Rheumatic Diseases 329
Pavel Vavřík and Stanislav Popelka

33 Paget's Disease of Bone. 343
Ines Guimaraes da Silveira, Melissa Cláudia Bisi, Aline de Souza Streck, Caroline Zechlinski Xavier de Freitas, Deonilson Ghizoni Schmoeller, Carlos Alberto von Muhlen, Jozef Holjenčík Jr, and Jozef Rovenský

34 Involutional Osteoporosis: Sarcopenia, Frailty Syndrome and Falls 351
Jiří Jenšovský

35 Systemic Enzyme Therapy in Comprehensive Treatment of Degenerative Rheumatic Diseases in the Elderly 363
Martin Wald and Jozef Rovenský

Index. 367

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1 Pathogenesis, Clinical Syndromology and Treatment of Rheumatoid Arthritis

Jozef Rovenský, Miroslav Ferenčík†, and Richard Imrich

1.1 Elderly-Onset Rheumatoid Arthritis

Rheumatoid arthritis (RA) starting after the age of 60 years is called elderly-onset rheumatoid arthritis (EORA) [1]. The age factor is very important as EORA accounts for 10–33 % of all RA cases and has certain specific clinical features. Another factor to be taken into account is that medications to treat elderly-onset RA may cause various adverse effects; therefore, the therapy must be carefully considered and continuously monitored. Older patients also typically suffer from more than one disease, and the drugs they receive may interact. Some of their physiological functions are impaired which has a negative impact on the drug bioavailability and metabolism.

The EORA female/male incidence ratio is lower than in patients with rheumatoid arthritis. An Italian study showed that the EORA female/male ratio is 1.6:1, as compared to 4.4:1 in the younger-onset rheumatoid arthritis (YORA) [2]. Another typical feature of EORA is its abrupt onset. Bajocchi et al. [2] have found out in their study that acute onset of EORA occurs in 33.6 % of cases, while in younger individuals, it is only in 13.6 %.

1.2 Pathogenesis of EORA

In pathogenesis of EORA are present abnormalities in regulation of immune functions, characteristic of old age, increase susceptibility of the elderly to infections, autoimmune and tumorous diseases.

A significant role in development of EORA is played by a complex of age-related changes in immunity mechanisms presented below. In addition to the mentioned disorders of the innate and acquired immunity, antibody and cell-specific immunity, the age-related changes include also defects in antigen processing or apoptosis of cells. An important factor in EORA pathogenesis may be a disorder of the immune system caused by gradual impairment of functions of T-lymphocytes, associated with development of a chronic inflammation [24]. It is assumed that immunological changes in the course of physiological ageing modify the (clinical and laboratory) progress of EORA [4].

†Author was deceased at the time of publication.

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The incidence of the rheumatoid factor (RF) is substantially lower in patients with EORA, and it is generally known that the presence of IgM RF increases during physiological ageing. Vencovský [4] states that the criterion of the presence of RF is from the viewpoint of diagnostic process less important in old age, as the positivity of RF ranges in individuals over the age of 60 without any obvious disease between 15 and 20 %, although the levels are not in most cases high [5].

Therefore, it is recommended to consider in elderly patients the first positive RF titre to be 1:1,280 in latex fixation test, as compared to 1:160 in the middle-aged individuals. Vencovský [4] also reports that in part of seronegative EORA patients, RF can be proved by a more sensitive method, and so the frequency does not differ that much, and it is rather a case of RF of another type [6]. ELISA test is used to determine RF isotypes. IgG RF is associated with the presence of vasculitis, IgA RF with development of bone erosion. In EORA, arthritic syndrome is typically confined more or less to large joints. An important issue is also the outcome prognosis in EORA patients.

1.3 The Basic Specific Features of EORA

1. Approximately equal incidence of the disease in women and men
2. Frequent acute onset of the disease
3. Frequent involvement of large joints
4. Frequent oligoarticular distribution
5. Frequent systemic manifestations at the beginning – high erythrocyte sedimentation rate, weight loss or fatigue
6. Higher incidence of "seronegativity", i.e. RF absence detected by common agglutination tests
7. Impaired functional ability and decreased quality of life of EORA patients
8. Slightly higher incidence of severe cases, with rapid development of significant functional involvement and destructive changes

Of great importance is also genetic examination of the role of HLA-DR4 and severity of rheumatoid arthritis. As concerns the HLA-DR4 relation in EORA, the research findings are contradictory. Terkeltaub et al. [11] observed a lower frequency of HLA-DR4 in EORA, while Hazes et al. [12] reported a slightly increased prevalence of DR4 with increasing age of the RA onset. A positive association was found with DR-B1*0101, *0405 and *1502 in the Japanese EORA patients as compared to YORA [13].

Scientists in Spain found out that EORA, unlike YORA, correlates with DRB1*01, but did not prove correlation with DRB1*04 [14]. According to another finding, seronegative EORA patients had an increased frequency of DRB1*13/*14. A similar finding is related to patients with polymyalgia rheumatica (PMR).

These differences are highly interesting both from the clinical and genetic viewpoints, as it seems that there exist two groups of EORA patients, one of which resembles YORA and the other is similar to polymyalgia rheumatica. The latter one is typically associated with a painful involvement of the shoulder girdle, acute onset, the absence of the rheumatoid factor, minimal extra-articular involvement and non-erosive course.

Recently, investigations have focused also on the incidence and prevalence of EORA in various countries. In Norway, RA incidence in the 1988–1993 period was reported at 25.7 (females, 36.7; males, 13.8) per 100,000 inhabitants. The incidence was increasing with age from 7.8 per 100,000 of inhabitants between 20 and 29 years of age to 61 in the age group of 70–79 years [15]. The same authors found the RA prevalence in the age group of 20–79 years to be 0.437 %, while in women older than 60 years, the RA prevalence exceeded 1 %. In a British study, increased RA incidence in the course of physiological ageing was observed in men; in women the disease typically started at the age of 45–65 years [16]. Similarly, the Finish researchers examined the impact of physiological ageing on RA. Analyses showed that in patients aged 65, 75, 80 and 85 years, the prevalence was higher – 2.4 % – particularly at the age of 65 years and tended to decline with age [17]. Based on the new findings that were published in the USA, RA prevalence in patients aged 60 years and more reached 2 %, regardless of age [18]. In Sweden the RA prevalence in patients in the age group of 70–79

years was 2–3 %. According to the data from the Netherlands, the RA prevalence at the age of more than 85 years was only 0.3 % [20].

Characteristics of rheumatoid arthritis and basic differences of the disease in the elderly RA is a chronic systemic inflammatory disease that primarily affects synovial membranes of joints, tendons and joint capsules. Its most prevalent clinical manifestation is chronic symmetrical polyarthritis. The systemic manifestations include the variable presence of extra-articular symptoms, the most frequent of which is serositis, vasculitis, nodule formation, general decalcification, marked production of proteins in the acute phase and production of autoantibodies.

RA occurs almost all over the world and affects on average about three times more women than men. The most typical manifestations are reflected by the diagnostic criteria. Prevalence of the disease ranges around 1 %. Although RA reduces lifespan on average by 5–10 years, it is a chronic, long-lasting disorder, and so its prevalence in the population over the age of 60 years ranges around 2–3 % [3].

Most of the patients suffer from RA in the long run, and therefore progressive conditions can be observed that due to destructive changes in the joints lead to severe deformities and functional changes. The disease starts as a rule between 30 and 50 years of age, but in almost one third of cases, it develops after the age of 60. As RA that has developed later in the life differs in certain aspects from RA in middle-aged individuals, i.e. younger-onset rheumatoid arthritis (YORA), it is sometimes defined as a separate entity, i.e. the elderly-onset rheumatoid arthritis (EORA) [1–4, 19].

1.4 Clinical Features of RA in Elderly Patients in View of Changes in Its Course

The range of RA clinical manifestations is variable and includes more subtle forms of mild synovitis and short-term morning stiffness, as well as severe and disabling conditions with a rapid destruction of the joint tissue and severe extra-articular symptoms.

The disease begins usually insidiously. Arthritis develops slowly in the course of 1 week up to months, sometimes in combination with prodromal symptoms such as increased temperature, fatigue, weight loss and anorexia. Less frequently RA begins with acute or peracute signs in the course of several days, although one study reports up to 26 % EORA patients with such an onset of the disease [7]. Typical of RA is a polyarticular, symmetrical joint involvement, even if at the beginning it may affect one or only a few joints, which is more frequent in EORA. Subcutaneous nodules were reported less frequently in elderly patients than in younger patients with RA. In older age, involvement of large joints is more frequent, particularly shoulders, where the disease quite often starts. In these cases it is difficult to distinguish it from polymyalgia rheumatica, the incidence of which at the onset of the disease is almost impossible [8–10].

Arthritis is accompanied by morning stiffness described by patients as a feeling of stiffness and tightness of fingers and inability to bend the small joints of the hand. Intervals of morning stiffness differ in length and may last for several hours. Stiffness can be relieved by warming or soaking hands in warm water.

RA may involve almost all synovial joints, as a rule with the exception of the distal interphalangeal joints of hands and feet. Hands display typical spindle-shaped swelling of the proximal interphalangeal joints and marked interosseous muscle atrophy. Gradual progress of the disorder together with destructive changes leads to radial rotation of carpal bones and ulnar deviation of fingers, metacarpophalangeal (MCP) joints in particular. There may occur subluxation and dislocation of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. Typical changes include swan neck deformity (flexion in MCP joints, hyperextension in PIP joints and flexion in distal interphalangeal (DIP) joints) and buttonhole deformity (flexion in PIP joints and hyperextension in DIP joints). A severe complication is the carpal tunnel syndrome caused by compression of the median nerve associated with swelling and synovial hyperplasia in the wrist. It manifests itself by sensory loss and piercing pain of the

first three fingers as well as the radial half of the fourth finger in combination with thenar muscle atrophy.

Involvement of elbows may lead to flexion contracture and only in later phases to limitation of flexion. Shoulder joints are affected quite often, both in the glenohumeral and acromio-clavicular joints. Rupture of the rotator cuffs can be seen in about 20 % of patients. Hip joints are involved more often in the elderly. A sign of unfavourable development is rheumatoid coxitis. The frequent involvement of knee joints results in axial deformities, ligamentous laxity leading to a lax knee joint and flexion contracture. Accumulation of the synovial fluid in the knee joint is easily provable and facilitates diagnosis. The fluid may penetrate into the popliteal cyst, also called a Baker cyst. Rupture of this cyst and leak of the fluid out into calf muscles cause painful swelling which may be misdiagnosed as phlebothrombosis. Ankle joints are affected mostly in severe RA forms. Involvement of metatarso-phalangeal (MTP) joints is much less frequent in EORA than in YORA and may cause a number of deformities (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11 and 1.12).

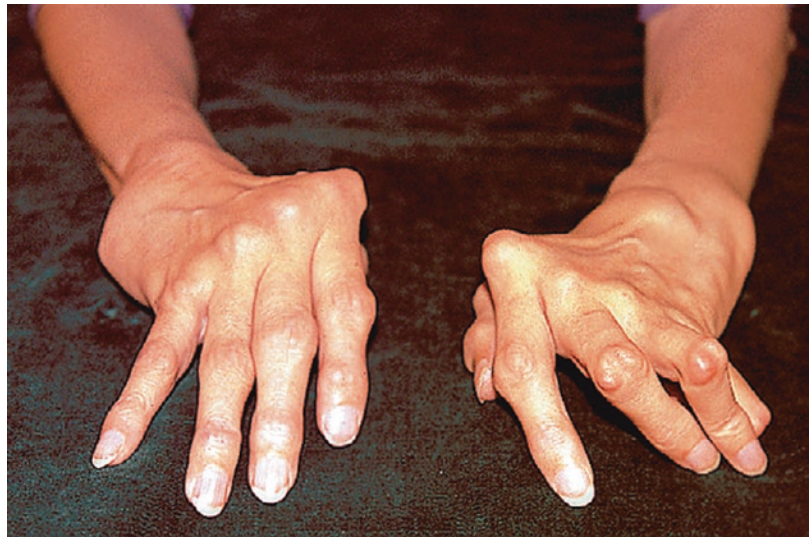

Fig. 1.1 Ulnar drift of hands in an EORA female patient, with associated tendovaginitis of extensors, interosseous muscle atrophy and rheumatoid nodules (Courtesy of Professor J. Vencovský, MD, DSc)

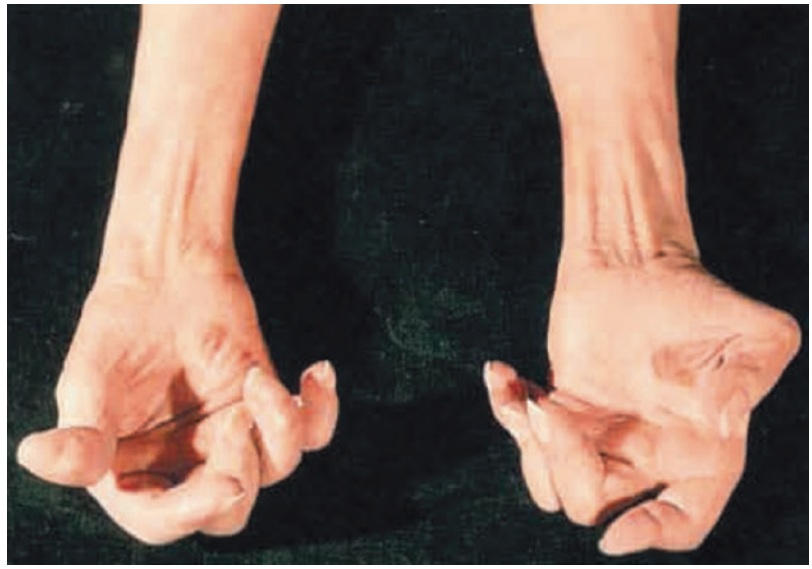

Fig. 1.2 Severe flexion contractures in an EORA female patient, with buttonhole deformities of fingers (Courtesy of Professor J. Vencovský, MD, DSc)

Posterior subluxation of proximal phalanges causes a hammertoe deformity that may considerably limit walking and standing. Patients often develop also hallux valgus. The disease may severely affect the cervical spine, primarily in the atlantoaxial joint. The transverse ligament, which fixes the dens in a stable relationship to the anterior arch of the atlas, may become lax as a result of inflammation and conduce to anterior subluxation of the atlas. Intervertebral discs and intervertebral joints may be also involved.

A relatively frequent arthritis of temporomandibular joints causes pain in chewing, and these symptoms are often attributed to a tooth disorder. Involvement of cricoarytenoid joints may lead to voice changes, hoarseness or even inspiratory stridor. Sternoclavicular and manubriosternal involvement is quite frequent but mostly clinically irrelevant.

A study published by Yazici et al. [21] states that EORA starts after the age of 60 years and is a distinctly different disorder from YORA. In younger patients the disease is characterised by acute onset, affecting about three times more women than men. In contrast, RA in middle age has typically an insidious and often vague onset. In elderly patients, there is a tendency for the onset of the disease to be acute and infectious-like, involving also large proximal joints, shoulders in particular, while RA in middle age affects mainly small (PIP and MCP) joints of the hands [1, 4] – see Table 1.1.

In elderly patients, the clinical features are sometimes similar to those of polymyalgia rheumatica or symmetrical synovitis with pitting

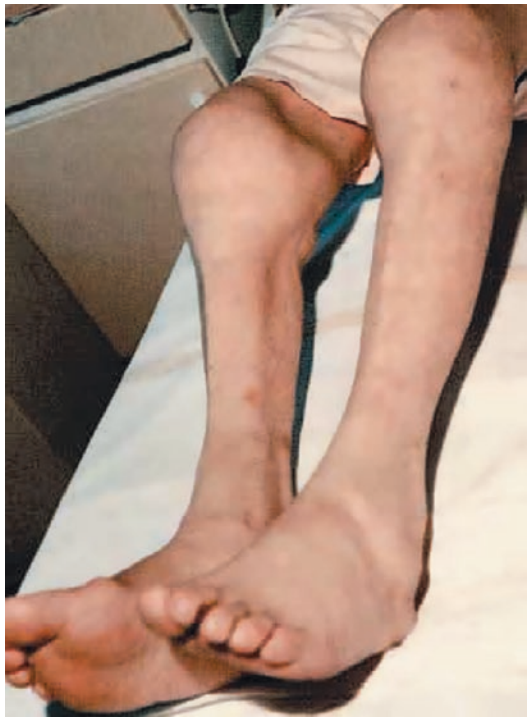

Fig. 1.3 Flexion contractures in knee joints in a patient with a long-term RA, including active gonitis and a marked muscle atrophy (Courtesy of Professor J. Vencovský, MD, DSc)

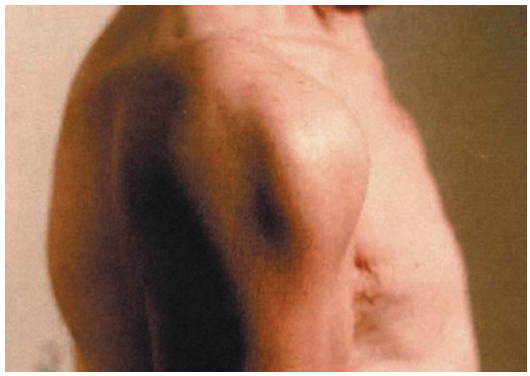

Fig. 1.4 Involvement of the shoulder joint in an EORA female patient. The joint capsule bulges with a massive effusion (Courtesy of Professor J. Vencovský, MD, DSc)

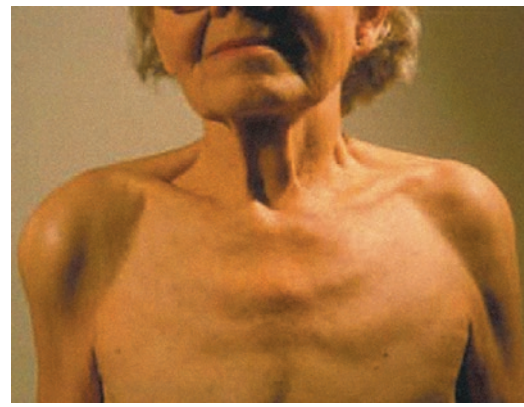

Fig. 1.5 Involvement of shoulder joints in an EORA female patient. Massive effusion is present in both shoulders, with a bulging joint capsule (Courtesy of Professor J. Vencovský, MD, DSc)

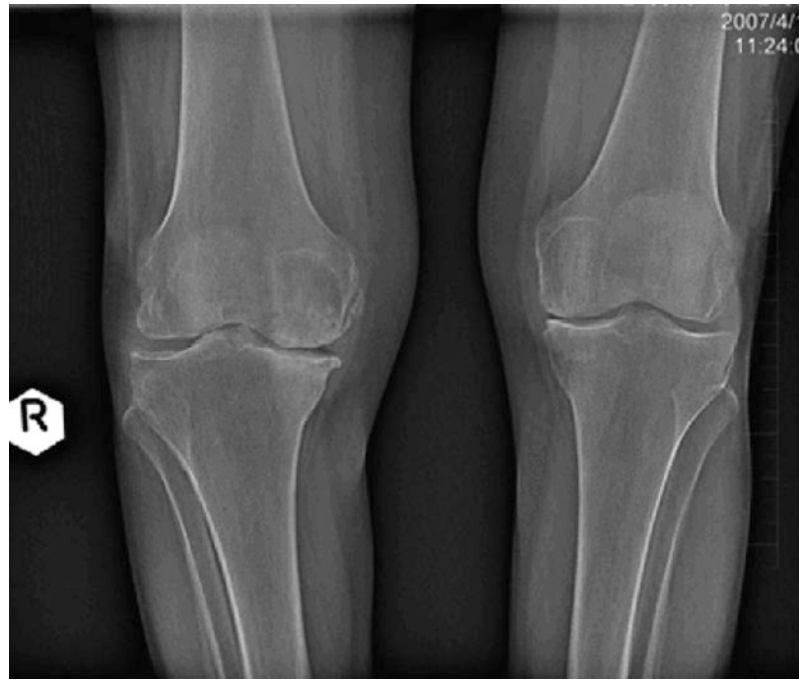

Fig. 1.6 Knee joints: *right* – stage III OA of the knee with varus deformity, joint space narrowing, subchondral sclerosis and osteophytes in the medial compartment. *Left* – slight joint space narrowing of the medial tibiofemoral joint and tibial erosion, in EORA

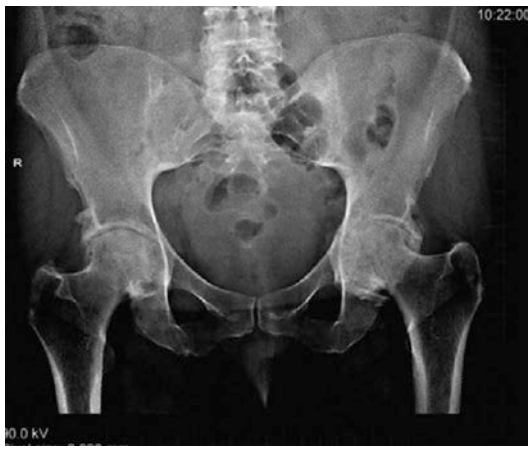

Fig. 1.7 Hip joints: stage II OA of the hip bilaterally and enthesophytes in typical locations. *Left* – coxitis in EORA, central joint space narrowing to minimum, thinning of the acetabular floor, even slight protrusion and mild subchondral cysts in the femoral head

oedema (RS3PE) syndrome. In older patients the onset of the disease is more often associated with systemic manifestations and a high sedimentation rate. Comparison of the specific features of the classical and of elderly-onset rheumatoid arthritis is shown in Table 1.1.

1.5 Extra-articular Symptoms

The number and severity of extra-articular symptoms vary with the duration and severity of the disease. A number of these symptoms may be combined with a disorder of the respective organ or with a process associated with another concomitant disease of a different type. As a result, more severe conditions can be often seen in elderly than in middle-aged patients.

Rheumatoid nodules are more often an extra-articular sign in RA and occur in about 20–30 % of patients, almost always together with the rheumatoid factor (RF). They usually develop under the skin over the proximal subcutaneous border of the ulna or over the olecranon. Multiple nodules over small joints of hands are termed rheumatoid nodulosis. Less often the nodules can be seen in the sacral or occipital region and quite rarely in the larynx, heart or lungs. Elderly patients are less likely to have subcutaneous nodules [9].

Tenosynovitis can be observed, mainly in the region of hands and wrists. Rupture of tendons, most frequently flexors or extensors of

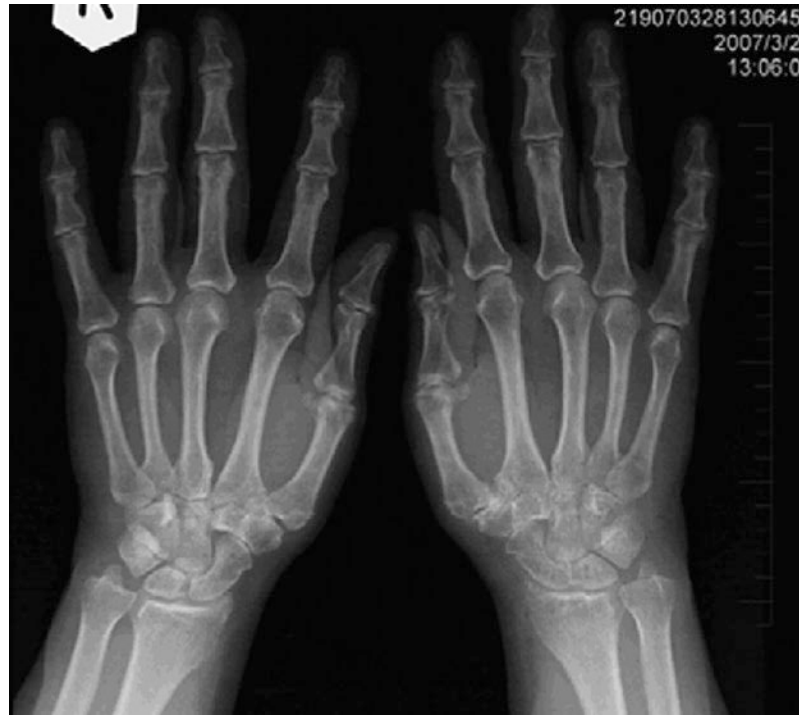

Fig. 1.8 Left wrist: stage II arthritis in the region of the DIP and PIP joints, stage II rhizarthrosis on the left, periarticular osteoporosis, slight joint space narrowing and widening of the shadow left wrist soft tissue – stage I arthritis within EORA

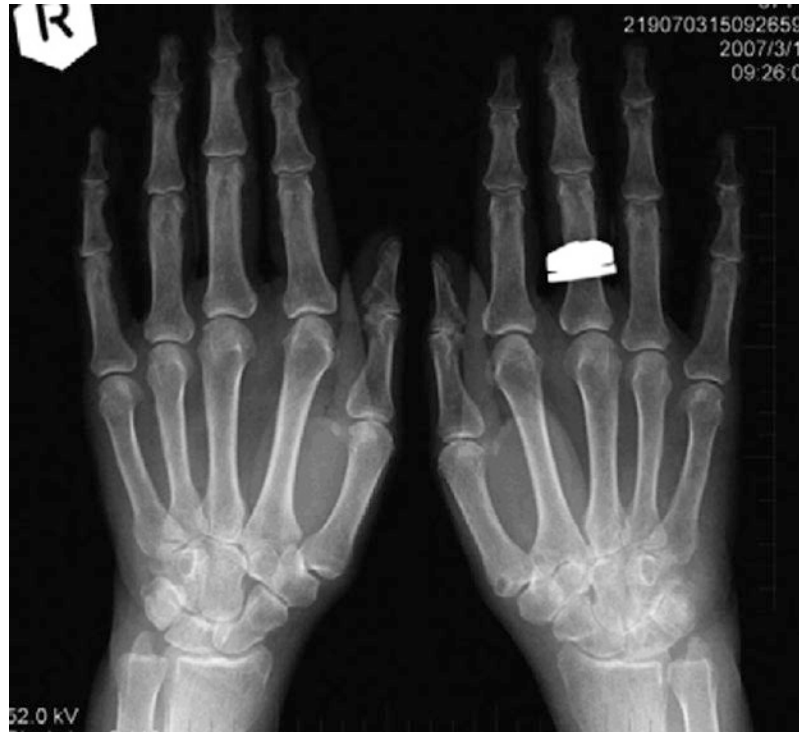

Fig. 1.9 Left wrist 2: stage II arthritis of DIP and PIP joints, joint space narrowing in the left wrist, mild periarticular osteoporosis, widened shadow of the soft tissue – degree I arthritis

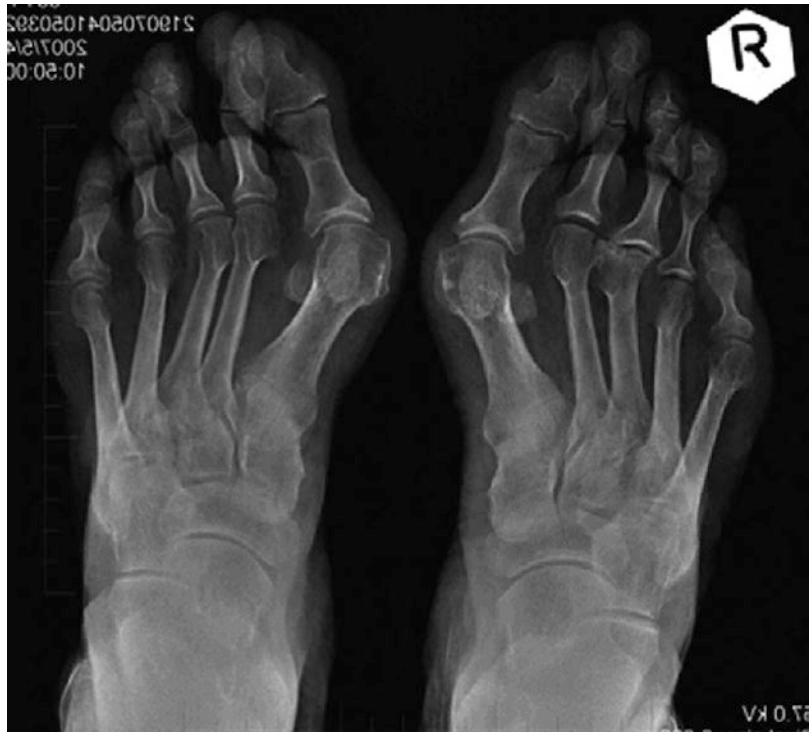

Fig. 1.10 Feet – hallux valgus with bunion and stage I arthritis of MTP joint bilaterally, condition after Köhler disease II. Erosion of MTP III on the right and erosion of MTP III on the left. Cysts and minor marginal erosion of the MTP V joint on the right in EORA

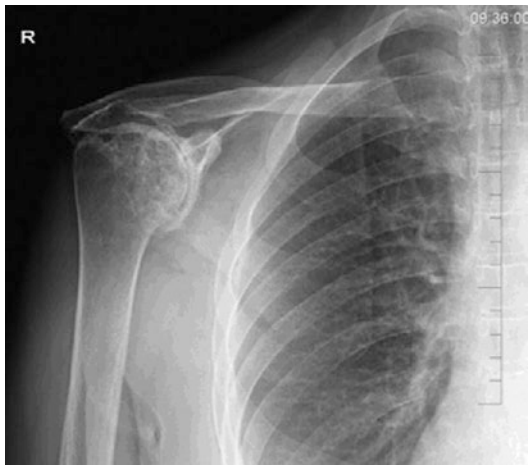

Fig. 1.11 Shoulder: joint space narrowing in the humeroscapular joint, erosion of the lateral edge of the articular surface of the humeral head, subchondral cysts of the humeral head in arthritis, simultaneous sclerosis and osteophytic spurs on articular surfaces – omarthritis, cranial migration of the humeral head towards the acromion – rotator cuff arthropathy in EORA

fingers, leads to development of deformities, with bursitis developing near joints. Muscles are involved quite often, and impaired mobility leads to atrophy and muscle weakness. In the elderly it is associated with the age-related loss of muscle mass. Also osteoporosis associated with RA may be more serious in elderly patients because of combination of several etiological causes.

A serious complication is vasculitis. Clinical manifestations include rash, cutaneous ulcers and both sensory and motor peripheral neuropathy. Pulmonary involvement may manifest itself by pleuritis, interstitial lung fibrosis or rheumatoid nodules. RA is often associated with a number of cardiac disorders, e.g. pericarditis, myocarditis, endocarditis, conductive defects and arteritis which as a rule do not cause symptomatic problems. Secondary amyloidosis occurs in 7 % of progressive RA, i.e. primarily in older patients with a long history of the disease. It is characterised mainly by impaired renal function that may be indirectly caused also by therapy. The most frequent ophthalmological disorder is dry eye syndrome, keratoconjunctivitis sicca (KCS), affecting about 10–35 % of patients.

EORA is sometimes divided into three groups: classic RA, seronegative RA similar to PMR (polymyalgia rheumatica) and a group with predominating Sjögren's syndrome symptoms. This division of EORA reflects a higher incidence of

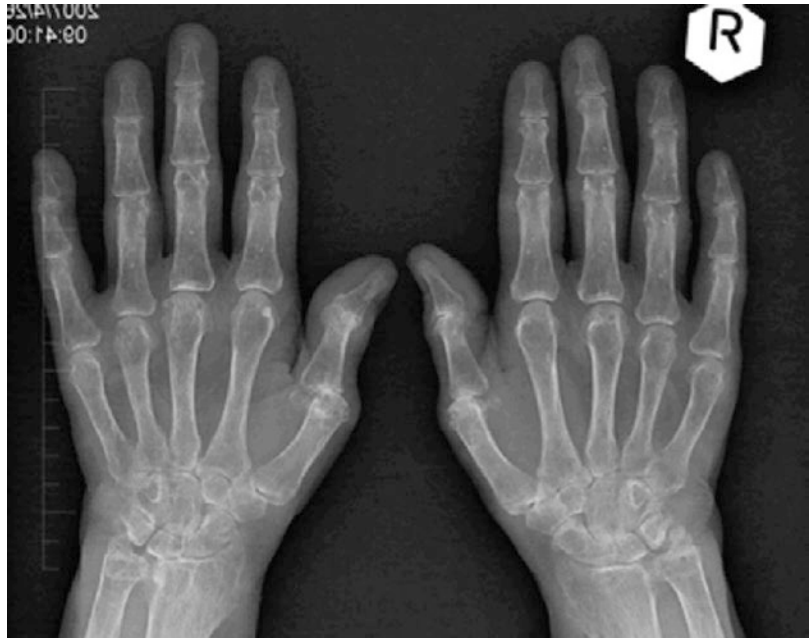

Fig. 1.12 Hands: diffuse osteoporosis mainly in the periarticular region of the left wrist; widened shadow of the soft tissue around PIP, MCP joints and in wrists; carpal and radiocarpal joint space narrowing bilaterally; cysts in the radiocarpal joint on the left; erosion of MCP I joint on the right, EORA; stages I and II arthritis of DIP, PIP joints, IP joints of thumbs and MCP III on the left side

Table 1.1 Comparison of classic versus elderly-onset RA

	Classic RA	Elderly-onset RA
Men/women ratio	1:3	1:1
Age at onset	30–50 years	More than 60 years
Onset	Gradual	Often acute, systemic manifestations
Number of joints	Polyarticular	Often oligoarticular
Involvement location	Small joints	Often large joints
Course of the disease	Variable severity	Often severe
Prognosis	Variable	Often severe
Rheumatoid factor	Predominantly positive	Predominantly negative

Modified according to Yazici et al. [21]

KCS and xerostomia. The most frequent haematological abnormalities include anaemia and thrombocytosis which develops mainly in the active stage of the disease [1, 4].

1.6 Immunological Changes During Physiological Ageing in Relation to Development of EORA and Immunopathological Condition

It is estimated that 25 % of human longevity is influenced by genetics, while the remaining 75 % is determined by lifestyle and environmental influences. In people aged 90 and more years, genetic factors are responsible for more than 25 % of their lifespan. The share of genetic factors in the general activity of the immune system differs in terms of natural and specific immunity. Natural immunity, including inflammation, is determined genetically, with almost no impact of environmental factors. Therefore, it is also called innate immunity. In contrast, specific immunity is genetically determined only roughly.

This concerns mainly the T-lymphatic component. Its activities are modified by specific environmental factors in the course of the human life.

The capacity of the human immune system is supposed to be the highest immediately after birth. Subsequently it gradually decreases due to various stress factors or a past history of inflammatory responses and diseases (mainly

chronic). One of the factors is also the fact that during evolution the human organism was set to live 40 or 50 years, but today the immune system must remain active for a much longer time. However, evolution changes take place in much longer period than in human lifespan. Accordingly, the annual age-dependent decline of immunity functions is higher than in other examined physiological functions.

The result of progressive changes in functioning of the immune system is immunosenescence. It is defined as abnormal regulation of immune responses, resulting in an increased susceptibility of the elderly population to infections and autoimmune, degenerative and tumorous diseases caused by cellular and molecular changes in mechanisms of the innate and acquired immunity. Innate immunity mechanisms are impaired by decline in dendritic cells that are the basic antigen-presenting cells inducing immune response. Macrophages have a decreased expression of toll-like receptors (TLRs) and, consequently, also reduced antimicrobial activity. On the other hand, their inflammatory activity grows as a result of increased production of pro-inflammatory cytokine IL-6. With the increasing age, expression of low-affinity Fc receptor for IgG (CD16) decreases on neutrophils, which results in a significant reduction of their phagocytic function. Activity of NK cells does not change or slightly grows. Elderly people have slightly lower levels of several complement components. The degree of its activation considerably decreases during infection which is another cause of their increased susceptibility to infectious diseases [22].

Another contributing factor is decreased capacity of antibody- and cell-mediated specific immunity. It is manifested mainly in responses to new infectious agents or vaccines. For instance, old people are substantially more susceptible to infectious complications after flu infection. In addition, the effect of flu vaccines on them is much less effective than in young and middle-aged adults [23]. The reason is primarily substantial changes in the T-lymphocyte repertoire. Adequately efficient immune response to a new infectious antigen depends on the function and repertoire diversity of naïve T-lymphocytes (which have not come into contact with the respective antigens, yet). These T-lymphocytes must be able to recognise a pathogenic antigen and, in response to it, to proliferate and differentiate into T-lymphocyte subpopulations with the necessary effector and regulatory functions. In addition, they must be able to migrate to the place of action. The key factor of this process is sufficient diversity of antigen receptors on the surface of naïve T-lymphocytes, providing a sufficient number of those of them that recognise antigenic determinants on a newly infecting pathogen. T-lymphocytes that have recognised it subsequently become activated and differentiate into helper Th-lymphocytes (CD4+), conditioning proper activity of B lymphocytes with a subsequent production of antibodies, or into cytotoxic Tc-lymphocytes (CD8+) with the respective effector functions.

In young people, the group of naïve T-lymphocytes is adequate to fulfil these functions, while in old people, it is significantly limited not only in terms of their numbers but also diversity of their antigen receptors that are able to recognise a new antigen. As a result, the function of effector and regulatory CD4+ and CD8+ T-lymphocytes, differentiating from them, is also reduced. On the other hand, the number of memory T-lymphocytes dramatically grows. They have already been in contact with their specific antigens and remember them, and therefore in repeated contact, they quickly become activated and may proliferate and form clones of effector cells. However, most of them are not able to become activated by new antigens. Reduction of the number and diversity repertoire of naïve T-lymphocytes and overfilling of the immunological space with memory T-lymphocytes is the main cause of impairment of anti-infection and antitumour immune defence of old people. In people older than 100 years, the naïve cytotoxic T-lymphocytes are already absent. Lymphocytes in their blood are almost solely of the memory phenotype. This change in the ratio of naïve and memory T-lymphocytes does not progress in a linear way during the life and changes dramatically in favour of memory T-lymphocytes mainly after the age of 60–65 years.

1.6.1 Paradox of Immunodeficiency and Stimulation of Chronic Inflammation During Ageing

This paradox consists on the one hand in deterioration of the function of the immune system caused particularly by progressive decreasing of the function of T-lymphocytes and, on the other hand, in development of chronic inflammation documented by the age-related increased levels of pro-inflammatory cytokines (IL-6, TNF, IL-1, IL-8), acute-phase proteins (C-reactive protein, serum amyloid A) and a higher frequency of chronic inflammatory diseases, such as Alzheimer's disease and Parkinson's disease, amyotrophic lateral sclerosis, elderly-onset rheumatoid arthritis (EORA), autoimmune diseases – elderly-onset systemic lupus erythematosus – atherosclerosis and other diseases [24].

What is the cause of these negative changes? Presumably the main causes of deteriorating function of lymphocytes are alterations in their response to the regulatory effect of certain cytokines (IL-2, in particular) and increased sensitivity to induction of the programmed cell death – apoptosis – through receptor for tumour necrosis factor (TNF). Throughout the whole life, the human body continuously responses by defensive inflammation to a wide range of infectious and other insults causing tissue damage. The triggering (alarm) cytokine, which is commonly released into circulation in the case of acute inflammation, is the tumour necrosis factor (TNF). Therefore, also its systemic concentration grows with age. This results in progressive increase of apoptosis and reduction of T-lymphocytes that have receptors for TNF on their surface. The cells that underwent apoptosis are phagocytosed by phagocytes, such as macrophages and dendritic cells, whose phagocytic function, however, decreases with age.

Therefore, they are not able to liquidate rapidly and efficiently apoptotic lymphocytes. As a result, the apoptosis process turns into secondary necrosis, with a developing chronic inflammation which damages the surrounding tissue.

During the process of ageing, development of chronic inflammation stimulates elevated levels of pro-inflammatory cytokines. Causes of such increase are not exactly known. However, they certainly include repeated defensive inflammatory responses with production of free radicals and other inflammatory mediators that are toxic not only for the damaging infection agent but also for cells of the surrounding tissue. Another factor is apoptosis of lymphocytes increasing with age and their inadequate removal by dendritic cells and macrophages. Apoptosis is associated with activation of caspases, some of which directly produce active pro-inflammatory cytokines IL-1β and IL-18.

This chronic systemic inflammatory condition, characteristic of ageing, is termed inflammaging. It is a low-grade chronic systemic stimulation of pro-inflammatory responses [24, 25]. It may be considered as a certain evolutionary relict that contributed in the past to survival of human population, particularly in the conditions of devastating epidemics and pandemics of infectious diseases. At that time, mainly individuals with a more efficient pro-inflammatory genotype survived. Inflammatory genotype predominates also in the current human population. As a defence against infectious diseases, it is more efficient in children, although this advantage has been recently debated in connection with epidemic spread of allergic diseases. In advanced age, this advantage of inflammatory genotype is erased, as it causes increased susceptibility to chronic inflammatory diseases, for instance, elderly-onset rheumatoid arthritis, polymyalgia rheumatica, giant cell arteritis and other autoimmune diseases (elderly-onset SLE, Werner's syndrome as a variant of systemic sclerosis and others).

A particular inflammatory genotype of each individual is determined by about 400 different genes with multiple polymorphisms that determine quantitative differences between their carriers. Based on them, two extreme genotypes may be distinguished. "More pro-inflammatory" genotype is characterised by low production of anti-inflammatory cytokine IL-10 and high production of pro-inflammatory cytokine IL-6, while "less pro-inflammatory" genotype by high production of IL-10 and low production of IL-6. Individuals with a genetic predisposition to produce high

levels of IL-6 and low levels of IL-10 have a lower ability of normal regulation of the inflammatory process and a decreased resistance to inflammatory and tumorous diseases. At the same time, they exhibit an increased incidence of syndromes of innate (natural) autoimmunity, and their chance to live long declines. This may be indicated also by the fact that a great majority of individuals in the age category of 90–100 years are only "producers" of high levels of IL-10 [27]. Syndromes of innate autoimmunity, including, for instance, atherosclerosis and the related pathological entities [28], should be distinguished from conventional autoimmune diseases, the pathogenesis of which is predominated by specific immunity mechanisms (autoantibodies, autoagressive T-lymphocytes).

On the other hand, disorder of immune homeostasis during physiological ageing may be involved also in the pathogenesis of conventional autoimmune diseases.

On the basis of the existing findings, it may be concluded that metabolic, functional and clinical manifestations associated with age quite well correlate with the functional activity of the immune system. The immune system is part of the neuroendocrine-immune system that plays a decisive role in regulation of homeostasis in humans. Therefore, its inadequate or otherwise abnormal function will be reflected also in homeostasis changes influenced by genetic, internal and external factors. Genetic factors determine the genotype of an individual that cannot be practically influenced. It has been shown that in terms of the quality of life and longevity, the genotype of producers of high levels of anti-inflammatory IL-10 and low levels of pro-inflammatory IL-6 is more advantageous than a genotype with the opposite characteristics of these two cytokines.

To a certain extent, it is possible to influence the phenotype of each individual. It is determined primarily by environmental factors, eating, working and social habits. Onset of immunosenescence may be postponed in individuals who live in a hygienic environment with a minimal exposure to persisting viral and parasitic infections, with available adequate medical care, vaccination, safe food, uncontaminated water and air, i.e. in an environment with minimal incidence of antigens and stress factors that would exhaust the immune system and lead to accumulation of chronic inflammatory responses. All these factors that were established in the advanced countries in the middle of the last century have contributed to lengthening of the average human lifespan but, on the other hand, quite probably also to epidemic development of allergic diseases. This is also the rationale behind the hygienic hypothesis that, namely, insufficient infectious stimuli and "excessive" hygiene, mainly in childhood, result in abnormally developed "maturity" of the immune system, which is manifested by increased susceptibility to development of allergic inflammatory responses. Their clinical forms include allergic eczema, nasal allergy, allergic hives and bronchial asthma.

Thus it seems that from the viewpoint of a normal development and activity of the immune system, its "inactivity" with a low pressure of antigens is equally disadvantageous as excessively repeated responses to the presence of infectious agents or other factors damaging its cells and tissues. Infectious agents may lead to a more rapid onset of immunosenescence and development of a systemic chronic inflammation with subsequent clinical manifestations, such as cardiovascular diseases, a majority of tumorous and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus, osteoporosis, osteoarthritis (OA), Alzheimer's and other degenerative diseases [26].

A new medical discipline – preventive anti-ageing medicine – focuses on postponing the onset and decreasing intensity of manifestations of immunosenescence, by extensive therapies and preventive procedures aimed at achieving an optimal lifespan and enhancing the quality of life.

Its goal is to influence the ageing process by pharmacological and psychotherapeutic means and reduce morbidity and disability in the old. Its important part is strengthening of immunity by various immunostimulatory means, such as probiotics, sufficient supply of proteins, certain vitamins and trace elements (especially selenium) and reasonable physical and mental activity.

1.7 Hormonal Findings and Cytokine Levels in Polymyalgia Rheumatica, EORA and EORA/ Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR) may in terms of differential diagnosis pose certain problems as concerns nosographic distinction between EORA and EORA with PMR-like onset (EORA/PMR). Cutolo et al. [29] and Sully et al. [30] studied levels of TNF-alpha and IL-6 in the above-mentioned nosological entities and found out that concentrations of TNF-alpha and IL-6 in plasma were higher in PMR, EORA and EORA/PMR as compared to the control group. The results also showed that IL-6 concentration was higher in PMR and EORA/PMR than in the group of EORA patients. Concentration of the IL-1Ra receptor antagonist was higher in EORA patients as compared to the controls, and similarly IL-1Ra was also more frequent in PMR and EORA/PMR patients. Concentration of adrenal androgen dehydroepiandrosterone sulphate (DHEAS) was lower in EORA/PMR than in EORA patients. Progesterone (PRG) levels were provably higher in all studied diseases. After administration of glucocorticoids, the levels of serum TNF-alpha and IL-6 provably decreased in all three nosological entities.

IL-1Ra provably increased in PMR patients as well as in the group of EORA/PMR patients. As expected, after glucocorticoid treatment the levels of cortisol, DHEAS and PRG decreased both in PMR and EORA/PMR patients.

The results of both studies have indicated that different cytokine and steroid profiles suggest that in PMR and EORA/PMR, the inflammatory response is more intensive than in EORA alone, and the effect of glucocorticoid treatment is more efficient than in EORA alone. The results of a recent research in this field (Cutolo et al. [29]) have confirmed in PMR a lower production of adrenal cortex hormones, such as cortisol and DHEAS in basal secretion [31]. It seems that the disorder relates to the impaired response of adrenal glands to Adrenocorticotropic hormone (ACTH) stimulation, e.g. elevated PRG levels in untreated patients and subsequently after 1-month glucocorticoid treatment with a decrease of levels of inflammatory mediators, such as IL-6. For this reason PMR may be classified as a disease with a concurrent hypofunction of the hypothalamic-pituitary-adrenal axis [32, 33]. Cutolo et al. [29] point out an important fact that the decrease of the cortisol level after 1-month glucocorticoid treatment was more significant in PMR and EORA/PMR than in EORA patients. This indicates that changes in the function of the adrenal axis in EORA patients might not be as marked as in PMR.

High basal PRG level in PMR and EORA/PMR may be related to the impaired response of adrenal glands to ACTH stimulation. PRG is a precursor of glucocorticoid biosynthesis in adrenal glands, and its elevated level in plasma may indicate a decreased function of the 21α-hydroxylase enzyme. And finally, reduction in DHEAS is considered to be a general feature of chronic inflammatory diseases, including RA [34].

Laboratory examinations show that PMR patients have a more intensive inflammatory response than EORA patients. This fact is confirmed also by the results of ESR, CRP and IL-6 levels. On the other hand, the detected higher IL-1Ra plasma level in EORA patients as compared to EORA/PMR patients may have a protective effect, mainly in terms of bone erosions. A higher IL-1Ra level indicates that EORA alone has a lower erosive activity, which is typical of a subgroup of elderly RA patients [34].

1.8 Laboratory Examinations

Erythrocyte sedimentation rate is in most patients markedly elevated and correlates with the disease activity. Elderly-onset RA is usually associated with higher ESR but also C-reactive protein than the classic RA [35, 36]. In YORA, rheumatoid factors are present in about 80–85 %, while in EORA in about 65 % of patients [6]. However, in elderly patients the criterion of RF presence is not so important from the diagnostic viewpoint, because RF seropositivity in population over 60 years of age without an evident chronic disease ranges between 15 and 20 %, although the levels

are not in most cases high [5]. Therefore, it is recommended to consider in elderly patients the first positive RF titre to be 1:1,280 in latex fixation test, as compared to 1:160 in middle age. In part of seronegative EORA patients, RF may be proved by a more sensitive method, and thus the frequence will not be obviously so different. It is rather a case of incidence of another RF type [4]. The ELISA method is used to determine isotypes of rheumatoid factors – IgG RF is associated with the presence of vasculitis, and IgA RF with development of bone erosions. New tests using anti-cyclic citrullinated peptides (CCP) antibodies are highly specific for RA and correlate with severe diseases. Their presence at the onset of the disease seems to have a significant prognostic value [4]. Anti-CCP, however, were not detected in EORA, unlike RF, where its presence is associated with persistence of arthritis, a more rapid and more severe functional impairment and a higher mortality [37].

1.9 Differential Diagnosis

The basic nosological entity that must be distinguished from EORA is PMR. In 1992, Healey [38] pointed out a marked incidence of similar clinical manifestations in patients with PMR and seronegative RA. Later, temporal arteritis (TA) was observed in patients with both diagnoses.

The author has stated that non-erosive symmetrical synovitis may be present in PMR or in polyarthritis mimicking elderly-onset RA. As shown by Gonzalez-Gay et al. [14], seronegative EORA is a sub-entity that is very similar to PMR, and both the diseases have a genetic predisposition in the form of the presence of HLA-DR-B1.

At the same time, it may be stated that both diseases are closely associated with this genetic trait from the HLA antigen group. It means that they may be triggered by a similar pathogenetic mechanism. The clinical features show the presence of arthritis with swelling of limbs, pitting oedema and incidence of tenosynovitis in all cases of PMR. In PMR, however, antibodies against cyclic citrullinated peptides (CCP) that are highly specific for RA are not as a rule present. In this connection the study published by Spanish authors should be noted; they have pointed out that the presence of anti-CCP antibodies in patients with PMR clinical symptoms suggests that the disease should be rather diagnosed as EORA [39]. Involvement of shoulders in EORA and PMR patients requires ultrasound examination which shows a symmetrical and massive inflammation of periarticular structures and joints in the case of EORA, while involvement of one shoulder only, with a low-grade inflammation, is typical of PMR. On the other hand, other studies of PMR patients revealed such involvement neither by ultrasound examination nor by magnetic resonance imaging. It may be summarised that EORA-like PMR could be rather PMR-like RA, and anti-CCP antibodies may play an important role in differential diagnosis [39].

1.10 Remitting Seronegative Symmetrical Synovitis with Pitting Oedema

It is a symmetrical acute synovitis involving small joints of hands and wrists or feet and ankles primarily in elderly patients, with male predominance [39]. Extensor tenosynovitis is a disorder responsible for pitting oedema of dorsum of hands and feet [40]. However, a similar clinical manifestation with a soft tissue swelling may occur in polymyalgia rheumatica, rheumatoid arthritis, spondyloarthritis as well as haematological and well-defined tumours. In these nosological entities, distribution of oedema is usually asymmetrical. As a rule, this disease is associated with elevated erythrocyte sedimentation rate and acute inflammatory phase reactants. Therapy with small dosages of glucocorticoids is highly efficient. However, it should be noted that signs of contractures of fingers, wrists and elbow joints may persist in the clinical presentation.

HLA-B27 is present in two thirds of cases, and this finding indicates that in terms of nosology, the RS3PE entity is different from EORA. Differential diagnosis of RS3PE should

take into account also potential incidence of paraneoplastic syndrome [41].

1.11 Spondyloarthritis

Spondyloarthritis includes ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated spondyloarthritis. They primarily affect thoracic spine, sacroiliac joints, but there may occur also extra-articular manifestations including peripheral enthesitis, tenosynovitis and bursitis. These manifestations are very important in terms of differential diagnosis of individual nosological entities. Peripheral symptoms and manifestations are usually asymmetrical. Imaging techniques, including radiograph, MR, CT and ultrasound, are usually used in examination and nosographic definition of individual nosological entities.

Ankylosing spondylitis (AS) typically affects young adults, and therefore its EORA-like form is very rare. Differential diagnosis to distinguish spondyloarthritis from EORA is often more difficult in older people with undifferentiated spondyloarthritis and in elderly-onset psoriatic arthritis. In 1989, Dubost and Sauvezie [42] described undifferentiated elderly-onset spondyloarthritis characterised by oligoarthritis, pitting oedema in lower limbs and minimal involvement of the axial skeleton. General symptoms of the disease are usually minimal. Laboratory findings include elevated erythrocyte sedimentation rate. The authors assume that undifferentiated elderly-onset spondyloarthritis might have such a clinical presentation. Only recently, clinical manifestations of undifferentiated spondyloarthritis have been detected not only in elderly people but also in children, adolescents and middle-aged population. A great majority of elderly patients with undifferentiated spondyloarthritis meet classification criteria of the European Spondyloarthropathy Study Group.

Rheumatologists often find it difficult to distinguish between symmetrical psoriatic polyarthritis without involvement of the axial skeleton in the elderly and rheumatoid arthritis in the first phases of the disease because not even imaging techniques are able to identify changes typical of either of them. Oedema of lower limbs may occur both in psoriatic arthritis and rheumatoid arthritis. Rheumatoid arthritis, however, is not associated with enthesitis and dactylitis that are typical of psoriatic arthritis. Determination of anti-CCP antibodies cannot serve as a reliable criterion distinguishing these two nosological entities as they are positive in 7–16 % cases of psoriatic arthritis [1].

1.12 Crystal-Induced Arthritis

Local symptoms of inflammation are more frequent in crystal-induced arthritis than in EORA. In gout, sodium urate microcrystals are usually present in the synovial fluid.

Clinical features often include repeated attacks of arthritis in one or more joints, with a good response to the treatment by non-steroidal antiphlogistic drugs or colchicine. Symmetrical polyarthritis is quite frequent. In men, gout starts typically in younger age groups, while in women it may start later. Radiological abnormalities, including urate deposits in soft tissues, paraarticular erosion and osteolytic lesions, are associated with advanced stages of the disease. Differential diagnosis must consider also the possibility of secondary gout (e.g. due to long-term diuretic therapy).

In the case of calcium pyrophosphate arthropathy, the radiograph will show speckled or linear calcifications in fibrous and articular cartilage and in joint capsules. These calcifications are not always associated with inflammatory symptoms and may be asymptomatic mainly in the elderly, which complicates differential diagnosis [44].

1.13 Various Pathological Conditions

Erosive osteoarthritis may be confused with RA development. However, erosive osteoarthritis affects usually DIP joints and exceptionally MCP

joints, while in EORA it is just the opposite. In erosive osteoarthritis, the bone erosion is located centrally as compared to marginal erosions typical of RA. Anti-CCP antibodies may be helpful in differential diagnosis as they are usually negative in erosive osteoarthritis. Due to the incidence of erosive osteoarthritis in older age groups, the RF parameter is usually not reliable because RF is more frequently positive in older individuals [4].

One of the two sub-entities of hepatitis C is characterised by the presence of arthritis mimicking rheumatoid arthritis and has to be taken into account in differential diagnosis in elderly individuals, particularly in groups with a more frequent incidence of hepatitis C virus infection. Arthritis is characterised by the absence of rheumatoid nodules and elevated erythrocyte sedimentation rate in half of the patients. The clinical course of the disease is usually milder than in RA (the absence of erosions); anti-CCP antibodies are as a rule not present in hepatitis C virus-related arthritis.

RA-like arthritis may be the first manifestation of occult malignancy [41]. Mok and Kwan [43] suggested that active polyarthritis, with unexplainable anaemia and general symptoms, not responding to adequate treatment, may be associated with an occult and unexplained tumorous disease. An efficient therapy of malignancy may then suppress arthritis in such pathological conditions.

1.13.1 Therapeutic Procedures in EORA Treatment

The basic therapeutic procedures in RA treatment are focused on:

1. Improvement of symptoms of active inflammation
2. Prevention of further tissue destruction
3. Preservation of function of joints
4. Prevention of joint deformities
5. Slowing down of the disease progression in view of morbidity

1.14 Non-pharmacological Treatment

The basic non-pharmacological procedures include special rehabilitation therapy methods aimed at preservation of the function of joints and of striated muscles. It has to be taken into account that RA patients are susceptible to development of cardiovascular diseases and osteoporosis. Therefore, adequate physical activity is very important. Nevertheless, it is very difficult to standardise rehabilitation techniques and compare their effects in various rehabilitation therapy programmes. In addition, rehabilitation therapy in EORA has not been developed on a scientific basis, yet. It has been generally accepted that a moderate or high intensity of exercises may improve breathing as well as functional capacity of the organism. High-intensity exercises focus mainly on small joints of hands and feet, but a long-term rehabilitation therapy should be prescribed cautiously in weight-bearing joints, as high-intensity workout may accelerate the progression of large joint damage. High-intensity rehabilitation procedures for weight-bearing joints may be applied only in RA patients with a slow loss of bone mass in hip joints. And finally, physical therapy may help reduce pain and the morning stiffness.

1.15 Pharmacological Treatment

Pharmacological treatment of EORA must reflect changes in the organism during physiological ageing, mainly in terms of pharmacokinetics and pharmacodynamics of drugs, coexistence of other diseases and drugs as during physiological ageing the effect of the same drug may be reduced. Decrease in clearance may be caused by reduction in liver volume, which results in lower enzymatic activity; pharmacokinetics may be decreased as a result of lower renal blood flow and reduced glomerular filtration and tubular function.

It is generally known that EORA patients receive more medications as compared to younger

patients, due to polymorbidity typical of older age, and there is a high risk of drug interactions.

Polypharmacy may lead to impairment of cognitive functions, vision, and other alterations.

Five groups of drugs are used in EORA treatment, namely, analgesics, non-steroidal antirheumatic drugs, glucocorticoids, classic drugs modifying the course of the disease and anti-cytokine therapy [45] (for anti-cytokine therapy, see page 52).

1.16 Analgesics

Non-narcotic analgesics, such as paracetamol, may be used as adjuvant therapy in a comprehensive treatment of arthritis mainly in patients with contraindication for other drugs. A dosage of paracetamol of less than 2 g per day is safe also in patients with liver diseases and alcoholics. However, adverse gastrointestinal events were reported with its higher dosage. It must be also taken into account that regular administration of drugs of paracetamol type is associated with an increased risk of chronic renal failure. Combination of paracetamol and codeine or other opioid analgesics should be prescribed very cautiously as it may cause excessive sedation, impairment of cognitive functions and obstipation in elderly patients.

1.17 Non-steroidal Antirheumatic Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to reduce pain in RA, but it has to be taken into account that in elderly patients, the risk of adverse effects is higher. These effects include primarily gastrointestinal, renal and cardiovascular events. In addition the effect on the central nervous system is more intensive in the elderly than in the younger patients. In the USA, gastroduodenal toxicity related to NSAID use accounts for 2,660 deaths annually – this is one of the crucial and most serious problems of RA patients. RA patients face a high risk of ulcer complications, including bleeding, perforation and obstruction, occurring in a total of 2–4 % of cases annually as compared to 0.5 % of patients without any risk factors. Risk factors for adverse effects of NSAID include the age over 60 years, previous history of ulcer disease or complications caused by ulcer disease, high NSAID dosage and use of glucocorticoids together with anticoagulants. The risk of development of NSAID-related gastrointestinal complications is naturally higher in patients with two or more risk factors. The aim of treatment is to reduce this risk by the following therapeutic procedures:

1. Administration of non-selective NSAIDs + misoprostol or proton pump inhibitors
2. Administration of selective COX-2 inhibitors

Currently only two selective COX-2 inhibitors – celecoxib and etoricoxib – are used in the therapy. The previously used coxibs, e.g. rofecoxib, were withdrawn from the market and deregistered as they were associated in the long run with increased risk of vascular events and myocardial infarction. Valdecoxib was deregistered due to incidence of adverse skin reactions. Celecoxib at the daily dose of up to 200 mg should be administered only in the lowest effective dose. The risk of myocardial infarction increases with its long-term use at the daily dose of more than 400 mg.

Eradication of *Helicobacter pylori* infection which occurs in more than 70 % of elderly individuals may reduce the risk of gastrointestinal complications arising from NSAID administration in patients with glomerular disease and pre-existing chronic kidney disease, hypercalcaemia or other conditions such as heart failure and decompensated cirrhosis. It is generally known that NSAIDs reduce renal blood flow and glomerular filtration rate and even cause an acute kidney injury. It has to be taken into account that both non-selective NSAIDs and selective COX-2 inhibitors may produce a serious adverse effect.

Other adverse effects of non-steroidal anti-inflammatory drugs may include sodium and fluid retention leading to development of a peripheral oedema, hypertension and severe congestive

heart failure. In addition, NSAIDs increase the risk related to antihypertension therapy in elderly people, and the intensity of the risk grows in proportion to the drug dosage. Adverse effects of NSAIDs include psychotic reactions, cognitive impairment and depression in elderly people.

Indomethacin may cause more problems than other NSAIDs, and therefore it should be prescribed with great caution in the elderly, as it may induce mental function disorder.

1.18 Glucocorticoids

Administration of glucocorticoids in EORA treatment is a subject of continuous debates in terms of both their efficiency and multiple adverse effects in elderly patients, particularly diabetes mellitus, cardiovascular changes, cataract, glaucoma, moon face and osteoporosis. Oral glucocorticotherapy lasting for more than 6 months increases 2.3 times the risk of newly developed diabetes in elderly people. Congestive heart failure may result in fluid retention caused by glucocorticoids, particularly in the case of supraphysiological doses. A daily prednisone dose of more than 7.5 mg is a risk factor for development of myocardial infarction, stroke and transient ischemic attack. The risk of heart damage is three times higher with administration of glucocorticoids as compared to patients who do not use these drugs.

It has been also found out that glucocorticoids may slightly impair cognitive functions in elderly people or exacerbate the pre-existing cognitive deficit.

Short-term administration of low doses of prednisone (less than 10 mg per day) or other medical preparations of this group may improve temporarily symptoms and signs of active rheumatoid arthritis and the function of joints before the clinical response to the basal therapy takes effect. Meta-analysis of ten randomised studies of oral administration of low doses of glucocorticoids (less than 15 mg per day) as compared to placebo or NSAIDs has confirmed that prednisolone is much more effective than placebo and NSAIDs in improving joint tenderness and grip strength [39]. Short-term low-dose glucocorticoid therapy is only rarely associated with serious adverse effects. Reports of the benefits of long-term low-dose glucocorticoid treatment of RA patients are contradictory. Some studies have demonstrated a protective effect of corticosteroids as compared to radiographic progression [39]; others have confirmed that there was no clinical or radiological benefit during more than 2 years of follow-up of patients who used glucocorticoids. However, long-term administration of low doses of corticosteroids may cause multiple adverse effects. It is necessary to administer the lowest possible doses (about $\leq$5 mg/day) and monitor loss of bone mass. The American College of Rheumatology (ACR) recommends the following therapy to prevent bone loss and fractures in patients receiving prednisone $\geq$5 mg/day for a period of 3 months: baseline and serial bone mineral density measurements, calcium intake of 1500 mg/day, vitamin D 400–800 IU and bisphosphonate therapy (alendronate or risedronate).

Pulse therapy with methylprednisolone at a dose of 1 g/day for three days may be used in the case of significant exacerbation of EORA. Minipulses at the dose of 100 mg are also highly effective. However, the effect of both dosage regimens is only temporary. On the other hand, pulse therapy has no adverse effects, which is an advantage as compared to long-term oral therapy [1].

Intraarticular administration of glucocorticoids, particularly those with a long-term effect such as triamcinolone, is safe and effective mainly in the case that acute inflammation involves only a few joints. Improvement of symptoms varies and ranges from several days up to months. Intraarticular glucocorticoids must not be applied more than four to six times in one joint during 1 year, as there is a danger of rapid damage to the articular cartilage.

1.19 Disease-Modifying Antirheumatic Drugs (DMARDs)

1.19.1 Methotrexate

Methotrexate (MTX) is used in many countries as a key drug from the group of disease-modifying antirheumatic drugs. It is usually administered

once a week orally or parenterally. The dose ranges from 7.5 to 25 mg/week, although recent studies have shown that a higher dose (15–45 mg/week) does not improve the course of the disease. Outcomes of MTX administration in EORA are not known. One study has analysed safety and efficacy of oral MTX at a dose of 7.5 mg/week in 33 RA patients with the mean age of 78.8 years. The results have shown that a low MTX dose in elderly individuals seems to be safe and the most significant risks may be eliminated by regular testing of the liver and kidney functions. Another study compared MTX efficacy and toxicity at a dose of 7.5–15 mg/week in patients older than 65 years and in younger persons. No differences in the quality of the effect were found out. Despite these facts it is necessary to take into account in MTX administration that its clearance decreases with age, similarly as creatinine clearance. The half-life of the drug is also provably longer in the elderly patients. MTX alone may also impair renal functions, and therefore it is recommended to give only low doses to the elderly patients.

Some other drugs, such as cyclosporine, naproxen, ibuprofen, ketoprofen and salicylates, may reduce creatinine clearance similarly as MTX. Sulphonamides, tetracycline, salicylates, phenytoin and chloramphenicol may replace MTX in plasma albumin.

Advanced age may be a risk factor for MTX-induced bone marrow suppression and may cause also changes in CNS. Protracted administration of MTX for more than 3 years and of prednisone ≤5 mg/day is associated with a higher loss of bone mass, mainly in the region of the lumbar spine, when compared to patients receiving prednisone alone.

Folic acid supplementation reduces liver impairment, especially abnormal liver tests, and gastrointestinal intolerance induced by MTX, but provably does not reduce the effect of the drug in RA. It is generally known that high levels of homocysteine in the blood are a risk factor for development of cardiovascular diseases. MTX may increase its level, probably by reduction of the renal function. Advanced age alone is characterised by the presence of hyperhomocysteinaemia. Its occurrence is effectively influenced by regular administration of the folic acid. In some countries the folinic acid is usually administered at a dose of 7.5 mg/week, which is more effective than the folic acid alone, in order to increase the volume of red blood cells in elderly RA patients [45].

1.19.2 Leflunomide

Based on our experience, leflunomide is a very interesting and effective DMARD. Its administration in elderly patients does not require any special precautions except for periodical monitoring of biochemical parameters as recommended in the summary of product characteristics (SPC) [46]. However, the results related to administration of leflunomide in EORA are missing. In any case it is suitable to check blood pressure as the drug in combination with physiological ageing may be associated with development of hypertension. Recent studies focused on frequency of adverse effects after administration of leflunomide have shown that it is well tolerated, similarly as MTX and sulfasalazine. A retrospective cohort study of a large US insurance claims database provided very good results concerning leflunomide administration [47]. On the other hand, the Dutch and French researchers pointed out a high number of discontinuations of the treatment due to adverse effects of leflunomide [48, 49]. In the view of a number of rheumatologists, adverse effects could be reduced by replacing the loading dose of 100 mg administered for three days by the common dose of 20 mg/day. Our results show that in some patients, a dose of 20 mg administered every other day is sufficient. However, this drug is not suitable for patients with liver impairments, and alcohol consumption may also severely damage the liver [1].

1.19.3 Cyclosporine

Cyclosporine is usually given to patients with autoimmune diseases. In RA, it had a similar effect as other DMARDs, and moreover cyclosporine inhibits radiographic progression and development of joint erosion. As the only DMARD drug, cyclosporine may be used in

elderly patients with severe RA, where MTX cannot be applied. There is so far lack of experience in administration of this drug in EORA; in elderly EORA patients, a medium dose of 2–2.5 mg/kg is recommended. Pharmacokinetics of cyclosporine is usually not influenced by age [50]; this drug may often cause hypertension and nephrotoxicity [51]. Renal failure may be acute, chronic and irreversible, as a result of interstitial fibrosis, tubular atrophy and hyaline degeneration of the afferent arteriole and its wall. Renal acute failure results from reversible imbalance between renal vasoconstrictors and vasodilators [51].

1.19.4 Sulfasalazine

Sulfasalazine is a drug which significantly dampens down RA activity, but its impact on radiographic progression seems to be low. Drosos et al. [52] have pointed out that sulfasalazine could be used as an alternative to MTX in the group of elderly patients treated for mild or moderate RA. In elderly people the size of sulfasalazine tablets and their gastrointestinal intolerance may pose a serious problem, as in older individuals the sulfasalazine degradation half-life is usually longer.

It has been also proven that acetylation is slower in the elderly, and the sulfasalazine degradation half-life increases from 13 to 20 h. Adverse effects are associated with the serum level of sulfapyridine which is a component of sulfasalazine [53, 54].

1.19.5 Hydroxychloroquine

In RA treatment, hydroxychloroquine is reported to be more efficient than placebo, but its efficacy is very low as compared to MTX [45]. Its application is very suitable in elderly patients with a nonaggressive RA form [52]. Its molecule is safe. Therapy with hydroxychloroquine does not require monthly blood pressure checks as in other basic drugs, but blood count tests and kidney and liver function tests on a quarterly basis are recommended. The most adverse effect of hydroxychloroquine is potential visual impairment, particularly its impact on the retina. Toxicity of the preparation may lead to continuous vision impairment and blindness. The latest studies examined 524 persons treated with hydroxychloroquine at a dose of 6.5 mg/kg/day and revealed that impairment of the retina during the first 6 years of the treatment was very low [55]. The group comprised patients without retinal findings, with normal kidney functions. On the other hand, in patients older than 65 years with kidney or liver disease, a dose of hydroxychloroquine of more than 6.5 mg/kg/day may be a certain risk factor in terms of development of retinopathy [56]. In some countries patients treated with hydroxychloroquine are examined every 3 months for eye ground changes. In view of some French ophthalmologists, ophthalmological examination is recommended every 12 months in patients with a risk factor and every 18 months in patients without risk factors. The examination should include clinical assessment and two tests of macular function (colour vision, static perimetry and also focal macular electroretinography) [56].

1.19.6 Gold Salts

Application of gold injections is being gradually abandoned as gold is one of the substances associated with a potential development of renal, haematological and skin complications and reactions leading to mucosal lesions. Kidney involvement is more frequent in elderly people or in people with impaired renal function. On the other hand, application of gold salts remains one of the few methods, which suppresses development of joint erosion and RA progression.

Auranofin is an oral, gold-containing chemical (salt) used for treating rheumatoid arthritis. Its effect is lower as compared to MTX or gold salt injections. The advantage of auranofin reported by various studies is its safety and higher efficacy than placebo and may be successfully used to reduce corticosteroids in EORA patients [57]. Potential adverse effects of this preparation

include mild intestinal disorders, such as diarrhoea and abdominal cramps [58].

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Osteoporosis in Rheumatoid Arthritis in Relation to Age

2

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Rheumatoid arthritis (RA) is associated with development of a chronic inflammatory process affecting the synovium of joints. Although the disease is caused mainly by focal involvement of joints, it is unquestionably a systemic disorder and the inflammatory process may affect the entire skeleton. In RA, bone may be affected by structural joint damage (bone erosions) in combination with development of juxta-articular osteopenia and osteoporosis that are the major radiodiagnostic signs of rheumatoid arthritis. In RA patients, the incidence of osteoporosis has been found out to be twice as high as in healthy population [1]. Osteoporosis increases the risk of fractures and, consequently, the morbidity and mortality rate. The causes of osteoporosis associated with RA are numerous, and in addition to primary risk factors, they include also inflammation, immobilisation and glucocorticoid treatment. Quantitative determination of periarticular and generalised bone loss may be in future reliable indicators of further progress of the disease. The main risk factors of development of osteoporosis and fractures associated with RA include duration of the disease, severity of its course, extent of immobilisation, age, female sex and use of glucocorticoids. It has been found out that the incidence of osteoporosis is twice as high in RA female patients of all age categories [1–3].

In the past, it was believed that bone changes in RA were caused by different mechanisms. However, the latest findings have shown that the main role in development of bone erosions and osteoporosis (both periarticular and generalised) is played by osteoclasts. The concept of mechanism of development of bone changes in RA assumes that cells with phenotypic features and functional abilities of osteoclasts (osteoclast-like cells) are responsible for a greater part of bone resorption typical of synovial lesions in RA. Osteoclast-like cells are present in resorption lacunae at the pannus-bone interface. Their origin in the RA lesions remains speculative. There is some evidence that they may derive from mononuclear cell precursors present within the inflamed synovium. Interaction with the bone surface and the effect of cytokines, particularly IL-1 and TNF-alpha produced locally in synovium that play an important role in pathogenesis of

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synovitis, potentiate differentiation of these cells into osteoclasts [4].

However, it is assumed that also other types of cells, such as synovial fibroblasts and macrophages, participate in bone resorption, but their resorption activity is very limited as compared to osteoclasts. Inflamed joint synovial tissue is a source of a recently discovered factor which regulates osteoclastic activity and differentiation. Various terms are used for this factor, such as osteoclast differentiation factor (ODF), RANK ligand (RANKL) and osteoprotegerin ligand (OPGL). ODF/RANKL is a member of the TNF-ligand family of cytokines, and it has been proven that many factors that increase the number or activity of osteoclasts act through increased expression of this cytokine. The primary sources of ODF/RANKL are T-lymphocytes in inflamed joint synovium and synovial fibroblasts. The therapy that interferes with activity of these cytokines slows down or prevents progression of bone changes. A better understanding of osteoclastic way of degradation of bone in RA allows introduction of new approaches to treatment of the disease [4–6].

Treatment with drugs blocking the effect of TNF-alpha and IL-1 has proved effective in prevention of joint destruction [7]. Nevertheless, there is still lack of information as to whether these drugs also positively influence periarticular and generalised bone mass loss.

As mentioned above, involved in the development of osteoporosis in RA patients are primary risk factors (age, female gender), as well as other, RA-specific factors, such as inflammatory process itself, limited mobility of RA patients, glucocorticoid effects and immunosuppressive treatment [8]. These factors complicate identification of the impact of a systemic inflammatory process alone on bone remodelling in RA. A number of studies have shown that there exists a relation between systemic osteoporosis and inflammatory activity of the disease expressed by erythrocyte sedimentation rate and serum level of C-reactive protein. In patients with a more severe course of the disease (higher inflammation activity) and a higher number of affected joints, also a higher bone loss was observed. But there is a lack of evidence as to whether suppression of inflammatory process is accompanied by prevention of further bone reduction. In general, a treatment modifying the disease should have a favourable effect also on the bone status of patients, which has been confirmed also by several studies, where radiological features of anti-inflammation treatment showed decrease in RA progression. Conventional DMARDs (sulphasalazine, methotrexate) did not cause reduction of bone in patients during the treatment.

The effect of administration of low doses of glucocorticoids on bone density in RA patients has been investigated for many years. The aim of corticotherapy was to improve symptoms of the disease and functional status. At the same time, a positive effect on bone density was expected. However, RA patients have lower bone density values than the comparable healthy population.

It has been proved that even without previous DMARD treatment, low-dose glucocorticoids halt radiographic progression of joint damage in RA patients, which may be beneficial for the treatment outcomes. The effect on bone density, however, remains questionable. A number of studies compared bone density in RA female patients in the premenopause with female patients without RA, with the conclusion that bone loss in RA might be potentiated by corticotherapy [4, 5]. Other studies compared prevalence of vertebral fractures in RA patients treated with glucocorticoids and in RA patients without glucocorticoid treatment. Patients receiving glucocorticoids showed an increased risk of vertebral deformities and symptomatic fractures, but the effect was not statistically significant. No significant correlation was found between glucocorticoid doses and bone density parameters (determined by quantitative ultrasound and DXA). Thus, the use of glucocorticoids alone is not in RA related to development of osteoporosis; its development is influenced by various factors present in this disease, namely, age, female gender, Caucasian race, immobilisation and previous history of a severe course of the disease.

Unlike postmenopausal osteoporosis, osteoporosis in rheumatoid arthritis is characterised

predominantly by preservation of bone in the axial skeleton and considerable bone loss in peripheral bones. Bone loss in RA occurs already in the early stages of the diseases, and therefore osteoporosis treatment should not be delayed. Generalised bone loss in RA is prevented by antiresorptive treatment of osteoporosis (bisphosphonates). Studies of patients undergoing antiresorptive treatment showed increase in bone mass as compared to patients who received calcium and vitamin D or untreated patients [8, 9]. In patients with a simultaneous antiresorptive and glucocorticoid treatment, bone loss was stopped while it went on in patients with glucocorticoid treatment without antiresorptive therapy. For this reason, it is necessary to highlight the need of osteoporosis management in RA patients. The question remains, how to select patients for diagnosis of osteoporosis by DXA measuring. Identification of patients should be based on assessment of risk factors in individual patients or on screening of all patients [6].

As concerns the correlation between age and rheumatoid arthritis, no significant differences were found in the course and severity of the disease and response to treatment. Development of RA at 50–65 years of age is called elderly-onset RA (EORA) and at a younger age younger-onset RA (YORA). The difference between EORA (Fig. 2.1) and YORA is minimal and consists in a more equal gender distribution in YORA patients, involvement of more joints and a higher RF positivity. It has been confirmed that there are no significant age-related differences in efficacy and outcome of treatment or development of adverse effects of treatment. However, in elderly patients, there is a higher tendency to terminate the treatment due to its adverse effects or low efficacy. It is necessary to take into account also the fact that age is the decisive factor for osteoporosis [3].

In spite of this, studies showed that the clinical course and radiographic progression of the disease were parallel in YORA and EORA patients

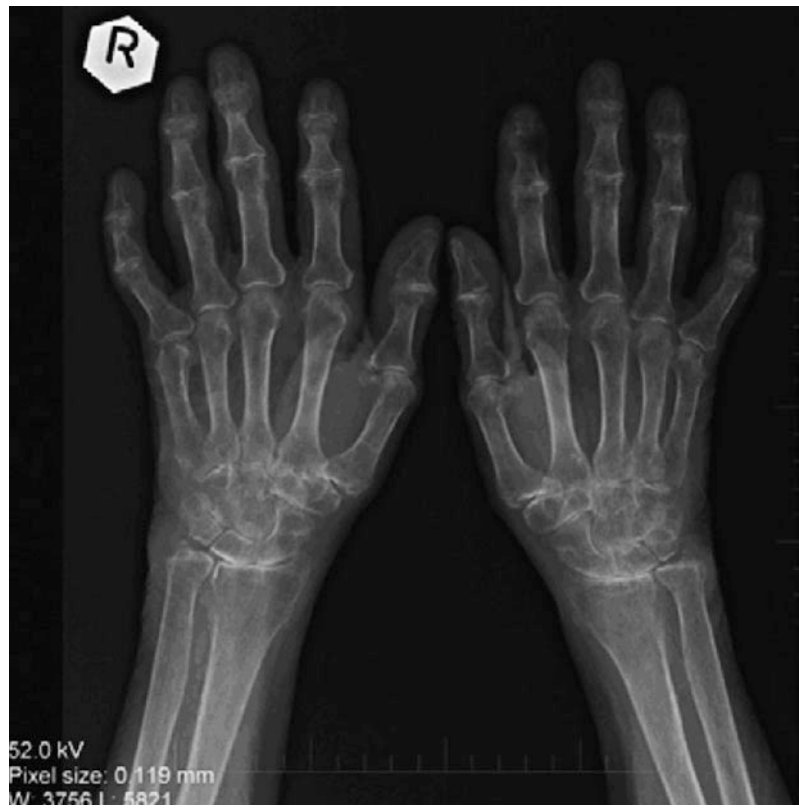

Fig. 2.1 Severe postmenopausal osteoporosis with EORA development

and the difference between them at the onset of the disease and at a 3-year follow-up was not statistically significant.

It may be concluded that the mechanism responsible for reduced bone density in patients with rheumatoid arthritis remains unclear. The incidence of osteoporosis in RA patients is twice as high as in the healthy population. Involved in development of osteoporosis in patients with RA are primary risk factors, as well as the inflammatory process itself, duration of the disease and severity of its course, extent of immobilisation and use of glucocorticoid treatment. The drugs influencing the course of the disease have a positive effect also on bone density. The reports concerning the relation between glucocorticoid treatment and reduced bone density remain controversial. However, it is believed that glucocorticoid treatment in combination with other risk factors for reduced bone density present in RA contributes to significant reduction of bone density. Therefore, it is suitable to apply also antiresorptive treatment in RA patients treated with glucocorticoids (at a dose of $\geq$5 mg/day of prednisone for more than 3 months) and with a low bone density (T-score <-2.0 SD). New approaches to RA treatment prove effective in prevention of joint damage; however, little is known yet about their effect on bone density.

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Biological Therapy for Rheumatoid Arthritis

3

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Rheumatoid arthritis (RA) is one of the most severe and most frequent inflammatory rheumatic diseases, which may develop at any age.

If it occurs at the age over 60 years, it is called elderly-onset RA (EORA). The age factor is very important as EORA accounts for 10–33 % of all RA cases. Elderly-onset RA has certain typical clinical features. This chapter is focused on these features as well as on targeted (biological) therapy of EORA.

The range of EORA clinical manifestations includes 1:1 male/female ratio as compared to 1:2 in classical RA developing in middle age; usually an acute onset associated with organ manifestations as compared to gradual beginning in classical RA; involvement of less joints (oligoarticular) while RA in middle age is most often polyarticular (involving more joints); and mainly involvement of shoulders and hips, i.e. large joints as compared to classical RA affecting especially small joints of hands and feet. Elderly-onset RA has often a severe course and prognosis.

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3.1 Treatment of Rheumatoid Arthritis

RA treatment aims at suppression of inflammatory manifestation of the disease, reduction of swellings, pain of joints, halting of radiographic progression (damage visible on radiographs), improvement of the quality of life and elimination of fatigue and depression. RA treatment starts with application of non-steroidal antirheumatic drugs which are followed by so-called basal or "disease-modifying" medications, including methotrexate, sulphasalazine, gold salts, antimalarial drugs, leflunomide and others. In the recent 10 years, the severe, resistant forms of RA have started to be addressed by a targeted elimination of inflammatory factors, pro-inflammatory cytokines, the most important of which is the tumour necrosis factor alpha (TNF-alpha).

TNF-alpha is the decisive factor that stimulates the immune system cells to generate additional inflammatory factors, involved both in inflammatory damage to joint structures and in organ, i.e. extra-articular, manifestations of RA.

Is biological therapy possible also in elderly-onset RA? According to prominent rheumatologists, such therapy is possible, and the outcomes are very good, although special care is required in the treatment of patients with hypertension, ischaemic heart disease, tumour disease or infections. It is essential that assessment to rule out hidden form of tuberculosis be carried out before the treatment is started. When respecting these

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criteria, the application of biological therapy is safe, poses no risks and achieves good outcomes, similarly as in the treatment of RA developed in middle age. RA treatment by TNF-alpha inhibitors leads provably to suppression of inflammatory activity, halting of radiographic progression and substantial improvement of quality of life also in EORA patients.

3.2 Anti-cytokine Therapy

Currently, nine biologic drugs are available for RA treatment, namely, five anti-TNF inhibitors (infliximab, adalimumab and etanercept, golimumab, certolizumab), anti-IL6-tocilizumab, anti-CTL4-abatacept, anti-CD20 rituximab and anti-IL1-anakinra. Most experience has been obtained in treatment of elderly patients with the use of anti-TNFs, etanercept, infliximab and adalimumab particularly.

In the group of patients older than 60 years, it is necessary to rule out active infection as elderly patients are more susceptible to secondary infection, including activation of latent tuberculosis, due to decreased non-specific immunity and increased comorbidity; a potential source of infection may be also a permanent catheter.

It should be noted in this respect that higher doses of TNF antagonists may be harmful in NYHA class III or IV patients in terms of heart failure. Frequency of heart failure was examined in 13,171 patients with RA, treated with TNF antagonists. It has been found out that in addition to common risk factors for heart disease, such as gender, hypertension and ischemic heart disease, the annual incidence of heart failure was 0.2 % of patients receiving etanercept or infliximab as compared to those without this medication [11].

Fleischmann et al. [4] have pointed out that long-term use of etanercept in inflammatory rheumatic diseases does not differ in terms of adverse effects between young and elderly patients. Assessment covered a total of 3296 persons younger and 597 persons older than 65 years. Demyelinating disease was observed in younger RA patients, whereas in persons over the age of 65 years, the demyelinating process was absent.

The frequency of respiratory infections was higher in patients under the age of 65. The analysis included 18 clinical studies of rheumatoid arthritis (RA), two studies of psoriatic arthritis (PsA) and two studies of ankylosing spondylitis (AS) patients. RA patients older than 65 years accounted for 17.3 %, PsA patients for 5.3 % and AS patients for 1.4 %; however, the frequency of respiratory infections was higher in patients under the age of 65. RA, PsA and AS are diseases that are associated with increased mortality, primarily due to cardiovascular and tumorous diseases and infections. The reduction of median life span ranges between 5 and 15 years [11].

In their studies, Fleischmann et al. [4] and Bathon et al. [1] reported that the application of etanercept is safe and persons older than 65 years are at no greater risk of adverse effects than younger subjects. Bathon's study [1] focused also on efficacy of treatment. The results of application of etanercept in both groups have confirmed that etanercept and MTX suppress RA activity in elderly as well as in younger patients. In the elderly group, the positive effect lasted for 6 years. Radiographic progression was low in both groups of patients treated with a combination of methotrexate and etanercept as compared to placebo or (MTX) group receiving methotrexate alone.

In other studies, the authors [1] concentrated on safety and efficacy of etanercept in RA patients from the viewpoint of their age. The results showed higher incidence of serious adverse effects in the group of elderly patients which, however, in this group did not differ from the control group, whether receiving placebo or MTX. In elderly patients, a slower response was recorded in ACR20, ACR50 and ACR70 values. In both groups, however, the disease activity decreased and functions improved as compared to the control group. The combination with MTX was in both groups more effective than monotherapy. Effects of treatment in elderly patients were sustained for 6 months during the follow-up period; radiographic progression did not differ between the two groups and was slower with combined treatment than with monotherapy.

The risk of infection is lower in the application of anakinra (anti-IL-1). On the other hand,

the effect of this biological agent on reduction of signs and symptoms and retardation of radiographic progression is lower than that of TNF antagonists. The incidence of infection requiring antibacterial therapy was 12 % in the placebo group and 16 % in the group receiving anakinra. Anakinra must not be used together with etanercept due to incidence of severe and frequent infections, when pulmonary infections in patients receiving anakinra affect primarily asthmatic patients [2].

Tutuncu et al. [9] studied two groups of patients with rheumatoid arthritis, namely, elderly-onset rheumatoid arthritis (EORA) group and younger-onset rheumatoid arthritis (YORA) group, based on the register of the Consortium of Rheumatology Researchers of North America (CORONA). Of 9381 patients with RA, there were 2101 EORA patients. The group of 2101 EORA patients was compared with 2101 patients with YORA. Differences in Disability Index of the Health Assessment Questionnaire were as follows: 0.30 vs 0.35; tender joint count, 3.7 vs 4.7; swollen joint count, 5.3 vs 5.2; Disease Activity Score 28, 3.8 vs 3.6; and patient global assessment, 29.1 vs 30.9.

Physician global assessment, 24.9 vs 26.3; patient pain assessment using VAS, 31.4 vs 34.4. The mean methotrexate dose among the YORA group was higher than that in the EORA group. The percentage of patients with EORA who were on multiple DMARD treatment (30.9 %) or on biological agents (25 %) was considerably lower than that of patients with YORA (40.5 % and 33 %, respectively). The difference was statistically significant ($p < 0.0001$). The number of patients using prednisone was higher in EORA (41 %) than in YORA (37.64 %, $p < 0.05$).

Differences in toxicity related to treatment were minimal in both groups, whereas toxicities related to methotrexate were more common in the YORA group. The most commonly observed MTX-associated toxicities included liver disorder ($n = 34$), lung disease ($n = 17$), nausea ($n = 15$), haematological disorder ($n = 15$), alopecia ($n = 7$), dyspepsia ($n = 7$), rash ($n = 4$), diarrhoea ($n = 4$) and peptic ulcer ($n = 1$). The use of methotrexate was more common in patients with EORA (63.9 % vs 59.6 %; $p < 0.01$). Patients with EORA received more frequently biological therapy without combination with other DMARDs.

Comorbidities were more common among the EORA group than among the YORA group: coronary artery disease, 8.9 % vs 3.7 %; myocardial infarction, 5.9 % vs 3.0 %; hypertension, 41.1 % vs 27.4 %; and stroke, 3.8 % vs 1.4 %, respectively.

The authors used regression analysis of the use of methotrexate, multiple DMARD and biologic drugs. In EORA, the Health Assessment Questionnaire (HAQ) Disability Index was low, and tender joint count, swollen joint count and patient global assessment correlated with use of methotrexate, whereas in YORA, the patients exhibited high Health Assessment Questionnaire Disability Index and high Disease Activity Score (DAS) 28, and tender joint count, swollen joint count, physician global assessment score, patient global assessment score and use of prednisone correlated with biological usage. In YORA, the high Health Assessment Questionnaire Disability Index, Disease Activity Score 28, tender joint count, swollen joint count, patient global assessment and use of prednisone correlated with use of multiple DMARDs.

Among the comorbidities investigated in this study population, only history of hypertension was a negative predictor of the use of biological agents and multiple DMARDs. The presence of other comorbidities did not seem to have an influence on the choice of therapeutic agents.

Although MTX was more commonly used by patients with EORA, the weekly methotrexate dose was considerably lower among them (mean = 11.96 mg) than in those with YORA (mean = 16.25 mg). MTX dose correlated with weight, tender joint count and use of prednisone [9].

An interesting study [3] followed up 295 RA patients receiving anti-TNF biological therapy, divided according to their age in two groups, including 190 patients in the age group of 17–65 years and 105 patients over 65 years of age. During the study, no significant difference was found between the two groups in terms of changes in DAS28, DAS44 and SDAI. HAQ

improved less in the elderly than in the younger patients ($p<0.05$) and CRP decreased less in elderly patients ($p<0.05$).

During 2 years, the treatment was discontinued in 38.05 % patients in the age group of 17–65 years and in 38.95 % patients over the age of 65, including discontinuation of treatment due to loss of efficacy (11.42 % vs 20.52 %), serious adverse effects (25.67 % vs 17.54 %), voluntary discontinuation of treatment or discontinuation for remission (0.95 % vs 1 %).

On the basis of their research, Villa-Blanco and Calvo-Alen [10] recommend in EORA patients application of the same therapeutic procedures as in younger patients, taking into account comorbidity and toxicity of drugs. There are no special contraindications for the use of DMARDs and biologic drugs in elderly patients.

Italian authors [6] studied application of biological therapy used in RA, PsA and AS patients over the age of 65 in real life. This retrospective study focused on the safety profile of etanercept, adalimumab and infliximab. The application of these drugs has been proven to be a safe option of a successful therapy, improving the quality of life. Adherence to the valid principles of screening of candidates for biological therapy minimizes the risk of serious adverse effects.

Koller et al. [5] examined two drugs, namely, adalimumab and infliximab, based on the data from two randomized controlled double-blind clinical studies of 1236 patients with early onset of RA, treated with adalimumab or infliximab + MTX or MTX alone, with 788 patients receiving TNF + MTX and 448 patients treated with MTX monotherapy. The authors have demonstrated that MTX efficacy was the same in all the groups (composite indices, physical functions, radiographic progression). The effect of anti-TNF inhibitors + MTX was the same in all the groups and the combination was in all cases more efficient than MTX monotherapy. The same effect as in the other groups was achieved also in the group of the oldest patients (61–82 years), comprising 10 % of the whole cohort.

Several studies have been published on the options of treatment of EORA. For instance, according to the Japanese authors [8], the increasing number of elderly patients with RA is paradoxically also a consequence of development of new therapeutic procedures, and they also document the higher incidence of the elderly-onset RA (EORA – defined as RA with the onset after the age of 60). The study has shown that in elderly patients, the combined treatment and biological medications are applied very cautiously although too much caution may lead to incorrect and inadequate therapy. It has been demonstrated that EORA patients receive more often corticosteroids rather than a combination of DMARDs and biological therapy. Parts of the patients are not adequately treated at the beginning of the disease, in its active phase, which results in a fast development of various destructions. In the authors' view, DMARDs and biological therapy should be preferred instead of corticosteroids in EORA patients.

Another Japanese study [7] included 969 patients with RA. It showed that elderly patients were receiving less DMARDs, a smaller percentage was receiving methotrexate (MTX) and the average MTX doses were lower.

Elderly patients received less biologic drugs and were inadequately treated despite laboratory evidence for poorly controlled disease status among the elderly, which may also contribute to the increased incidence of complications of this disease.

Annually several tens of randomized clinical studies are conducted, with a focus on efficacy and safety of new drugs. However, these studies include carefully selected groups of patients, and therefore their results are not always applicable to a broader population. In fact most treated patients would not meet the criteria for enrolment in a randomized controlled clinical study. One of the exclusion criteria for enrolment in a study is, for instance, comorbidities which are quite usual in most elderly patients. Data on efficacy and mainly safety produced by studies cannot be automatically transposed into daily practice. Of great importance in terms of monitoring of elderly patients in real life are registers of patients receiving biological therapy. One of them is, for instance, the Swiss Clinical Quality Management Programme for RA – SCQM-R A that collected between January 1997 and November 2005 data on 1571 patients, of which 334 patients over the

age of 65. According to these data, the group of elderly patients included more seropositive patients (89 % vs 79 %), the disease lasted longer (14.3 vs 11.5 years), more patients were taking glucocorticoids (60 % vs 49 %), more patients were receiving sulphasalazine (7.6 % vs 3.3 %) and less patients were treated with MTX (35.2 % vs 42 %). The median duration of biological therapy was the same in both groups, and DAS28 decrease did not differ between the two groups (assessed at 6, 12 and 24 months), although a lower percentage of elderly patients achieved good EULAR response points (7.2 % vs 11.2 %). Median EULAR response did not differ in the two groups (32 % vs 37 %). HAQ changes were more marked in the group of younger patients; however, after elimination of patients over the age of 75, there were no differences. In the group of elderly patients, the incidence of tumours was higher (2 vs 0). The frequency of infections was not higher in the group of elderly patients, and allergy reactions were more common in the group of younger patients (10.7 % vs 20 %).

Other studies demonstrated additional benefits of biological therapy in elderly patients. One of them was evidence of a positive effect of anti-TNF therapy on lipids by changing HDL-C anti-oxidative capacity, which may be clinically relevant, with a documented protective effect of anti-TNF treatment on cardiovascular morbidity. Another study has proved that treatment with etanercept leads to a significant and long-lasting decrease of the ApoB/ApoA-I ratio in patients with a good and median EULAR response to etanercept. This may have a positive effect on the cardiovascular risk in these patients. New findings point out the potential role of TNF-alpha high levels in pathogenesis of Alzheimer disease. RA itself accelerates atherosclerosis and increases the risk. At the same time, the prevalence of cognitive improvement is higher in RA patients than in other patients.

Another option in biological therapy of RA patients is tofacitinib. Its safety profile is strictly controlled and the benefits of the therapy outweigh the risk of adverse effects. Due to polymorbidity of elderly RA patients, biological therapy with a shorter biological half-life (etanercept) seems to be more beneficial.

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Systemic Lupus Erythematosus

4

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Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystem disorder with a wide range of clinical and laboratory manifestations.

Etiopathogenetic factors that may be involved in the development of SLE include primarily genetic susceptibility, environmental triggers (superantigens, viruses, UV radiation, drugs, chemicals) as well as internal factors (hormones), age, and probably other, yet unknown, factors. They impair immunological homeostasis, induce creation of antibodies that react with their own antigens, and subsequently cause tissue damage [1].

During aging, the immune system undergoes continuous morphological and functional changes. In general, it may be stated that defensive capacity of the immune system against foreign pathogens decreases with age, while reactivity of autoantigens increases. In the population of healthy elderly people, the incidence of antinuclear antibodies and rheumatoid factors grows [2]. In the course of aging, the number of naive CD45RA T-lymphocytes decreases and the number of memory CD45RO T-lymphocytes increases, the ratio between CD4 and CD8 T-lymphocytes expressing the CD28 receptor changes, and the proliferative capacity of peripheral blood lymphocytes decreases after mitogenic stimulation [3, 4]. Levels of serum cytokines and acute phase reactants rise twice to four times during aging [5]. These changes may participate in atypical course or incidence of some inflammatory diseases in older age.

SLE affects most often women between second and fourth age decade [6, 7]. Elderly-onset SLE (SLE-E) constitutes a specific subgroup of diseases defined by the onset of the disease at the age of 50–65 years [8–10]. The incidence of SLE-E is lower and accounts for 12–18 % of all cases [6, 7, 10, 11]. Prevalence of women remains unchanged, although the female/male ratio is decreasing (1.1:1–7:1) as compared to SLE with earlier onset (5.7:1–9:1) [3, 8, 9, 12]. SLE-E affects predominantly the Caucasian population [11, 13].

Elderly-onset SLE may have a different clinical course, a more insidious onset at presentation, with nonspecific first symptoms. The first clinical manifestations include arthralgia, weakness, fatigue, muscle pain, body weight loss, higher body temperature, and impairment of cognitive functions [7, 14, 15]. The clinical course of SLE-E tends to be more benign (Table 4.1). Cutaneous manifestations (Fig. 4.1),

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Table 4.1 Clinical manifestation of SLE-E

Authors	Number of patients	Age at the onset of the disease	Incidence	
			Decreased	Increased
Maddison [7]	19	≥60	Arthritis, alopecia, Raynaud's phenomenon, lymphadenopathy, anti-RNP	Lung involvement, Sjögren's syndrome, anti-Ro, anti-La, rheumatoid factor
Baker et al. [11]	31	≥50	Lymphadenopathy, neuropsychiatric manifestations, alopecia, Raynaud's phenomenon	Lung involvement, pericarditis, pleuritis
Wilson et al. [16]	17	≥50	Nephritis, rash, hypocomplementemia, anti-dsDNA	Pleuritis, pericarditis, arthritis, rheumatoid factor
Cattogio et al. [14]	13	≥55	Arthritis, alopecia, anti-RNP	Lung involvement, anti-Ro, anti-La, rheumatoid factor
Mak et al. [17]	13	≥50	Butterfly erythema, photosensitivity, alopecia	Serositis
Bertoli et al. [13]	73	≥50	Nephritis, anti-Sm	Neurological complications
Koh and Boye [18]	26	≥50	Arthritis, alopecia, butterfly erythema	Peripheral neuropathy, myalgia, pancytopenia
Ho et al. [19]	25	≥50	Nephritis, butterfly erythema	Rheumatoid factor

Fig. 4.1 Butterfly exanthema in a female patient with elderly-onset SLE

photosensitivity, arthritis, and nephritis were in the SLE-E patient group less frequent than in SLE with earlier onset [7, 11, 14, 16].

In SLE-E, a higher incidence was reported of serositis, lung involvement, and Sjögren's syndrome [7, 11, 14, 16, 20]. A lower incidence of nephritis, CNS involvement, and skin manifestations in SLE developed after the age of 50 were described by Formiga [8], who simultaneously evaluated the disease activity score. SLEDAI score in these patients was at the onset and in the first year of the disease lower than in patients with earlier onset of SLE. The milder course of the disease was more frequent in SLE-E (75%) than in younger patients (27%). Lower incidence of nephritis and more frequent neurological complications in SLE-E were reported also by Bertolt [13].

A controversial study was published by Mak [17] who described predominantly in the Chinese population the similar incidence of organ complications (involvement of the heart, lungs, kidney, and CNS) in both groups of SLE patients, with SLE-E patients having a lower incidence of skin complications and a higher incidence of serositis. Maddison [21] reported, in a group of 86 patients with SLE developed after the age of 54, a higher incidence of cardiovascular, ocular, musculoskeletal complications and malignancies. Involvement of the skin, kidneys, and CNS was similar in both groups. Organ complications

Table 4.2 Clinical and immunological manifestations of SLE-E – analysis of literature data [25]

	SLE > 50 y	SLE < 50 y	$p =$
Number of patients	714	4700	
Women/men	4.4:1	10.6:1	$3 \cdot 10^{-14}$
Serositis	36.7 %	28.6 %	$7 \cdot 10^{-4}$
Pneumopathy	21.2 %	11.3 %	$6 \cdot 10^{-8}$
Butterfly erythema	31.1 %	62.4 %	10^{-44}
Photosensitivity	26.2 %	38.2 %	$6 \cdot 10^{-6}$
Skin vasculitis	13.4 %	25.9 %	$9 \cdot 10^{-4}$
Alopecia	24 %	44.9 %	$3 \cdot 10^{-11}$
Raynaud's phenomenon	24.8 %	37.2 %	$3 \cdot 10^{-7}$
CNS	15.3 %	20.2 %	0.025
Lymphadenopathy	9.1 %	19.6 %	$2 \cdot 10^{-4}$
Nephritis	28.6 %	42.7 %	$2 \cdot 10^{-10}$
Nephrotic syndrome	8.1 %	24.3 %	0.015
Rheumatoid factor	32.7 %	20.1 %	$3 \cdot 10^{-5}$
Anti-RNP	10.4 %	20.9 %	$9 \cdot 10^{-5}$
Anti-Sm	9.1 %	17.1 %	0.001
Hypocomplementemia	45 %	64.9 %	0.002

were assessed by SDI score which takes into account 12 organ systems but does not specify their cause. As a result, these complications may be caused by comorbidity, the administered treatment, or SLE clinical manifestations.

Elderly-onset SLE may exhibit a different autoantibody profile. In SLE-E patients showed a higher incidence of rheumatoid factors, anti-Ro, and anti-La antibodies and on the other hand a lower incidence of anti-RNP antibodies and hypocomplementemia [7, 12, 14, 22]. The incidence of anti-dsDNA antibodies is in patients with elderly-onset SLE lower [16, 20] or the same [10, 15] as in younger patients. A higher incidence of anti-dsDNA antibodies in SLE-E was described by Padovan [12], however, these antibodies did not correlate with organ complications associated with the disease.

Differences in results reported by individual studies may arise from relatively small groups of patients, a differently defined age at the SLE onset, ethnic differences, retrospective collection of data, and different techniques used for examination of autoantibodies. Cervera [23] studied prospectively a group of one thousand SLE patients. In 90 patients (9 %), the disease developed after the age of 50. At the onset of the disease, these patients displayed lower incidence of arthritis, rash, and nephropathy. In the course of the disease, the prevalence of arthritis, rash, photosensitivity, nephropathy, and anti-La antibodies was decreasing, and the prevalence of Sjögren's syndrome was increasing. Based on a meta-analysis, Ward [24] reported a higher incidence of interstitial lung disease, serositis, Sjögren's syndrome, and positivity of anti-La antibodies in SLE-E. Less frequently, these patients suffered from neuropsychiatric diseases, Raynaud's phenomenon, alopecia, fever, lymphadenopathy, and hypocomplementemia. No differences were found in the incidence of nephritis, photosensitivity, myalgia, leukopenia, rheumatoid factors, and anti-dsDNA antibodies. Boddaert [25] analyzed data collected from the literature and compared the incidence of clinical manifestations and autoantibodies in a group of 714 late-onset SLE patients and 4700 early-onset SLE (Table 4.2). The group of SLE-E patients displayed a higher incidence of serositis, lung involvement, and rheumatoid factor positivity and a lower incidence of butterfly exanthema, photosensitivity, cutaneous vasculitis, alopecia, Raynaud's phenomenon, neuropsychiatric manifestations, lymphadenopathy, nephrotic syndrome, and nephritis, based on the laboratory positivity parameters of anti-RNP, anti-Sm antibodies, and hypocomplementemia.

SLE diagnosis is determined in all age groups on the basis of the presence of clinical and laboratory symptoms according to diagnostic criteria [26].

Due to a slow course, often nonspecific manifestations at the onset, lower frequency of SLE in older population, as well as the time needed to rule out other diseases, SLE-E diagnosis is often delayed. The interval between manifestation of the first symptoms and diagnosis of the disease is longer (19–50 months) as compared to early-onset SLE (5–24 months) [3, 7, 8, 12, 14]. The most frequent incorrect diagnoses are polymyalgia rheumatica, rheumatoid arthritis, osteoarthritis, infection and malignancies, less often Raynaud´s phenomenon, discoid lupus erythematosus, chronic active hepatitis, and fibrosing alveolitis but also tuberculosis, infectious endocarditis, idiopathic thrombocytopenic purpura, chronic renal failure, and photodermatitis [7, 11, 14]. As elderly-onset SLE affects as a rule patients with a higher comorbidity that often requires a combined pharmacological treatment, the differential diagnosis must take into account also drug-induced lupus. Clinical presentation of this nosological entity is dominated by joint and muscle pain, lung involvement, fever, and loss of body weight. The laboratory findings show presence of antinuclear antibodies, absence of anti-dsDNA antibodies, and hypocomplementemia. The drugs most frequently inducing SLE include procainamide, isoniazid, methyldopa, carbamazepine, acebutolol, hydralazine, chlorpromazine, sulfasalazine, D-penicillamine, and others [27].

Despite discrepant findings in the incidence of organ complications, the cause of death of SLE-E patients is not usually SLE manifestation but rather infection, cardiovascular diseases, malignancies, or drug-induced complications [9, 10, 13].

As the cause of SLE is not known, treatment of the disease is focused on suppression of symptoms and autoimmune inflammatory responses. SLE treatment depends on severity of its clinical manifestations. Associated diseases, as well as concomitant therapy, often limit the possibilities of SLE-E treatment. The choice of treatment must also reflect potential drug interactions, drug-induced diseases, and changes in absorption, distribution, metabolism, and elimination of drugs in elderly patients, which increase the risk of adverse effects.

Joint and skin disorders, as well as serositis, are usually treated with antimalarials (hydroxychloroquine) in combination with NSAIDs and at the beginning of the therapy usually also with low-dose glucocorticoids. According to the latest recommendations, antimalarials should be administered to all SLE patients, unless contraindicated. The treatment may be long term. Patients receiving antimalarials must be regularly checked for their blood count, liver enzymes, ocular fundus, or any changes of cognitive functions [28].

The treatment of lupus pneumonitis and hematologic abnormalities require higher doses of glucocorticoids and, where necessary, immunosuppressants, administered preferably orally and in case of more severe complications intravenously. Lupus nephritis is managed similarly as in younger patients by glucocorticoids and cyclophosphamide, with regular monitoring of blood count, liver enzyme, and urine sediment tests as an inevitable component of the treatment. In case of contraindication of cyclophosphamide, it is replaced by azathioprine. Neuropsychiatric complications in elderly patients are treated symptomatically, with immunosuppressants added in case of SLE-related manifestations. Hypertension and the presence of antiphospholipid antibodies increase the risk of cerebrovascular events. In order to prevent such a complication, adequate treatment of hypertension and administration of acetylsalicylic acid in antiaggregation doses or indirect anticoagulants are required [2, 3, 10].

Adverse events of glucocorticoids include hypertension, dysbalance of minerals, diabetes mellitus, hyperlipidemia, CNS symptomatology (depressions, anxiety, insomnia), fluid retention, an increased risk of pathologic fractures in long-term treatment of osteoporosis, avascular necrosis, cataracta, glaucoma, and increased susceptibility to infections. In order to minimize the risk of these adverse events, it is necessary to reduce gradually glucocorticoids to the lowest effective dose as soon as remission has been achieved.

Patients are administered concominant therapy with calcium, vitamin D supplements and gastroprotective drugs.

Biological therapy has become part of SLE treatment only recently. The first approved medication for SLE treatment is belimumab. It is a human monoclonal antibody which binds cytokine (B-Lys) responsible for prolonged survival of B-cells. Belimumab is indicated in patients unresponsive to common pharmacological treatment, with frequent relapses and long-term use of higher doses of glucocorticoids. It is administered at the dose of 10 mg/kg in intravenous infusion, with the first three doses applied at 2-week and subsequently at 4-week intervals. Belimumab treatment decreases autoantibody levels, increases complement, and reduces relapses of the disease which has allowed reducing of the dose of glucocorticoids in most patients.

An important part of SLE treatment is appropriate education of patients about the regimen and lifestyle they have to follow, rehabilitation, physical activity limitations, avoidance of direct sunshine, and importance of regular medical follow-up.

The care of elderly patients with systemic lupus erythematosus is multidisciplinary, starting from diagnosis up to treatment. It requires close cooperation of rheumatologists, general internists, gerontologists, hematologists, pneumologists, nephrologists, neurologists in case of neurological complications, and other specialists, according to the clinical manifestation of the disease.

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Sjögren's Syndrome

5

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Sjögren's syndrome is a chronic autoimmune disease that affects exocrine glands and the lacrimal and salivary glands in particular. The patients complain of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) caused by lymphocytic infiltration of lacrimal and salivary glands. Sjögren's syndrome is considered primary when present alone or secondary when associated with another autoimmune disease, most often with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It should be pointed out that in one third of patients, Sjögren's syndrome is associated with extraglandular manifestations. Patients may develop arthritis, vasculitis, nephritis, neuropathy, and interstitial lung disease. This study will focus on clinical features of the Sjögren's syndrome in elderly patients.

5.1 Incidence

The disease affects primarily women during the fourth and fifth decades of life, and the female/male ratio is 9:1 [1]. In the Greek geriatric population (≥65 years), the prevalence of primary Sjögren's syndrome amounted to 4.8 % [2].

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The abovementioned group had an objectively confirmed keratoconjunctivitis sicca and sometimes xerostomia with a positive biopsy of salivary glands. In contrast, a study published in Great Britain confirmed incidence of Sjögren's syndrome in 3.3 % of elderly patients, but the diagnosis was not confirmed by histological examination [3].

5.2 Pathogenesis

An important role in the pathogenesis is played by involvement of salivary epithelial cells and vascular endothelial cells with expression of pro-inflammatory cytokines and co-stimulatory molecules [4]. Sjögren's syndrome is associated with abnormal regulation of apoptosis and the presence of anti-Ro and anti-La [5] antibodies. Venables et al. [6] pointed out a possibility of virus infection, especially by retroviruses.

In addition to the given factors, the pathogenesis of the disease is probably influenced also by the environmental and immunologic factors that ultimately lead to the development of this syndrome.

The following American-European diagnostic criteria are currently used that were recommended by the American-European Consensus Group [7]:

1. Ocular symptoms (dry eyes)
2. Oral symptoms (dry mouth)

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3. Ocular signs (confirmation of dryness by objective tests)
4. Positive histopathological finding (focal lymphocytic sialadenitis)
5. Objective evidence of salivary gland involvement
6. Presence of autoantibodies (anti-Ro and/or anti-La)

For a primary Sjögren's syndrome diagnosis, the clinical features must meet *four of six diagnostic criteria*, with histopathological changes confirmed by histopathological findings, biopsy of labial salivary glands, or positive serology with presence of anti-Ro or anti-La autoantibodies.

In addition, three of four objective criteria must be met to confirm the diagnosis. When these criteria are used, their sensitivity and specificity range around 96 % and 94 %, respectively. Diagnostic criteria apply to the primary Sjögren's syndrome. Its secondary manifestation occurs in combination with systemic connective tissue diseases, such as RA, SLE, systemic sclerosis (SSC), polymyositis (PM), dermatomyositis (DM), mixed connective tissue disease (MCTD), polyarteritis nodosa, but also with primary biliary cirrhosis, chronic active hepatitis, autoimmune thyroiditis, and mixed cryoglobulinemia. Cases when another systemic disease develops in patients with already diagnosed Sjögren's syndrome are called by some authors an overlap syndrome or Sjögren's syndrome associated with a systemic connective tissue disease [8].

The currently used diagnostic criteria are based on a combination of clinical, pathological, and serological examinations [9].

Positive Schirmer's test in persons over the age of 60 should not be included in classification criteria [8]. When diagnosis is considered in elderly persons, it is necessary to check their medical history for use of tricyclic antidepressants and antipsychotics that may cause dry mouth. Dry eyes or dry mouth were observed in approximately 27 % of persons in the age group between 65 and 84 years [10].

Prevalence of dry mouth increases with age and can be found in about 17 % of elderly population. Al-Hashimi [11] points out that up to 40 % of elderly patients (≥60 years) with Sjögren's syndrome suffer from xerostomia, while Sjögren's syndrome occurs in 20 % of them. The symptoms correlate with reduced production of saliva, which is one of the problems of establishment of diagnosis in elderly patients. Elderly persons may present also with salivary gland swelling. For the purpose of differential diagnosis, it is necessary to rule out also other causes of salivary gland swelling, such as acute and chronic infection (both viral and bacterial infections, tumors, alcoholism, granulomatous disease, e.g., sarcoidosis).

As concern the presence of anti-Ro/SS-A or anti-La/SS-B antibodies, elderly patients (≥60 years) with a diagnosis of Sjögren's syndrome exhibited lower prevalence of serological findings as compared to a group of younger patients with Sjögren's syndrome, and no provable difference was detected in the clinical manifestation [12–14]. As concerns clinical laboratory parameters in Sjögren's syndrome, autoimmune hemolytic anemia was detected in an 81-year-old woman. Her medical history included progressive anemia and jaundice in 2004. Twenty years prior to the disease, she was diagnosed with sicca syndrome, with persistent xerostomia and xerophthalmia. The patient underwent subtotal thyroidectomy for hypertrophy of thyroid gland. Laboratory parameters indicated low hemoglobin level, positive direct and indirect Coombs test, as well as presence of antinuclear antibodies (ANA), granular pattern (at a titer > 1:1280), and anticentromere antibodies; the presence of LE cells was low, and the level of CH50 and C3 and C4 was also lower. Other autoantibodies were negative (rheumatoid factor, anti-ds-DNA antibodies, anti-Ro/SS-A, anti-La/SS-B, anti-Jo-1, anti-Scl-70).

In diagnostic terms the patient's condition was assessed as Autoimmune hemolytic anemia (AIHA), complicating the course of the primary Sjögren's syndrome [15].

After administration of oral prednisolone at the dose of 30 mg/day, the hemoglobin level returned to normal within 4 weeks. Authors of the study demonstrated development of progressive anemia on the basis of late-onset AIHA in a female patient with the primary Sjögren's syndrome.

Garcia-Carrasco et al. [14] compared clinical and laboratory symptoms in case of the primary Sjögren's syndrome in middle-aged and elderly population. Their group included 233 patients (204 women and 29 men, with the mean age of 53 years, range 15–87 years). In 31 patients (26 women and 5 men, 14 % of the whole group), the disease developed after the age of 70 (with the mean age of 74 years, range 70–87 years).

Extraglandular manifestations included articular involvement (29 %), hepatic involvement (20 %), peripheral neuropathy (16 %), and interstitial pneumopathy (13 %). The authors compared the prevalence of glandular and extraglandular manifestations and immunological features (cryoglobulinemia, hypocomplementemia and positivity for RF, anti-Ro/SS-A, or anti-La/SS-B) with the group of younger patients and came to the conclusion that the signs indicative of Sjögren's syndrome were similar in both groups.

Garcia-Carrasco et al. [14] have concluded that although Sjögren's syndrome is typically a disease of middle-aged adults, it may be diagnosed also in elderly patients, without differences in their clinical and immunological features (Tables 5.1, 5.2, 5.3, 5.4, and 5.5).

Table 5.1 Clinical manifestations of the primary Sjögren's syndrome

Clinical manifestations	Prevalence (%)
Xerostomia	92
Xerophthalmia	95
Enlarged parotid gland	50–60
Arthralgia/arthritis	75
Raynaud's phenomenon	40
Lung involvement	40
Interstitial nephritis	10–15
Glomerulonephritis	1–2
Lymphadenopathy	15–20
Hepatopathy	15–30
Vasculitis	5–10
Peripheral neuropathy	2–5
Myositis	1
Lymphoma	4

Table 5.2 Laboratory findings in Sjögren's syndrome

Laboratory sign	Incidence (%)
Increased SE	70–80
Leukopenia	10–30
Thrombocytopenia	10
Rheumatoid factor	80–90
Hypergammaglobulinemia	80
ANA	80–90
Anti-Ro by ELISA method	85–95
By gel precipitation	40–60
Anti-La by ELISA method	70–85
By gel precipitation	25–40
ACLA	15
AMA	5
ASMA	30
Anti-TPO	25

Table 5.3 Revised international classification criteria for Sjögren's syndrome

American-European Consensus
I. *Ocular symptoms* – a positive response to at least one of the following questions:
Have you had daily, persistent, troublesome dry eyes for more than 3 months? *Do you have a recurrent sensation of sand or gravel in the eyes*? *Do you use tear substitutes more than 3 times a day*?
II. *Oral symptoms* – a positive response to at least one of the following questions:
Have you had a daily feeling of dry mouth for more than 3 months? *Have you had recurrently or persistently swollen salivary glands as an adult*? *Do you frequently drink liquids to aid in swallowing dry food*?
III. *Ocular signs* – that is, objective evidence of ocular involvement defined as positivity for at least one of the following two tests:
Schirmer's I test, performed without anesthesia (<5 mm in 5 min) Rose bengal score or other ocular dye scores (>4 according to van Bijsterveld's scoring system)
IV. *Histopathology*: In minor salivary glands (obtained from normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm [2] of glandular tissue
V. *Salivary gland involvement*: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
Unstimulated whole salivary flow (<1.5 ml in 15 min) Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
VI. *Autoantibodies*: presence in the serum of the following autoantibodies:
Antibodies to Ro(SS-A) or La(SS-B) antigens or both

Table 5.4 Revised rules for classification of Sjögren's syndrome

Primary Sjögren's syndrome diagnosis:
The presence of any 4 of the 6 criteria, as long as either criterion IV (histology) or VI (serology) is positive The presence of any 3 of the 4 objective criteria (i.e., items III, IV, V, VI)
Criteria for secondary Sjögren's syndrome (for instance, associated with a systemic connective tissue disease):
The presence of criterion I or II plus any 2 from among items III, IV, and V
Exclusion criteria:
Past head and neck radiation treatment Hepatitis C infection and AIDS Preexisting lymphoma Sarcoidosis Graft-versus-host disease Use of neuroleptics, antidepressants, antihypertensives or parasympatholytic drugs Sialadenosis

Table 5.5 Differential diagnosis of sicca syndrome

Xerostomia	Xerophthalmia	Bilateral enlargement of parotid gland
Viral infections	Inflammatory diseases	Viral infections
Medications:	Stevens-Johnson syndrome	Infectious parotitis, flu
Psychopharmaceuticals	Pemphigoid	EBV, cytomegalovirus
Parasympatholytics	Chronic conjunctivitis	Coxsackie A, HIV, CMV
Antihypertensives	Chronic blepharitis	Sarcoidosis
Psychogenic conditions	Toxic effects	Amyloidosis
Post-radiation syndrome	Drugs	Metabolic diseases:
Diabetes mellitus	Neurological diseases	Diabetes mellitus
Shock condition	Impaired function of lacrimal glands	Hyperlipoproteinemia
Advanced age	Impaired function of eyelashes	Chronic pancreatitis
	Shock condition	Liver cirrhosis
	Hypovitaminosis	Endocrine diseases:
	Advanced age	Acromegaly
	Scars on eyelids	Gonadal hypofunction
		Unilateral enlargement
		Salivary gland neoplasia
		Infection
		Sialolithiasis

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Systemic Scleroderma

6

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Systemic scleroderma (SSc, progressive systemic sclerosis) is a generalized connective tissue disease which clinically manifests itself by thickening – fibrosis – and cutaneous sclerosis of various extents (scleroderma) and a typical involvement of multiple internal organs [1]. At the same time, there occur fibrotic and sclerotic changes in vascular walls, disturbances of microvascularization, and disorders of humoral and cellular immunity. It affects 3–8 times more women than men. It develops usually in middle age, with an annual incidence of about 3 – 19 new cases per million population. One of the major clinical manifestations is Raynaud's phenomenon with trophic changes, skin induration, and involvement of gastrointestinal tract, lungs, heart, and kidneys [2].

The patients with late-onset SSc, may exhibit visceral pathology in the earlier stages of the disease, as documented by the study published by Volkov et al. [3]. The authors compared clinical manifestations in patients under and over the age of 50 and gender-dependent changes. Late-onset SSc patients developed SSc visceral manifestations in the first 3 years of the disease. Men with late-onset SSc had predominantly the diffuse cutaneous form of the disease with progressive skin involvement and induration and significant microcirculation changes. In contrast, the study by Hügle et al. [4] comparing SSc patients under and over 75 years demonstrated that the patients over the age of 75 had more frequently limited than diffuse SSc.

Myalgia, arthralgia, and arthritis are nonspecific symptoms in SSc, while tendon friction rubs at finger flexors are thought to be diagnostic of SSc. Late-onset SSc patients had a more marked muscle weakness [5]. Peripheral trophic changes are relatively less frequent in late-onset SSc than in early-onset SSc.

Fibrotic changes in the digestive tract result in retardation or arrest of the passage of the intestinal contents and dilatation of the distal esophagus. This is manifested by dysphagia, pyrosis, gagging, abdominal pain or even colic, sometimes malabsorption and emptying disorders, constipation in particular. These symptoms are usually accentuated in late-onset SSc patients.

Pulmonary involvement occurs in the form of interstitial lung disease or pulmonary arterial hypertension. A more frequent form is alveolitis with the subsequent interstitial fibrosis. Frequency of the interstitial process probably increases with age and often leads to secondary pulmonary hypertension. However, the study by Hügle [4] proved this difference neither by radiographic methods nor by function tests.

Primary pulmonary hypertension without interstitial lung disease is according to the American authors twice as frequent in late-onset SSc with the beginning of the disease after the

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age of 60 [6]. Similarly, the study by Manno [5] showed a higher risk of pulmonary hypertension in late-onset SSc patients. Cumulative incidence during 5 years was higher in the late-onset SSc group (9 %) as compared to early-onset SSc patients (2.7 %; $p<0.001$) [7]. The study by Hügle [4] also revealed in the group of patients over the age of 75 a more prevalent pulmonary hypertension (measured by echocardiography) as well as systemic hypertension and diastolic dysfunction.

Cardiac involvement may have several forms, e.g., a frequent finding of often asymptomatic pericarditis. Myocardial involvement is manifested in the conductive system by abnormal heart rhythm and atrioventricular blocks. These findings are more frequent and more serious in late-onset SSc [3], which was confirmed by the study published by Manno [5].

Renal manifestation is reported in 8–10 % of patients. The most severe form is scleroderma renal crisis with abrupt onset of hypertension and rapid development of oliguria or even anuria. A higher frequency of renal manifestation has been documented also in an American cohort study [5].

The laboratory findings usually include a mild normochromic normocytic anemia and thrombocytopenia. Acute phase reactants values are often slightly elevated or normal and thus do not reflect the disease activity. Immunological tests show the presence of rheumatoid factors and cryoglobulins in up to 40 % of patients. Antinuclear antibodies are positive in up to 90 % of cases, usually with granular immunofluorescence pattern. A more specific anticentromere antibody test is positive in about 70 % of patients with limited cutaneous SSc [8]. The study published by Manno evaluated 2,300 SSc patients and showed that incidence of anticentromere autoantibodies was considerably higher in patients older than 65 years as compared to younger individuals (42 % vs. 27 %; $p=0.001$) (Table 6.1). This was confirmed also by a large cohort study based on the EUSTAR/EULAR database [4]. In contrast, anti-DNA topoisomerase I antibodies (anti-Scl-70) are found in up to 40 % of patients with the diffuse cutaneous form.

Table 6.1 Clinical symptoms and laboratory findings in systemic scleroderma with younger- versus late-age onset

Manifestation	SSc, younger-age onset	SSc
Anticentromere antibodies (ACA)	Positive mainly in limited cutaneous form	In general higher incidence
Pulmonary hypertension, muscle weakness, involvement of the heart and kidneys	More frequently in diffuse cutaneous SSc	In general higher incidence
Peripheral vasculopathy	Frequent	Less frequent
General prognosis	Better	Markedly worse

Modified according to Manno et al. [5] and Hügle et al. [4]

Prognosis of the disease is usually given by severity of pulmonary involvement; the interstitial process usually gradually leads to development of global respiratory insufficiency with fatal consequences. Pulmonary arterial hypertension, on the other hand, is characterized by rapid progress with a very poor diagnosis. The age over 75 years is in late-onset SSc associated with a substantially worse prognosis than in patients older than 60 years [9]. In the cohort from the EUSTAR/EULAR database, mortality due to SSc was higher in the late-onset group, but the survival time from diagnosis was longer compared with the younger patients. The disease is manifested by a far more severe involvement of individual organs, and the condition is often complicated by various comorbidities; therefore, diagnosis must be established as soon as possible. In the patients, special attention should be paid to the incidence of malignant processes, including solid tumors in men with extensive skin involvement; pulmonary fibrosis as a predisposition to lung cancer, breast cancer in women, and chronic reflux esophagitis; and Barrett's esophagus as a predisposition to esophageal carcinoma.

SSc treatment must be always comprehensive. The basic process cannot be usually controlled by pharmacological treatment as the effect of most preparations can be observed only in the cutaneous form of the disease. In the edematous phase of the disease, patients receive corticosteroids

with methotrexate and in active alveolitis corticosteroids on a long-term basis and repeated intravenous pulses of cyclophosphamide [10]. Other procedures are organ specific and have only a symptomatic effect. In late-onset SSc treatment, the basic therapeutic procedures do not differ substantially from treatment of younger patients, only it is complicated by frequent visceral organ involvement and neurological comorbidities and the associated risk of serious drug interactions. The future of a complex SSc treatment lies in biological preparations that will be targeted at individual phases of the immunopathological process. The results of clinical trials focused on the current biologic drugs used to treat rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis are not unequivocal.

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Vasculitides

7

Radim Bečvář and Jozef Rovenský

7.1 Introduction

Vasculitis is an inflammatory disease of blood vessels leading to destruction of the vessel wall, subsequent proliferation and obliteration of their lumen. The clinical syndromes are associated with ischaemia of tissues supplied by the involved blood vessels and general manifestations of inflammatory diseases. Vasculitis may develop de novo as a primary involvement of the vessel wall of unknown aetiology or as a secondary disorder in other common or rarer primary processes.

Classification of vasculitis is a complex problem, as the cause of the disease is mostly unknown; clinical features are highly variable and may overlap. The final diagnosis is usually given by the histological finding from biopsy specimens; in some cases radiographic contrast examination or another imaging method is sufficient.

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Several classifications have been developed during the recent decades by the American College of Rheumatology (ACR) [1], and one generally accepted nomenclature was introduced at the conference in Chapel Hill in 1993 [2]. The main criterion is the size of the affected blood vessels. Table 7.1 includes a combination of ACR classification and the classification presented at the conference in Chapel Hill [3].

Except for giant cell arteritis, the incidence of vasculitides in the elderly is not very frequent. Different diagnoses are reported only in individual cases or small groups of patients. Relatively larger cohorts were studied in case of the Behçet's disease.

7.2 Large-Sized Vessel Vasculitis

7.2.1 Takayasu's Arteritis

Definition Takayasu's arteritis (TA) is a chronic inflammatory disease affecting large arteries, primarily the aorta and its main branches [4]. It most commonly occurs in young women in the Middle and East Asia.

Aetiology and Pathogenesis Aetiology of the disease is unknown. Several aetiologic factors have been proposed, including streptococcal infection and hypersensitivity to tuberculin test. A potential role of circulating immune complexes and circulating antibodies to aortic

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Table 7.1 Classification of primary vasculitides by the size of damaged blood vessels

Frequent	Less frequent
Large blood vessels – giant cell (temporal) arteritis Takayasu's arteritis	Sarcoidosis (affects large, medium or small blood vessels) Cogan's syndrome (affects large or medium blood vessels)
Medium blood vessels Polyarteritis nodosa and cutaneous form Familial Mediterranean fever Kawasaki disease	
Medium to small blood vessels Granulomatosis with polyangiitis (Wegener's granulomatosis) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) Microscopic polyangiitis (polyarteritis) Behçet's disease (affects large blood vessels)	Primary angiitis of the central nervous system Thromboangiitis obliterans
Small blood vessels Cutaneous leucocytoclastic vasculitis IgA vasculitis (Henoch-Schönlein purpura) Cryoglobulinaemic vasculitis	Degas' disease Urticarial vasculitis Myelodysplastic syndromes Erythema elevatum diutinum Hyperimmunoglobulinaemia D

Modified according to Ball et al. [3]

wall components has also been mentioned. Immunogenetic studies have revealed associations with BW52 and DR4 haplotypes.

Clinical Manifestations The clinical features typically include *symptoms of vascular insufficiency* of upper limbs, described as arm claudication or arm numbness; loss of pulse or low blood pressure in an arm; and bruits heard most often over the carotids and abdominal aorta, less frequently over the subclavian and femoral arteries. There is often a *difference in blood pressure* between the arms of more than 30mmHg. *Postural nausea* is a sign of occlusion of the carotid and vertebrobasilar arterial systems, which may cause a typical partial flexion of the cervical spine. *Visual disorders* include blurred vision, diplopia or transient unilateral amaurosis. A regular finding is hypertensive retinopathy. Microaneurysms, dilatation of veins and bleeding resemble diabetic retinopathy. Late sequelae include optic nerve atrophy, retinal detachment and vitreous haemorrhage. In the early stages *arthralgia*, sometimes lower limb synovitis or symmetrical polyarthritis can be observed. *Myalgia* is frequent and may be misleading. The inflammatory phase of the disease may last for months. Patients are treated for a "fever of unknown origin" for several years before symptoms of vascular insufficiency develop. *Skin lesions* have often the form of erythema nodosum and lower leg ulcers. *Cardiac involvement* consists in changes of coronary artery orifices or of their proximal sections. Heart failure is most frequently caused by this disorder or systemic hypertension; myocardial biopsy has proved also myocarditis. Involvement of large- and medium-sized *pulmonary arteries* is common and leads to pulmonary hypertension, often without a marked clinical manifestation.

Other repeatedly reported clinical features include mesangial proliferative *glomerulonephritis* or renal amyloidosis. Renal artery stenosis may be multiple and bilateral and is manifested by hypertension.

Laboratory Findings Most patients exhibit high *ESR* and *CRP*, mild *anaemia* and *leucocytosis*, with a finding of elevated levels of all immunoglobulin classes, but no antibodies.

Additional Examinations The key role is played by angiographic examination focused on all branches of the aorta. Additional arteriography depends on the respective clinical

features; the currently most frequently used method is digital subtraction angiography. CT scans show aortic wall thickness and its treatment-induced changes. Early inflammatory phase can be well imaged by positron emission tomography (PET). Histologically, the granulomatous phase represents the period of active inflammation with changes in media and adventitia with a mixed cellular infiltrate of lymphocytes, plasma cells and histiocytes together with typical giant cells. In the late stage, the disease is represented by a mild fibrous intimal hyperplasia, medial degeneration and fibrosis of the adventitia.

Diagnosis TA diagnosis is based on typical distribution of changes in main branches of the aorta, primarily in the left subclavian artery, superior mesenteric artery and other branches of the abdominal aorta. About 85 % of patients exhibit only stenosis and the rest have combined changes.

Differential Diagnosis In the first place it is necessary to exclude atherosclerosis – TA primarily affects young individuals without risk factors of this disease. Other diseases to be excluded are SLE, Behçet's disease, aortitis in ankylosing spondylitis, rheumatic fever, Crohn's disease and syphilitic aortitis. TA may also resemble GCA, congenital coarctation of the aorta, ergotism and thromboangiitis obliterans.

Therapy The medications of choice are *corticosteroids*; in the inflammatory phase, prednisone is administered at the initial dose of 0.5–1 mg/kg/day or another preparation with a slow reduction in dose. Therapy is long term, with a continuous ESR control and, after several months, also PET control. Several cases were reported of regression of inflammatory stenosis. Where the dosage of corticosteroids cannot be successfully reduced, cytotoxic treatment should be initiated, including cyclosporine A, cyclophosphamide pulses or azathioprine and lately also methotrexate. In refractory forms, excellent results were achieved with anti-TNF alpha blockers.

Surgical treatment is reserved for selected cases in the case when the disease is under control and includes percutaneous angioplasty, bypass, endarterectomy, resection of aneurysms and valve replacement and often also renal artery surgeries.

Disease Prognosis The prognosis depends on specific manifestations (Takayasu's retinopathy, secondary hypertension, aortic insufficiency, aortic and arterial aneurysms).

Patients with stabilised disease survive in 98 % for 6 years. The main cause of death is heart failure and cerebrovascular stroke.

Two cases of late onset of TA were reported by Nakabayashi et al. [5]. The patients developed the disease at the age over 60, with involvement of distal branch arteries and association with rheumatoid arthritis. *Angiography* showed in both patients a typical involvement of abdominal aorta and subclavian artery stenosis. In addition, the first patient had occlusive lesions of the superficial femoral arteries, and the latter one manifested occlusion of the axillary artery. Laboratory findings showed increased ESR and CRP in both patients and, in the first of them, a positive rheumatoid factor. Both patients presented with swelling, pain and tenderness in small joints. In one of the patients, radiographic examination revealed destructive changes in joints that were absent in the other patient. The histological findings from femoral artery biopsy showed lesions typical of TA. Based upon these findings, the authors diagnosed the two patients as having atypical Takayasu's arteritis with arthritic manifestations.

7.3 Medium-Sized Vessel Vasculitis

7.3.1 Polyarteritis Nodosa

Definition Polyarteritis nodosa (PAN) is a disease of small- and medium-sized arteries involving all three arterial wall layers, leading to multiple aneurysms, thrombi and tissue

infarction. PAN may be a manifestation or a complication of RA, SSc and other connective tissue disorders.

Aetiology and Pathogenesis Aetiology is unknown. The pathogenesis is attributed to deposition of *immune complexes* in various tissues, probably also to *hepatitis C* (less frequently B) *virus*, *HIV* and *cytomegalovirus* and *parvovirus*. The role of *ANCA* antibodies and *hypersensitive reaction* has not been clarified, yet.

Clinical Manifestations The severity of the disease may range from a limited condition up to a rapidly progressing form which is usually fatal [6]. Most patients present with *general symptoms*, such as fever, weakness, weight loss and sometimes rash, peripheral neuropathy and polyarthritis. Sometimes only a single organ is affected, e.g. the skin, peripheral nerves or kidneys. *Cutaneous manifestations* may include palpable purpura, ulceration, livedo reticularis and ischaemic changes in distal phalanges. *Joint involvement* includes arthralgia or arthritis. Asymmetrical episodic nondeforming polyarthritis affects the joints of lower extremities. *Neurological symptoms* may develop in the form of peripheral neuropathy with an abrupt onset including pain and paresthesia of the peripheral nerve, followed by loss of motor function. Gradual involvement of nerves may result in asymmetrical polyneuropathy. *Renal insufficiency* is manifested by proteinuria; in the early stages, there may occur haematuria. Involvement of renal arteries or glomeruli often results in hypertension. The disease-related *GIT disorders* are associated with abdominal pain, and their location correlates with the affected organ. In case of diffuse pain, mesenteric artery thrombosis should be considered.

This pain causes also abdominal distension, sometimes even peritonitis, quite often with gastrointestinal bleeding. *Cardiac involvement* includes heart failure is caused by coronary insufficiency or hypertension. *Myalgia* induces diffuse involvement of muscle arteries, sometimes in the form of intermittent claudication. *Eye* manifestation is commonly in the form of retinal detachment or toxic retinopathy.

Laboratory Findings Include elevated *ESR*, *normochromic anaemia*, *thrombocytosis* and lower serum albumin levels. Part of the patients is *HCV* or *HBsAg positive*. The sign of disease activity is decreased complement levels. In the active phase, circulating immune complexes (CICs) are usually elevated.

Additional Examinations Arteriography appears to be of great value, usually showing saccular or spindle-shaped aneurysms or conical narrowing of arteries. Aneurysms can be found in renal, hepatic, mesenteric, cerebral, lumbar, intercostal, lower phrenic, hypogastric and gastroduodenal arteries. The common examination method is biopsy of skin, skeletal muscles, the sural nerve and the testes. Histological findings include involvement of small- and medium-sized arteries with a predilection at the site of arterial ramification. Typical signs include *fibrinoid transformation and massive infiltration of all three arterial wall layers with polymorphonuclear cells and eosinophils*. Thromboses and aneurysms typically occur at the sites of changes. Inflammatory foci heal with fibrous tissue causing arterial occlusion. Glomerulonephritis is in most cases segmental and proliferative.

Diagnosis Diagnosis should be always verified by biopsy, if the affected organ is accessible or by arteriography which shows typical aneurysms.

Differential Diagnosis It is important to distinguish between IgA vasculitis (IGAV) (formerly Henoch-Schönlein purpura) and anti-GBM nephritis. The renal biopsy finding may be identical to granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis) and to eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome). A number of PAN clinical symptoms may occur also in other diseases. Unless aneurysms are clearly seen, a similar angiographic image can be found in GPA, vasculitis in SLE, thrombotic throm-

bocytopenic purpura, infective endocarditis and tumours metastasizing to peritoneum. A problem may be dissecting arterial aneurysms.

Therapy All patients receive *corticosteroids*, at the beginning preferably in the form of intravenous bolus of methylprednisolone. In case of rapidly progressing extensive visceral involvement, *cyclophosphamide* pulse therapy should be added. In case of contraindication of cyclophosphamide, *azathioprine* or *methotrexate* may be used instead. If these combinations are ineffective, plasmapheresis is used as an adjuvant therapy. In cases associated with hepatitis B, corticosteroids are administered for several days, in combination with antiviral medications. Local, primarily cutaneous, forms respond well to colchicine in combination with topical corticosteroids.

Disease Prognosis The prognosis depends on the scope of involvement of vital organs. Uncontrollable vasculitis (heart failure and stroke) or infectious complications during immunosuppressive treatment may have fatal consequences.

With the treatment based on corticosteroids alone, 60 % of patients survive for 5 years.

Several cases were described, of PAN *with the onset in old age* [7]. The reported cohort included also three patients, namely, two women (86 and 75 years old) and one man (75 years old), two of which suffered from hypertension and one from ischaemic heart disease. Of the main signs, all patients had at the onset of the disease fever and fatigue, two of them also polyneuropathy, one had a history of stroke, and two of them had arthritis. Laboratory tests in all of them showed high inflammatory reactants and one positive urine finding. Two patients were positive for perinuclear (pANCA) and one for cytoplasmic (cANCA) antineutrophil cytoplasmic antibodies. All of them were treated with corticosteroids, two with antibiotics and one with addition of cyclophosphamide. Two patients died and in one patient the disease was stabilised.

7.3.2 Kawasaki Syndrome

Definition Kawasaki syndrome (KS) is a vasculitis affecting coronary arteries with formation of aneurysms and occlusions and a tendency to spontaneous remission. It is characterised by long-term fever, oral mucosal inflammation, skin disorders and cervical lymphadenopathy. It most often affects *children younger than 5 years*, with a slight *predominance in boys*.

Aetiology and Pathogenesis The aetiology remains unknown. It has been hypothesised that it is related to a microbial agent (*Propionibacterium acnes*) due to the acute course, a tendency to spontaneous remission and endemic incidence. Association between KS and HLA-Bw22 was found in Japanese patients and between KS and HLA-Bw51 in Caucasian patients.

Clinical Manifestations The clinical course of the disease is conventionally divided into three stages: acute, subacute and convalescent [8]. The acute stage is characterised by high fevers and is followed by the subacute stage when the fever and symptoms have gradually abated; the convalescent phase is marked by complete resolution of clinical signs of the illness. *Fever* up to 41 °C is not responsive to antibiotics and can persist for up to 3 weeks if untreated. Typical complaints include irritability, restlessness, vomiting and diarrhoea. *Rash* resembles scarlet fever, measles or erythema multiforme. Reddening of palms and soles, followed sometimes by induration of hands and feet and finally desquamation of the digits, is often observed in the acute phase of the disease. Exanthem is often accentuated in the perineal region, where early desquamation may occur. Oropharyngeal changes include congested oropharynx, red tongue with prominent papillae (strawberry tongue), erythema and swelling, cracking, and bleeding of the lips. *Neck lymph nodes* are tender to palpation and markedly enlarged. All the mentioned symptoms resolve without sequelae. *Involvement of coronary arteries* is much more severe and is often asymptomatic. In addition, about 20 % of patients develop aneurysms during convalescence.

Laboratory Findings Show increase in *acute phase indicators*, marked *leucocytosis* and normocytic normochromic *anaemia*, sometimes also increased *liver test* values. Typical of the convalescent stage is a marked thrombocytosis and acute increase and subsequent decrease of levels of all immunoglobulin classes.

Increased levels of circulating immune complexes (CICs) were repeatedly observed. Of special interest is the evidence of antibodies against endothelial cell antigens. Sometimes the patients also suffer from temporary pyuria.

Additional Examinations ECG shows changes suggesting myocarditis that must be verified by two-dimensional echocardiography and coronarography. Myocarditis is manifested in about 20 % of cases, by enlargement of the heart shadow on the chest radiograph and episodes of heart failure or arrhythmias. Autopsy reveals heart hypertrophy and in about half of the cases a pericardial effusion. A principal finding is *multiple coronary artery aneurysms* with *thrombus* in the stems. With the aneurysm, the arterial wall grows progressively thinner; the intima and media are damaged and show massive infiltration of polymorphonuclear cells. The inflammation involves also perivascular tissues. In later stages there occur scarring in major coronary arteries, arterial wall calcification and recanalization. Intimal thickening causes stenosis and occlusion. These changes progress to coagulation necrosis with a subsequent fibrosis, resulting in endocardial fibroelastosis.

Diagnosis Typical skin and mucosal changes with fever and cardiac involvement facilitate early diagnosis which is extremely important because mainly the youngest children develop disorders of coronary arteries quite early. Sometimes the clinical presentation is incomplete. Such condition is called atypical KS.

Differential Diagnosis First of all, it is necessary to exclude scarlet fever, measles and rubella that are not associated with cardiac involvement.

Therapy Infusion therapy is applied if the patient rejects food. Antibiotics are often administered until infection is excluded. Diuretics and inotropic medications are used in case of signs of myocarditis; sometimes even pacemaker stimulation is required. The medication of choice in the acute and subacute stages of the disease is aspirin. Intravenous gamma globulin therapy reduces the period of fevers and the incidence of aneurysms. In case of uncertain diagnosis, only gamma globulins are applied. Intracoronary thrombolysis is indicated in case of a pathological coronarographic finding. Occlusion of larger branches requires aortocoronary bypass.

Disease Prognosis Although the disease tends to remit spontaneously, it leads to a high rate of irreversible changes in coronary arteries and myocardium, if untreated. Mortality in treated patients amounts to about 0.5 %.

KS onset *after the age of 20 years* is quite rare. Italian authors [9] described a case of a 21-year-old man with this disease who suddenly died. Autopsy revealed thromboses and aneurysms of coronary arteries and myocarditis, resulting probably from a past history of KS. A British group of authors [10] reported a case of a teenager who was repeatedly examined for a fever persisting for 2 weeks. Despite administration of intravenous immunoglobulins, corticosteroids and TNF-alpha blockers, cardiovascular complications kept progressing. Echocardiographic findings were indicative of a heart disorder, and only the subsequent CT angiographic examination clearly proved the presence of giant coronary artery aneurysms.

7.4 Small-Sized Vessel Vasculitis

7.4.1 Granulomatosis with Polyangiitis (Wegener's Granulomatosis)

Definition GPA is a necrotizing vasculitis affecting the respiratory tract through formation of granuloma and glomerulonephritis. It is most

common in men, as a rule between 50th and 60th year of age [11].

Aetiology and Pathogenesis The cause of GPA is not yet known. A certain role may be attributed to hypersensitivity to an unspecified allergen. It is hypothesised that the pathological factor is immune complex deposition along the basement membranes.

Clinical Manifestations The common general symptoms include fatigue, weight loss and fever. Involvement of the upper respiratory tract is manifested by epistaxis, chronic rhinitis and sinusitis. Otitis media and conductive hearing loss are frequent. A disorder of the lower respiratory tract is signalled by cough, haemoptysis or chest pain. Granulomas may get into the pleural cavity and cause pneumothorax. Renal involvement is common and may lead to renal insufficiency. A wide range of ocular disorders include conjunctivitis, episcleritis, corneal ulcers, retinal vasculitis, neuropathy of the optic nerve and exophthalmos. The most common form of involvement of *peripheral nerve* involvement is mononeuritis multiplex. The signs of involvement of the *gastrointestinal tract* include diarrhoea, bleeding and abdominal pain and sometimes bowel perforation. The musculoskeletal symptoms include *arthralgia* and *myalgia* or even erosive arthritis.

Laboratory Findings Show anaemia, leukocytosus, sometimes also thrombocythaemia, as well as elevated *ESR* and *CRP* and *hypergamaglobulinaemia*, particularly the raised IgA level. In the early phase microscopic glomerular erythrocyturia is commonly observed, with a mild or medium proteinuria. Renal function may be impaired. Sometimes also the rheumatoid factor (RF) is positive, and circulating immune complex (CIC) levels are elevated. Laboratory examination includes also positivity of tests for cANCA autoantibodies.

Additional Examinations Granulomas in the upper respiratory tract and sinuses can be well seen on MRI scans. Histological findings from biopsy material may include minor granulomas or necrosis with secondary infection. Radiograph of the lungs shows typical "butterfly" opacity; a more specific image is provided by HRCT. In addition to transient infiltrates, extensive granulomas with central degradation can be sometimes seen in alveoli. Renal biopsy findings include focal up to diffuse segmental necrotizing glomerulonephritis. Histology may reveal also small-sized vessel vasculitis. Endoscopy is used to detect haemorrhage or even ulcerations in the duodenum.

Diagnosis It is based on the typical clinical features of the upper and lower respiratory tract involvement with granulomas, of the eyes and, in later phases, also of the kidneys.

Differential Diagnosis The pulmonary renal, so-called Goodpasture's syndrome, should be excluded, preferably by immunofluorescence examination based on renal biopsy, aimed at detection of linear deposition of immunoglobulins along glomerular basement membranes. Eosinophilic granulomatosis with polyangiitis (EGPA) is typically associated with asthma and blood and organ eosinophilia without renal impairment. In PAN, the lung involvement is substantially less frequent than in GPA.

Therapy has two main goals, namely, to achieve remission of the disease by aggressive combined immunosuppression and to prevent its relapse by maintenance treatment. Prednisone with cyclophosphamide or methotrexate is used to induce remission. In life- or organ-threatening cases, intravenous methylprednisolone is added at the dose of 1 g for three consecutive days. In an early systemic form of the disease, methotrexate is recommended. Local granulomatous forms may be treated with a trimethoprim/sulfamethoxazole combination. Refractory forms require addition of high doses of intravenous immunoglobulins or repeated plasmapheresis. Azathioprine or methotrexate, leflunomide and trimethoprim/sulfamethoxazole are administered in the maintenance phase. The most promising of biologic drugs seems to be so far rituximab in combination with cyclophosphamide and corticosteroids.

Disease prognosis depends on the scope of involvement of the kidneys and opportunistic infection. One of the fatal acute causes of death is massive pulmonary haemorrhage. The disease relapses in up to 50 % of patients even several years after the diagnosis. Antineutrophil cytoplasmic antibodies (ANCA) are a useful parameter that may signal a relapse of the disease.

A case of a 74-year-old woman with ANCA-negative granulomatosis of the upper respiratory tract was reported [12]. The patient responded well to a combined treatment with prednisone and cyclophosphamide. Subsequently, she developed painless nodes in ankles that disappeared after a high dose of corticosteroids. Satchell et al. [13] studied the correlation between the age and the course of renal vasculitis in the elderly and the treatment effects for a period of 2 years. The mean age of the patients at the beginning of the follow-up was 69 years. A total of 48 % of patients required dialysis treatment, and the total mortality was 33 %. In agreement with other studies, they concluded that the incidence of vasculitis grows with the age and the general prognosis is getting worse.

7.4.2 Microscopic Polyangiitis (MPA)

Definition It is a small-sized vessel vasculitis with focal segmental necrotising glomerulonephritis without granuloma formation in the airways. It is part of the group of vasculitides associated with antineutrophil cytoplasmic antibodies (ANCA) [14].

Clinical Features In addition to nonspecific symptoms (arthralgia, arthritis and myalgia), the clinical features include glomerulonephritis, hypertension, lung involvement, lower extremity ulceration, sometimes peripheral neuropathy and often also involvement of the digestive system and eyes.

Incidence MPA is a rare disease with the annual incidence of about 5 cases per one million population and is more common in the *middle-aged male* Caucasians.

Aetiology and Pathogenesis The aetiology is not known. Association has been described with *HLA DR2* antigen and factor B (BfF) phenotype of the alternative complement pathway activation. Pathogenetic role of antineutrophil cytoplasmic antibodies (ANCA), particularly activation of neutrophils stimulated by TNF-alpha, has been proved in vivo.

Another pathogenetic factor seems to be anti-endothelial cell antibodies (AECA) that increase adhesion of leukocytes to endothelial cells. In predisposed patients MPA may be induced by certain drugs, penicillamine and hydralazine in particular. Seasonal incidence of the disease indicates a potential correlation with infectious (viral) diseases.

Clinical Manifestations At the beginning the symptoms are usually nonspecific – myalgia, arthralgia or arthritis. The typically predominating clinical feature is renal disorder – a rapidly progressing glomerulonephritis manifested by microscopic haematuria and mild proteinuria. Hypertension is present in about 20–30 % of patients.

Pulmonary involvement is represented by alveolar haemorrhage, and sometimes interstitial pulmonary fibrosis may develop. *Cutaneous lesions* can be found in about half of the patients, having a wide range from macular skin lesions to lower extremity ulceration. About one third of patients suffer from some type of *peripheral neuropathy*, most frequently mononeuritis multiplex. CNS involvement is much rarer. About 50 % of patients present with GIT disturbances, with pain and bleeding from small and large intestinal ulcers. *Ocular manifestations* include eyelid inflammation, iridocyclitis, scleritis and retinal vasculitis. Sometimes there occurs mild sinusitis.

Laboratory Examination Acute-phase reactants are usually increased. The common presenting features include *microscopic haematuria*, mild to moderate *proteinuria*, with a various degree of renal function impairment and *positive pANCA* directed primarily against

myeloperoxidase, less often against elastase and other enzymes.

Additional Examinations Renal involvement is histologically characterised by *focal segmental necrotising glomerulonephritis* with a various degree of glomerular crescent formation in individual phases of the development. Immunofluorescence is negative, or there are only slightly positive immunoglobulins or complement. Histological finding of renal impairment is identical to the lesions seen in GPA, with absence of granulomas. A skin biopsy finding may indicate leukocytoclastic vasculitis of small-sized vessels.

Diagnosis Diagnosis is based on a typical histological finding in the kidneys, involvement of at least one more organ and absence of necrotising granuloma.

Differential Diagnosis The above-mentioned facts show that it is often difficult to distinguish between the "idiopathic" focal segmental necrotising glomerulonephritis and GPA. Microscopic granulomas may be present and not always detected by biopsy. MPA is usually not associated with lung granulomas.

Therapy Medications and treatment regimens used in MPA and GPA do not differ. All patients with MPA diagnosis should receive corticosteroids, at the beginning either in the form of pulses or orally. The effect of intravenous cyclophosphamide pulse therapy is not as straightforward as in GPA. The maintenance treatment is almost identical as in GPA. Plasmapheresis does not provide prolonged survival in case of severe renal failure, the effects of intravenous immunoglobulins have not been clearly determined in MPA.

Disease Prognosis The prognosis of MPA patients largely depends on the level of renal functions at the time of diagnosis; the highest mortality (about 50 %) is reported in the patients requiring dialysis in the early stage of the disease. However, the most frequent mortality causes are pulmonary manifestations – pulmonary haemorrhage and pneumonia. The group reported by Turcu et al. [7] included also two patients with MPA – an 85-year-old man and a 75-year-old woman. The man suffered from extreme fatigue, polyneuropathy and urticaria and later died of stroke. The woman had a past history of stroke and subsequently died of multiple organ failure.

7.4.3 Behçet's Disease

Definition Behçet's disease (BD) is a chronic relapsing inflammatory process affecting multiple tissues and organs. The underlying condition is small-sized vessel vasculitis, although involvement of large arteries and veins can be also found [15].

Clinical Features Typical clinical signs include recurrent aphthous stomatitis with genital aphthous ulcers, uveitis, skin nodules or pustules, synovitis or meningoencephalitis. Other common clinical symptoms include inflammation of large arteries, phlebitis and intestinal ulceration.

Incidence The disease is most common in Japan, in East Mediterranean countries, in the USA and in the Middle East, while uveitis is more frequent and more severe in South East Asia and Turkey. Males and females are equally affected.

Aetiology and Pathogenesis BD aetiology and pathogenesis are not known. Incidence of HLA-B5 and B51 subtype is in patients with BD 3–6 times higher than in healthy population. Especially the presence of B51 subtype may be a predictor of a severe course of the disease. Although it is known that the vasculitis process is triggered by immunological mechanisms, there is no evidence that BD would involve an autoimmune process. Numerous studies have focused on identification of *microbial agents*, viruses in particular, that would activate T lymphocytes and their Th1 subpopulation. Prolonged euglobulin lysis time was revealed in the acute phase of the disease, indicating inhibition of spontaneous plasma fibrinolysis, perhaps in connection with disorders of tissue plasminogen activator release. The relevance of this finding is not quite clear.

Clinical Manifestations One of the main symptoms is *mouth* and *genital ulcers*. Oral lesions differ from viral aphthous ulcers; they have well-defined borders and are accompanied with reduction of the number of fungiform papillae on the tongue, plaque-like lesions of the pharynx and mouth odour. Ulcers on penis and scrotum are usually painful, unlike those on vulva and vagina which often go unnoticed. The common *skin manifestations* include pyoderma with pustules of various size, erythema nodosum and gangrenes. GIT involvement is manifested by ulcers ranging from aphthae to large intestinal ulcers. A classic *ocular symptom* is iritis with hypopyon. There may occur also episcleritis, conjunctivitis, keratitis, iridocyclitis, retinal thrombophlebitis, papilloedema or even atrophy of the optic nerve that, if untreated, may result in blindness.

The prognosis of certain patients is given by the degree of CNS involvement, primarily meningitis, myelitis and the brainstem syndrome. In clinical terms, the neurological disorders include spastic haemiparesis or quadriparesis, often with cerebellar ataxia. Thrombosis of the superior or inferior vena cava, superficial or deep veins of limbs, is identified in about 7–37 % of cases. Occlusion of intracranial cavernous sinus is manifested by chronic headache and blurred vision without papilloedema. Aneurysms and large artery occlusions were described in autopsy material of up to 37 % of patients. Occlusions were often caused by emboli from the mitral valve endocardium. *Pulmonary arterial* aneurysms communicate with bronchi, which results in massive haemoptysis. *Joint involvement* is mono- or oligoarticular and is rather of arthralgic than of arthritic nature. Most frequently it affects knees, ankles, wrists and sacroiliac joints.

Laboratory Findings Include increased values of acute phase reactants, anaemia and typically also polyclonal gammopathy. Immunological tests show only nonspecific increase of levels of circulating immune complexes (CICs levels) and the presence of cryoglobulins in 20–25 %.

Table 7.2 Diagnostic criteria for Behçet's disease

Main criterion
Recurrent oral ulceration (aphthous or herpetiform) observed by physician or reliably reported by patient minimally 3times in 1 year
Plus two of the following secondary criteria
Recurrent genital ulceration (scrotum, penis, labia, vagina)
Eye lesions (anterior/posterior uveitis, retinal vasculitis) observed by ophthalmologist
Skin lesions: erythema nodosum, pseudofolliculitis, papulopustular or acneiform lesions in postadolescent patients, not receiving corticosteroids
Pathergy test checked by physician after 24–48 h

Additional Examinations Histological findings of lesions of oral mucosa and genitals are characterised by infiltration with lymphocytes and plasma cells with IgM and C3 deposits in blood vessels and perivasculitis; sometimes leucocytoclastic vasculitis is detected. Neurological manifestations are indicated for brain CT and MRI examination. Thromboses are proved by phlebography; arterial involvement can be best confirmed by digital subtraction angiography. Diagnostic examination of involvement of pulmonary arteries is based on their arteriography. Pyoderma may be induced by a skin prick test (using a sterile needle) causing a papule or pustule development within 24–48 h (pathergy test).

Diagnosis Disease criteria were developed in 1990 by the International Study Group for Behçet's disease. BD diagnosis requires compliance with the main criterion and with two secondary criteria (Table 7.2).

Differential Diagnosis BD differential diagnosis must reflect the fact that there often occur incomplete forms with recurring aphthae and involvement of only one of the organs.

Reactive arthritis (Reiter syndrome) is characterised by oral and genital ulcerations, while in BD lesions are located more often on the scrotum than on the glans penis. In addition, BD is usually not associated with urethritis. SLE with

secondary antiphospholipid syndrome may mimic BD but is commonly without marked mucosal manifestations. Erythema exsudativum multiforme (Stevens-Johnson syndrome) is associated with skin and mucosal manifestations, but ocular manifestations occur only in conjunctiva and cornea; the chronic relapsing uveitis typical of BD is absent, similarly as thrombophlebitis and arterial aneurysms. Colitis ulcerosa is sometimes associated with mucosal and skin lesions and episcleritis that cannot be distinguished from BD. Certain BD neurological symptoms may resemble the multiple sclerosis.

Therapy with corticosteroids has rather a palliative effect in BD. Topical corticosteroids are used in mucocutaneous manifestations of the disease. This therapy is combined with administration of antibiotics. Prednisone suppresses to a certain extent the vasculitis phase, but it has to be supplemented with a preparation of long-term action. In Japan, colchicine was used due to its proved antichemotactic effect on neutrophils. The condition of several patients considerably improved as a result of administration of methotrexate. In ocular manifestations corticosteroids are used in combination with azathioprine, and in case of its inefficacy, it is replaced by cyclosporine. The latest preparations of biological therapy, which have already proved efficient, include interferon-α and infliximab.

Disease Prognosis Although BD does not significantly reduce life expectancy, neurological symptoms and large artery involvement should always be a warning signal. These manifestations are associated with increased mortality, mainly in young men; after the age of 40 the mortality decreases.

Ocular involvement may occur as a severe BD manifestation in the elderly. Citrink et al. [16] described retrospectively ocular involvement in 16 individuals from a cohort of patients with BD, namely, eight men and four women with the mean age of 53.8 years. A total of 68 % of patients had panuveitis, 17 % had anterior, and 25 % of patients had posterior uveitis. Panuveitis affected more frequently men, and the late-onset BD showed their marked predominance, with the 3:1 ratio.

Another Turkish study focused on demographic, clinical and ocular features in BD patients with the onset of the disease after the age of 40 [17]. The cohort comprised 42 patients, of which 26 had uveitis and 16 had no eye disorder. The two groups differed in terms of age, gender and the initial symptoms of the disease. The most frequent initial symptoms were oral ulcerations, and the most common ocular manifestation was anterior uveitis (73.1 %), followed by panuveitis (19.2 %). Bilateral uveitis occurred in 80.8 % of patients; the incidence of anterior uveitis was increasing and of panuveitis was decreasing with growing age.

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Polymyalgia Rheumatica and Giant Cell Arteritis

8

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Rheumatic diseases in the elderly are quite frequent, and their spectre largely varies. Some of them are typical of younger patients, having certain different clinical features if present in the elderly; others occur predominantly in the elderly patients. Typical diseases of the latter group are polymyalgia rheumatica (PMR) and giant cell arteritis (GCA).

Polymyalgia rheumatica and giant cell arteritis are systemic inflammatory diseases affecting as a rule patients older than 50 years and have a number of similar clinical features.

PMR is a clinical syndrome characterised by pain and stiffness of the neck, shoulder and pelvic girdles, often associated with general symptoms. GCA is a primary systemic vasculitis affecting large- and medium-sized arteries, most commonly the major arteries branching off the aortic arch, the external carotid artery branches in particular. Due to a frequent involvement of the temporal artery, the disease is also called temporal arteritis. The two disorders may occur simultaneously. Half of the patients with GCA have also PMR, and 10 % of patients with PMR have clinical symptoms of GCA [1, 2].

PMR clinical symptoms were described for the first time in 1888 by William Bruce and those of temporal arteritis in 1890 by Hutchinson. In 1932, Horton presented the histopathological finding of granulomatous inflammation in relation to the clinical syndrome. Later the pathologist Gilmore found out that temporal arteritis may involve also other arteries and introduced the term "giant cell arteritis" [3].

8.1 Incidence

The two nosological entities are characterised by the onset of the disease in patients older than 50 years. PMR incidence ranges between 12.7 and 52.2 cases per 100 000 persons annually, with more than 90 % of cases occurring at the age above 60 years. Women are affected about 1.5 times more often than men [2, 4].

GCA occurs in 0.49–141.7 of cases per 100 000 persons annually, and its incidence increases with increasing age. It affects twice as many women than men [5–9].

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In addition, ethnic differences have been identified in the GCA prevalence, with the highest incidence in the Scandinavian countries [6, 10].

8.2 Aethiopatogenesis

Aethiopatogenesis of these diseases remains unknown. A certain genetic predisposition is assumed due to the fact that the disease occurs more often in the Caucasian race. Association has been also described of GCA with the histocompatible antigen of HLA-DR4/HLA-DRB1 * 04 allele [11, 12].

Several studies have suggested that GCA is an autoimmune syndrome induced by an immune response targeted against vascular wall antigens. As GCA occurs in elderly individuals, it may be also hypothesised that it is inflammation of an atherosclerotic blood vessel triggered by a so far unknown endogenous or exogenous factor [13], bacteria or virus or other factors that have not been identified, yet [14, 15].

The GCA pathology is characterised by transmural inflammatory infiltration of the vascular wall, intimal hyperplasia and occlusion of the lumen of the affected blood vessel.

The key role in the whole process is played by T-lymphocytes and macrophages. Activated macrophages located in adventitia of the blood vessel produce pro-inflammatory cytokines. Oxidative reaction in the media damages smooth muscle cells. Nitric oxide and free oxygen radicals together with metalloproteinases lead to fragmentation of the internal elastic lamina. Increased permeability of the intima allows for entry of migratory fibroblasts that later cause its hyperplasia. Immunopathological process consists in excessive production of pro-inflammatory cytokines (especially IL-1, IL-6) that induce a systemic inflammatory reaction with a marked response of inflammatory reactants. Cytokines are present also in the vascular wall circulation. IFN-γ produced by T-lymphocytes in the vascular wall plays an important role in intimal hyperplasia. The ultimate result of these changes is occlusion of the lumen of the affected blood vessel. High levels of certain cytokines correlate with inflammatory activity of the disease [16–20].

It is assumed that an important role in pathogenesis of the disease is played also by the changes in the endocrine system and the subsequent neuroendocrine responses. This assumption is supported by the fact that administration of glucocorticoids results in a rapid suppression of the inflammatory activity [21–23].

8.3 Clinical Features

Both diseases are often associated with nonspecified general symptoms, such as lethargy, fatigue, subfebrile temperature, loss of appetite and weight and overall weakness.

PMR usually shows an abrupt onset. The main clinical findings include pain and stiffness of at least two of the following regions: shoulder girdle, pelvic girdle and neck muscles, persisting for more than a month. The pain is usually symmetrical, occurring during physical inactivity and at night, accompanied by morning stiffness, which often dominates. Physical examination reveals limited shoulder elevation and pain in intra-rotation, limited hip rotational motion and trapezius pain during neck movements. If untreated for a long time, the disease leads to gradual muscle atrophy [1].

Patients relatively often complain of arthralgia. The findings of joint involvement are mostly insignificant. A total of 10–60 % of patients may have oligoarticular synovitis of peripheral joints in the initial stage of the disease [24]. It affects most frequently the wrists, knees and metacarpophalangeal joints. Synovitis of joints is usually episodic and quickly subsides when treated by low doses of glucocorticoids [25].

Clinical symptoms of GCA are induced by ischaemic changes in the region supplied by the affected blood vessel. The onset of the disease may be abrupt or gradual. A typical clinical manifestation of GCA is sharp, throbbing headache, located mainly in the temporal, less frequently in the occipital area. It occurs in about two thirds of patients as a new or altered headache,

unresponsive to common analgesics. Patients often complain of palpation tenderness in the temporal area, which they feel especially during hair combing. The affected temporal artery is usually thickened, tender, with reduced pulsation, and the patient has red patches on the scalp, including localised hair loss [26, 27].

Ocular Manifestations of GCA One of the most frequent and the most severe manifestations of GCA is visual disturbance. It occurs in about one third of patients and may be manifested by temporary loss of vision, vision problems of various severity or diplopia [28]. Permanent loss of vision occurs in about 14–17 % of patients [29] and is quite often preceded by amaurosis fugax. It involves usually one eye, and its onset may be abrupt or gradual in the course of several days. Visual problems often develop quickly, overnight, and may have a form of decreased visual acuity, diplopia, light scotoma, narrowing of the visual field or even transient or irreversible blindness. If untreated, the other eye is likely to become affected within 1 week.

Ophthalmologic complications are most often triggered by anterior ischaemic optic neuropathy, less often by inflammatory occlusion of the cilioretinal artery, central retinal artery and posterior ischaemic optic neuropathy.

Individual ischaemic lesions, however, may occur in combination [28]. A rare cause of loss of vision is embolization into the central artery of the retina. The fundus shows ischaemic changes and haemorrhagic deposits that may result in atrophy of the optic nerve papilla.

Neurovascular Manifestations of GCA GCA affects the central nervous system (CNS), cranial nerves as well as the peripheral nervous system. Neurological symptoms occur in about 20–30 % of patients. They most probably result from vasculitis of nutritive blood vessels or from spreading of inflammation from arterial walls in the surrounding tissues. Clinical manifestations may comprise hearing loss, hemiparesis, depressions, confusion and in 10–15 % of patients peripheral neuropathy. Neuropathies are often diagnosed before GCA diagnosis is established. A review published in the English literature reports 50 cases of neuropathy caused by GCA, of which in 40 % the involvement was bilateral, affecting most frequently the median nerve. The brachial plexus may also be involved which makes it difficult to distinguish the disease from oppression of the C5-C6 root [30].

A common presenting feature of the disease is involvement of facial muscles in the form of masseter claudication while chewing solid food, pain in the tongue, rarely microstomia or trismus [31, 32].

Cerebrovascular disorders, such as strokes or transient ischaemic attacks (TIA), are according to Nesher [30] quite rare in GCA. In a cohort of 166 patients with biopsy-proven GCA, TIA occurred in 6 % and stroke in 3 % of patients. GCA shows a higher incidence of ischaemia of vertebrobasilar blood vessels (40–60 %) as compared to atherosclerosis (15–20 %).

Neuropsychiatric manifestations of GCA include disorientation, dementia, impairment of cognitive and memory functions, mood changes (depression) and psychoses. Visual hallucinations have been reported in patients with a vision impairment or loss. It should be noted that GCA is one of the manageable causes of dementia, and glucocorticoid therapy in these patients may stabilise its symptoms and improve the patient's condition. As the hormone therapy alone aggravates at the beginning psychotic manifestations, it has to be combined with antipsychotics [33]. Audiovestibular manifestations were detected in about 7 % of patients, most often in the form of unilateral or bilateral hearing loss, vertigo and tinnitus.

8.4 Involvement of Extremities in GCA Patients

One of the quite rare GCA manifestations is involvement of the arteries of the upper and lower extremities, namely, branches of the subclavian and the brachial arteries in the upper

limbs and branches of the femoral superficial and popliteal arteries in the lower extremities. Patients are at risk of a sudden occlusion of the blood vessel with ischaemia and subsequent gangrene in the respective region. The initial symptom of ischaemia in extremities is usually claudication pain.

Only a few patients with the histologically proven GCA in lower extremities have been reported in the literature up to now. Garcia Vazquez et al. [34] report a 52-year-old woman with ischaemia of upper and lower extremities, suffering from ischaemic pain for 6 months. Bruits could be heard along the course of both femoral arteries.

No risk factors typical of atherosclerosis, such as smoking, hypertension, hypercholesterolemia and triglyceride levels or diabetes mellitus, were identified in the patient. Ischaemia in the left lower extremity was gradually getting worse, reaching degree III according to Fontaine's score, including bilateral loss of pulsation. Temporal arteries were palpable but not painful. The patient had a high sedimentation rate and increased serum albumin values. Angiography revealed narrowing of both subclavian arteries, segmental stenoses and filiform stenosis of the left superficial femoral artery and multiple lesions and stenoses of the whole right artery**.** The bioptic material taken from the temporal and femoral arteries contained multiple giant cells, confirming GCA diagnosis. Bilateral sympathectomy was performed with poor results, while glucocorticoid treatment with 40 mg daily dose was efficient. Another angiographic examination performed after 2 years showed a marked improvement of lesions in both subclavian arteries and in the right superficial femoral artery. Although many segmental narrowings were found on the left side, there developed large collateral connections improving blood supply of the distal extremity.

In 1997, Dupuy et al. [35] reported two patients with GCA involving lower extremity blood vessels, where the initial manifestation of the disease was claudication pain.

Claire Le Hello et al. [36] published a study of eight patients with GCA (six women and two men). They all had leg claudication of recent onset, which was the first symptom of the disease in six of them. Angiography of the lower extremity showed numerous bilateral smooth stenoses and thromboses. Five patients met three criteria for GCA diagnosis according to the American College of Rheumatology (ACR). Biopsy of the affected lower extremity arteries provided histological evidence of GCA in four patients. In one patient GCA was confirmed post-mortem. Three patients had no histological evidence of GCA in lower extremities. However, one of them had biopsy-proven temporal arteritis, and another two had headaches, upper extremity claudication and angiography-proven arteritis in upper extremities. All patients received glucocorticoids, three had bypass, and one patient underwent endarterectomy. After 24–100 months (mean, 50.6 months), five patients were asymptomatic. In one case the extremity had to be amputated.

The most severe symptom of a vascular disease of extremities is an abrupt onset of bilateral and rapidly progressing claudication with reduced or even absent peripheral pulsation. Due to the severity of the disease, the authors point out the importance of considering GCA in all cases of unexplained peripheral arterial obliterating diseases in middle-aged and elderly individuals, referring to autoptic findings indicating that GCA is not so rare a disease as was initially supposed. In addition, they accentuate the need to perform lower extremity artery biopsy, if the aetiology of the disease remains unclear. Peripheral arterial obliterating disease of lower extremities is not always caused solely by atherosclerosis, and vasculitis may be also involved in its aetiology. Positive laboratory tests of inflammation strongly support GCA diagnosis. Hesitation to commence treatment with steroids may have severe consequences for the patient, including the extremity amputation.

8.5 Other Clinical Manifestations

Cardiac involvement is not very frequent. Clinical manifestations include myocardial infarction in case of involvement of coronary arteries [37, 38], very rarely pericarditis or myocarditis. Aortitis

with a subsequent development of thoracic, less frequent abdominal aneurysms occurs not only in the acute phase of the disease but may be also a late complication with a clinical manifestation after up to several years [39–42].

Liver involvement, usually not severe, is found in about 20 % of patients with GCA. It is characterised by elevation of liver enzymes. The symptoms resolve with administration of corticosteroids. The bioptic finding is commonly normal, although there may occur a portal or intralobular inflammatory infiltration, and rarely also granulomatous inflammation [43].

GCA may be rarely manifested also by pulmonary involvement (pleural effusion, intra-alveolar bleeding) [44, 45].

Renal involvement is infrequent and includes microscopic hematuria, mild proteinuria and only exceptionally nephrotic syndrome or impairment of renal functions [46]. Vanderschueren [47] found microscopic hematuria in 20 of 42 patients with histologically verified GCA, which was significantly more than in the group of patients with PMR and in the control group. Hematuria was asymptomatic in all patients and subsided after glucocorticoid treatment.

8.6 Laboratory Findings

Laboratory findings of both PMR and GCA are in general typical, predominated by a high, often three-digit erythrocyte sedimentation rate (ESR). However, literature sources report also cases of both diseases with lower or normal ESR values [48–50].

A significant GCA inflammation marker is C-reactive protein (CRP). Unlike ESR, it is usually not influenced by age, gender or hematologic abnormalities. CRP level increases during 4–6 h and responds more promptly to the treatment than ESR. Both these parameters are examined routinely [28].

Most patients exhibit a mild normochromic or hypochromic normocytic anaemia [51]. Thrombocytosis occurs in about 60 % of patients, while the number of leukocytes usually remains unchanged [28, 52].

The values of alpha 2-globulins, less often of alpha 1-globulins, gamma globulins and fibrinogen, are increased. Muscle enzymes are within standard limits. Examination of liver enzymes reveals a mild increase especially of alkaline phosphatase [43, 53].

Interleukin 6 (IL-6) is a pro-inflammatory cytokine. It has been demonstrated that its elevated levels better correlate with the disease activity than ESR. Elevated IL-6 levels may persist also during glucocorticoid treatment as a subclinical manifestation of clinically silent inflammation [20, 54].

Von Willebrand factor is a high-molecular-weight glycoprotein which is involved in the process of haemocoagulation. It is produced by thrombocytes and endothelial cells. Increased values of this factor were detected also in patients with PMR and GCA, but its use as a marker of the disease activity has not proved efficient in practice, yet [55].

Some patients may exhibit also a low-titre rheumatoid factor [56], but anticitrulline antibodies were not found in any of the patients with PMR [57]. The presence of this marker may help in differential diagnosis of PMR, and rheumatoid arthritis developed in advanced age.

Several studies have recently focused on the share of T-lymphocyte subpopulation in the peripheral blood. However, their results remain controversial. Corrigall et al. [58] recommend routine monitoring of the number of CD8+ T-lymphocytes, as they consider their decrease as a specific and sensitive PMR parameter. They base their statement on a long-term follow-up of patients with PMR. In ten patients with clinical symptoms of PMR and normal values of CD8+ T-lymphocytes, RA manifested itself after 24 months, and in another six patients, malignancy was diagnosed after a longer period. Salvarini et al. [59] did not find a statistically significant decrease in CD8+ T-lymphocytes as compared to the RA and control groups, although they observed a trend of decreasing number of CD8+ T-lymphocytes in patients with PMR as compared with seronegative elderly-onset RA. Similar results were found also in our group of 16 patients with PMR, where decreased, even if statistically

insignificant, values of CD8+ T-lymphocytes were seen [60]. On the other hand, other studies did not confirm decrease of CD8+ T-lymphocytes in untreated patients with PMR/GCA [61, 62].

8.7 Diagnosis

PMR diagnosis is based on a careful assessment of clinical and laboratory parameters of the disease and primarily on exclusion of other diseases that may manifest by polymyalgia syndrome. These include especially infections, malignancies, multiple myeloma, hypothyreosis, rheumatoid arthritis or other systemic connective tissue diseases [63]. Several criteria have been set for PMR diagnosing.

Criteria according to Bird [64] include seven parameters:

1. Bilateral shoulder pain and/or stiffness
2. Onset of illness of less than 2 weeks' duration
3. ESR higher than 40 mm/h
4. Duration of morning stiffness exceeding 1 h
5. Age 65 years or more
6. Weight loss
7. Bilateral tenderness in the upper arm

PMR diagnosis is probable if at least three of these criteria are met or if at least one criterion coexists with a clinical or pathological abnormality of the temporal artery. A positive standardised test makes the diagnosis of PMR certain.

Jones and Hazleman [65] require all the criteria listed below to be met for PMR diagnosis:

1. Shoulder or pelvic girdle pain
2. Morning stiffness
3. Duration of symptoms exceeding 2 months
4. ESR higher than 30 mm and/or CRP more than 6 mg/l
5. Absence of rheumatoid arthritis, infectious arthritis and malignancy
6. Absence of objective manifestations of another muscle disease
7. A rapid and significant response to glucocorticoid treatment

GCA diagnosis should be considered in all patients older than 50 years with a new onset of headache, visual disorders, myalgia, elevated ESR and fever of unknown origin. It has to be taken into account that loss of vision sometimes occurs as early as during manifestation of the first complaints, often without prodromal symptoms. Examination should be focused on palpation tenderness along the course of arteries of the head, neck and extremities, their swelling or change in their colour, detection of murmurs, symmetrical checking of peripheral pulsation in both upper and lower extremities and measuring of blood pressure in both upper extremities.

The gold standard in establishment of GCA diagnosis is biopsy. A positive histological finding is part of diagnostic criteria [66]. However, a negative result of biopsy (in about 15 % of patients) with typical clinical features does not exclude GCA diagnosis. A sample is as a rule taken from the temporal, less often from the occipital or facial artery. In order to reduce the risk of false-negative results due to segmental involvement of the artery, the sample taken in biopsy should be adequately long. In case of macroscopic evidence of changes in the artery (rigid to palpation, tortuous, painful), a 2–3 cm sample is representative. Where typical local manifestations of temporal arteritis are not shown, additional arterial segment has to be sampled [63, 67]. Biopsy is usually unilateral. Hall [68] studied a group of 88 patients with a negative unilateral temporal biopsy, and only in one of them he subsequently found a positive bioptic finding on the opposite side, however without secondary ophthalmological or neurological complications.

GCA histological features typically show segmental involvement of the blood vessel where the involved segments alternate with normal sections.

Granulomatous nature of the inflammation with fragmentation of the internal elastic lamina, intimal hyperplasia and the presence of giant multinucleated cells can be seen in about 50 % of patients with typical GCA manifestations. The other 50 % of patients with positive histological findings show panarteritis with a mixed inflammatory infiltrate, but without giant cells.

The inflammatory infiltrate is composed largely of mononuclear cells, less of neutrophils and eosinophils. Foci of fibrinoid necrosis may also be present [69].

Sampling is usually performed prior to glucocorticoid treatment. As the disease is associated with a risk of severe ischaemic complications, the treatment must be commenced as soon as possible. Where it is impossible to perform biopsy immediately, commencement of treatment is a priority. According to the data in the literature, bioptic sample of the temporal artery is positive in 74 % of patients during the 1st month [67, 70].

A non-invasive and relatively easily available examination is colour Doppler ultrasonography. Ultrasound findings of GCA in the superficial temporal artery include hypoechoic (dark) oedematous wall swelling of the affected blood vessels and changes in the blood flow velocity in this vessel. Specificity of these findings in GCA diagnosis varies in reports of individual authors [71–74]. Part of the ultrasonography examination in case of suspected extracranial involvement is examination of the aortic arch and its branches.

In the diagnosis of aortitis, particularly in its acute phase, positron emission tomography or magnetic resonance is indicated [67]. Within a long-term follow-up, the patients should be regularly checked for a risk of development of aortic aneurysm and examined by ECG. Angiography is used due to its invasive nature only after failure of the above-mentioned options.

Part of the comprehensive examination of patients with suspected GCA must be ophthalmologic and other specialised examinations based on the clinical manifestations.

In 1990, the American College of Rheumatology published classification criteria developed on the basis of comparison of 214 patients with GCA with a group of 593 patients with other forms of vasculitis [66]. Traditional ACR classification consists of five criteria:

1. Age at disease onset ≥50 years
2. New onset of or new type of localised pain in the head
3. Temporal artery tenderness or decreased temporal artery pulse
4. Elevated ESR exceeding 50 mm/ h
5. Biopsy sample showing necrotizing arteritis, characterised by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells

A patient is said to have GCA if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5 % and a specificity of 91.2 %.

Differential diagnosis must be used to exclude other causes of headache that are quite frequent in this age group, such as ischaemic manifestations of CNS, inadequately compensated hypertension, intracranial tumours or metastases of other tumours. Headache may be associated with migraine but also with the use of certain medications.

The drugs that cause headache in elderly patients include mainly nitrates, hypotensive drugs (reserpine, atenolol, nifedipine), digoxin, benzodiazepines, barbiturates, nonsteroidal antiphlogistic drugs (indomethacin), H2 receptor blockers, aminophylline, theophylline, trimethoprim-sulfamethoxazole and other drugs. In case of pain located in the jaw, it is necessary to exclude stenocardia, gastroesophageal reflux, tooth disorders, otitis, neuralgia and osteoarthritis of the temporomandibular joint [63, 75].

8.8 Therapy

Polymyalgia rheumatica and giant cell arteritis are diseases that respond exceptionally well to glucocorticoid treatment. A prompt response to low doses of glucocorticoids is part of certain PMR diagnostic or diagnosis supporting criteria [64, 65].

A common daily dose of glucocorticoids in PMR usually does not exceed 15 mg, and an even lower initial dose was reported in the literature. Based on the experience, the most suitable initial dose is 15 mg of prednisone a day. Alternate day therapy is less efficient than a

single daily dose. Marked improvement can be observed as early as during 48–72 h of the commencement of glucocorticoid treatment. After resolution of clinical symptoms and decrease of inflammatory reactants, the prednisone dose is gradually decreased. In practice, the dose of prednisone is reduced most often by 2.5 mg every 4 weeks. Maintenance doses should range between 5 and 7.5 mg of prednisone daily and should be administered for at least 12 months. Part of the patients requires such treatment for the period of 2 years and some of them even for 4–5 years. Nonsteroidal antiphlogistic drugs are added to glucocorticoids in order to control musculoskeletal symptoms, mainly during the period of reducing the prednisone dosage. In case of failure of therapeutic response after a 2-week treatment with prednisone at the dose of 15 mg/day, it is necessary to reconsider the PMR diagnosis [1, 76].

Until recently efficiency of the treatment was assessed only according to the present clinical symptoms and ESR values. In 2004, a group of clinical and laboratory parameters was published that were recommended for monitoring of PMR therapeutic response: CRP, visual analogue scale of pain evaluated by the patient (VASp), overall evaluation of the disease activity by the physician (VASph), duration of morning stiffness in minutes (MST) and elevation of upper limbs (EUL).

The PMR activity score (PMR-AS) is calculated using the following formula:

$$\mathrm{CRP}(\mathrm{mg/dl}) + \mathrm{VASp}(0-10) + \mathrm{VASph}(0-10) + \left[\mathrm{MST}(\mathrm{min}).0{,}1\right] + \mathrm{EUL}(3-0).$$

The value PMR-AS < 7 indicates a low disease activity, PMR-SA of 7–17 a medium and PMR-AS > 17 a high PMR activity [77].

Unlike PMR treatment, GCA therapy begins with higher doses of prednisone or its equivalents. The main principle is to commence the glucocorticoid treatment in patients with suspected GCA as soon as possible, upon meeting of three or more ACR criteria or in case of GCA history with exacerbation of neuro-ophthalmologic complications, including jaw claudication, amaurosis fugax and other visual disturbances. The initial dose of prednisone ranges around 40–60 mg daily. In case of a risk of severe ischaemic complications (amaurosis fugax, monocular vision loss, initial manifestations of visual disturbances in the other eye), the patient receives intravenous pulse methylprednisolone therapy at the dose of 500–1000 mg daily for three days, which then continues in the form of oral treatment. Alleviation of subjective complaints is reported by patients within 48–72 h of commencement of treatment. During 2–4 weeks, inflammatory parameters (ESR, CRP) decrease or return to normal. The initial dose is administered usually for 4 weeks, and then it is gradually reduced, maximally by 10% of the total daily dosage at 1- or 2-week intervals [7, 78, 79].

Patients are monitored during the treatment due to a risk of both disease relapse and of adverse effects of the therapy. At the beginning of the disease, checks must be more frequent, with the recommended intervals at week 0, 1, 4, 8 and 12 and afterwards at month 3, 6, 9 and 12 during the 1st year [67]. Disease relapse should be considered with ESR > 40mmHg and the presence of at least one GCA clinical manifestations: fever (≥38 °C), PMR, headache or scalp tenderness, loss of vision, pain in the tongue/jaw or jaw claudication, claudication pain in extremities, thickening, palpation tenderness or swelling of the temporal or occipital arteries, angiographic changes indicating vasculitis of the aorta or its branches, TIA or stroke [67, 80].

The risk of ischaemic complications in patients with GCA is reduced by antiplatelet or anticoagulation therapy [81].

In order to reduce the cumulative dose of prednisone, also other DMARDs are added to glucocorticoid treatment, particularly methotrexate, however with a varying effect on reduction of the monitored parameters reported in individual studies [80, 82]. Several recent studies have presented promising results of anti-cytokine

therapy (primarily infliximab and etanercept) used in patients with PMR and GCA, although the cohorts of patients were small [83, 84].

The drug of choice for treatment of both PMR and GCA still remain glucocorticoids. In order to reduce the risk of adverse effects, the patients receive simultaneously H_2 receptor blockers or proton pump inhibitors, calcium and vitamin D supplementation and where appropriate bisphosphonates, depending on the bone density values.

The British Society for Rheumatology published the following guidelines for GCA treatment [67]:

- Initial treatment of uncomplicated GCA: prednisolone 40 mg daily until resolution of symptoms and laboratory abnormalities.
- Initial treatment of complicated GCA (visual disturbances, amaurosis fugax): i.v. methylprednisolone 500–1000 mg daily for 3 days.
- Monocular vision loss (prevention of involvement the contralateral eye): prednisolone 60 mg daily, addition of 75 mg daily, calcium and vitamin D supplementation, where appropriate addition of proton pump blockers.
- Reduction of the dose: the dose starts to be reduced after resolution of clinical symptoms and laboratory abnormalities; reduction of the dose must be slow due to a risk of disease relapse. It is recommended to administer a dose of 40–60 mg prednisolone for 2–4 weeks until resolution of clinical and laboratory manifestations of the disease. Subsequently, the dose is reduced by 10 mg every 2 weeks to 20 mg daily, then by 2.5 mg every 2 weeks to 10 mg and finally by 1 mg every month.
- Relapse treatment: cephalgia, increasing of the dose of prednisone prior to its last reduction:
  - Cephalgia + jaw claudication: 40 mg prednisolone daily
  - Visual disturbances: 60 mg prednisolone or i.v. methylprednisolone

Treatment of PMR and primarily GCA must be multidisciplinary due to their systemic nature. Early diagnosis, a timely and appropriate treatment and lifelong follow-up of patients in view of the risk of ischaemic complications may prevent both development of severe complications of the disease and adverse effects of the treatment (Figs. 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, and 8.7).

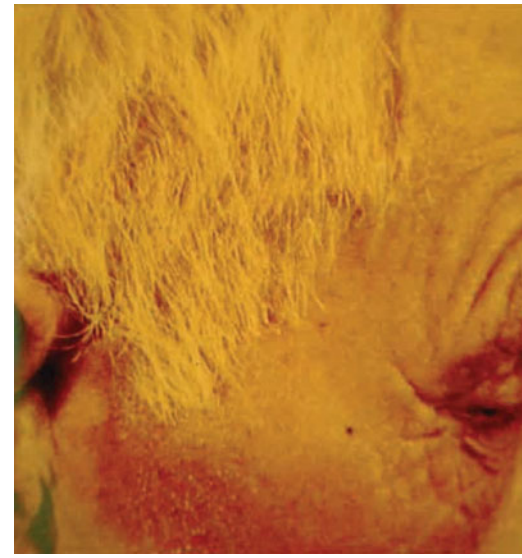

Fig. 8.1 A patient with histologically proven temporal arteritis

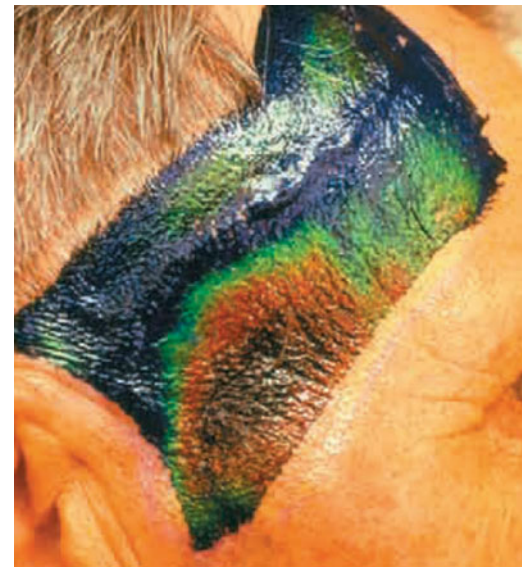

Fig. 8.2 Thermographic image of the temporal arteritis site showing increased temperature gradient in the area of superficial temporal artery

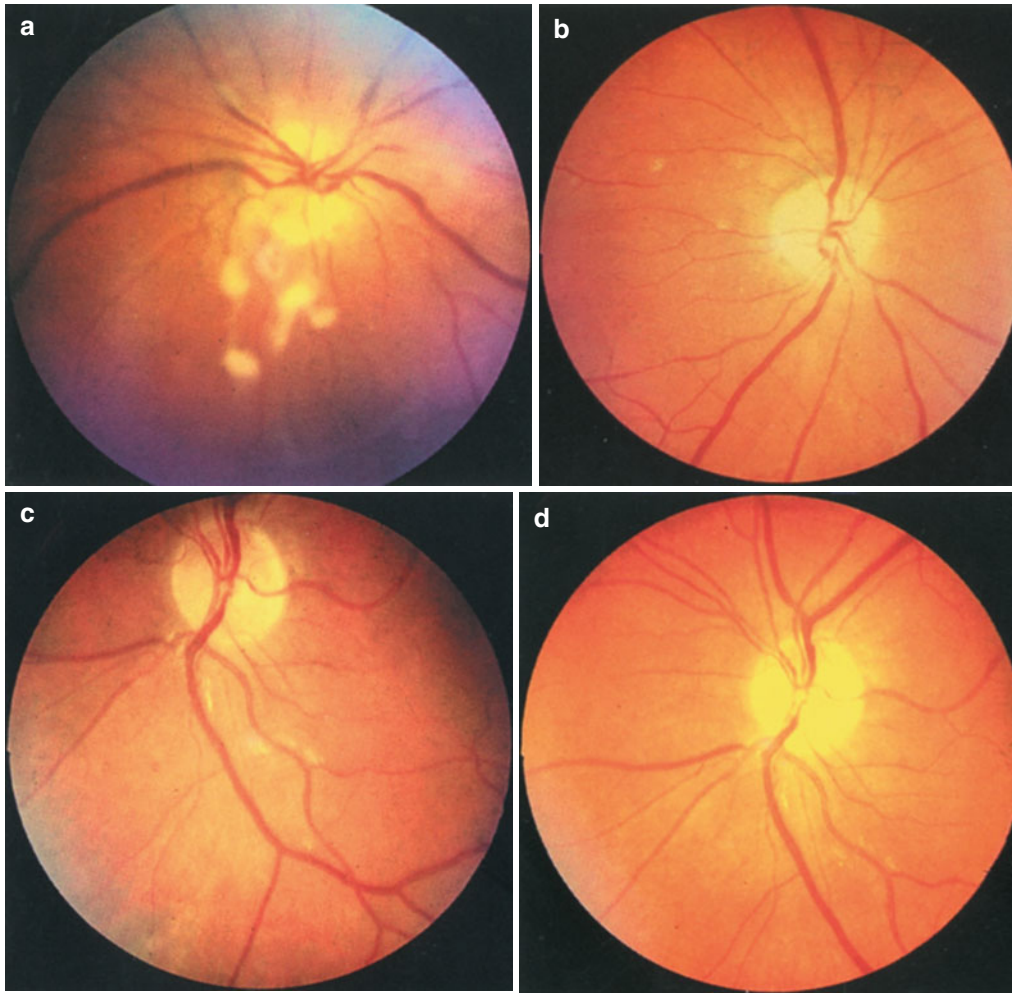

Fig. 8.3 GCA complications in one of our patients. Pictures **(a)** and **(b)** are show ischaemic changes of optic nerve disc and retina prior to corticosteroid treatment; pictures **(c)** and **(d)** show fundus after corticotherapy. Treatment with high glucocorticoid doses saved the patient's sight

Fig. 8.4 GCA associated with oculomotor nerve palsy (convergence insufficiency, left eyelid ptosis)

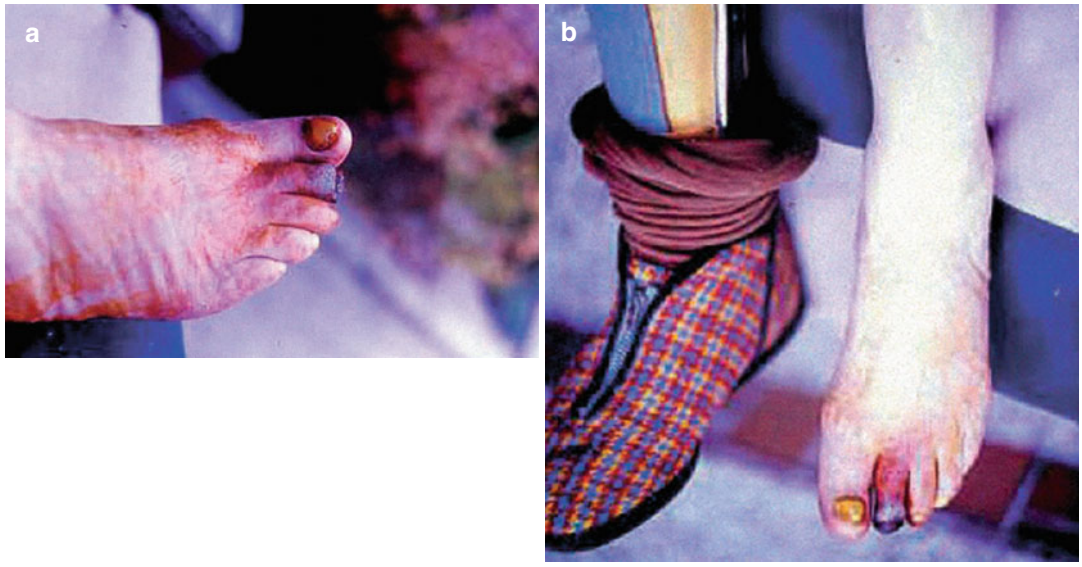

Fig. 8.5 GCA complications in one of our patients. Fatal consequences of PMR/GCA in histologically proven arteritis of peripheral blood vessels of lower extremities with a subsequent gangrene and amputation of the right lower leg and the condition of the left foot. After the last complication, the patient's condition was complicated by embolization into the pulmonary artery

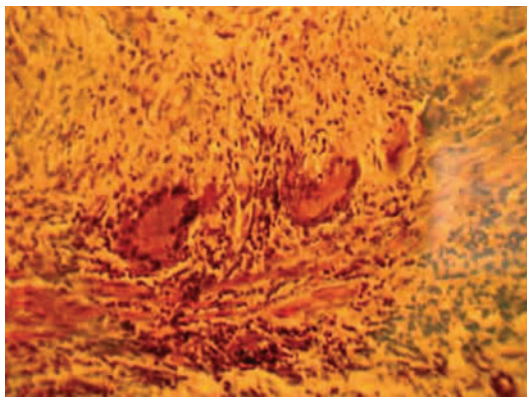

Fig. 8.6 Histopathological image of giant cells with mononuclear cell infiltration near the wall of the temporal artery

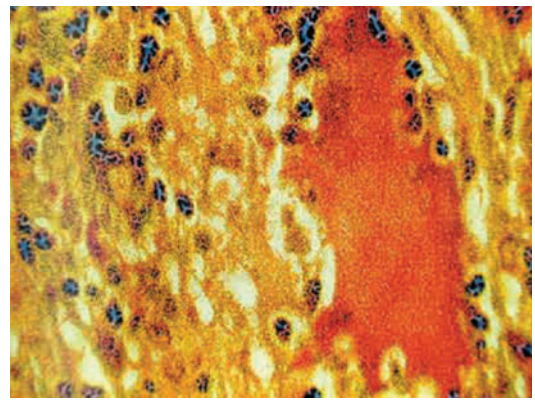

Fig. 8.7 A detail of a giant cell according to Horton in giant cell arteritis

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Aortic Aneurysm as a Cause of Death in Giant Cell Arteritis

9

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Aneurysm is a serious, life-threatening disease, often with fatal consequences. The aorta and its pathology deserve more attention than it currently receives, although it may seem that it serves only as a transportation system between individual parts of the human body. Aortic aneurysm is one of the most severe vascular surgical diseases [23].

Aneurysm may be defined as a permanently localized dilatation of an artery to 1.5times the width of the artery common in the given segment [10].

9.1 There Are Three Types of Aneurysms

1. True aneurysm (aneurysma verum – dilatation of the artery involving all layers of the arterial wall)
2. Dissecting aneurysm (aneurysma dissecans) – resulting from hemorrhage that causes lengthwise splitting of the arterial wall, producing intramural hematoma and establishing communication with the lumen of the vessel
3. False aneurysm (aneurysma spurium seu falsum – perivascular hematoma)

The etiology of aneurysms includes atherosclerosis but also infections (bacterial, mycotic, syphilitic), trauma (traffic accidents, falls), congenital defects (e.g., Marfan syndrome or Ehlers-Danlos syndrome), Erdheim idiopathic cystic medial necrosis, as well as systemic vasculitis. In primary systemic vasculitides, aortic aneurysms occur mainly with giant cell (Horton) arteritis and in Takayasu's arteritis. About 11 % of thoracic aortic aneurysms are caused by giant cell arteritis [22].

Giant cell arteritis (*GCA*) is a systemic granulomatous vasculitis of unknown etiology that typically affects branches of the carotid (temporal artery, in particular) but may involve any medium- or large-sized artery, which then makes the diagnosis much more difficult [1, 13, 24]. Temporal arteritis is the most frequent form of giant cell arteritis [6].

The term "temporal" is sometimes put into brackets as it describes a frequent, however not obligatory involvement of the temporal artery in this disease. Temporal artery may be affected also in other types of vasculitis, such as Wegener's

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granulomatosis or microscopic polyarteritis. On the other hand, inflammation of the temporal artery is not necessarily present in all patients with giant cell arteritis [7].

Temporal arteritis (i.e., arteritis affecting the temporal artery) is not a fatal disease, with the mean longevity of the patients being the same as in the healthy population. However, giant cell arteritis involving large- and medium-sized arteries may have lethal consequences and is often dramatically manifested in the elderly by aortic dissection or rupture [12].

9.2 Case Reports

Patient 1

An 84-year-old woman with a history of arterial hypertension and coronary artery disease was admitted to a hospital for quantitative disturbance of consciousness (sopor to coma) with 110/70mmHg blood pressure. ECG showed sinus bradycardia (with 50/min frequency) with no signs of an acute coronary accident. Her blood count showed severe anemia (hemoglobin–5.4 g/l) and leukocytosis (11 x 10^9/l). Cerebral CT did not show any fresh ischemic or hemorrhagic lesion. The patient died 6 h after hospitalization for cardiorespiratory failure.

Macroscopic examination during the autopsy discovered a 3.5 cm long longitudinal tear at the posterior wall of the aorta 2 cm above the aortic valve; the tear formed a hematoma cavity between the adventitia and the media. The cavity continued to the abdominal aorta, and there, at the level of the celiac trunk, a crosswise 1 cm long fissure was found at the posterior wall of the aorta through which the blood poured back to the lumen of the aorta (Fig. 9.1).

Figure 9.2 shows histotopography (photo of the histological specimen – glass) of the part of the aortic wall with the adventitia and dissection of the media (stained with phosphotungstic hematoxylin).

Similarly, Fig. 9.3 shows dissection in the media, where blue color represents fibrin, which is a proof of blood flowing in the false lumen of the dissecting aneurysm.

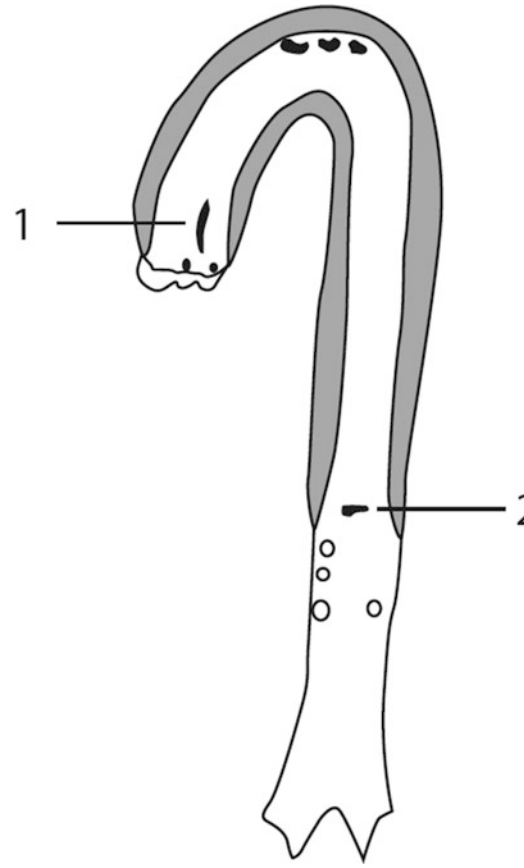

Fig. 9.1 Scheme of the dissecting aneurysm of the thoracic and abdominal aorta in an 84-year-old woman; (*1*) beginning of dissection, (*2*) end of dissection

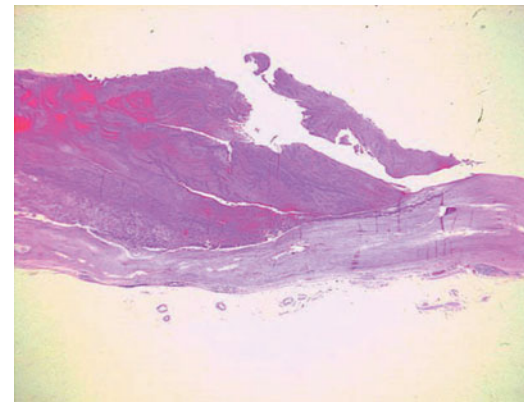

Fig. 9.2 Histotopography. Dissection of the media

Panarteritis is formed by a mixed inflammatory infiltrate composed of polymorphonuclear leukocytes, lymphocytes, and plasma cells.

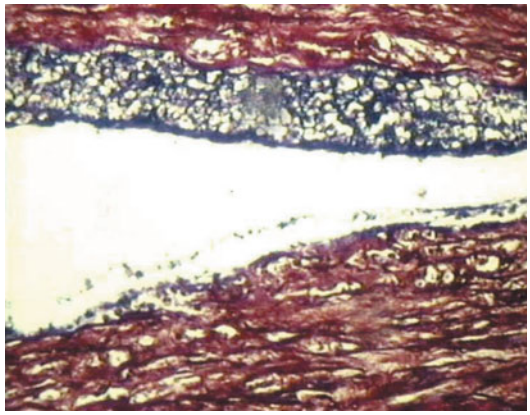

Fig. 9.3 Dissection of aortic media

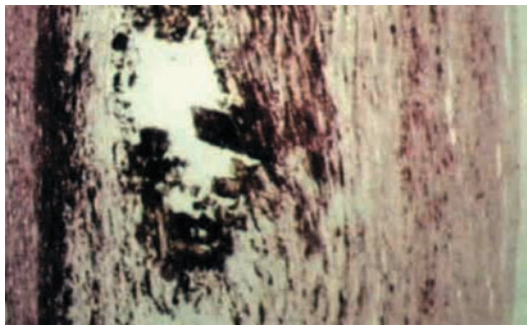

Fig. 9.4 Typical deposits of calcium salts in the area of the internal elastic lamina and atherosclerotic plaque with calcium in the intima (Kossa + HE staining)

Figure 9.4 (Kossa + HE staining) shows the intima and part of the media. In the intima an atherosclerotic plaque with calcium and deposits of calcium can be seen in the area of the internal elastic lamina, which is a typical sign of GCA.

The pathological-anatomical diagnosis and the cause of death were dissecting aneurysm of the ascending thoracic aorta continuing to the descending thoracic and abdominal aorta as far as the origin of the celiac trunk that developed due to giant cell arteritis.

Patient 2

An 81-year-old patient with a history of two myocardial infarctions with an implanted pacemaker was admitted to the hospital for intense pressure pain over a large area in the front part of the chest. ECG showed a pacemaker rhythm with

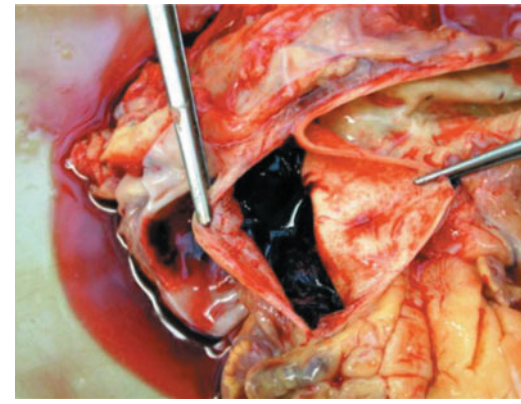

Fig. 9.5 Dissecting aneurysm of the aorta

a frequency of 70/min and the condition after anteroseptal and lateral myocardial infarction. The values of indicating enzymes of myocardium damage – CK, AST, and ALT – were normal, similarly as the blood count. Twenty hours of admission to the hospital, the patient had a sudden respiratory and cardiac arrest indicating another acute heart attack.

At the autopsy, a 4 cm long longitudinal tear was discovered at the posterior wall of the aorta 0.4 cm above the aortic valve. The tear created a sac between the adventitia and the media, 8 cm long, filled with about 150 ml of dark red clots. A 20 cm section of the adventitia of the ascending and descending aortas was filled with blood. Macroscopic image of the aortic arch shows a split aortic wall with blood clots (Fig. 9.5).

The histological features showed inflammation in the media composed largely of lymphocytes and a mixed inflammatory infiltrate, histiocytes, and giant cells in the adventitia (Fig. 9.6)

The cause of the patient's death was giant cell arteritis with a dissecting aneurysm of the ascending aorta. Clinically suspected fresh myocardial infarction was not confirmed by the autopsy.

Patient 3

An 86-year-old patient with a multiyear history of ischemic heart disease and duodenal ulcers, after anteroseptal myocardium infarction 2 years before, was admitted to the hospital for a pressure

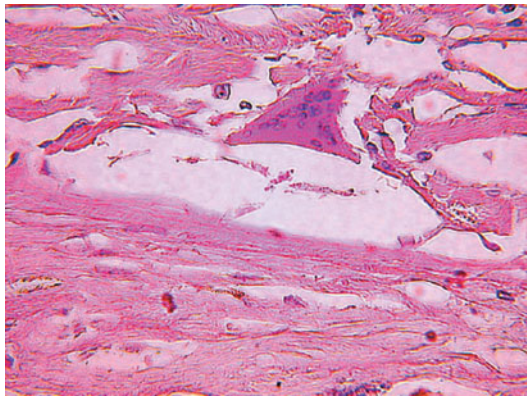

Fig. 9.6 Typical multinucleated cells

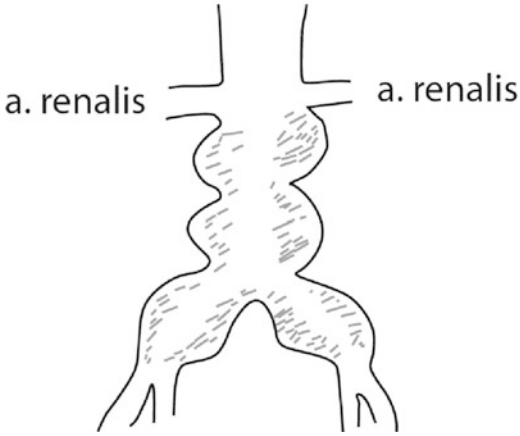

Fig. 9.7 Scheme of aneurysm of the abdominal aorta and both iliac arteries in an 86-year-old man

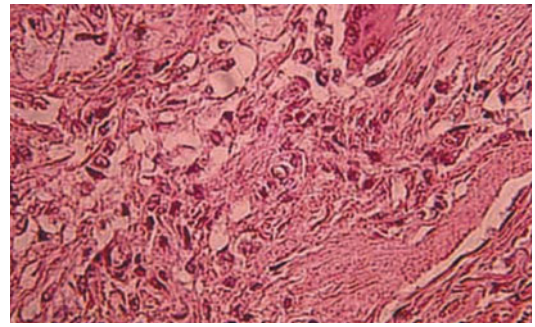

Fig. 9.8 Granuloma in the media of the abdominal aorta

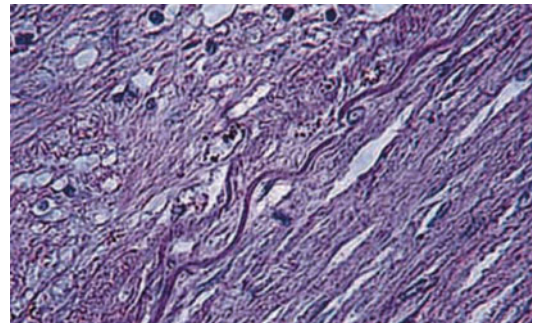

Fig. 9.9 Split and fragmentation of the internal elastic membrane

chest pain lasting for 2 h. At the time of admission, his blood pressure was 90/60mmHg, and the ECG showed acute myocardial infarction of the anterior wall. Urgent thrombolysis could not be carried out in the patient because of the melena finding probably due to bleeding from a duodenal ulcer. Eighteen hours after admission to the hospital, the patient suddenly died.

The autopsy revealed a fresh extensive myocardial infarction of the anterior and posterior walls of the left ventricle and of papillary muscles of the mitral valve. When examining the abdominal aorta, two circular (ringlike) widenings of the lumen (aneurysms) by about 0.5 cm and mural thrombi were observed below the level of the origin of renal arteries, and the common iliac arteries were extended in a balloon-like way having 1.2 cm in diameter (Fig. 9.7).

One of the typical histopathological findings in GCA is a granuloma or a granulomatous inflammation of the media, as seen in Fig. 9.8 in the abdominal aorta in the 86-year-old patient (stained with HE).

The inflammatory infiltrate is composed predominantly of histiocytes and plasmatic cells, not so many lymphocytes, and one giant multinucleated cell.

In the area of the granuloma, the structure of elastic fibers disappears. All the arterial wall layers are involved, but most of them the media. The internal elastic lamina membrane is split and fragmented, as seen in Fig. 9.9, showing the same patient.

Figure 9.10 shows another GCA typical histological finding, namely, multinucleated giant cells.

Thus, aneurysms of abdominal aorta and lumbar arteries developed due to giant cell arteritis.

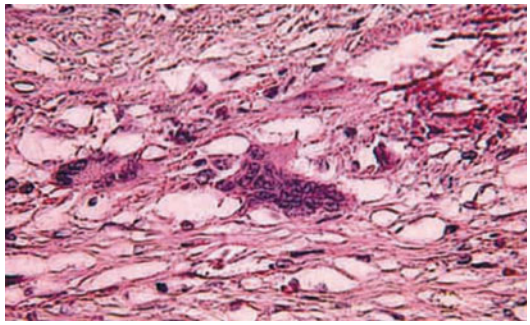

Fig. 9.10 Typical multinucleated cells

9.3 Discussion

Involvement of the aorta and its branches is observed in about 10–15 % of GCA patients. The symptoms indicating involvement of large arteries include Raynaud's phenomenon, paresthesia, and claudication in extremities. Aneurysmal dilatation of the root of the ascending aorta causes insufficiency of the aortic valve [22]. In a group of 72 patients with involvement of the aorta and/or its branches in histologically verified GCA, the ascending aorta and the aortic arch were affected in 39 patients, the subclavian and the axillary arteries in 26 patients, and femoropopliteal arteries in 18 patients; 9 patients underwent amputation of an upper or lower extremity [15].

Involvement of the aorta can be life-threatening due to the development of a dissecting aneurysm or rupture of the aorta [3]. In the group of 24 patients with a dissecting aneurysm of the aorta, reported in the literature, giant cell arteritis was for the first time diagnosed during autopsy as the cause of dissection of the aorta and the subsequent death in up to 46 % of patients [16]. Similarly, both our patients with a diagnosis of a dissecting aneurysm had GCA diagnosis detected as late as during autopsy. Lie [15] reports in 18 patients with extracranial GCA the following causes of death: rupture of aortic aneurysm in 6 patients, dissection of aorta in 6 patients, cerebral infarction in 3 patients, and myocardial infarction in 3 patients. Säve-Söderbergh [21] describes the following causes of death in 9 GCA patients: two patients died of dissecting aneurysm of the aorta, another two of myocardial infarction, and five of sudden cerebral accident. None of the described patients was receiving adequate corticoid therapy.

Although lesions of coronary arteries are not very frequent in GCA, acute myocardial infarction was also several times reported in the literature as the cause of death, namely, by Lie [12] in an 84-year-old man, by Martin [17] in a 77-year-old woman, and by Säve-Söderbergh [21] in 74-year-old and 85-year-old women.

A prospective epidemiological study conducted in Olmsted County in Minnesota that included 96 patients with GCA in the period of 1950–1985 has revealed that in patients with GCA, the probability of development of aneurysm of the thoracic aorta is 17.3times higher and that of the abdominal aorta 2.4times higher as compared to healthy population [2]. In a group of 11 patients with aneurysm of the thoracic aorta (of a total of 96 followed-up patients with GCA), two patients developed aneurysm as the first GCA symptom, but in the remaining nine patients, aneurysm appeared on average 5.8 years after the disease was diagnosed. Part of these 11 patients with aneurysm of the thoracic aorta died suddenly of dissection of the aneurysm.

In 1990, the American College of Rheumatology developed classification criteria for GCA diagnosis [5], based on comparison of 214 patients with GCA with a group of 593 patients with other forms of vasculitis. The following five criteria have been selected:

1. Age at disease onset ≥50 years
2. New onset of or new type of localized pain in the head
3. Temporal artery tenderness to palpation or decreased pulsation
4. Elevated ESR (exceeding 50 mm during the first hour)
5. Abnormal artery biopsy

A patient is said to have GCA if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5 % and a specificity of 91.2 %. Assessment of

the given diagnostic criteria is relatively simple as it requires only clinical examination in addition to biopsy. Biopsy which is the only invasive procedure is performed under local anesthesia and is associated with minimum of complications.

Histological diagnosis is established on the basis of a characteristic finding obtained during biopsy of the temporal artery or the material sampled intraoperatively. Typical GCA-related histopathological changes include granulomatous inflammation; presence of giant cells, predominantly in the media; smooth muscle atrophy and destruction of elastic fibers; splitting and fragmentation of the internal elastic lamina; as well as deposits of calcium salts in the area of the internal elastic lamina, diffuse inflammation of the vessel wall, and ingrowth of capillaries (neovascularization, Figs. 9.11 and 9.12). As the involvement of blood vessels is segmental and biopsy may miss the affected location, it is recommended to examine several sections of 5–8 cm portion of the temporal artery [8], however, a minimum of 2–3 cm. If biopsy of the selected portion of the artery shows a negative result in terms of arteritis, but there is still a clinical suspicion of GCA, examination of the temporal artery on the other side is recommended [14].

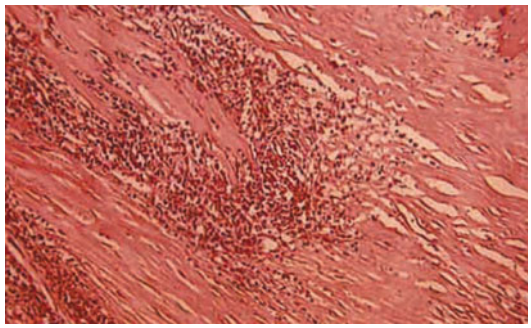

Fig. 9.11 Neoangiogenesis with inflammatory infiltrate

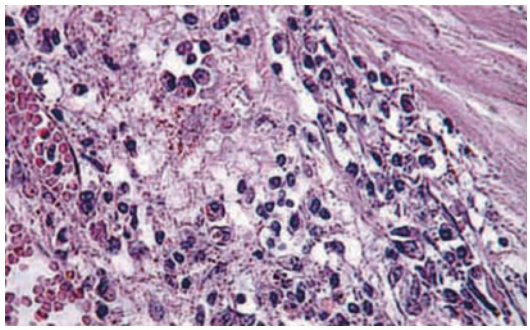

Fig. 9.12 The same figure magnified

Biopsy is important in terms of confirmation of the diagnosis as well as assessment of the disease activity. It should be performed prior to commencement of therapy, as corticosteroid treatment reduces the value of bioptic examination. Biopsy is efficient in up to 80 % if performed before the therapy, in up to 60 % if made during the 1st week of the therapy, but only in 20 % of patients when performed 1 week after full corticosteroid treatment [19].

Typical features of granulomatous inflammation are observed in about 50 % of patients; the other half of patients with a positive histological finding are examined for panarteritis with a mixed inflammatory infiltrate, which is primarily of lymphomononuclear nature, with a few neutrophils and eosinophils, but without giant cells [14]. Giant cell arteritis must be always clinically and histologically distinguished from the syphilitic aortitis and Takayasu's aortoarteritis [4]. In GCA aneurysms develop most frequently in the area of the ascending aorta, while in Takayasu's arteritis, they can be seen more often in the area of the abdominal aorta [11]. Sometimes atherosclerotic changes ("secondary atherosclerosis") can be observed in the aortic wall initially affected by inflammation [11, 25].

Since involvement of large arteries in GCA may have fatal consequences, examination of all patients should be targeted at changes in these arteries.

Blood pressure should be measured in both upper extremities. The methods used to assess the scope of involvement of the arterial system include ultrasound and angiography examinations. Angiography alternately shows smooth contoured stenosis and slightly dilated sections and sometimes also occlusions. A typical feature is bilateral location and segmental involvement of the aorta and its branches [8, 9]. Angiographic finding may support clinical suspicion of giant cell arteritis, and in case of ischemia unresponsive to conservative treatment, it is used as a

strategy guide for the intervention. Negative biopsy does not exclude GCA diagnosis if there is still clinical suspicion of the disease [18].

Survival of patients is not significantly reduced by giant cell arteritis [6] provided that the treatment is timely and adequate. However, GCA increases the risk of development of aortic aneurysm which is often a late complication of the disease that causes death. Therefore, it is important to check actively all patients for aneurysms and schedule their regular duplex ultrasound and where necessary also CT or MRI examination. A consistent treatment of patients with a diagnosed GCA is of vital importance. Most patients who experienced dissection of the aorta were not adequately treated because their sedimentation rate at the time of dissection was high (on average 62 mm during the first hour [16]). Of great importance is also treatment of hypertension as high blood pressure was detected in up to 77 % of patients with dissection of the aorta. Untreated or inadequately treated hypertension is among key factors conducing to dissection of the aorta [20].

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Relapsing Polychondritis

10

Jozef Rovenský and Marie Sedláčková

10.1 Historical Background

The first to describe the disease was Jaksch-Wartenhorst from the Faculty of Medicine of the German University in Prague, in 1923 [1], who called it polychondropathy. Later the disease was referred to as systemic chondromalacia, panchondritis, chronic atrophic polychondritis, and rheumatic chondritis. The most fitting term for this disease was introduced by Pearson in 1960 who called it relapsing polychondritis (RP).

10.2 Epidemiology

A total of 800 cases of this rare disease were reported in the world literature. Onset is most likely between the ages of 40 and 60, although it can occur also shortly after birth and in advanced age. Familial aggregation of the disease is unknown, and no correlation has been found between increased RP incidence and HLA Class I antigens. The incidence of RP is estimated to be 3.5 cases per million population per year. Five-year survival has been recorded in 74 % of patients, while in the systemic vasculitis subgroup, survival is similar to that of patients with polyarteritis (up to 5 years in 45 % of patients). The period of survival is reduced mainly due to infection and respiratory compromise.

10.3 Etiology and Pathogenesis

The most prominent RP manifestation is inflammation of cartilaginous structures resulting in their destruction and fibrosis. It is characterized by a dense inflammatory infiltrate, composed of neutrophils, leukocytes, lymphocytes, macrophages, and plasma cells. At the onset, the disease affects only the perichondral area; the inflammatory process gradually leads to loss of proteoglycans, destruction of the collagen matrix, and ultimately chondrocyte necrosis. The damaged cartilage is replaced by granulation and fibrous tissue.

The cause of the disease remains unknown, but detailed studies have shown that immunological processes play an important role in the pathogenesis. Cartilage consists of collagen, proteoglycans, and elastin that have many antigen determinants of normally sequestered cells of the immune system. Impaired integrity of the cartilaginous structure could be an important

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stimulus for the immunological response to these components that are contained in the cartilage of the respiratory system, the eye structures, and the cardiovascular system. Specific antibodies against type II collagen, primarily IgG, were detected in the serum of 50 % of patients with RP. Ebringer et al. [3] found high titers of antibodies against type II collagen in the early phase of the disease that may be related to its activity. However, it should be noted that these antibodies are not RP-specific and were identified also in RA; they are directed against various epitopes of the collagen molecule. Participating in RP development may be also humoral immunity, as indicated by findings of Arundell and Haserick [4], who described a case of RP development in a newborn of a mother with RP. The child was later cured. In the disease pathogenesis, deposits of immunoglobulins and complement, indicating involvement of immune complexes, were found in chondrofibrous junction of the affected auricles. A reduced complement concentration was detected in the middle ear fluid. These findings indicate that humoral immunity may contribute to RP development, but a role of cell-mediated immunity in this respect should be considered as well, because cellular immunity is involved in immunity reactions together with proteoglycans and collagen.

10.4 Clinical Features

The subjective symptoms include auricular and nasal pain and tension, sometimes eye pain and arthralgia. Episodes of inflammation of the cartilage of one or both auricles and nose often develop suddenly and last for several days. Recurrent protracted inflammations destroy cartilage and produce various deformities, e.g., a saddle-nose deformity and red and swollen auricles tender to palpation (Fig. 10.1). In the Slovak Republic, a report of the RP course was published by Tomík et al. in 1977 [2].

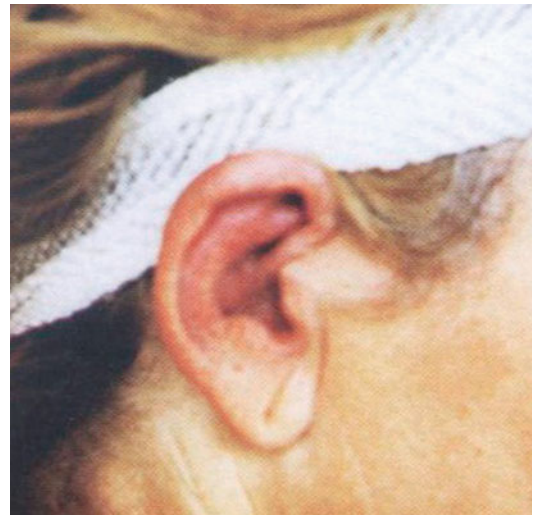

Fig. 10.1 Red and swollen auricles tender to palpation in relapsing polychondritis

10.5 Arthropathy in Relapsing Polychondritis

RP quite often involves joints usually independently of other manifestations. The clinical features show episodic asymmetrical inflammatory involvement of large and small joints, including parasternal articulations and sacroiliac joints, that lasts for several days or weeks. In general, it manifests itself as a nondeforming, nonerosive, and seronegative (negative RF) polyarthritis. Radiographic examination of joints as a rule reveals joint space narrowing without erosion, which is given by the fact that pathological process causes only loss of the hyaline cartilage. A typical histopathological finding shows a lighter space with multinucleated bodies around chondrocytes and unspecific proliferation of epithelial cells in the middle and deep layers of the synovial membrane. The clinical course as well as radiographic and histopathological findings serves as the basis for distinguishing pure RP polyarthritis from polyarthritis of the rheumatoid type.

10.6 Organ Manifestations of Relapsing Polychondritis

In a half of the patients, RP affects the respiratory system which may result in a breakdown of the architecture of bronchi and trachea and air collapse during the respiratory cycle. The first involved are usually the larynx and the upper part of trachea, with subglottic inflammation. The process may progress and involve also the lower part of the trachea and main bronchi. Dominant clinical symptoms include dysphonia, cough, stridor, and dyspnea. During the active phase of the disease, there may occur increased tenderness over the thyroid cartilage and the trachea. Neilly et al. [5] have found out that young patients with upper airway compromise, developed as early as at the onset of the disease, are often resistant to the treatment and have a poor prognosis. Involvement of the respiratory system may be the only dominant symptom of the disease and may be mistaken for a banal chronic bronchitis. In such case, it is beneficial to establish the diagnosis on the basis of flow-volume curve that will reveal an abrupt onset of acute obstruction of the upper airways.

On the contrary, the bronchitis loop shows a chronic obstructive disorder with a peak in the periphery (Fig. 10.2).

Involvement of cardiovascular system occurs in about 10 % of patients, particularly in the form of thoracic and abdominal aortic aneurysms. Another disorder may be aortitis causing thinning of the media and aortic root dilatation with ruptures of the aortic valve. Systemic polyarteritis nodosa was identified in 9 % of cases. The range of effects of inflammation on the blood vessels is quite broad. If it affects small blood vessels, it has a form of cutaneous leukocytoclastic vasculitis, while in large blood vessels that of the Takayasu's arteritis. Inflammation may affect also the aortic and mitral valves and cause their functional insufficiency due to aortic root dilatation, valvulitis, or papillary muscle dysfunction. In addition to these symptoms and findings, there

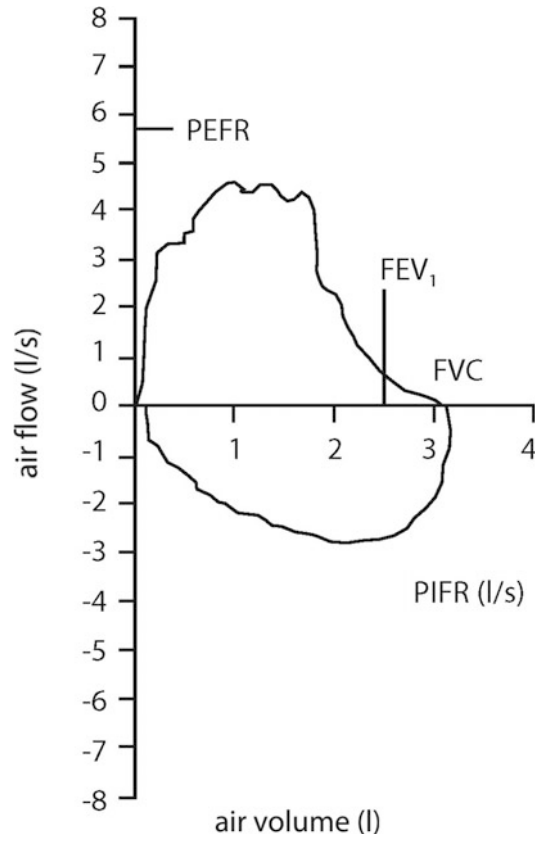

Fig. 10.2 F-V loop. The flow-volume ratio in the lungs. The flow-volume loop shows a defect of air flow in expiration (deformation of the soft trachea by expiration pressure). *FEV1* forced expiratory volume per 1 s, *FVC* forced vital capacity, *PEFR* peak expiratory flow rate, *PIFR* peak inspiratory flow rate

may occur several abnormalities, such as arrhythmia, heart block, and supraventricular tachycardia caused by myocarditis of the conductive system.

Renal involvement was detected in 20 % of patients with RP. It manifests itself predominantly in the form of segmental proliferative necrotizing glomerulonephritis. Immunofluorescence and electron microscopy examination showed a small amount of sediments of IgG and IgM immunoglobulins and of C3 component of the granular complement deposited in the subendothelial and mesangial areas. The course of the

disease in patients with renal involvement is usually quite severe and may be associated with manifestations of extrarenal vasculitis and unfavorable prognosis.

10.7 Ocular Involvement

A severe disorder in RP is inflammation of the eyeball, most often episcleritis, scleritis, and corneal thinning, that may cause perforations associated with other complications, leading ultimately to the loss of vision. Other ocular manifestations in RP include uveitis, retinal vasculitis, and optic neuritis that may also ultimately result in loss of vision. In addition, this disease may be associated with paralysis of eye muscles, inflammation of the orbit, and papilla swelling.

Skin symptoms in RP include purpura, rash, and angioedema, less frequently livedo reticularis, migratory superficial thrombophlebitis, erythema nodosum, erythema multiforme, and panniculitis.

Neurological complications in RP include cranial neuropathy, headache, encephalopathy, hemiplegia, and ataxia, sometimes also transverse myelitis, mononeuritis multiplex, and temporal non-granulomatous vasculitis. In up to 22 % of patients, RP is accompanied by quite a high fever.

Bellamy and Dewar [6] described a case of a 25-year-old woman who presented with chondritis at 14 weeks of pregnancy. The patient was receiving high doses of glucocorticoids. Pregnancy and delivery of the child were physiological. The child developed normally after the birth, and the disease did not reactivate in the postpartum period. Later the patient gave birth to another healthy child, again without reactivation of the disease.

10.8 Relapsing Polychondritis in the Elderly

Sallam et al. [7] described an unusual manifestation of relapsing polychondritis presenting initially with isolated ocular signs, mimicking infective keratitis. It was a case report of a 75-year-old man who presented with marked left ocular irritation and photophobia. Ophthalmological examination disclosed corneal intrastromal infiltrate and hypopyon which failed to respond to intensive antimicrobial drops. Later he developed bilateral auricular chondritis. Relapsing polychondritis was diagnosed. Treatment with topical and oral corticosteroids resulted in marked improvement of the corneal infiltrate and resolution of the auricular inflammation. The authors highlighted the importance of considering connective tissue inflammatory conditions in any stromal keratitis unresponsive to antimicrobial treatment, in the context of a developing relapsing polychondritis or another connective tissue inflammatory condition. In 2010, Starr et al. [8] presented a case report of a 70-year-old man with an unusual clinical manifestation of the relapsing polychondritis in the form of alopecia areata.

Erten-Lyons et al. [9] detected in a 50-year-old lawyer with the diagnosis of relapsing polychondritis the presence of subacute dementia associated with the disease. Another patient, a 68-year-old man, with the diagnosis of relapsing polychondritis presented with myalgia, headache, fever, and bilateral swelling of auricles. For 8 months, the patient's condition was gradually aggravating, with typical weight loss, conjunctiva involvement, and loss of cognitive functions. The patient was unable to perform activities of daily living without assistance and had speech difficulties lasting for several hours. Psychological examination revealed impaired verbal and visual memory indicating an early stage of dementia.

10.9 Incidence of Relapsing Polychondritis in Association with Other Diseases

Relapsing polychondritis may occur simultaneously with ulcerative colitis, Behçet's syndrome, Wegener's granulomatosis, Sweet's syndrome, systemic lupus erythematosus, and other inflammatory diseases of the connective tissue (rheumatoid arthritis, Sjögren's syndrome, systemic

scleroderma, psoriatic arthritis, polyarteritis nodosa), but also in association with tumorous diseases, such as chronic lymphocytic leukemia [10].

The "MAGIC syndrome" (mouth and genital ulcers with inflamed cartilage syndrome) is a combination of the Behçet's disease and relapsing polychondritis [11].

Duda and Botka [12] described a rare association of RP in a 64-year-old female patient with Sjögren's syndrome, tubulointerstitial nephritis, and autoimmune thyropathy. During the first year, tubulointerstitial nephritis became aggravated in the form of renal failure with hypokalemia and hyperuricemia. Later it was followed by a stroke and development of pancytopenia even after elimination of cyclophosphamide from the treatment. After 1 year and 7 months, the patient died of catheter-related sepsis and bronchopneumonia.

The presented case reports indicate that a severe relapsing polychondritis may occur even in an older age category.

10.10 Laboratory Findings

The common feature of laboratory parameters in RP is increase in acute inflammatory phase reactants and the presence of anemia and thrombocytosis, sometimes also a mild leukocytosis. Serological tests have shown that the serum in 50 % of patients was positive for antibodies against type II collagen. In most cases, the finding includes circulating immune complexes and antibodies against intracellular antigens (approximately in 20 % of cases). A finding of circulating anticoagulants was also described, which explains the clinical finding of severe thromboses.

10.11 Diagnosis

RP should be considered as confirmed if the following clinical criteria are met:

1. Recurrent chondritis of both auricles
2. Nonerosive polyarthritis
3. Chondritis of nasal cartilages
4. Inflammation of ocular structures (including conjunctivitis, keratitis, scleritis, episcleritis, and uveitis)
5. Involvement of laryngeal or tracheal cartilage
6. Cochlear or vestibular damage

The abovementioned criteria were published by McAdam et al. [13] and later slightly modified by Damiani and Levine [14]. They included three or more of these criteria; however, the diagnosis requires at least one clinical criterion and a histological finding of chondritis in separate anatomical locations with response to the treatment.

Based on 112 cases of the disease, the diagnostic criteria were modified in 1986 in Minnesota as follows: RP has to be suspected when the inflammatory bouts involve at least two of the typical sites – auricular, nasal, and laryngotracheal – or one of the typical sites and two others, ocular and statoacoustic disturbances (hearing loss and/or vertigo) and arthritis.

10.12 Differential Diagnosis

Although the course of RP is quite typical, under certain conditions it may make the diagnosis difficult. It has to be taken into account that the auricle is highly sensitive to trauma, chemical agents, and frostbite. Similarly, the trachea is highly sensitive to protracted endotracheal intubation. Similar symptoms as in perichondritis may be found in acute streptococcal infection, mycotic infection, syphilis, and leprosy, which may be a cause of erroneous RP diagnosis. Therefore biopsy should be performed in order to establish a correct diagnosis. Nasal cartilage may be affected also by granulomatous processes (Wegener's granulomatosis, lymphomatoid granulomatosis, lethal midline granuloma). Involvement of eyes may be manifested as necrotizing scleritis or keratitis also in inflammatory rheumatic diseases, such as RA, Wegener's granulomatosis, polyarteritis nodosa, Behçet's disease, or Cogan's syndrome. Differential diagnosis must exclude pulmonary or renal vasculitis affecting CNS or other organs. The aortic root may be involved in case of Ehlers-

Danlos syndrome, Marfan syndrome, and idiopathic cystic medial necrosis associated with ankylosing spondylitis.

10.13 Therapy and Prognosis

RP therapy depends on the forms of the disease. Milder forms affecting the auricle or arthritis are treated with nonsteroidal anti-inflammatory drugs and low doses of prednisone. Severe forms of the disease, such as laryngotracheal or ocular involvement, severe involvement of the ear and nasal cartilage, systemic vasculitis, aortitis, or glomerulonephritis, require administration of prednisone at the dose of 1 mg/kg of body mass daily. In certain cases, the prednisone doses may be successfully reduced and maintain reliable remission, while sometimes reduction of doses of glucocorticoids results in exacerbation of the disease [6]. In these cases, a combined immunosuppressive treatment (cyclophosphamide, azathioprine, chlorambucil, cyclosporine) should be attempted. Van der Lube et al. [15] used anti-CD4 monoclonal antibody in the therapy. Recently, autologous transplantation of stem cells has been introduced in the RP treatment.

Within the basic RP treatment (Handler [16]), a 68-year-old woman with confirmed RP diagnosis (with auricular involvement) received 100 mg of leflunomide daily for 3 days, followed by 20 mg daily.

Within 2 weeks the auricular inflammation resolved, and the treatment reliably maintained remission for the period of 3 years [16, 17]; in the resistant form, the inflammatory process could not be managed by glucocorticoids, methotrexate, azathioprine, and antimalarials. Auricular and nasal cartilage was effectively treated with leflunomide at a dose of 20 mg and then 30 mg daily; however, the treatment had to be discontinued due to febrile hematologic adverse response.

Recently, the resistant forms of RP have started to be treated with biological therapy by TNF inhibitors (infliximab, adalimumab, etanercept), anti-IL-6 receptor inhibitor (tocilizumab), Il-1 receptor inhibitor (anakinra), and rituximab (antibody against B lymphocytes).

In 2002, Ehresmann [18] used infliximab in the treatment of a 35-year-old man with a 10-year history of RP. Due to resistance resulting from high doses of glucocorticoids in combination with MTX, the patient received infliximab at a dose of 5 mg/kg, in the form of infusion at weeks 0, 2, and 6 and then every 8 weeks. MTX and glucocorticoids were gradually eliminated from the treatment. The therapy appeared to be safe and well tolerated. In the treatment of a 42-year-old woman with RP [24], who developed resistance to treatment with glucocorticoids in combination with MTX and later with azathioprine, infliximab was added at a dose of 3 mg/kg (dosage [10, 14, 24]). Her condition improved as early as after the second infusion. After the third infusion, arthritis subsided, and the basal treatment could be radically reduced to 10 mg of prednisone and 7.5 mg of MTX weekly.

Carter [19] used etanercept in a 46-year-old female patient with a resistant form of RP, at a dose of 25 mg twice a week, in combination with glucocorticoids and MTX (20 mg daily). This therapy allowed gradual elimination of prednisone from the treatment (starting from the dose of 30 mg daily) and administration only of MTX at a dose of 15 mg daily. With combination of MTX and etanercept, the disease remained clinically in remission. And finally, Seymour et al. [20] successfully applied adalimumab at a dose of 40 mg every 2 weeks after previous treatment with infliximab for the period of 10 months. Due to disease relapse, adalimumab was introduced in the treatment. Remission was maintained for 4 years of replacement of infliximab by adalimumab. This was the first case report of RP with associated aortitis where adalimumab was successfully used in the treatment.

Similar problems, as in developed resistance of biological therapy to infliximab in RP, were addressed in resistance to classic immunosuppressive treatment (cyclosporine, azathioprine, cyclophosphamide, and various doses of glucocorticoids). Infliximab proved to be inefficient after three infusions, and therefore anakinra was used, the effect of which was immediate. It has been proved that anakinra may be an alternative

drug in patients with a resistant form of RP requiring high doses of glucocorticoids to suppress the disease [21]. Kawai et al. [22] pointed out the possibility of administration of tocilizumab in case of development of a resistant form of RP or exacerbation of the disease due to attempts at reduction of prednisone dosage.

However, there may occur also acute conditions during RP, such as acute airway obstruction. Such cases require aggressive treatment with pulse methylprednisolone at a dose of 1 g [23].

The patient must be followed up by a rheumatologist as well as by an otolaryngologist (indirect laryngoscopy, CT scanning of trachea, urgent tracheostomy for symptomatic subglottic stenosis). The disease may have fatal consequences in case of airway collapse of the bronchial stroma. Heart valve replacements and aortic grafts have also been used in the treatment.

Despite the abovementioned therapeutic possibilities, RP prognosis remains to be severe, especially in the forms affecting the laryngeal cartilages and individual organs (heart, respiratory system, eye). Therefore, rheumatologists should pay increased attention to this rare disease.

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RS3PE: A Disease or a Syndrome? 11

Jozef Rovenský

RS_3PE (remitting seronegative symmetrical synovitis with pitting oedema) was described by McCarty et al. [1] in 1985 and by Russel et al. [2] in 1990 in 23 elderly patients.

Clinical features included:

1. Acute severe onset
2. Bilateral symmetrical synovitis (wrists, MCP and small joints of the hands)
3. Inflammation of digital flexor tendons and their sheaths
4. Flexor synovitis largely contributing to swelling of the dorsum of hands
5. Pitting oedema (boxing glove-like hands)

Unlike in rheumatoid arthritis (RA), the disease affected elderly men. All patients were rheumatoid factor negative. Synovitis was subsiding and remained in remission, although the therapy by antirheumatic drugs was gradually eliminated. Later association was found of the clinical condition with the incidence of HLA-B7 incidence, less of DR4, as was documented in severe forms of RA. The pitting oedema may occur also in lower extremities, in the pretibial region and ankles and knee and hip joints. In the upper extremities, it was observed in the region of elbows and shoulders.

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The pitting oedema is highly sensitive to the glucocorticoid therapy ensuring long-term remission after withdrawal of drugs, although flexion contractures may persist for an indefinite period [3]. In a few cases, also unilateral involvement of the hands was reported [4, 5]. As compared to RA, there was no radiological evidence of destruction of articular structures in RS_3PE [3].

11.1 RS_3PE Syndrome and Polymyalgia Rheumatica

Recent studies have debated whether there exists a "pure" RS3PE syndrome or whether it is part of the clinical features of polymyalgia rheumatica (PMR) [3, 4], i.e. that these two syndromes would be part of the same disease, without any difference between them. Cantini et al. [6] have suggested that the two syndromes may be part of one nosological entity, based on the following clinical features associated with RS3PE and PMR: there were no patients under the age of 50 in the follow-up cohort; the frequency of the disease was increasing in the course of physiological ageing, with the peak in the age group of 70–79 years. The clinical symptoms rapidly remitted after a brief period of administration of low doses of glucocorticoids. No patient developed RA during the follow-up. However, in the pure form of the RS3PE syndrome, the glucocorticoid therapy

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was shorter, requiring lower cumulative glucocorticoid dose, and a lower frequency of systemic symptoms and relapses of clinical symptoms was recorded.

In the pure RS_3PE syndrome group, evidence of hand and/or foot synovitis was present in all the 23 patients. On the other hand, in the group of 177 consecutive patients with PMR diagnosed over a 5-year period, 21 patients (12 %) had distal extremity swelling with pitting oedema. Comparison of the two groups revealed no significant differences in the sex, age at onset of disease, acute phase reactant values at diagnosis, frequency of peripheral synovitis and carpal tunnel syndrome, and frequency of HLA-B7 antigen. Hands and feet MRI showed evidence of tenosynovitis in five patients and joint synovitis in three patients. Cantini et al. [6] found only a low frequency of residual hand contractures and thickening of wrist extensor and flexor tendon (9 %), as compared to the original studies by McCarty et al. [1] and Russel et al. [2] who reported the above finding in 61 % of patients.

Based on the above-mentioned facts, it may be concluded that RS3PE syndrome may be part of the clinical features of PMR, or it may occur separately. Several studies reported also the incidence of giant cell arteritis in the patients' history, with a subsequent development of RS3PE syndrome [7].

11.2 Rheumatoid Arthritis, Psoriatic Arthritis, Other Inflammatory Rheumatic Diseases and RS3PE Syndrome

Schaeverbeke et al. [8] evaluated the outcomes of a retrospective study of patients with RS3PE in order to establish whether it is a syndrome or a disease. The group comprised 24 patients with polyarthritis and pitting oedema who met the criteria for diagnosis of RS3PE syndrome, as described by McCarty [1]. Two patients died and four patients could not be traced. In five patients who could not be seen after the initial period of follow-up, relevant data were obtained from their general practitioners. In the remaining 13 patients, clinical, radiological and biological evaluations were performed. The follow-up period ranged between 1 and 18 years. Eleven patients had one or several recurrences of articular manifestations, of which eight had repeated episodes of mild arthritis, two of them developed spondyloarthropathy and one patient rheumatoid arthritis.

The interval until the first recurrence was 18 months to 12 years after the first attack. Thirteen patients had no recurrence of arthritis, one was rheumatoid factor positive, one was positive for antinuclear antibodies (1/2000) and one had Sjögren's syndrome. Two patients were positive for HLA-B7 and one of them also for HLA-B27. This patient had a radiologically proven sclerosis of sacroiliac joints. Another HLA-B27-positive patient had a relapse of oligoarthritis with pitting oedema 18 months after the first episode. Another two patients were HLA-B22 positive and yet another patient HLA-B35 positive. This patient had a mild oligoarthritis. The results of the study indicate that long-term follow-up of RS_3PE may differentiate certain nosological entities from the group of rheumatic diseases. RS_3PE appears to be a syndrome related to age-related rheumatic diseases, such as elderly-onset rheumatoid arthritis (EORA) and late-onset spondyloarthropathy.

Bhakta and Pease [9] published a prospective study comparing the clinical and radiological outcome of patients with elderly-onset RA presenting with (22 patients) and without (81 patients) pitting oedema of the hands. The outcome was defined by development of erosions of the hands, wrists or feet and the number of patients in remission. The results indicated that IgM RF was less frequent in EORA patients with pitting oedema who also were less likely to develop erosions, as compared to the group of EORA patients without pitting oedema. On the

other hand, IgM RF-seropositive patients were more likely to develop erosions.

Based on a number of studies, the following clinical findings have been obtained:

1. Oedema may involve also lower extremities (feet, ankles, knee and hip joints and sometimes also elbows and shoulders).
2. RS3PE syndrome is usually RF seronegative, with high activity of acute inflammatory phase reactants; 59 % of patients are HLA-B27 positive, as compared to 24 % in healthy population.
3. Low doses of glucocorticoids suppress oedema and the disease remits.
4. Flexion contractures of fingers, wrists and elbows may, however, persist for an indefinite period.
5. RS_3PE (remitting seronegative symmetrical synovitis with pitting oedema) may, however, occur also in the form of a unilateral involvement of the hand.
6. Destructive radiological changes are absent.
7. RS3PE syndrome is often associated with B7 antigen, which distinguishes it from PMR.
8. Responsible for development of a subcutaneous oedema is extensor synovitis and peritendinitis in the soft tissues of the dorsum of the hand, which may occur both in RS3PE and PMR.

RS3PE syndrome occurs in the following nosological entities:

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Articular chondrocalcinosis
- Sarcoidosis, systemic lupus erythematosus, dermatomyositis, MCTD, Sjögren's syndrome and systemic sclerosis
- Late-onset spondyloarthropathy
- Whipple's disease
- Paraneoplastic syndromes
- Amyloid arthropathy
- BCG instillation

11.3 RS3PE and Tumours

The first finding of RS3PE was described by Roldan et al. [10], who observed development of the disease 4 months before the patient was diagnosed with non-Hodgkin lymphoma. Later, Olivé et al. [11] found in 27 patients with RS3PE also its paraneoplastic form, i.e. T lymphomas and myelodysplastic syndrome, during onset of polyarthritis. It has been found out that RS3PE may occur also in solid tumours, e.g. in endometrial adenocarcinoma [12]. One case was also reported of a patient with gastric carcinoma [13], and finally, one patient had a pancreatic carcinoma. Sibilia et al. [14] focused on description of RS3PE in six male patients with solid tumours. All six patients, with the mean age of 74 years, met the following criteria: bilateral pitting oedema of both hands, sudden onset of polyarthritis, age >50 years and absence of rheumatoid factor. Four patients suffered from prostatic carcinoma, one had gastric carcinoma and one patient had colonic adenocarcinoma. The clinical presentation was characterised by the classical form of RS_3PE syndrome and by exacerbation of the general condition, sometimes with fever. All the patients were seronegative, with the absence of the rheumatoid factor and antinuclear antibodies in the serum. In these six patients, the articular manifestations regressed totally or partially in response to corticosteroids, sometimes at low doses, associated in most cases with specific antitumour therapy. The mean survival following detection of RS_3PE was 11 months. Five patients died of metastatic dissemination of their cancer and one of myocardial infarction. Based on these clinical findings, the authors have concluded that RS_3PE is a heterogeneous syndrome that can reveal a solid tumour, notably an adenocarcinoma.

The authors assume that although the pathogenic mechanism is unknown, this could involve a type of paraneoplastic polyarthritis linked to the synthesis of a factor such as IL-6. Further

studies have shown that surgical resection of the tumour or chemotherapy contributed to resolution of the oedema [3]. It seems that in paraneoplastic syndromes, the anatomical target in paraneoplastic processes may be tenosynovial extensor sheaths.

Some authors share the opinion that RS3PE syndrome is often associated with a number of inflammatory rheumatic diseases, mainly in older age and in connection with malignancy [15–17].

11.4 Oedema and Hand Arthritis: Differential Diagnosis in Other Nosological Entities

Based on differential diagnosis, the isolated RS3PE syndrome must be distinguished from a mixed connective tissue disease (Sharp's syndrome), chondrocalcinosis, reflex sympathetic dystrophy (Sudeck's disease, algodystrophic syndrome), amyloid arthropathy, spondyloarthropathy of psoriatic type or spondyloarthropathy in Reiter's syndrome as well as from the above-mentioned diseases, such as rheumatoid arthritis and polymyalgia rheumatica [18].

Typical of Sharp's syndrome is oedema on the hands, primarily sausage-like swelling in the fingers.

In a majority of cases (up to 80 %), it is manifested by thickening and tension of the skin typically occurring in young women (Raynaud's phenomenon). Laboratory parameters include a speckled pattern of antinuclear antibodies (U1-RNP specificity).

Sharp's syndrome (unlike RS3PE) is characterised by its prevalence in younger patients with the mean age of about 36 years, women in particular (84 %), and sometimes also the presence of Raynaud's phenomenon (84 %). Sometimes there occur ulcerations and erythematous lesions mimicking a similar condition as in dermatopolymyositis. From the immunological viewpoint, the disease is characterised by the presence of U1-RNP and high-titre ANA with a speckled fluorescence pattern.

11.5 Articular Chondrocalcinosis

In elderly patients, articular chondrocalcinosis (CPPD) is often associated with oedema on the dorsum of hands and lower extremities (Fig. 11.1).

Oedema may have both an acute and subacute form; it is often asymmetrical and affects mostly women. General inflammatory manifestations are usually slightly increased. Examination of synovial effusion under the polarising microscope may show calcium pyrophosphate dihydrate crystals, and radiological diagnosis may confirm calcification of hyaline cartilage. These findings together with a good response to non-steroidal antirheumatic drugs may contribute to proper diagnosis.

11.6 Reflex Sympathetic Dystrophy (Sudeck's Disease)

Oedema on the hands may result in bilateral reflex sympathetic dystrophy. Marked pain limits active and passive motion; it is associated with vasomotor disorders, usually without arthritis. The predisposing factors include a history of myocardial infarction and sudden stroke; systemic inflammatory manifestations are not among the factors. The diagnosis of Sudeck's atrophy may be supported by radiographic examination, bone scintigraphy and MRI.

11.7 Amyloid Arthropathy

Amyloid arthropathy is also often associated with pitting oedema of hands; sometimes it occurs in light chain disease within multiple myeloma. Oedema develops slowly and is rarely accompanied by short-term episodes of morning stiffness. It is a pseudoedema that has slightly inflammatory parameters and is relatively rigid by palpation. Diagnosis is based on clinical findings, including renal insufficiency with proteinuria.

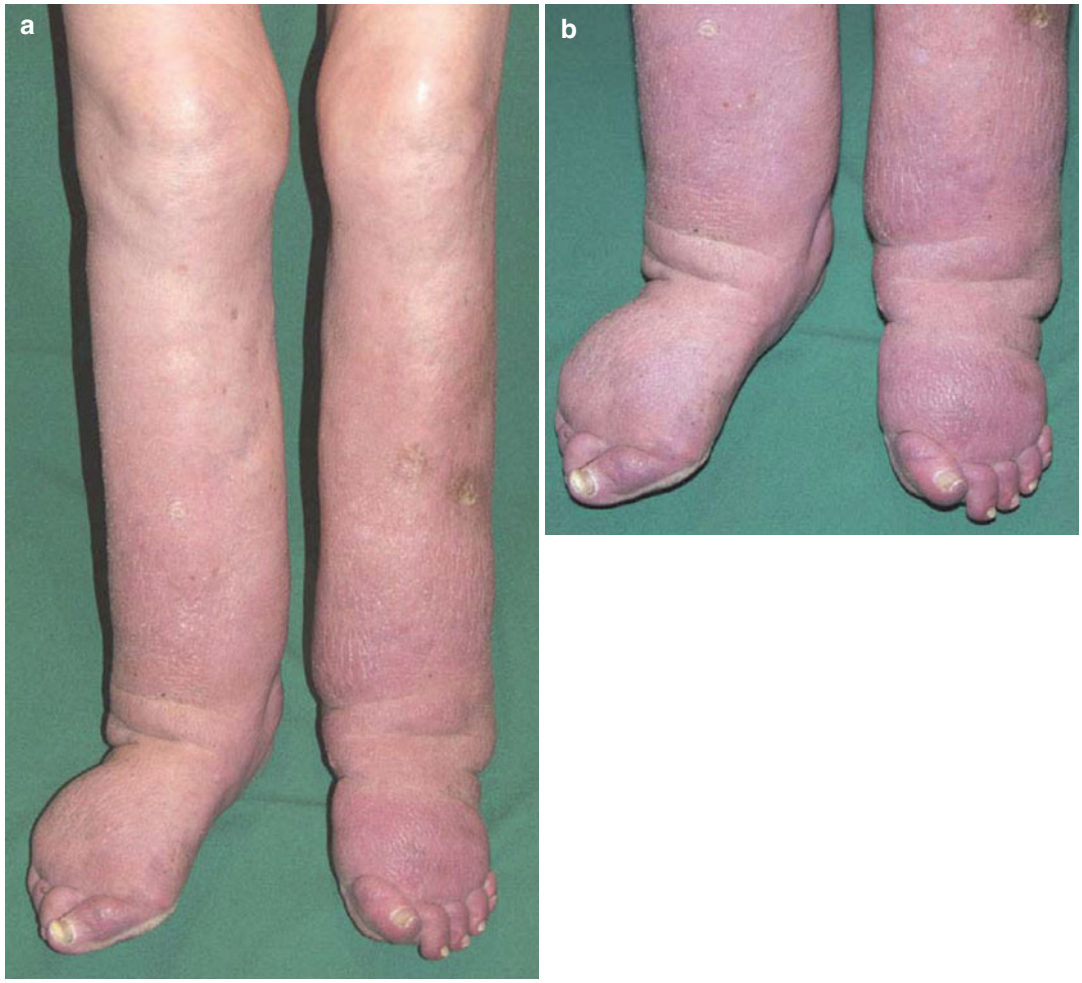

Fig. 11.1 (**a**, **b**) Severe symmetrical lymphedema with development of elephantiasis in both lower limbs in a patient with the familial form of articular chondrocalcinosis (RS3PE)

Bioptic examination of the synovial membrane or synovial fluid may reveal the presence of amyloid which shows apple-green birefringence in polarised light when Congo red stained.

11.8 Late-Onset Spondyloarthropathy

Pitting oedema may be a manifestation of late-onset peripheral spondyloarthropathy [19]. It affects mainly lower extremities, less frequently hands, and is often asymmetrical [19, 20]. The patients are mostly middle-aged men, while RS3PE syndrome affects primarily individuals at the age of about 60 years. The patients present with mild oligoarthritis in lower extremities. The axial skeleton remains as a rule intact; the response to non-steroidal antirheumatic drugs and glucocorticoids is weak, and the disease usually evolves over the years. HLA-B27 is usually positive [21].

11.9 Sarcoidosis

Cantini et al. [22] studied RS_3PE syndrome in lower extremities in acute sarcoidosis. Remitting distal extremity swelling with pitting oedema was the presenting manifestation in five (29 %)

of 17 consecutive patients with acute sarcoidosis seen during a 2-year period. The swelling and pitting oedema were most prominent over the dorsum of both feet and ankles. In perimalleolar areas the oedema followed the distribution of tibial and peroneal tendons. MRI confirmed in three patients a severe tenosynovitis of peroneal, tibial and extensor tendons that was primarily responsible for the oedema in the subcutaneous and peritendinous ankle and foot soft tissues.

11.10 Whipple's Disease

Olivieri et al. [3] reported five cases of RS3PE associated with the Whipple's disease, manifested by pitting oedema over the dorsum of the hands and feet.

Conclusion

RS3PE syndrome is a sub-entity of seronegative symmetrical synovitis that occurs in elderly men with a marked pitting oedema, affecting primarily the hands. The disease is highly sensitive to the glucocorticoid therapy ensuring long-term remission after withdrawal of drugs. However, it should be pointed out that RS3PE syndrome may be also part of the paraneoplastic syndrome. Such a syndrome should be suspected particularly in cases where the response to glucocorticoid treatment is inadequate.

Differential diagnosis has to take into account that RS3PE syndrome does not always occur as an isolated disorder but may be part of the clinical features of other inflammatory and metabolic rheumatic diseases.

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12 Clinical and Laboratory Manifestations of Paraneoplastic Rheumatic Syndromes

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Clinical manifestations of paraneoplastic rheumatic syndromes may coincide with a malignancy and follow or precede the diagnosis of cancer. According to Fam [1], the paraneoplastic syndromes should meet the following criteria:

1. Personal or family history of cancer, exposure to carcinogens
2. Late onset of symptoms, at the age over 50
3. General symptoms: fever, fatigue, loss of weight
4. A rapid onset and atypical course
5. Time correlation between the onset of paraneoplastic symptoms and tumorous disease
6. Absence of metastases in bones or joints
7. Absence of rheumatoid factor, negative cultivation in the synovial fluid, absence of crystals in the synovial fluid
8. Inadequate response to conventional therapy
9. Improvement of symptoms after a successful therapy of a malignancy
10. Recurrence of paraneoplastic symptoms with recurrence of the tumour

In paraneoplastic syndromes, involvement of joints or muscles is not attributable to direct tumour invasion. It is generally known that it may be sometimes difficult to distinguish strictly between musculoskeletal manifestations of malignancy and paraneoplastic syndromes. The cause of the disorder may be probably attributed to induced hormones, peptides, autocrine and paracrine mediators, autoantibodies and cytotoxic leukocytes. Highly differentiated tumours may secrete autocrine and paracrine hormones. Some paraneoplastic mediators are normal cellular products that are, however, secreted in excessive quantities by a large tumorous mass. Others may result from tumour cell death, due to release of autoantigens. As a result of impairment of integrity of the basement membrane and during tumour invasion, autoantigens may get into contact with the immune system cells and activate them.

The subsequently developing circulating antibodies or cytotoxic lymphocytes target tumour and the surrounding tissues and may damage endothelial, synovial, epithelial and mesenchymal cells [2].

Paraneoplastic rheumatic syndromes are divided into cutaneous, muscular, vascular and mixed [1, 3, 4]:

- Cutaneous paraneoplastic syndromes – multicentric reticulohistiocytosis, palmar fasciitis, pruritus, Sweet's syndrome, gangrenous pyoderma, scleroderma-like syndrome
- Muscular paraneoplastic syndromes – dermatomyositis and polymyositis, Lambert-Eaton myasthenic syndrome

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- Paraneoplastic arthropathy of solid tumours – carcinomatous polyarthritis, palmar fasciitis and polyarthritis, hypertrophic osteoarthropathy, Jaccoud's arthropathy
- Paraneoplastic arthropathy of hematologic malignancies – leukemic arthritis, polyarthritis, polyarthralgia with lymphoma, amyloid arthropathy
- Vascular paraneoplastic syndromes – paraneoplastic vasculitis, Raynaud's syndrome, digital gangrene, erythromelalgia
- Mixed paraneoplastic syndromes – algodystrophic syndrome, lupus-like syndrome, antiphospholipid syndrome, catastrophic antiphospholipid syndrome, relapsing polychondritis, polymyalgia rheumatic and giant cell arteritis, multicentric reticulohistiocytosis, oncogenic osteomalacia
- Arthropathy associated with cancer immunotherapy

Although paraneoplastic syndromes are quite infrequent in autoimmune diseases, they are clinically very important for individual patients as their early diagnosis, with a timely chemotherapy and surgical intervention, may radically change the patient's fate.

12.1 Algodystrophic Syndrome

Algodystrophic syndrome may occasionally occur in pulmonary, colorectal, pancreatic and ovarian cancer and chronic myeloid leukaemia. In the English literature, it is referred to as the reflex sympathetic dystrophy syndrome. The clinical features include primarily marked pain of the affected part of the body, autonomous vasomotor and sudomotor dysfunction, skin changes and subsequent limited range of motion of the extremity involved. Radiologically it is characterised by regional osteoporosis of the affected area. Pathogenesis of the relation between cancer and this syndrome is unknown. The disease may precede the diagnosis of cancer, and its symptoms may resolve after a successful treatment of the malignancy [1].

12.2 SLE-Like Syndrome

Another paraneoplastic syndrome deserving attention is SLE-like syndrome. Solans-Laqué et al. [5] reported a case of SLE-like syndrome that could not be clinically distinguished from classic SLE (the patient suffered from fever, maculopapular exanthema, symmetrical polyarthritis and lethargy). Laboratory manifestations included anaemia, leukopenia, thrombocytopenia, decreased levels of C3 and C4, elevated erythrocyte sedimentation rate, and positivity of granular antinuclear antibodies (1:320), and other antibodies – anti-dsDNA, anti-SS-A, anti-SS-B and anti-Sm – were negative. After unsuccessful treatment by prednisone, the patient's condition improved only partially. It was found out that the patient suffered from Burkitt lymphoma that was successfully managed by chemotherapy and the paraneoplastic syndrome resolved. However, mixed paraneoplastic syndromes are associated with SLE only rarely.

Another case report was published by Loch et al. [6]. A 68-year-old patient with systemic lupus erythematosus simultaneously developed epidermoid pulmonary carcinoma. The patient's condition improved after successful lobectomy for lung cancer, because SLE remitted during 2 months. A simultaneous incidence of thymoma, systemic lupus erythematosus and hypertrophic pulmonary arthropathy was diagnosed in an 11-year-old boy [7]. Cohen [8] reports that up to 20 % of patients with SLE have two concurrent diagnoses, namely, B-cell hematologic malignancy and systemic lupus erythematosus, and that several case studies may be found in the literature, on simultaneous incidence of SLE and non-Hodgkin syndrome or myeloma. There are even several reports of patients with a SLE-like onset that may be associated with hematologic malignancy, clinically manifested by mucocutaneous paraneoplastic syndrome which heralds development of lymphoma or myeloma. And finally, subacute cutaneous lupus erythematosus was reported in six patients in combination with solid tumours, including cancer of breast (two female patients),

lung (two male patients), stomach (one male patient) and uterus (one female patient). In these patients, the cutaneous lupus erythematosus developed 8 months prior to diagnosis of malignancy and the skin changes resolved within several hours up to 6 months following commencement of anticancer therapy [8].

12.3 Antiphospholipid Syndrome and Catastrophic Antiphospholipid Syndrome

Another disease associated with the incidence of mixed paraneoplastic syndrome is antiphospholipid syndrome (APS) and catastrophic antiphospholipid (CAPS). APS occurs in association with thymoma; cancer of the kidneys, lungs, and ovaries; B-cell lymphoma; spleen lymphoma; chronic myeloid leukaemia; and non-Hodgkin lymphoma.

The clinical features show that thromboembolic events in the elderly patients are often associated with the incidence of antiphospholipid antibodies. Their presence may be also the first sign of malignancy manifestation. It means that the presence of antiphospholipid antibodies in patients with malignancy may signal development of APS which is complicated by the malignancy [9].

Trigger mechanisms such as infection, trauma, surgery, anticoagulation problems, neoplasia and others may turn APS into catastrophic antiphospholipid syndrome (Asherson's syndrome, CAPS). Miesbach et al. [10] examined 262 patients from the CAPS register and found out that malignancy was associated with this syndrome in 23 patients, i.e. 9 % (Table 12.1).

Hematologic malignancies were present in six patients (26 %), four patients had lung cancer (17 %) and two patients (9 %) colon cancer. In most patients, it was confirmed that CAPS was triggered by cancer. One patient developed CAPS during allogeneic stem cell transplantation due to acute lymphoblastic leukaemia. CNS tumours were also highly frequent and were a significant risk factor for CAPS development. Another risk factor, in addition to malignancy, were also surgical interventions.

12.4 Relapsing Polychondritis

Relapsing polychondritis is a very rare disease that affects multiple organs. It is characterised by recurrent episodes of inflammation of cartilaginous structures and other connective tissues, rich in glycosaminoglycan. Clinical symptoms concentrate in auricles, nose, larynx, upper airways, joints, heart, blood vessels, inner ear, cornea and sclera. Several cases were reported in the literature of relapsing polychondritis with features of a mixed paraneoplastic syndrome in combination

Table 12.1 Malignancy in patients with CAPS

Patient no.	Malignancy
1	Uterine cancer
2	Lung biopsy (adenocarcinoma)
3	Cancer of unknown origin
4	Stomach adenocarcinoma
5	Lung adenocarcinoma
6	Gallbladder cancer
7	Lymphoma
8	Abdominal surgery to restore the function of the large intestine; former colectomy
9	Breast cancer
10	Colonic adenocarcinoma
11	Primary lung carcinoma
12	Epithelial carcinoma of unknown primary origin
13	Resection of meningioma
14	Leiomyosarcoma
15	Carcinoid tumour, surgery
16	Lung adenocarcinoma
17	Non-Hodgkin lymphoma
18	Angiocentric lymphoma
19	Chronic myelomonocytic leukaemia
20	Peripheral T-cell lymphoma
21	Ovarian cancer
22	Allogeneic transplantation of stem cells for acute lymphoblastic leukaemia
23	Hodgkin's lymphoma

According to Miesbach et al. [10]

with leukaemia, lymphomas, myelodysplastic syndrome and rarely with carcinoma [11, 12]. Chondritis may precede or follow the diagnosis. Malignancy-induced relapsing polychondritis as paraneoplastic syndrome is most often reported in association with myelodysplastic syndrome [13, 14].

Cohen [8] states that in addition to myelodysplastic syndrome, paraneoplastic polychondritis is often associated with the incidence of other hematologic malignancies. Less often relapsing polychondritis is related to solid tumours.

12.5 Polymyalgia Rheumatica and Giant Cell Arteritis

Recently, increased attention has been paid to the mixed paraneoplastic syndromes in polymyalgia rheumatica (PMR) and giant cell arteritis. Polymyalgia rheumatica may occasionally occur also in association with colon cancer [15, 16]. It is important to follow up the patient not only in terms of PMR clinical symptoms but also of potential malignancy (weakness, exacerbating anaemia and elevation of erythrocyte sedimentation rate), after previous treatment of the syndrome with glucocorticoids and its recurrence [15, 16]. After diagnosis of colon cancer and successful radical treatment, reliable remission was achieved both of polymyalgia rheumatica and the malignancy. It should be pointed out in this respect that PMR may occur also in association with ductal breast cancer, where the above-mentioned paraneoplastic syndrome may be signalled by younger age of female patients, relatively lower erythrocyte sedimentation rate and finally by a weaker response to glucocorticoids [17].

Paraneoplastic syndrome in PMR may occur also with prostate cancer [18]. Three patients presented with clinical symptoms of PMR, and laboratory tests revealed raised prostate-specific antigen (PSA) and were subsequently diagnosed with carcinoma of the prostate. The authors highlight the importance of clinical and laboratory screening, as well as examination of the skeleton in order to detect potential metastases of the prostate carcinoma (in one of the three diagnosed patients). Megalakaki et al. [19] presented a case report of chronic idiopathic neutropenia preceding polymyalgia rheumatica (5 years), with acute myeloid leukaemia that developed after another 3 years, and the patient died of sepsis. The causal relationship between the described diseases cannot be established in this case, but a possible coincidence of the three diseases cannot be excluded, either.

As for paraneoplastic mixed syndromes, the relation should be mentioned between development of polymyalgia rheumatica and myelodysplastic syndrome. Liozon et al. [20] described cases of concurrent giant cell arteritis (GCA) and malignancy. They report malignancy frequency at 7.4 % and point out myelodysplastic syndrome (MDS) as the precipitating factor for development of GCA.

The relation between MDS and frequency of autoimmune or systemic disease of connective tissues has been reported in the literature at 7–60 % [21–23]. Polymyalgia rheumatica is considered to be the consequence of MDS [24, 25]; on the other hand, GCA does not occur too often in association with MDS [26]. Several reports were, however, published of a concurrent incidence of aortitis and MDS [27, 28]. The available findings show that vasculitis, although not very frequent, may be often a complication in patients with MDS/MPS (myelodysplastic and myeloproliferative) disease. Therefore, clinical examination in the presence of PMR/GCA should exclude a potential share of MDS in the development of paraneoplastic syndrome associated with PMR/GCA (Table 12.2).

12.6 Multicentric Reticulohistiocytosis

Another disease which is part of the group of mixed paraneoplastic syndromes is multicentric reticulohistiocytosis (MR). It is a rare multisystemic disorder of unknown aetiology, which is manifested by papulonodular skin, mucosal and synovial lesions and potentially destructive symmetrical polyarthritis with a tendency to involve

Table 12.2 Overview of studies on frequency of malignant tumours in patients with PMR and temporal arteritis

Author	Number of patients	Diagnosis	Number of patients with malignancies	Tumour location/type
Kalra and Delamere	Case report	PMR	PMR	Monoclonal gammopathy – acute myeloid leukaemia, myeloma, suspected Waldenström's macroglobulinaemia
Montanaro and Bizzarri	Case report	PMR-like syndrome	1	Non-Hodgkin lymphoma later turning into lymphoblastic leukaemia
Haga et al.	185	PMR and/or TA	28	Cancer of the uterus (3), rectum (5), kidney (2), pancreas (1), ovaries (1), vagina (1), penis (1), breast (3), stomach (1), testis (1), prostate (1), large intestine (5), lung (1), lymphatic nodes (2)
O'Keefe and Goldstraw	Case report	PMR	1	Lung cancer
Tabata and Kobayashi	Case report	PMR	1	Papillary thyroid cancer
Kohli and Bennett	Case report	PMR	3	Myelodysplastic syndrome
Shimamoto et al.	Case report	TA	1	Acute myelogenous leukaemia
Mertens et al.	111	PMR and/or TA	12	Breast (1), skin (2), large intestine (2), stomach (2), renal cancer (2), ovaries (1), lungs (1), Waldenström's macroglobulinaemia (1)
Lie	Case report	TA	1	Lung adenocarcinoma
Dasgupta et al.	Case report	PMR	1	IgA k paraproteinaemia
Genereau et al.	Case report	PMR	1	Urinary bladder
Gonzales-Gay et al.	Case report	TA	1	Chronic lymphocytic leukaemia
Assi et al.	Case report	TA	1	Spinocellular cancer
Bahlas et al.	149	PMR and/or TA	4	Multiple myeloma (2), spinocellular cancer, carcinoid, lymphoma
Liozon et al.	271	TA	20	Thyroid, rectum, prostate, large intestine, mediastinum, bladder, stomach, neuroendocrine tumour, uterus, astrocytoma, B-cell chronic lymphocytic leukaemia, resistant anaemia, chronic myelomonocytic leukaemia, acquired idiopathic sideroblastic anaemia, chronic myeloid leukaemia

According to Rovenský and Tuchyňová [48]

multiple organs. Histopathology reveals characteristic histiocytic and multinucleated giant cell infiltrate with eosinophilic ground-glass cytoplasm, with secondary lipid inclusions [29]. It typically develops in fifth age decade, and its incidence is higher in women [30]. Data in the literature show that almost 28 % of patients with MR have a malignancy [31–33]. MR is often associated with cancer of breast, stomach, cervix, ovary and pancreas.

Hematologic malignancies were also reported in association with this disease, as well as axilla sarcoma, melanoma and mesothelioma. Chun-Hsiung et al. [34] reported a case of a 60-year-old female patient who developed papulonodular skin eruptions with progressive osteolytic bone damage bilaterally over the hands, humeral head and acromioclavicular joints within 2 years. CT examination revealed increased thickness in the retropharyngeal wall and submucosal nodular

lesions in the region of arytenoid structures of the larynx.

Histological examination confirmed reticulohistiocytoma, infiltration of numerous CD68(+) histiocytes and multinucleated giant cells with abundant eosinophilic ground-glass cytoplasm. Aggressive treatment with methylprednisolone and MTX was effective and remission of the disease was achieved.

12.7 Osteogenic Osteomalacia

Osteogenic osteomalacia is a very rare syndrome. Musculoskeletal symptoms may appear several months up to several years prior to diagnosis of a tumour. It occurs most often in association with benign tumours of the bones (haemangioma) or soft tissues of mesenchymal origin, less frequently with malignant tumours (haemangiopericytoma, angiosarcoma, myoma, angiofibroma, osteoblastoma, chondroblastoma, neurinoma) [1, 35, 36]. These tumours produce humoral factor phosphatonin that affects proximal renal tubules and inhibits phosphate reabsorption. Another mechanism is increased calcitriol and metabolism abnormality, resulting in decrease of the serum levels [2]. Typical clinical features include muscle pain and weakness, pain in the back, joints and diffuse bone pain. Removal of the tumour improves the patient's condition in the course of several days or months postoperatively. Where it is impossible to remove the whole tumour, substitution therapy with calcitriol and phosphate should be applied [35].

12.8 RS3PE

Remitting seronegative symmetrical synovitis with pitting oedema (RS_3PE) syndrome has been recently included in the group of paraneoplastic syndromes. It was first reported by McCarty [37]. It has been found out that the disease may occur in association with rheumatic diseases in elderly patients, including rheumatoid arthritis, spondyloarthropathy, polymyalgia rheumatica, rarely sarcoidosis, polyarteritis nodosa and giant cell arteritis. In 1988, Sibilia et al. pointed out that RS3PE was detected also in tumorous diseases. The first to describe it were Roldan Molina et al. [38], who observed the disease 4 months before the patient was diagnosed with non-Hodgkin lymphoma. Later, Olivé et al. [39] found in 27 patients RS3PE and also its paraneoplastic form, namely, T-lymphomas and myelodysplastic syndrome, during onset of polyarthritis.

It has been found out that RS3PE may occur also in solid tumours, e.g. in endometrial adenocarcinoma [40]. One case was also reported of a patient with gastric carcinoma [41], and, finally, one patient had a pancreatic carcinoma. Sibilia et al. [42] focused on description of RS3PE in six male patients, with the mean age of 74 years, with solid tumours. All six patients met the following criteria: bilateral pitting oedema of both hands, sudden onset of polyarthritis, age >50 years and absence of rheumatoid factor. Four patients suffered from prostatic carcinoma, one had gastric carcinoma and one patient had colonic adenocarcinoma. The clinical presentation was characterised by the classical form of RS3PE syndrome and by exacerbation of the general condition, sometimes with fever. All the patients were seronegative, with the absence of the rheumatoid factor and antinuclear antibodies in the serum. In these six patients, the articular manifestations regressed totally or partially in response to corticosteroids, sometimes at low doses, associated in most cases with specific antitumour therapy. The mean survival following detection of RS_3PE was 11 months. Five patients died of metastatic dissemination of their cancer and one of myocardial infarction. Based on these clinical findings, the authors have concluded that RS_3PE is a heterogeneous syndrome that can reveal a solid tumour, notably an adenocarcinoma. The authors assume that although the pathogenic mechanism is unknown, this could involve a type of paraneoplastic polyarthritis linked to the synthesis of a factor such as IL-6.

Some authors share the opinion that RS3PE syndrome is often associated with a number of inflammatory rheumatic diseases, mainly in the older age and in connection with malignancy [43–45].

12.9 Incidence of Antinuclear Antibodies in Malignant Diseases

A significant issue is the incidence of antinuclear antibodies in malignant diseases. Solans-Laque et al. [5] conducted a study to determine the prevalence of antinuclear antibodies (ANAs) in patients with malignancies and to investigate if their presence might be related to the development of musculoskeletal symptoms or paraneoplastic rheumatic syndromes. Antinuclear antibodies were detected in 76 of 274 (27.7%) patients with malignancies and in nine of 140 (6.4%) healthy subjects.

Twenty patients reported paraneoplastic rheumatic symptoms or syndromes. Two of them developed clinical symptoms mimicking rheumatoid arthritis (rheumatoid-like arthropathy), one systemic lupus erythematosus (SLE-like syndrome), one dermatomyositis and four cutaneous vasculitides. Musculoskeletal symptoms and paraneoplastic rheumatic symptoms and syndromes were both more frequently observed in patients with positive antinuclear antibodies (Table 12.3).

Antinuclear antibodies were present primarily in patients with solid tumours of the breast, colon and lungs or in lymphoproliferative disorders.

The study published by Solans-Laqué et al. [5] reported positive ANAs in 19 (28.2%) of 68 patients with colorectal cancer (in titres from 1:80 to 1:320), in 17 (26.6%) of 64 patients with lung cancer and in 7 (31.8%) of 22 patients with lymphoproliferative diseases in titres from 1:80 to 1:320. Speckled fluorescence pattern was observed more often than homogeneous nuclear fluorescence. At higher titres, above 1:320–1:640, the patients exhibited more frequently rheumatic symptoms or clinical features of diffuse connective tissue diseases. However, these symptoms did not occur in all patients with higher ANA titres. A total of 65 patients had arthralgia, arthritis, myalgia and myositis at the time of diagnosis or during the follow-up period. Twenty-nine patients (44.6%) were positive for ANA. Part of these patients had metastases of the primary tumour, affecting joints, synovial membrane or juxta articular bone. On the other hand, there were 16 persons with a tumorous disease (24.6%), in which the metastatic process was excluded and purely paraneoplastic syndrome was diagnosed. Musculoskeletal symptoms developed simultaneously with the tumorous disease or preceded it. In this subgroup of patients with paraneoplastic syndrome, six patients had in the titre range of 1:80–640 the speckled and five patients the homogeneous fluorescence pattern.

Table 12.3 Antinuclear antibodies in patients with malignant diseases

Tumours	Patients	ANA-positive patients	ANA titre range
Breast cancer	39	11 (28.2%)	1 : 80–1 : 320
Colorectal adenocarcinoma	68	19 (27.9%)	1 : 80–1 : 640
Stomach adenocarcinoma	13	1 (7.7%)	1 : 80–1 : 160
Liver cancer	10	3 (30.0%)	1 : 80–1 : 320
Hypernephroma	6	2 (33.3%)	1 : 80–1 : 160
Lung cancer	64	17 (26.6%)	1 : 80–1 : 320
Lymphoma	22	7 (31.8%)	1 : 80–1 : 320
Hodgkin's sy	5	1 (20.0%)	
Non-Hodgkin sy	17	6 (35.3%)	
Pancreatic adenocarcinoma	10	2 (20.0%)	
Prostate adenocarcinoma	17	4 (23.5%)	1 : 80–1 : 320
Gynaecologic cancer	16	7 (43.5%)	1 : 80–1 : 320
Ovarian cancer	7	2 (28.6%)	
Uterus cancer	9	5 (55.5%)	
Urinary bladder cancer	9	3 (33.3%)	1 : 80–1 : 320

According to Solans-Laque et al. [5]

In terms of clinical features in the individuals with paraneoplastic symptoms, four patients developed asymmetrical polyarthritis, four had diffuse connective tissue disease and two patients developed symmetrical polyarthritis, mimicking rheumatoid arthritis (rheumatoid-like arthritis). One patient had colon cancer and the other non-Hodgkin lymphoma. The presence of rheumatoid factors was not confirmed in paraneoplastic syndromes (Table 12.4).

The relation between tumorous and rheumatic diseases is a highly complex issue. A tumorous disease may be associated with development of rheumatic syndromes, and after suppression of the tumorous disease, the clinical syndromes may resolve.

It has to be taken into account that both cytostatic and immunomodulation therapy may result in the development of an autoimmune condition associated with rheumatic manifestations [2]. A specific issue is the presence of certain autoantibodies, particularly ANA, RF and anti-smooth muscle antibodies. All these facts point out the necessity of close cooperation of rheumatologists and oncologists.

Another patient developed dermatomyositis that preceded development of haepatocarcinoma. The patient's serum contained ANA of speckled pattern (1:320), with a proved presence of anti Jo-1 antibody. Despite the treatment, the patient died as a result of the underlying disease.

Another reported disorder is paraneoplastic syndrome from the group of vasculitides. It related to clinical presentation of necrotising vasculitis with purpura together with the presence of cancer of the lungs, prostate and colon and Hodgkin's lymphoma. Resolution of vasculitis was seen in three patients after a successful chemotherapy (Table 12.5).

The presence of ANA in paraneoplastic syndromes has not been resolved, yet. It is not known whether it is an epiphenomenon or an autoimmune response to nuclear antigens resulting from cell transformation.

In this context, a large group of tumour-associated autoantibodies should be pointed out, which are directed against nuclear proteins, such as P53, c-myc, c-myb, CENP-F, DNA topoisomerase II and nucleolar protein, in patients with cancer. The clinical significance of the above-mentioned antibodies remains unclear [46, 47].

Table 12.4 Patients with paraneoplastic syndromes (musculoskeletal symptoms or manifestations of autoimmune diseases)

Tumours	Sex	Age	Symptoms	ANA titres	ANA image	Anti-ENA	anti-ds DNA	RF
	M	73	Dermatomyositis	1:320	Speckled	Anti-Jo+	Negative	Negative
Liver cancer	F	73	Polyarthritis	1:32	Speckled	Negative	Negative	Negative
Colon cancer	F	76	RA-like syndrome	1:640	Speckled	Negative	Negative	Negative
Colon cancer	M	72	Polyarthralgia	1:80	Homogeneous	Negative	Negative	Negative
Colon cancer	M	67	Polyarthralgia	1:160	Homogeneous	Negative	Negative	Negative
Colon cancer	F	75	Polyarthritis	1:160	Homogeneous	Negative	Negative	Negative
Colon cancer	M	75	Polyarthralgia	1:320	Speckled	Negative	Negative	Negative
Prostate cancer	M	82	Polyarthralgia	1:80	Homogeneous	Negative	Negative	Negative
Urinary bladder cancer	M	85	Polyarthralgia	Negative	–	–	–	Negative
Small cell lung cancer								
Small cell lung cancer	M	45	Polyarthritis	1:160	Speckled	Negative	Negative	Negative
Lung adenocarcinoma								
Lymphoma	M	44	Polyarthralgia	Negative	–	–	–	Negative
Lymphoma	F	26	SLE-like syndrome	1:320	Speckled	Negative	Negative	Negative
Pancreatic cancer			RA-like syndrome	Negative	–	–	–	Negative
Ovarian cancer			Polyarthralgia	1:320	–	–	–	Negative
Hypernephroma	M	52	Polyarthritis	Negative	Homogeneous	Negative	Negative	Negative
	F	65	Polyarthralgia	Negative	–	–	–	Negative

According to Solans-Laqué et al. [5]
ANA antinuclear antibodies, *anti-DNA* antibodies against DNA, *anti-ENA* antibodies against extractable nuclear antigens, *RF* rheumatoid factor

Table 12.5 Patients with paraneoplastic vasculitides

Tumours	Age	ANA titres	ANA image	Anti-ENA	Anti-DNA	RF
Lung adenocarcinoma	80	1:160	Speckled	Negative	Negative	Negative
Prostate adenocarcinoma	72	1:80	Speckled	Negative	Negative	Positive
Colonic adenocarcinoma	73	Negative	–	–	–	Negative
Hodgkin's lymphoma	78	1:160	Speckled	Anti-Ro+	Negative	Positive

According to Solans-Laqué et al. [5]
RF rheumatoid factor

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Osteoarthritis

13

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Osteoarthritis (OA) affects most commonly the musculoskeletal system and is often associated with pain and limited range of motion of the involved part of the body. The study presents the latest findings in the field of its aetiology, etiopathogenesis and treatment. Especially in the active phase of the disease, changes in cartilage homeostasis are similar to inflammatory processes, e.g. in rheumatoid arthritis. Numerous studies have described the role of pro-inflammatory cytokines, growth factors and nitric oxide in cartilage destruction and changes of the synovial fluid. An indispensable part of OA therapy is appropriate education of patients, adjustment of their lifestyle and the use of non-pharmacological treatment [1]. Currently a new group of non-steroidal anti-inflammatory drugs (NSAIDs) has been added to pharmacotherapy, namely, coxibs. They inhibit only cyclooxygenase 2 (COX-2) and do not affect cyclooxygenase 1 (COX-1), which is responsible for frequent adverse effects on the GIT. Certain coxibs, however, have proved to increase the risk of cardiovascular diseases and have been therefore withdrawn from the market [2, 3]. Future trends in the operative treatment will include primarily transarthroscopic methods of cartilage restoration and tissue engineering methods, transplantation of autologous chondrocytes or cartilage itself.

Osteoarthritis is the most common disorder of rheumatic diseases, which affects the musculoskeletal system and at the same time the most frequent cause of pain resulting from limited range of motion of the involved part of the body.

Due to many potential causes of its development, OA has not been defined as a nosological entity, yet, and remains to be a heterogeneous group of overlapping articular syndromes with similar biological, pathological, radiological and clinical manifestations. It consists in failure of a joint due to a metabolic disorder, mainly of the articular cartilage, causing changes in its mechanical properties. However, according to the latest opinions, OA does not develop in the cartilage but probably in the subchondral bone.

13.1 Epidemiology

During the recent decades, OA incidence has been increasing worldwide, among other things due to ageing of the population.

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Up to the age of 30, OA incidence is very low; up to the age of 65, it dramatically increases, and in the age group over 65 years, more than 70 % of population have radiologically proven arthritic changes in joints, although not always associated with subjective complaints. Up to the age of 45, OA affects more often men, while in the age group over 45 years, it prevails in women, usually with involvement of multiple joints. According to Kellgren, of all rheumatic diseases, OA of joints and spine is in the English population the most common cause of work disability. Other national databases show that OA resulting in disability occurs more often in the Southern than in the Northern Hemisphere. According to the latest reports, it affects equally men and women of all races [3].

13.2 Socioeconomic Impact

Socioeconomic impact of osteoarthritis is enormous, but it is not easy to obtain valid data about the cost of its treatment. Based on the studies conducted by Mayo Clinic in the USA, the costs of treatment in a group of patients with OA were substantially higher than in a group of patients with the same diseases, but without symptomatic OA. Recent reports from the USA point out that OA is becoming one of the "most expensive" diseases due to high costs of medicaments, rehabilitation, spa therapy, operative treatment and the number of disability pensions paid [4].

Findings in the field of OA aetiology and pathogenesis are still incomplete and inadequate. One of the reasons is the fact that the initial stage of OA often goes unnoticed for a long time, and the general health state or biomechanical or morphological changes in the respective joint are not known prior to its development. Although many important findings of initial stages of artificially induced arthritis have been obtained recently on animal models, they cannot not be always fully applied in the human medicine. The fact is that OA in humans results not only from various risk factors but also from the elementary developmental differences, ranging from the upright posture to an increasing number of stressful situations.

13.3 Pathogenesis

OA affects not only the cartilage but also all periarticular structures including the subchondral bone, synovial membrane, joint capsule, ligaments and the surrounding muscles. Independently of aetiology, the common sign of OA is irreversible damage of the cartilage with splitting of fibrils, formation of fissures and ulcers and ultimately complete loss of the cartilage [5].

Healthy cartilage homeostasis consists in a dynamic balance between its new formation and degradation. Chondrocytes as the only cell type present in articular cartilage, responsible for its metabolism, lose gradually in the course of the arthritic process the ability to maintain balance between synthesis and degradation of macromolecules of extracellular matrix.

Cytokines, mainly interleukin 1 (IL-1) and tumour necrosis factor (TNF) become active also during OA. As a result, degradation changes are combined with inflammatory processes in the synovial membrane. Interleukin 1 and TNF trigger a cascade of additional catabolic processes in the cartilage by stimulating the formation of degradation enzymes – metalloproteinases (stromelysin, collagenases, gelatinases, aggrecanases) and other enzymes, such as elastases, cathepsin G, cathepsin B and others. The formation of free radicals of oxygen and nitric oxide is also activated that further potentiates the degradation process. Involved in the degradation of collagen and core proteins of proteoglycans are primarily metalloproteinases. A certain role in degradation mechanisms is played also by anti-inflammatory cytokines – transforming growth factor beta (TGF-β) and insulin-like growth factor 1 (IGF-1) – that suppress the effect of interleukins and TNF, as well as the effect of metalloproteinases, stimulate formation of type II collagen and induce aggrecan synthesis.

Over the past two decades, significant progress has been made with respect to new concepts about the pathogenesis of osteoarthritis, particularly changes in the subchondral bone where some authors locate the origin of OA changes [6]. At the beginning, increased osteolysis can be

seen in the subchondral bone, which is associated with elevated bone resorption markers. At a later OA stage, the subchondral bone becomes sclerotic, which is manifested by increased bone density. However, this process results from increased formation of osteoid tissue rather than from increased mineralisation. An intensive interaction is assumed of metabolic processes and their acting on the subchondral bone and cartilage.

Simultaneously with the inflammatory processes in the synovial membrane, there occur also changes in the synovial fluid. Pro-inflammatory cytokines, free radicals and nitric oxide from the inflammation-induced changes in the synovial membrane diffuse into the synovial fluid. Oxygen and nitrogen free radicals decrease concentration and molecular weight of hyaluronic acid in the synovial fluid, altering substantially its viscoelastic properties, reducing its viscosity and elasticity. Some patients may develop synovialitis, when various proteinases and free radicals in larger volumes diffuse into the synovial fluid and subsequently into the articular cartilage. In clinical terms, this process is called activated OA [7]. Usually it is synovialitis that makes patients seek medical care.

The mechanism of development of OA-related pain is not uniform and depends on specific features of the disease and the stage of its development in each particular patient. The cartilage is avascular and aneural, and as such it cannot be the source of pain. Pain is caused by secondary changes of other joint tissues, such as the synovial membrane, periosteum, muscle origins and insertions and subchondral bone [8]. A relatively frequent source of pain is inflammation of the synovial membrane – synovitis, when the respective joint becomes swollen, tender and warm. Synovial membrane inflammation affects only certain parts of the membrane and is much less intensive than in rheumatoid arthritis.

The presence of inflammation is proved also by the fact that orally administered NSAIDs and intra-articular glucocorticoids have a good analgesic effect. Pain may be caused also by microfractures in the subchondral bone. Other potential causes of pain in OA are summarised in Table 13.1.

Table 13.1 Causes of OA-related pain

Synovitis
Stretching of the joint capsule
Periosteal elevation
Pain at tendon and ligament insertion sites (enthesopathy)
Muscular hypertonus
Increased intra-articular pressure
Bone microfractures

13.4 Risk Factors of OA Development

In addition to the pathobiochemical factors, the following risk factors may participate in the OA pathogenesis:

1. Genetic factors
2. Congenital and developmental defects
3. Overloading of joints during physical work or sporting activities
4. Obesity, reduction of body weight slows down the disease progression, e.g. in OA of the knee
5. Impaired joint innervation (dysfunction of protective reflex mechanisms)
6. Metabolic and endocrine diseases
7. Hypermobility

A number of studies have described a family history of Heberden's nodes inherited as a single autosomal dominant gene, with a strong female predominance. In the generalised nodal form, association has been revealed with HLA-A1 and B 8 and with α1-antitrypsin MZ phenotype. Early onset of OA was found also in familial diseases, such as chondrocalcinosis and ochronosis. The list of genetic associations with OA is quite broad, including the genes encoding molecules of extracellular matrix, collagen COL2A1 or COMP (cartilage proteoglycan), genes controlling skeletal development, such as BMP proteins (bone morphogenetic proteins; ASPN, BMP2) or Wnt signalling genes, as well as genes for inflammatory cytokines (IL-1, IL-6, IL-10 [9]). Meta-analysis of human genome-wide association studies has confirmed a susceptibility locus for knee osteoarthritis on chromosome 7q22 [10].

Factors contributing to OA development are also age-related involutionary changes of the musculoskeletal system, although the specific features of an ageing joint differ from the arthritic one in morphological, radiological as well as biochemical terms. In OA, cartilage fibrillation results in disintegration of chondrocytes and their general loss due to catabolic processes, while the ageing cartilage is characterised by loss of chondrocytes due to reduction of their replication ability [19].

13.5 Clinical Features

The main OA symptom is pain in the affected joint, occurring initially only after increased load. Tolerance to load gradually decreases. So-called start-up pain which usually works itself out after a few steps is typical of weight-bearing joints. At later OA stages, there occurs pain also during physical inactivity and at night, signalling further OA progression.

Sometimes it is impossible to move the joint through its full range of motion without any obvious cause, and sometimes the limited flexibility is caused by increasing pain. Morning stiffness, if any, subsides relatively quickly as compared to rheumatoid arthritis. A small effusion may be also present in certain cases.

Objective Symptoms of Osteoarthritis

- Crepitus – popping and cracking sounds in joints indicating an uneven articular surface
- Thickening and condensation of bone structures – joint deformation and remodelling (osteophytes)
- Restricted range of motion – advanced OA stage
- "Stretching" pain – in extreme ROM positions (periarticular structures)
- Loss of axial alignment – varus/valgus deformity (knees, hips), deformities (DIP)
- Joint instability – ligament injury
- Pain at night often resulting from increased blood supply to the subchondral bone
- Muscle atrophy – due to inactivity

13.6 Osteoarthritis Forms

13.6.1 Osteoarthritis of the Hip

OA of the hip is the most severe form of osteoarthritis [3], with pain concentrated initially in the groins, the region of greater trochanter and the buttocks. Most often the pain radiates through the anterior thigh and below the knee. Progression of the disease is potentiated by imbalance between muscle groups that stabilise the pelvic girdle, which results in flexion, adduction and external rotation of the lower extremity. Muscle weakness affects most of the hip extensors and abductors. As a rule, the first affected muscle is the gluteus medius, which is of an important diagnostic value (Trendelenburg sign).

Complaints are intermittent; in the active phase, all symptoms deteriorate, pain is more intensive and the range of motion of the joint is limited. However, the disease prognosis is not always poor, as its progression may be halted and the intensity of its symptoms may decrease (Figs. 13.1 and 13.2).

13.6.2 Osteoarthritis of the Knee

OA of the knee is the most prevalent form of arthritis [11]. In younger age groups, it affects more men, while with advancing age, its incidence is higher in women. As a rule it occurs bilaterally and is often associated with obesity. Clinical manifestations of OA of the knee depend on the prevailing locations of osteoarthritic changes in the knee joint. It involves more frequently the medial tibiofemoral compartment and results in a typical varus deformity of the knee joint. The frequency of involvement of the patellofemoral compartment is almost the same.

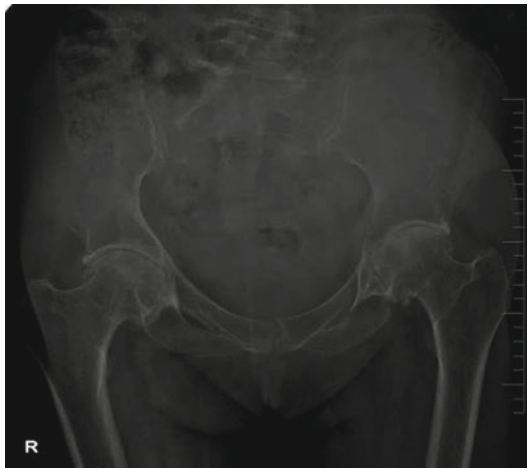


Fig. 13.1 Pelvis: OA of the hip, degree III, bilateral, with a thick concentric osteoplastic lining of the rims of articular surfaces of both femoral heads, subchondral sclerosis, geodes and central joint space narrowing in both hips, thinning of the acetabular floor with initial protrusion and bilateral varus deformity of both hips, SI joints intact

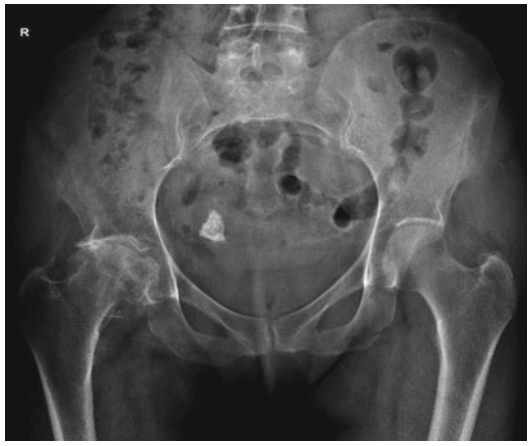


Fig. 13.2 Pelvis – right hip: deformity of the right femoral head after osteonecrosis with secondary osteoarthritic changes, shortening and varus deformity of the femoral neck, left hip intact, SI joints intact, calcified formation in the small pelvis, probably a calcified myoma

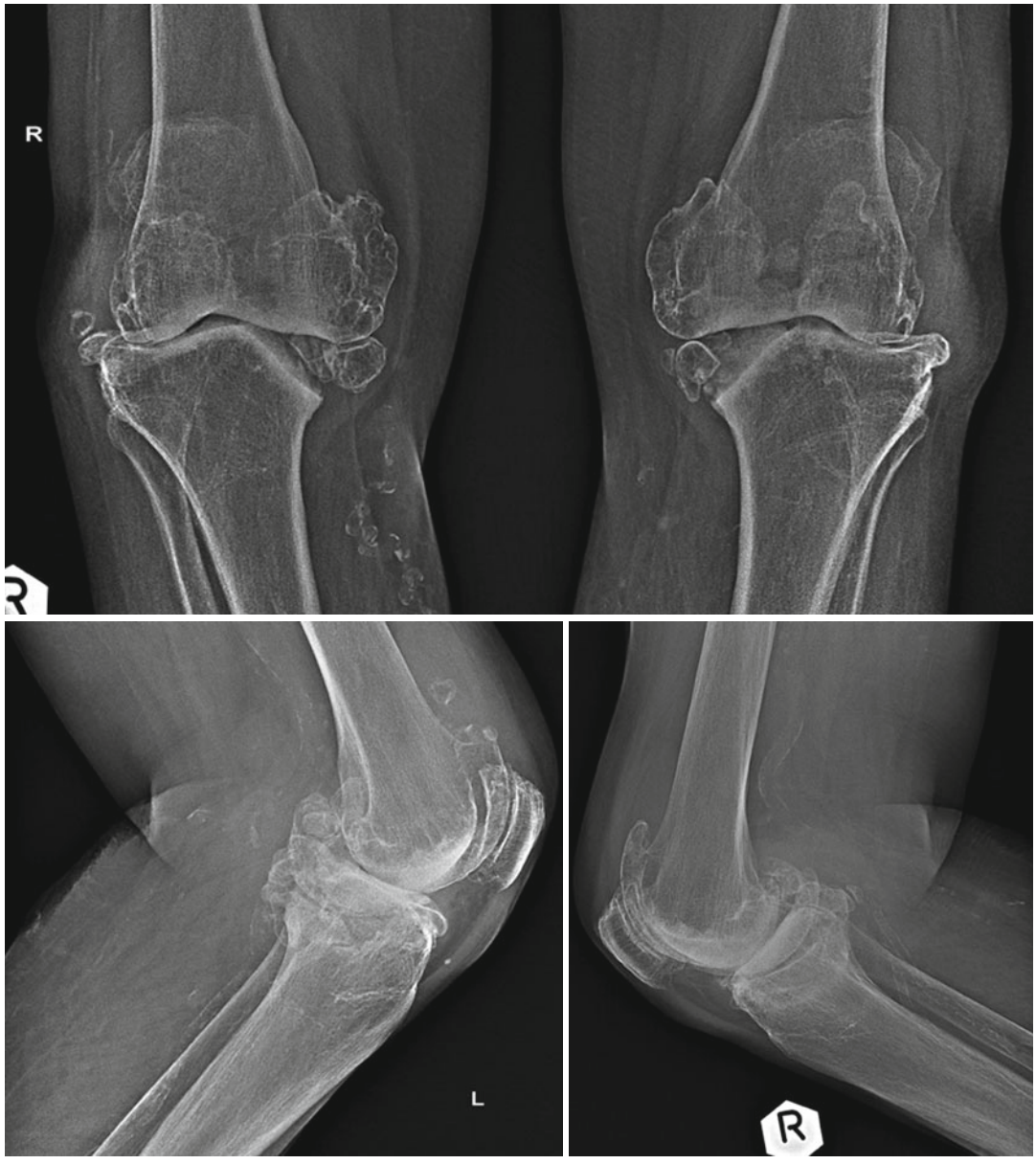
Typical pain in the knee joint gets worse during climbing up and down the stairs and walking on uneven ground. Short-term pain may be experienced with the transition from sitting to standing or with passive motion, forced hyperextension in particular. OA of the knee lasting for a longer time results in atrophy of the quadriceps, mainly the vastus medialis, and there develop painful enthesopathies of the patellar tendon and the pes anserinus. OA of the knee is often associated with the generalised OA form, and its prognosis is worth than in OA of the hip (Figs. 13.3, 13.4, 13.5, 13.6, 13.7 and 13.8).

13.6.3 Arthritis of the Joints of the Hand

The joints commonly affected by the disease are DIP joints (Heberden's nodes) or PIP joints (Bouchard's nodes), when bony nodules develop on their posterior and lateral borders of IP joints. These nodules are usually preceded by gelatinous cysts. Occasionally the pain in the joint may get worse, with swelling and reddening of the joint. Gradually there develop typical deformities, such as lateral subluxations and deviations primarily of the DIP joints. Arthritis of both the DIP and PIP joints has a good prognosis, and the function of the affected joints is not usually affected (Figs. 13.9, 13.10, 13.11 and 13.12).

Arthritis of the first carpometacarpal joint – *rhizarthrosis* – is characterised by pain and tenderness at the base of the thumb, mainly during pinching or grasping objects. Mobilisation of the thumb is associated with crepitus; at later stages there occurs thumb adduction contracture, often with hyperextension of the proximal phalanx, and the base of the thumb squared in shape. Unlike arthritis of the DIP and PIP joints, this OA type has a marked and permanent negative impact on the function of the hand. The condition may be improved by surgery.

A rare disorder of small joints of the hand (PIP and DIP joints) is *erosive osteoarthritis*. It is characterised by inflammatory manifestations, particularly painful swelling of these joints. Radiological examination shows subchondral erosions. The disease occurs in episodes and may

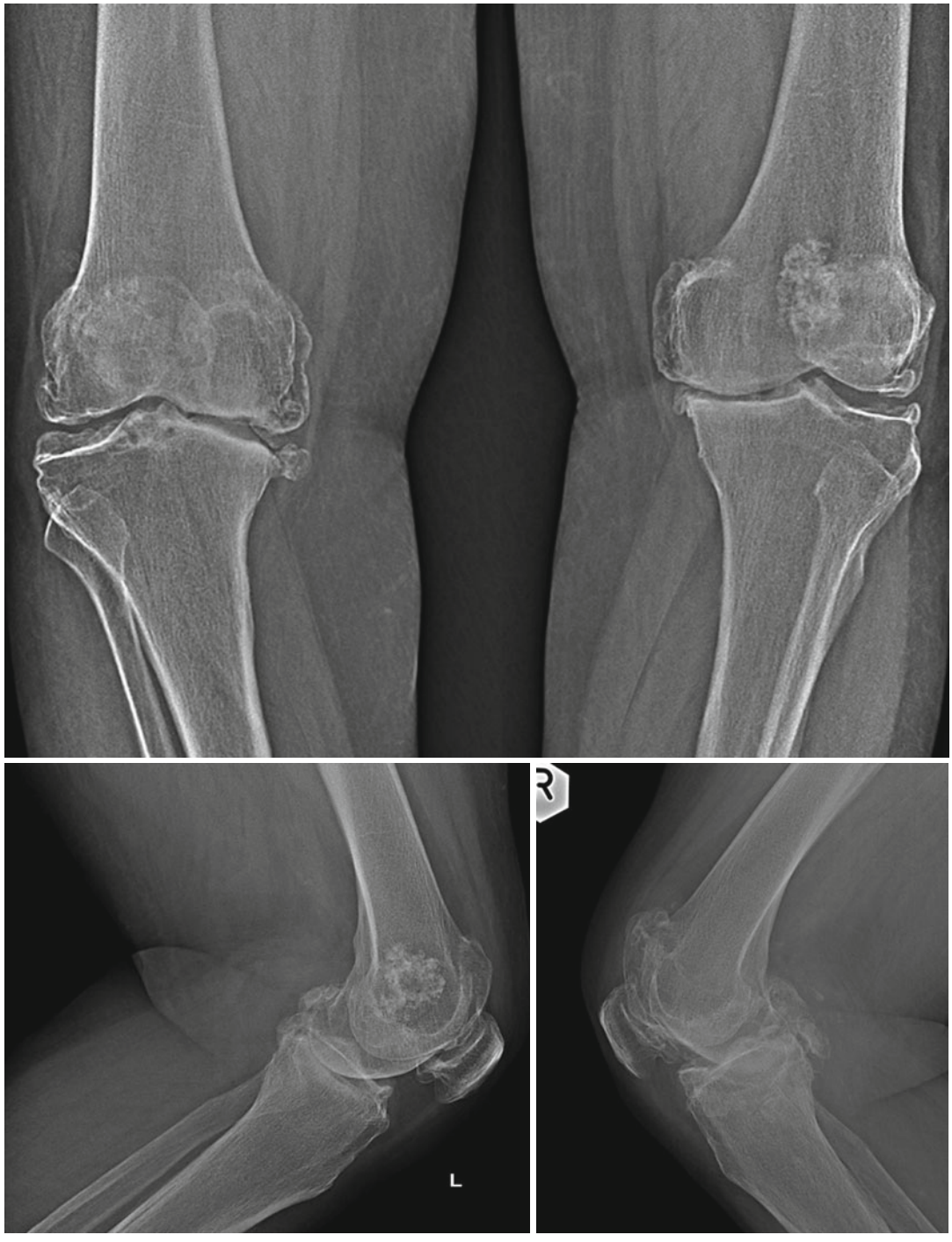


Figs. 13.3, 13.4 and 13.5 Knee joints: varus deformity in both knee joints, subchondral sclerosis and osteophytosis of the rims of articular surfaces particularly on both femurs – degree III arthritis, bilateral, necrosis of medial tibial condyle and periarticular ossification

result even in ankylosis of one or more joints [17]. Clinical examination of OA should be combined with radiological examination which reflects pathological processes in the cartilage and the subchondral bone.

Radiological Findings in Osteoarthritis

- Osteophytes – marginal bony outgrowths (remodelling)
- Joint space narrowing as a result of reduction of the cartilage height



Figs. 13.6, 13.7 and 13.8 Knee joints: degree III OA of the knee, bilateral, varus deformity, bilateral subchondral sclerosis of both tibiofemoral and patellofemoral joints with marginal osteophytes; on the right, necrosis of the medial tibial condyle and probably calcified enchondroma in distal femoral metaphysis

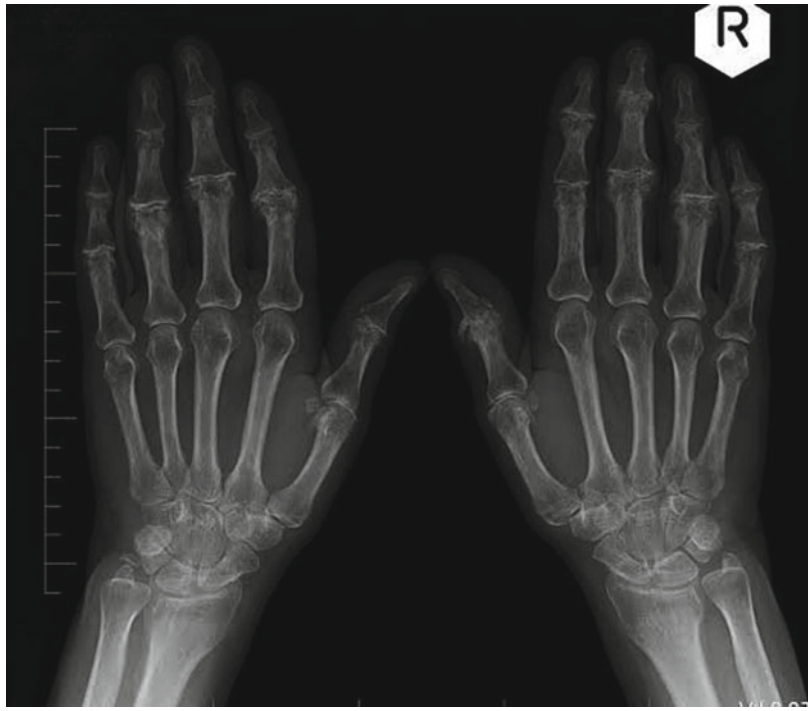


Fig. 13.9 Hands, prevalence of arthritis in the PIP joints: Degree III arthritis both in the DIP and PIP joints of both hands, with progressive marginal osteoproductive changes dominating mainly in the PIP joints bilaterally, degree I rhizarthrosis, bilateral

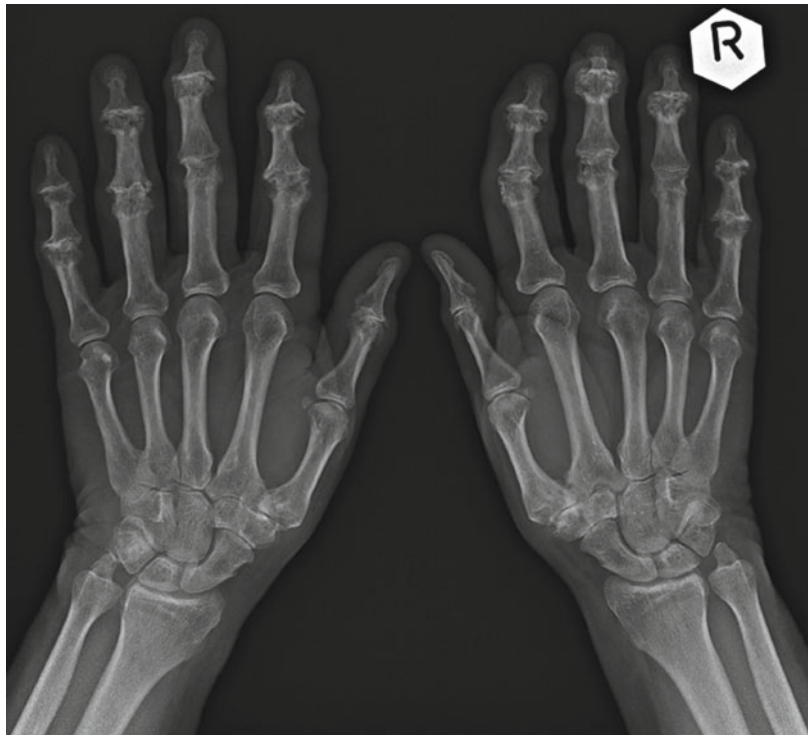


Fig. 13.10 Hands, prevalence of arthritis in the DIP joints: joint space narrowing in the PIP but mainly in the DIP joints of both hands, subchondral sclerosis, marked marginal osteoproduction, semi-flexion and initial ulnar drift – degree III arthritis bilaterally, degree II rhizarthrosis bilaterally

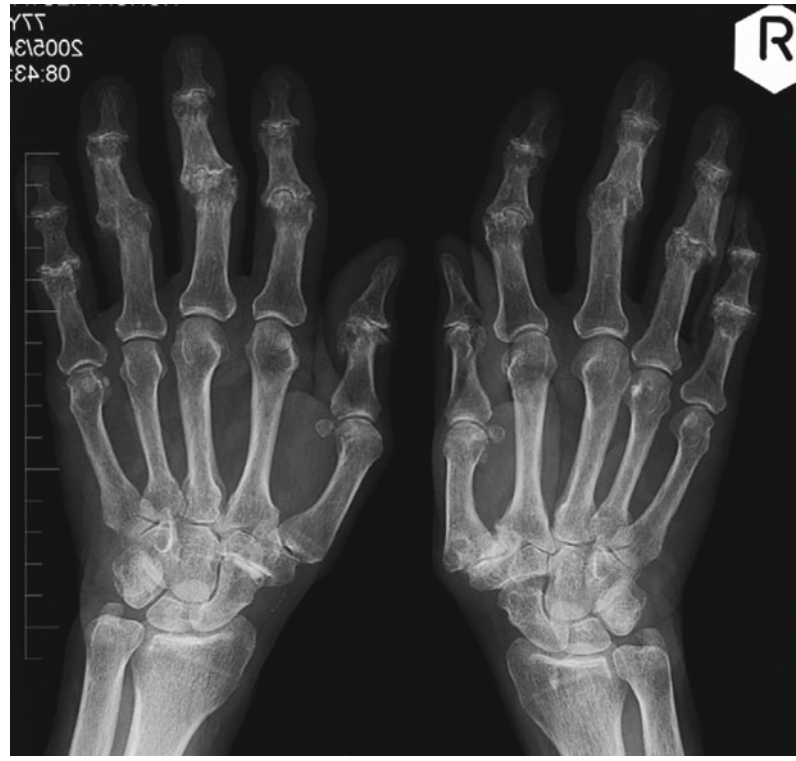


Fig. 13.11 Hands, erosive osteoarthritis: Degree III polyarthritis in the DIP and PIP joints of both hands with marked deformities, ulnar drift, in some of the PIP joints arthritis is almost of erosive nature, in PIP3 on the right and PIP4 on the left even ankylosis – degree IV arthritis, degree III rhizarthrosis on the right, degree II rhizarthrosis on the left, degree II arthritis of the trapezioscaphoideal joint bilaterally

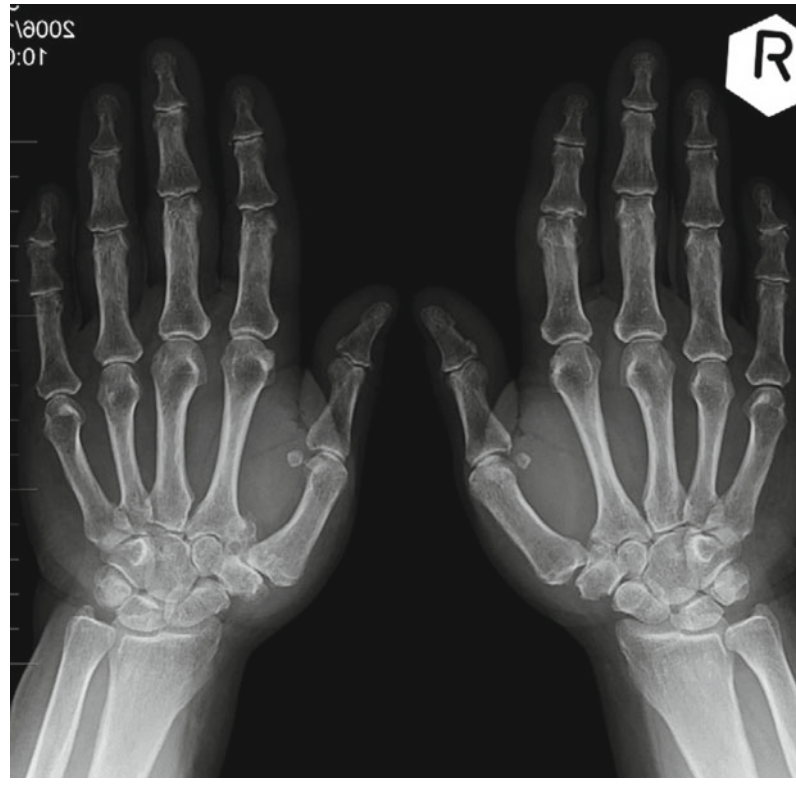


Fig. 13.12 Hands: degree II arthritis in the DIP joints bilaterally and in PIP2 on the right, degree III rhizarthrosis on the left, degree I on the right

- Subchondral bone sclerosis – manifestation of pathological processes in the subchondral bone
- Subchondral cysts proving the impaired cartilage integrity
- Remodelling of the bone surface and change of the bone shape

Relevant radiographic visualisation of the relationships in the joint depends on accuracy of the techniques used. Even the smallest deviations may distort the information about the width of the joint space and consequently about the height of the articular cartilage. It may be stated that typical OA symptoms in bones and joints already prove an advanced stage of the disease (Figs. 13.13, 13.14, 13.15, 13.16, 13.17, 13.18, 13.19, 13.20 and 13.21). In order to obtain more information about the condition of the cartilage, radiographic images may be magnified, or digital analysis may be made of the images stored in digital form.

Ultrasonography is increasingly used, which reveals even a small joint effusion and provides valuable information about the condition of periarticular structures.

Discrepancies may be found between the radiological and clinical findings as progressive radiological changes do not necessarily have a clinical response and vice versa [3].

13.7 Classifications

1. *Idiopathic OA* may involve:
   - Hands (Heberden's and Bouchard's nodes, CMC I) erosive form
   - Feet (MTP 1)
   - Hip joints
   - Knee joints
   - Spine (C and L segments)

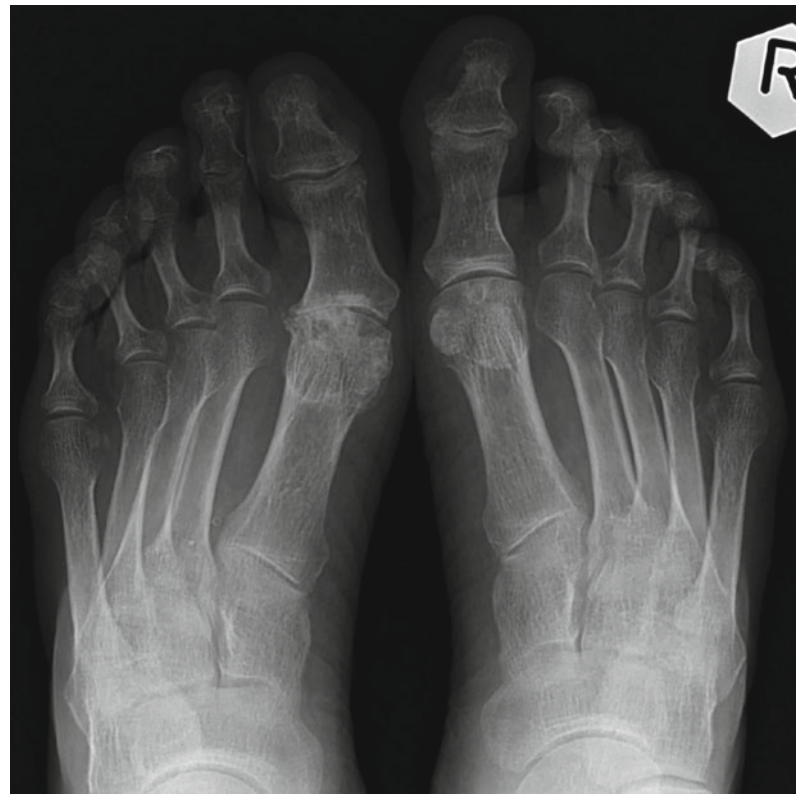
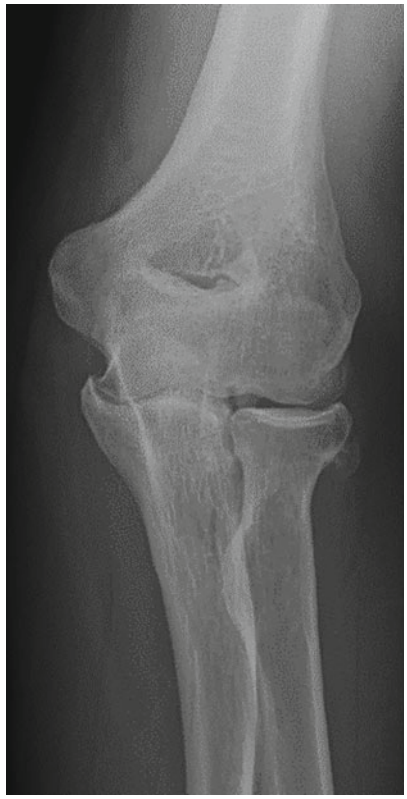
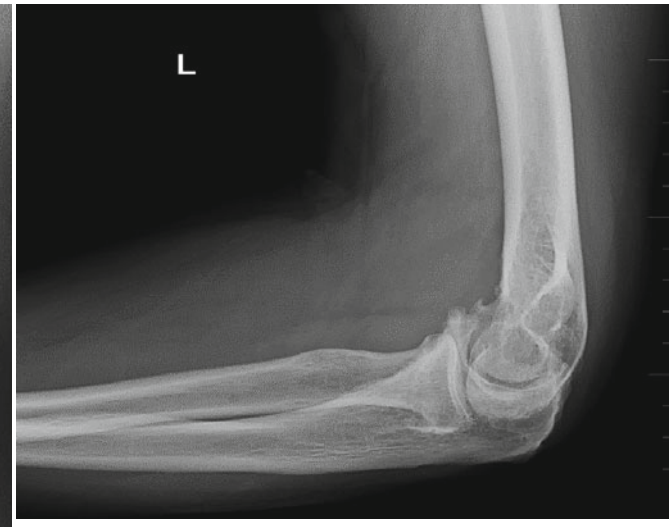
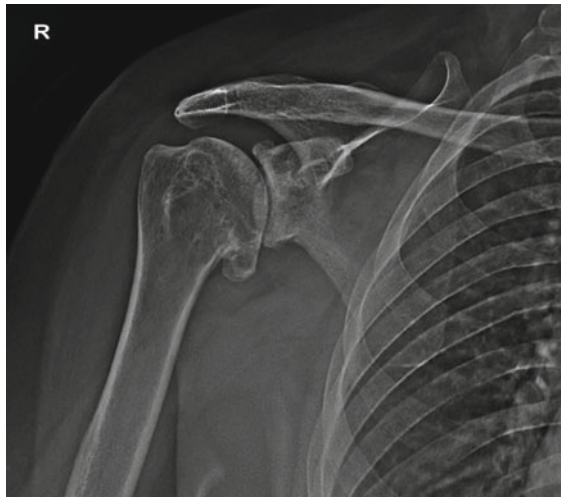


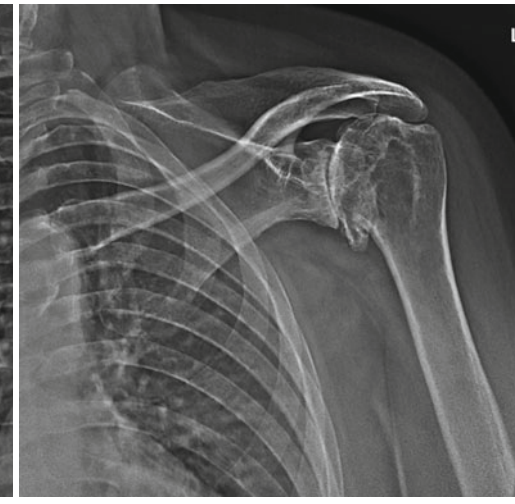
Fig. 13.13 Feet: hallux valgus, asymmetrical lateral joint space narrowing to minimum and marginal osteophytes – degree III arthritis in the MTP1 joint on the left





Figs. 13.14 and 13.15 Left elbow: degree II arthritis with joint space narrowing and marginal osteophytes mainly in the humeroulnar articulation, varietal small bones below the ulnar epicondyle of the humerus





Figs. 13.16 and 13.17 Shoulders: joint space narrowing in both glenohumeral joints – more progressive pronounced on the left, deformed humeral head and reduction of subacromial space, with a large inferior osteophyte, subchondral sclerosis and small geodes – degree II omarthritis on the right, degree III on the left

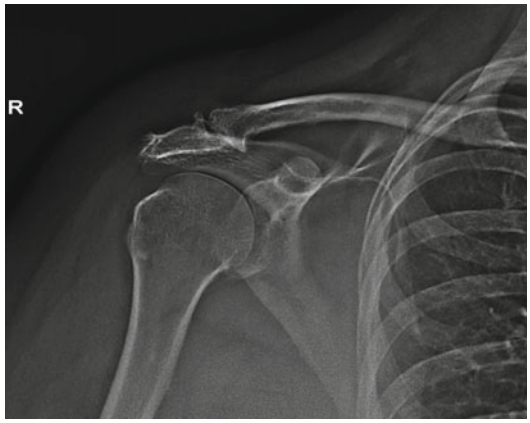


Fig. 13.18 The right acromioclavicular articulation: large osteophytes and joint line narrowing – degree II–III arthritis of AC joint on the right

Generalised OA affects at least three joints.

2. *Secondary OA* results from:
   - Trauma (fractures, mainly intra-articular, soft tissue injuries)
   - Microtraumas (overload caused by practising intense physical exercise or work)
   - Anatomical changes
   - Epiphysiolysis, developmental dysplasia of the hip
   - Hypermobile syndrome, unequal limb length
   - Metabolic diseases (Gaucher's disease, hemochromatosis and others)
   - Endocrinopathy (acromegaly, diabetes mellitus, hypothyroidism, hyperparathyroidism)

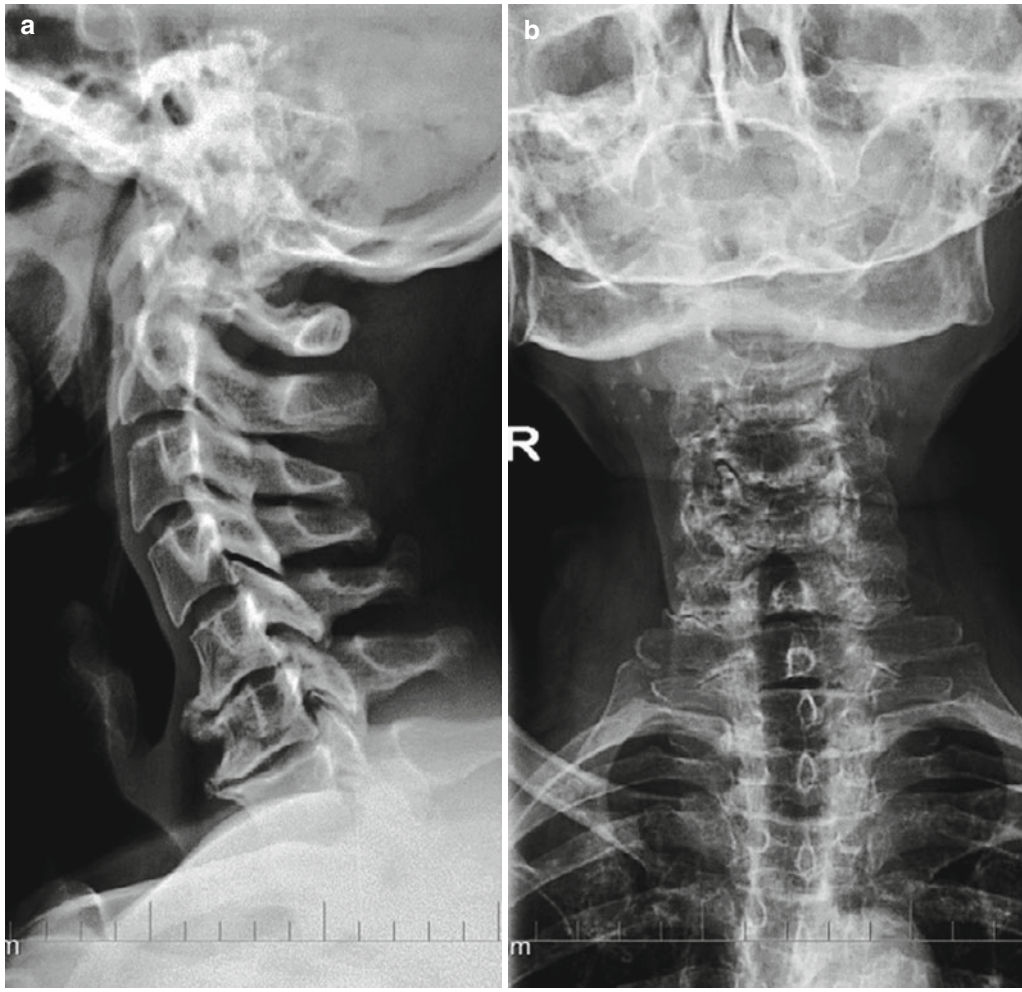


Fig. 13.19 (**a**) C spine: cervical lordotic compensation, polydiscopathy of the type of osteochondrosis of degree II to III in the entire C segment, anterior contours of vertebral bodies with a hyperostotic lining reaching the maximum on the anterior part of C4 vertebral body. (**b**) C spine: uncarthrosis of degree II to III in the entire C segment

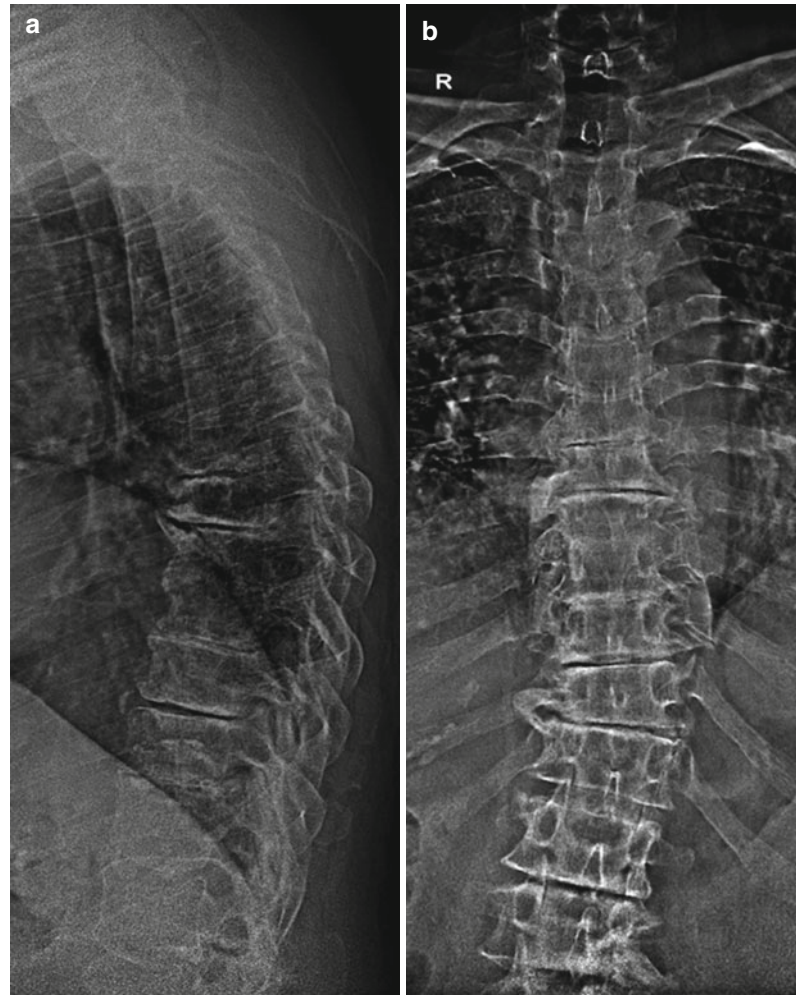


Fig. 13.20 Th spine: sinistro-convex scoliosis, degree II osteochondrosis of Th6–8, degree III osteochondrosis of Th9–12, with vacuum phenomenon and pronounced anterior and lateral spondylosis, in Th8–9 segment synostosis of vertebral bodies, reduced and wedge-shaped deformity of Th7 vertebral body at the apex of kyphotic curve. (**a**) LL view (**b**) AP view

- Crystal deposits (calcium pyrophosphate, hydroxyapatite, uric acid)
- Inflammatory diseases (rheumatoid arthritis, infectious arthritis)

Arthritis may affect all joints, with prevalence in small joints of the hand and the spine. A severe complication is involvement of weight-bearing joints, knees and hips, which restricts the patients' general mobility, permanently decreases their quality of life and quite often results in total disability.

13.8 Diagnostic Criteria

Criteria for establishment of OA diagnosis have been developed by ACR (the American College of Rheumatology; 2000; 13).

Diagnosis of Osteoarthritis of Small Joints of the Hand Is Confirmed if the Following Symptoms Are Present

1. Pain, aching or stiffness in the hands for the majority of days during the last month
2. Hard tissue enlargement involving at least two of ten selected joints
3. Swelling of two or more metacarpophalangeal (MCP) joints
4. Hard tissue enlargement of at least two distal interphalangeal (DIP) joints
5. Deformity of at least one of the ten selected joints

The ten selected joints include bilateral DIP II, III; PIP II, III; CMS I.

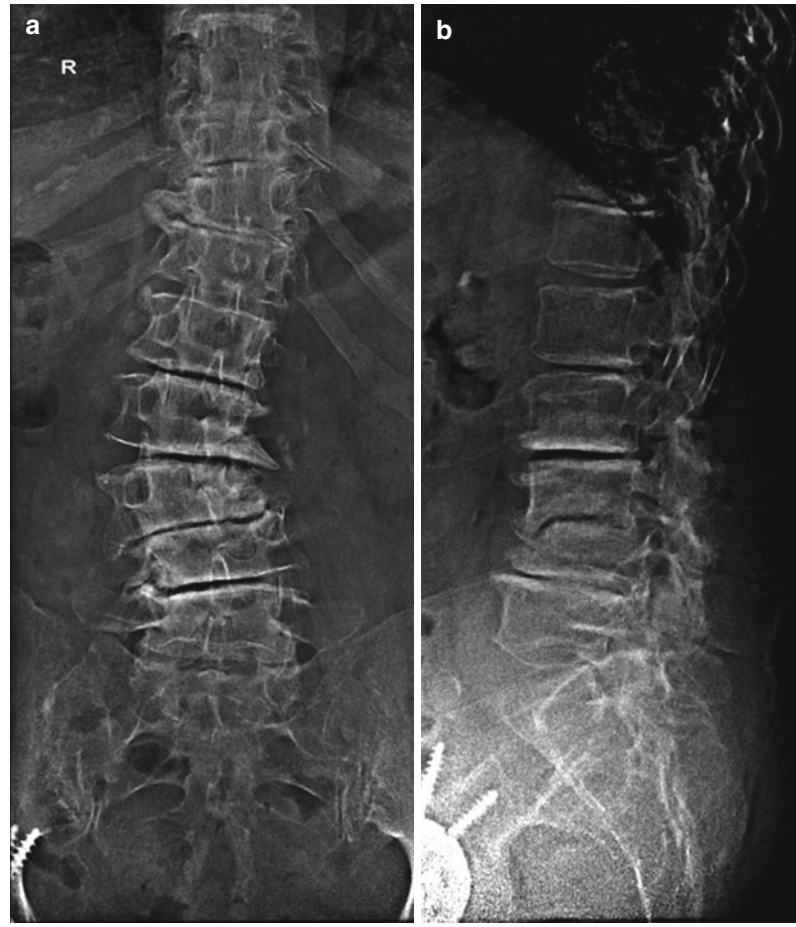


Fig. 13.21 LS spine: dextroscoliosis with a slight rotation of vertebral bodies, in L1–5 segments degree III osteochondrosis with vacuum phenomenon, subchondral sclerosis of endplates and marked spondylosis, the most prominent changes in the L3–L4 segment, L3 vertebral body causes impression of the anterior part of L4 vertebral body, degree I retrolisthesis of L5. (**a**) AP view (**b**) LL view

OA is diagnosed if the criteria 1, 2, 3 and 4 or 1, 2, 3 and 5 have been met.

Diagnosis of OA of the Hip

1. Hip pain for the majority of days during the last month
2. ESR less than 20 mm/h
3. Radiographic femoral or acetabular osteophytes
4. Axial joint space narrowing

OA of the hip is diagnosed if criteria 1 and 2 or 1, 3 and 4 have been met.

Diagnosis of OA of the Knee

1. Knee pain for the majority of days during the last month
2. Osteophytes along articular edges
3. Non-inflammatory joint effusion
4. Age over 40 years
5. Morning stiffness for less than 30 min
6. Crepitus on active motion

OA of the knee is diagnosed if criteria 1 and 2 or 1, 3, 5 and 6 or 1, 4, 5 and 6 have been met.

13.9 Therapy

The aim of all therapeutic interventions is to reduce or resolve pain, maintain the joint mobility and slow down the disease progression [13, 14]. In order to be efficient, OA treatment requires a timely diagnosis, examination of the scope of functional involvement and knowledge of the patient's activities of daily living. Patients should follow certain general

measures that will allow them to overcome more easily the OA-related complications.

General Measures in the Management of Osteoarthritis
- Weight loss (for persons who are overweight)
- Observance of principles of well-balanced diet
- Maintenance of general physical fitness
- Load-bearing exercises without overusing the affected joint
- More frequent bed rest in the active phase of the disease
- The use of appropriate assistive devices

Treatment should always begin with non-pharmacological therapy.

Therapeutic Programme Includes
- Patient education
- Physical therapy
- Physical medicine
- Appropriate footwear, braces, crutches and assistive devices
- Pharmacological treatment
- Surgical treatment

Patient Education Patients with OA should be appropriately informed about the nature and course of the disease, its treatment options and the need for their active cooperation, particularly in terms of observance of general recommendations [15].

Rehabilitation Therapy The aim of physical therapy in OA treatment is maintenance of the range of motion, muscle strength, muscle balance and improvement of the patient's general condition [16, 17]. Physical therapy is required in the spine involvement and is inevitable in the management of hip and knee OA. Imbalance of the hip and knee joints developed already at early stages of OA of weight-bearing joints results in incorrect movement patterns. Of great importance is maintenance of the strength of the quadriceps and the gluteus maximus that are often considerably weakened, but their adequate cooperation allows the patient to perform activities of daily living (rising from a chair, stair climbing). Low-impact exercises in suspension or aquatic physical therapy are highly efficient in this respect. Aerobic exercises, preferably walking, are indicated in stabilised periods of the disease. Physical therapy in the management of OA of the spine should focus on achievement of balance between the chest and back muscles and abdominal muscles.

Physical Therapy Physical therapy may help relieve pain, improve local metabolism or reduce inflammatory manifestations [18]. Thermotherapy (paraffin wax, hot wet pack) and electrothermotherapy are used during stabilised periods of the disease activity, while in its active phase, cryotherapy and electroanalgesia (TENS and medium frequency currents) are locally applied. Pain in OA of the knee is successfully managed also by acupuncture. Both reflexive and classic massage techniques may be used to manage muscle spasms and reflexive mechanisms, mainly in osteoarthritis of the spine. Spa therapy is in OA indicated as a priority together with other forms of physical therapy.

Orthopaedic (Orthotic) Devices In OA of the weight-bearing joints and the spine, it is necessary to correct abnormal position. Transverse and longitudinal flat foot should be addressed by appropriate insoles or orthopaedic footwear. Of great importance is correction of the limb length prior to the use of insoles. Varus or valgus deformity of the knee or its instability should be treated with custom-made braces. In case of more progressive OA of the knee or hip joints, the patients must use forearm walking crutches. Patients are recommended to adjust their home setup by raising chairs or toilet seat, installation of hand rails in the bathtub, etc. Radicular pain in OA of the spine may be relieved by a lumbar support belt to treat low back pain or a cervical collar to support the cervical spine.

Table 13.2 Pharmacological treatment of osteoarthritis

(a) Symptomatic drugs
1. With a short-term rapid-onset effect:
Non-steroidal anti-inflammatory drugs
Analgesics
Intra-articular glucocorticoids
Local treatment
2. With a long-term slow-onset effect of glucosamine sulphate:
Chondroitin sulphate
Hyaluronic acid
Diacerein
ASU (unsaponifiable extract from avocado and soybean oil)
(b) Structure-modifying drugs
(c) Experimental treatment

13.10 Pharmacological Treatment of Osteoarthritis

Breakdown of pharmacological OA treatment is shown in Table 13.2.

13.11 Rapid-Onset Drugs

Their rapid onset of action within a few hours terminates after discontinuation of the therapy. These drugs do not influence the course of the disease, but have analgesic and anti-inflammatory effect [3, 19].

13.11.1 Non-opioid Analgesics

This group includes primarily paracetamol, but also low doses of salicylates and metamizol. Although they do not have an anti-inflammatory effect, their advantage is a low incidence of adverse gastrointestinal effects and a low price.

According to OARSI (Osteoarthritis Research Society International) pharmacological recommendations for treatment of the knee or hip osteoarthritis, paracetamol (up to 4 g/daily) should be the first choice. In patients with a more intensive pain and synovial tissue irritation (synovitis), the first alternative medication is, as a rule, non-steroidal anti-inflammatory drugs (NSAIDs). They should be used at the lowest effective dose for the shortest duration of time. Except for one study that has not found any difference between the mechanism of action of paracetamol and ibuprofen, clinical trials have proved a higher effect of NSAIDs, primarily in patients with more marked pain manifestations. In spite of this, up to 40 % of patients consider paracetamol to be equally effective as NSAIDs. The incidence of subjective gastrointestinal adverse effects (dyspepsia, abdominal pain) is with the use of paracetamol at a higher dose than 2.5 g/daily, comparable to NSAIDs. But more importantly, endoscopic studies have not proved a higher incidence of ulcers and their complications associated with the paracetamol treatment. In addition, paracetamol has a beneficial cost-risk-effect ratio. Patients with a good response to paracetamol should not be converted to NSAIDs.

13.11.2 Non-steroidal Anti-inflammatory Drugs

NSAIDs have analgesic, anti-inflammatory and antipyretic effects. In the presence of OA, they are indicated in case of inadequate efficiency of non-pharmacological treatment or administration of analgesics. They have various chemical structures, similar pharmacodynamics and pharmacokinetic properties and a similar mechanism of action and therapeutic effect [19–22].

NSAIDs Classification Non-steroidal anti-inflammatory drugs are divided according to the chemical structure, plasma elimination half-life and cyclooxygenase 1 (COX-1) to cyclooxygenase 2 (COX-2) inhibition ratio.

In terms of chemical structure, they are derivatives of organic (carboxylic) acids. The only exception is nabumetone which is of non-acidic nature.

According to the plasma elimination half-life, they are classified as:

- NSAIDs with a short plasma elimination half-life, up to 6 h: diclofenac, ibuprofen, ketoprofen, flurbiprofen
- NSAIDs with a long biological half-life, more than 12 h: naproxen, piroxicam, meloxicam, celecoxib, etoricoxib

In terms of COX-1 to COX-2 inhibition ratio, they are:

- Non-selective NSAIDs that inhibit both COX-1 and COX-2 – all the NSAIDs used
- Selective COX-2 inhibitors: celecoxib and etoricoxib

NSAIDs have comparable efficacy but different adverse effects. According to a meta-analysis, up to 84 % of comparative studies found no significant differences in the effect between individual NSAIDs, but 41 % of studies proved differences in adverse effects.

Mechanism of Action of NSAIDs The main mechanism of action of NSAIDs is inhibition of cyclooxygenase enzyme (COX [21]), blocking production of prostaglandins. Cyclooxygenase occurs in two isoforms – COX-1 and COX-2. COX-1 is constitutive and is responsible for synthesis of prostaglandins that ensure physiological functions of thrombocytes, gastrointestinal system and kidneys. COX-2 is inducible and is found at the site of inflammation and in the damaged tissues and serves as a mediator of synthesis of pro-inflammatory prostaglandins. COX-2 inhibition decreases production of prostaglandins (PGs) that participate in pathogenesis of inflammation and generation of pain impulses. However, it has also certain physiological functions in kidneys, central nervous system and female urogenital system. COX-2 inhibition decreases prostaglandin I2 production in the vascular endothelium, which increases the risk of thrombosis. However, the NSAID effect is complex, and in addition to COX inhibition, they have also other mechanisms of action (Table 13.3).

Table 13.3 Mechanism of action of NSAIDs

Inhibition of prostaglandin synthesis (COX inhibition)
Inhibition of synthesis of cytokines, leukotrienes
Membrane enzyme blocking (leukocyte NADPH-oxidase, C-macrophage phospholipase)
Blocking of oxidative phosphorylation in mitochondria
Inhibition of release of lysosomal enzymes
Blocking of superoxide radicals
Inhibition of polymorphonuclear activity
Inhibition of inducible nitric oxide synthesis

Table 13.4 Adverse effects of non-steroidal anti-inflammatory drugs

Gastrointestinal	Dyspepsia Gastro-oesophageal reflux Peptic ulcer GIT – perforation and bleeding Small intestine bleeding
Hepatic	Cholestasis Hepatocellular toxicity Raised transaminase concentration
Renal	Temporary increase in creatinine Hypernatraemia Acute renal failure Interstitial necrosis Hyperkalaemia Analgesic nephropathy
Hematologic	Thrombocytopenia Neutropenia Bone marrow aplasia Haemolytic anaemia
Skin	Photosensitivity Erythema multiforme Toxic epidermal necrolysis
Respiratory	Bronchospasm Pneumonitis
Central nervous system	Headache Vertigo Personality change Aseptic meningitis
Cardiovascular	Thrombotic events Myocardial infarction

Development of adverse effects is associated mainly with COX-1 inhibition (Table 13.4). NSAIDs exert their analgesic effect through peripheral inhibition of prostaglandin synthesis decreasing irritation of nociceptors and spinal synaptic endings. Anti-oedematous effect

decreases push-pull irritation of mechanoreceptors. NSAIDs are not suitable for management of neuropathic pain. The analgesic effect of NSAIDs starts several minutes to hours after administration of the drug, while the anti-inflammatory effect starts after 7–14 days of regular use.

Certain NSAIDs, indomethacin and acetylsalicylic acid in particular, have a catabolic effect on cartilage metabolism.

Gastrointestinal Adverse Effects of NSAIDs NSAIDs are reported to cause dyspepsia in 30–50 % of patients, upper gastrointestinal ulceration in 20 % and ulcer complications (bleeding and perforation) in 1 % of patients. The risk factors of NSAID gastropathy are shown in Table 13.5, and this risk increases with increasing age. Of all NSAIDs, the highest risk of ulceration and its complications (bleeding, perforation) – up to 4.4 times higher – is associated with non-selective COX-1 and COX-2 inhibitors.

This fact is an impetus for identification of possibilities to reduce adverse effects of NSAIDs on GIT:

- Combination of NSAIDs with PGE2 analogue – misoprostol, combination of NSAIDs with proton pump inhibitors – decreases the risk of recurrent peptic ulcers, but does not prevent lesions in the distal parts of the digestive system.
- Enterosolvent preparations may also cause mucosal lesions in the small intestine
- Medications in the form of injections and suppositories: although these medication forms do not directly affect the mucosa of the stomach or duodenum, they cannot prevent systemic adverse effects induced by COX-1 inhibition.
- Nitro derivatives: nitric oxide (NO) bound to a molecule of effective agent (nitroflurbiprofen, nitrofenac) via esteric bond decreases gastrointestinal adverse effects of the original drug. Nitro derivatives, however, tend to decrease also blood pressure.
- NSAIDs bound to cyclodextrin. Standard NSAIDs have a crystal structure, but binding of one NSAID molecule to one β-cyclodextrin molecule will markedly accelerate absorption and onset of the effect of the drug and decrease drug-mucosa contact time. This will reduce the incidence of stomach lesions and increase the patient's tolerance after oral administration. Currently piroxicam – β-cyclodextrin (Flamexin) – is used. This technology was developed by Cram, Pedersen and Lehn for which they were awarded the Nobel Prize.

Table 13.5 Risk factors of adverse effects of NSAIDs on GIT

Combination of several NSAIDs
High doses and long-term use of NSAIDs
Age >60 years
Personal history of gastropathy
Decreased renal functions (hypertension, swelling)
Combination with glucocorticoids, anticoagulants, antiaggregants
Female gender
Hyperalbuminaemia
Helicobacter pylori infection
Alcohol, smoking coffee

Certain non-selective NSAIDs are provably associated with a lower incidence of adverse effects on GIT. In the phase of decompensated OA, meloxicam is administered at the dose of 7.5–15 mg daily and nimesulide at the dose of 2 × 100 mg.

Selective COX-2 Inhibitors In vivo, they specifically inhibit COX-2 and do not influence COX-1, and therefore the incidence of their GI adverse effects is significantly lower, while their analgesic and antiphlogistic effect is comparable with non-selective NSAIDs [2, 23]. These results were provided already by initial studies of both celecoxib and rofecoxib. The VIGOR study revealed in patients using rofecoxib a significantly higher incidence of cardiovascular events. Increased risk of cardiovascular events was confirmed also by other studies, and in 2004 the pharmaceutical company MSD voluntarily withdrew rofecoxib from the world market. Increased

risk of cardiovascular complications was reported also in relation to celecoxib; therefore, it is not recommended for use by patients with ischemic heart disease, cerebrovascular damage and peripheral vascular disease.

Currently second-generation selective COX-2 inhibitors of celecoxib and etoricoxib are available. Also these specific COX-2 inhibitors have been proved to be associated with a significantly lower incidence of gastroduodenal ulcers. In OA and RA, celecoxib is administered at the dose of 200 mg once daily, etoricoxib at the dose of 30, 60 or 90 mg once daily. Specific COX-2 inhibitors have certain indication and prescription restrictions.

They are indicated in patients with OA and rheumatoid arthritis, using glucocorticoids, anticoagulants and with a history of ulcer verified by gastrofibroscopy, in the last 5 years. Their disadvantage is a relatively high price, but taking into account treatment of GI complications in patients at risk and elderly persons, their use is economically beneficial.

13.11.3 Opioid Analgesics

Weak opioids – dihydrocodeine, oxycodone, propoxyphene and tramadol – are used to treat painful OA exacerbation [24]. They are suitable for short-term treatment of acute painful conditions, to relieve moderate pain and in case of NSAID contraindication.

Tramadol is a centrally acting analgesic, with a dual mechanism of action; it binds to the opioid receptor in the central nervous system and mildly inhibits also biogenic amine reuptake. Tramadol is rapidly and almost completely absorbed, with onset of analgesia within 1 h following oral administration. It is suitable for treatment of chronic non-cancer pain. The recommended dose is 100–200 mg daily. Its mechanism of action is comparable to that of diclofenac. It can be used as a monotherapy or in combination with paracetamol or NSAIDs. Dihydrocodeine is used at the dose of 60–120 mg daily.

13.11.4 Local Transdermal Treatment

Local transdermal treatment is based on the use of salicylates, capsaicin and NSAIDs [25]. Salicylates permeate poorly through the skin, and therefore their effect is low. Capsaicin found in chillies has a broader range of application. It irritates nerve endings and thus induces depletion of nociceptive pain transmitters. NSAIDs may be used in the topical treatment also in the form of creams, ointments, gels and sprays. This therapy is beneficial particularly at the early OA stages to treat local pain of muscles, tendons and ligaments where the concentration of the active substance is more effective than systemic therapy. Elimination of GIT and hepatic involvement makes transdermal treatment suitable for treatment of pain in arthritis, particularly in elderly patients.

13.11.5 Intra-articular Treatment with Glucocorticoids

Intra-articular application of glucocorticoids suppresses secondary synovitis in the phase of activated arthritis [21, 26]. Intra-articular treatment should not be applied too often in joints without symptoms of inflammation. Glucocorticoids may be used no more than four to five times a year, in the same joint. The most frequent medications include triamcinolone acetonide (Kenalog) or betamethasone + dipropionate (Diprophos) and methylprednisolone. This treatment usually has a short-term effect, reported as a rule between 2 and 4 weeks.

13.12 Symptomatic Slow-Acting Drugs

Symptomatic slow-acting drugs for OA (SYSADOA) are also referred to as *disease-modifying OA drugs* (DMOADs) or more lately, *structure-modifying OA drugs [*21, 27]. Their chondroprotective effect has been proved by multiple experimental studies and recently also by

long-term human clinical trials. However, the structure-modifying effect of these drugs has not been generally accepted and will require additional long-term studies, more precise detection methods and biochemical markers to characterise structural changes in the cartilage and the surrounding structures. SYSADOA are slow-acting drugs, but the effect lasts for up to 2 months after their withdrawal. As compared to NSAIDs, their action is more physiological. SYSADOA positively influence metabolism of chondrocytes of the articular cartilage and inhibit degradation processes induced by pro-inflammatory cytokines, oxygen and nitrogen radicals, metalloproteinases, lysosomal proteases and glycosidases. Hydroxychloroquine is sometimes used to treat erosive arthritis primarily of the hands, if associated with inflammation. It is not however commonly used to treat osteoarthritis.

13.12.1 Glucosamine Sulphate

Glucosamine sulphate (GS) is a basic substrate for glycosaminoglycan synthesis. It consists of two molecules of aminoglucose and the sulphate group. Up to 80 % of the substance is absorbed from the small intestine, with the peak plasma concentration 1 h after administration. In vitro, it stimulates proteoglycan production and decreases activity of matrix metalloproteinases (MMPs), phospholipase, aggrecanase and lysosomal enzymes. Glucosamine is available in the form of glucosamine sulphate and glucosamine hydrochloride. Most clinical trials focused on glucosamine sulphate. A meta-analysis including 20 randomised double-blind placebo-controlled studies demonstrated a more significant pain reduction and improvement of function as compared with placebo, in patients with OA [28]. Two studies lasting for 3 years confirmed slowing down of radiographic progression of OA in the treatment by glucosamine sulphate, which indicates that this substance has a structure-modifying effect [29, 30]. It is not recommended in patients with glucose intolerance and diabetes. The effective dosage is 1500 mg daily, divided into 2–3 doses. Treatment takes as a rule 2–3 months and is repeated three times a year. Occasionally, patients may develop gastrointestinal problems or skin reactions.

13.12.2 Chondroitin Sulphate

Chondroitin sulphate (CS) is a macromolecular substance which is a physiological part of the major proteoglycan of the hyaline cartilage, aggrecan. Chondroitin sulphate is a sulphated glycosaminoglycan. As a part of aggrecan, it binds with water, increases osmotic pressure of the extracellular matrix of the cartilage, enhances the flexibility and controls the tension of the collagen fibre network. It has a favourable effect on chondrocyte metabolism, stimulates synthesis of collagen type II and proteoglycans and at the same time inhibits the activity of degradation enzymes and release of lysosomal enzymes [31]. It has an anti-inflammatory effect and inhibits chemotaxis, migration of leukocytes and phagocytosis. The bioavailability after oral application is about 12 %.

In a double-blind placebo-controlled study of knee and hip OA, chondroitin sulphate reduced pain at rest, stiffness and algofunctional index. The effect lasted for 2 months after its withdrawal [32, 33]. Two recent long-term (3-year) randomised double-blind placebo-controlled studies demonstrated a certain reduction in the rate of joint space narrowing with application of 1500 mg crystalline glucosamine sulphate in knee OA, as compared to placebo. Chondroitin sulphate is administered continuously at the dose of 800 mg daily. No severe adverse effects were observed.

13.12.3 Diacerein

Diacerein is an acetylated form of rhein, the rhubarb extract. Its primary mechanism of action is inhibition of synthesis of interleukin-1 and TNF-alpha. At the same time, it retards cell chemotaxis, leukocyte phagocytosis and oxygen radical production. Its long-term use stimulates production of macromolecular cartilage components:

collagen, glycosaminoglycans and proteoglycans [35]. Its efficacy in knee and hip OA has been proved by several clinical trials, particularly for its marked analgesic effect. A meta-analysis of 19 randomised clinical trials has shown superiority of diacerein over placebo in the pain management and improvement of joint function in the knee or hip osteoarthritis [36]. As compared to NSAIDs, the analgesic effect of diacerein is slightly delayed, but from the first month until the end of the therapy, it is the same as that of NSAIDs [37]. Morphological studies demonstrated marked slowdown of the radiographic progression of OA.

The daily dosage of 100 mg is administered in two doses, after meals, for at least 6 months. At the beginning of the treatment, intake of diacerein frequently leads to diarrhoea.

13.12.4 Avocado Soybean Unsaponifiables

A combination of unsaponifiable soybean oil (200 mg) and avocado (100 mg), so-called ASU, is registered under the name Piascledine 300 as a medication for OA treatment. ASU suppress IL-1, TNF-alpha, COX-2, iNOS gene expression and prostaglandin E2 and nitric oxide production in articular chondrocytes and monocyte/macrophages [38]. Avocado/soya unsaponifiables enhance the expression and synthesis of transforming growth factor beta 1 and beta 2 (TGF-β1 and TGF-β2) that may account for the beneficial effects on cartilage metabolism [39]. Clinical trials demonstrated their positive effect on symptoms of osteoarthritis [40]. A meta-analysis of randomised controlled studies of ASU, which included 664 patients, showed a significant decrease in Lequesne's index and VAS [41]. The therapeutic effect was evident after 3 months and was more marked in knee OA. ASU also reduced the rate of joint space narrowing in hip OA [42]. It is used once a day with meals and is usually well tolerated. Occasionally there may occur regurgitation of gastric contents with a taste of fat in the mouth, skin allergy or a slight elevation of liver enzymes.

13.12.5 Hyaluronic Acid

Hyaluronic acid (HA) in the form of hyaluronate salts is part of connective tissues, e.g. skin, vitreous body and cartilage, but most hyaluronans are found in the synovial fluid – 0.5–4 mg/ml. HA high concentration and high molecular weight in the synovial fluid is the basic precondition of viscoelastic properties of the synovial fluid and proper function of joints. In the course of OA, the HA molecular weight decreases as a result of impaired metabolism of synovial fibroblasts, free radical-induced depolymerisation and intracellular hyaluronidase and other glucosidases in synoviocytes and leukocytes of the synovial membrane [43, 44]. Several HA forms for intra-articular application are available for commercial distribution, which differ by molecular weight, origin (animal and bacterial) or chemical modification. In terms of molecular weight, HAs are divided into low molecular ($0.5–0.7 \cdot 10^6$ Da), intermediate molecular ($0.8–1.5 \cdot 10^6$ Da) and high molecular ($>1.5 \cdot 10^6$ Da [45]) ones. The aim of chemical modification is to increase molecular weight, improve rheological properties and extend the biological half-life in the joint. Chemically modified hyaluronans – hylans (Hylan GF-20, Synvisc) – have the molecular weight of up to $6 \cdot 10^6$ Da [46]. As the pharmacological effect has been documented only for the low-molecular-weight sodium hyaluronate, the European Medicines Agency has recommended to register it as a medication, while its high-molecular-weight version should be used as supplementary preparations [44]. The hyaluronic acid is metabolised in the joint cavity within 3–5 days after intra-articular application, but its favourable effects last for several weeks. Due to this fact, the viscosupplementation concept does not quite explain the HA clinical effect. Hyaluronans bind to specific cell-surface receptors, including CD44, intracellular adhesion molecules (ICAM-1) and hyaluronan-mediated motility receptor (RHAMM), which are expressed in various cells, including those participating in the pathological process during OA [43, 45]. Through these receptors, hyaluronans may get involved into various biological

processes. A significant property of intra-articular HA is its ability to induce synthesis of endogenous HA in synoviocytes and chondrocytes. In addition, HA has anti-inflammatory effects: inhibition of IL-1, prostaglandin E2 (PGE2) and bradykinin, inhibition of chemotaxis and phagocytosis of granulocytes and monocytes and decrease of metalloproteinases activity.

In terms of clinical effect, the optimal value of HA molecular weight is not known, yet. Randomised studies [46], as well as a meta-analysis published by Reichenbach et al. [47], have concluded that there are no significant differences between individual preparations. In patients treated with hylan, a higher incidence of adverse effects was recorded. HA intra-articular application was shown to improve subjective complaints (pain relief), and arthroscopic evaluation of the effect of hyaluronan proved its favourable effect on structural changes in the cartilage [48].

HA administration is indicated in knee OA of degrees I–III in case of intensive pain and insufficient effect or intolerance of NSAIDs.

Intra-articular injections of hyaluronans are applied three times with 1-week intervals. The therapeutic cycle may be repeated twice a year. Intra-articular injections of high-molecular hylan (Synvisc) are applied in three doses with 1-week intervals. Adverse effects are neither frequent nor severe; local reaction, pain or transient synovitis at the puncture site is reported in 10–20 % of patients. Adverse effects are minimised by proper technical application and observance of hygienic principles. When using hyaluronans isolated from rooster comb, special attention must be paid to patients with allergy to egg protein.

13.13 Experimental Therapy

13.13.1 Orthokine Therapy

Orthokine therapy in OA treatment was developed by Peter Wehling, a spinal surgeon, and Julio Reinecke, a molecular biologist, from the Department of Orthopaedics of the Heinrich-Heine University in Düsseldorf, Germany. They have based their concept on the role of generation of the cytokine IL-1 that significantly conduces to inflammation and degradation of the cartilage, in OA patients. The effect of IL-1 may be slowed down or reversed by the receptor antagonist (IL-1Ra). IL-1Ra neutralises the effect of IL-1 and has anti-inflammatory, analgesic and chondroprotective effect. In the orthokine method, various anti-inflammatory and growth factors such as IL-1Ra are obtained from the patient's own blood. The blood is taken from the patient's arm and collected into special syringes containing medical-grade glass beads that serve as activation substance. The whole-blood syringes are incubated at 37 °C to allow synthesis of anti-inflammatory proteins such as IL-1Ra, growth factors and others. Then it is centrifuged and the obtained serum is ready for use and may be injected back to the affected joint. One therapeutic cycle consists of six injections applied to the joint once a week. A clinical trial of patients with knee OA proved efficacy of this therapy. In a randomised, multicentric, double-blind, placebo-controlled study, Yang et al. [50] found a provable improvement in patients undergoing the orthokine therapy as compared to placebo, with a decreased WOMAC score and other assessment parameters of joint pain and function. Currently, this method is used in orthopaedics to treat knee OA and damaged cartilage, inflammation of tendons, injuries to muscles and tendons and lately also in neurology to address chronic irritation of a nerve by a damaged disc, or its prolapse, or to treat small joints of the spine. In Slovakia this therapy was first introduced in the National Institute of Rheumatic Diseases in Piešťany and in the Railway Hospital and Health Centre in Košice. Currently it is applied in more healthcare facilities. Its advantage is that it is provided in the form of outpatient treatment.

13.13.2 Therapy Focused on the Subchondral Bone

The research of OA pathophysiology has brought interesting findings related to the subchondral bone.

Changes in the subchondral bone structure can be seen already in the early phase of OA [51], when resorption is usually associated with increased osteoresorption markers. Sclerosis of the subchondral bone develops later, at advanced stage of OA as a result of increased volume of bone tissue, rather than of increased mineralisation. There is an ample evidence of interaction between the subchondral bone and cartilage. Various molecules/factors spread from the subchondral bone into the cartilage, most probably through small channels and fissures in the tidemark, that can be observed in the early OA phase. The findings related to changes in the subchondral bone and interaction of the subchondral bone and cartilage have offered new possibilities in the OA treatment.

Phase II and phase III clinical studies of medications used in OA treatment are currently in process. These medications include bisphosphonates, strontium ranelate, calcitonin, cathepsin K inhibitor, vitamin D and others. Experimental studies on animals have shown that, for instance, calcitonin has both a preventive and therapeutic effects in OA. The results of a small study of patients with knee OA have shown that calcitonin decreases the Lequesne's index and joint metabolism markers. Cathepsin K inhibitors are also promising in this respect as they may influence remodelling of both the subchondral bone and cartilage [53]. The effects of bisphosphonates are not quite clear. Currently, several clinical trials are being conducted, focused on antiresorption and bone formation medications in OA treatment, that may expand the range of medications for this disease.

13.13.3 Vitamins, Minerals and Nutritional Supplements

OA affects mainly the elderly population. Therefore, most dietary supplements for OA prevention and treatment contain in addition to glucosamine, chondroitin sulphuric acid or both, also vitamins, minerals and other dietary supplements [54]. As concerns vitamins, positive effects on the OA symptoms have been proved at high doses of vitamin C [55]; application of vitamin E and beta carotene has shown no particular effect. Application of vitamin B^{12} and the folic acid (folate) decreased hand pain and stiffness in patients with OA. A higher incidence of OA was recorded in patients with lack of vitamin K, typical of the elderly, which should be supplemented. There is also a certain association between a higher incidence of OA and boron deficiency; therefore, boron is part of some dietary supplements. Selenium is used as antioxidant. Manganese is significantly involved in the metabolism of collagen and glycosaminoglycans and similarly as selenium it is contained in the dietary supplements used in OA treatment.

Of the natural plant substances, the extract from the raisin of the *Boswellia serrata* tree is often used, which can be found mainly in India where the extract has been used for centuries in the Ayurvedic medicine. It contains a large amount of boswellic acid which has anti-inflammatory and antioxidative effects and reduces OA symptoms [56]. A product that has been invented in Scandinavia is an extract from the sub-species of *Rosa canina*, which contains the active substance galactolipid, known as GOPO.

This substance has a marked anti-inflammatory effect. It inhibits chemotaxis of leukocytes and reduces their oxidation reactions. In patients with OA, it relieves pain and stiffness and increases mobility [57].

Animal products include a small amount of native type I and II collagen. Native, undenatured collagens have anti-inflammatory and immunomodulating effects [58, 59]. In patients with OA, they provably reduce pain, stiffness and increase the joint mobility. Gelatine is a source of important amino acids, such as glycine and proline, needed for collagen synthesis and regeneration of the cartilage. It is often combined with glucosamine and the chondroitin sulphuric acid. Lately, several preparations have appeared in the market that contain microbial hyaluronic acid or hyaluronic acid isolated from rooster comb. Application of isotopically labelled hyaluronan has proved that even orally administered hyaluronan may reach the joint.

Milk contains so-called micronutrients that have extraordinary biological properties. As their content in milk is very low, a milk concentrate, microlactin, from cows immunised by multibacterial vaccine is used. Clinical trials have demonstrated its anti-inflammatory and antiarthritic effects [60].

Several recent studies have proved anti-inflammatory effect of omega 3 fatty acids in both arthritis and arthrosis [61]. These polyunsaturated fatty acids favourably influence cellular metabolism and the structure of cellular membrane and reduce production of pro-inflammatory cytokines and prostaglandins. Application of polyunsaturated fatty acids, most often in the form of fish oil, which contains about 30 % of eicosapentaenoic acid and docosahexaenoic acid, has a positive effect on the symptoms of both arthrosis and arthritis. In addition, it has a protective effect in terms of cardiovascular diseases.

Methylsulfonylmethane (MSM), a naturally occurring sulphur compound found in the body, a source of the organic sulphur needed for production of glycosaminoglycans and collagen and important cartilage components, is frequently used in nutritional supplements for OA.

13.14 Operative Treatment of Osteoarthritis

Surgical interventions play an important role in OA treatment and are used after both pharmacological and non-pharmacological treatments have failed and in severe forms of hip and knee OA. Indications for surgical intervention include continuous intensive pain and markedly limited range of motion of the affected joint.

Currently, the most frequent and the most effective intervention is total hip or knee arthroplasty. Most patients are able to return to normal everyday activities. Improvement of the quality of the materials used in the development of endoprostheses ensures their long-term survival (10–15 years), as well as the possibility of their subsequent replacement [62].

13.15 Transarthroscopic Methods of Joint Debridement and Cartilage Repair

Tiny debris of the cartilage that irritates the synovial membrane is removed by *arthroscopic lavage of the joint*. This method may be combined with transarthroscopic debridement or shaving of the cartilage. Based on evidence, this combined procedure brings pain relief and improves the function of the joint. However, it does not initiate cartilage repair.

Several microsurgical arthroscopic techniques have been developed, aimed at cartilage repair, e.g. drilling of small holes into the subchondral vascular network to stimulate ingrowth of fibrocartilaginous tissue into the subchondral bone. Good results have been achieved also by so-called spongialisation consisting in excision of damaged cartilage along with the involved subchondral bone. The technique is particularly applicable to chondromalacia patella.

Another method of reconstruction of a damaged cartilage is the use of chondral auto- and allografts to reconstruct posttraumatic osteochondral defects in young patients. Multiple autologous small plugs (mosaicplasty) or precisely prepared osteochondral grafts are press fitted into the defective site.

Another option may be frozen autologous grafts that are, however, associated with a risk of immunological reaction. Similarly as chondral grafts, periosteal and perichondral tissue is used to fill chondral defects. The main problem of this method is fixation of the grafts at the defective site and their frequent calcification. Within tissue engineering a small biopsy may be performed, for instance, of the nasal cartilage to obtain autologous cells and implant them directly into the subchondral bone [63].

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Haemochromatosis Arthropathy

14

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Hereditary (primary) haemochromatosis of type I is one of the most frequent autosomal recessive genetic diseases in Europe. Similarly as other types of haemochromatosis, it results from mutations in one of the genes coding a protein that regulates iron metabolism. Although the resulting disorder may be identical, hereditary haemochromatosis must be distinguished from secondary haemochromatosis, i.e. haemosiderosis due to repeated red blood cell transfusions and other rare disorders leading to iron overload (aceruloplasminaemia, atransferrinaemia).

14.1 Pathophysiology of Hereditary Haemochromatosis

Hereditary haemochromatosis is a disorder of iron metabolism regulation, leading despite sufficient iron stores in the body to increased absorption of iron from the gastrointestinal tract, with iron deposition in tissues. With the physiological inability of the organism to eliminate excessive iron, such condition inevitably leads to progressive iron overload of the organism, with a subsequent toxic effect of the deposited iron in organs [1]. The disorder becomes clinically manifested when the iron content in the organism is 5–20 times increased as compared to its physiological stores. Depending on the type of the genetic defect, it may affect children or adolescents (juvenile type), but most commonly it occurs in adults after up to several decades of untreated disease (type I haemochromatosis).

In iron metabolism, hepcidin is the key regulator which responds to the iron stores and through its effect on ferroportin (the sole known iron exporter of enterocytes and macrophages) determines the rate of iron absorption. With low or normal iron stores, HFE protein (high Fe), haemojuvelin (HJV) and transferrin receptor 1 (TFR1) create a molecular complex on the surface of hepatocytes that is unable to induce hepcidin production. However, increase of the serum iron level generates a complex of HFE and HJV with transferrin receptor 2 (TFR2). This acts as a sensor of iron status and subsequently stimulates production of hepcidin which triggers ferroportin internalisation and degradation [2]. As a result, resorption of iron from the intestine decreases. Defects of these proteins participating in this regulation cascade result in hepcidin deficit (hereditary haemochromatosis of types 1, 2 and

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3), insufficient function of ferroportin (type 4A) or its resistance to the action of hepcidin effect (type 4B). All these disorders contribute to uncontrolled absorption of iron despite its increasing stores. Thus, it is a disorder of hepatic regulation rather than solely of intestinal resorption. This correlates also with the finding in experiments in mice that only HFE gene deletion in the liver [3], and not enterospecific HFE gene deletion [4], induces iron overload. Similarly, liver transplantation in patients with hepatic cirrhosis due to hereditary haemochromatosis effectively prevents further accumulation of iron [5].

14.2 Genetics of Hereditary Haemochromatosis

Although the disease is autosomal, it affects more frequently men. This is the result of regular physiological blood loss during menstrual bleeding, which until menopause, partially protects women from iron accumulation. So far, four types of the disease have been identified, depending on the location of the genetic defect [6] (Table 14.1). The most common in Europe (>80–90 % of patients), and basically the only clinically relevant form, is type I hereditary haemochromatosis caused by the C282Y homozygous mutation (replacement of cysteine by tyrosine) in the HFE gene [7, 8]. It occurs in 0.5 % of individuals in the Caucasian population and is almost absent in the African and Asian populations and in Australian Aborigines [9]. The C282Y mutation is believed to be of Celtic origin, which is supported by the highest prevalence of hereditary haemochromatosis in Britain, Ireland and the Bretagne, with a decreasing tendency eastwards. Introduction of molecular testing of the HFE gene in Britain in 1996 doubled the incidence and prevalence of hereditary haemochromatosis in the following decade [10]. Prevalence of heterozygotes in the Slovak population is estimated at 7 %, and thus the estimated prevalence of homozygotes does not significantly differ from other populations [8].

Soon after discovery of the C282Y mutation of the HFE gene, it became apparent that iron overload of the organism does not develop in all homozygous mutation carriers, and the clinical spectrum in homozygotes includes asymptomatic carriers as well as early severe cases with organ failure [11]. Thus, the phenotype does not always correlate with the genotype; penetrance of the disease in homozygous mutation carriers ranges between 30 and 50 % in males and about 2 % in females [12, 13]. However, the extent of clinical symptoms correlates with the extent of iron overload [12]. Additional modifying factors contributing to the manifestation of complications include excess alcohol consumption, chronic hepatitis [14], diabetes mellitus, joint over-use, smoking and male gender.

The H63D mutation (replacement of aspartic acid by histidine) in the HFE gene is common both in Caucasian and non-Caucasian populations. As its effect on iron metabolism is less marked than in the case of the C282Y mutation, it only rarely leads to manifest disease even in the homozygous form. The same applies to so-called compound heterozygotes (C282Y + H63D) and C282Y heterozygotes that may only in rare cases

Table 14.1 Types of hereditary haemochromatosis and their genetic basis

Type	Form	Mutated gene	Location	Heredity
1	Adult	HFE (high Fe)	6p21.3	AR[a]
2A	Juvenile	RGMc/HJV (hemojuvelin)	1q21.1	AR[a]
2B	Juvenile	HAMP (hepcidin antimicrobial peptide)	19q13.1	AR[a]
3	Adult	TFR2 (transferrin receptor 2)	7q22	AR[a]
4A/4B	Adult (Bantu siderosis)	SLC40H1 (ferroportin)	2q32	AD[b]

[a]Autosomal recessive
[b]Autosomal dominant

(about 0,5%) exhibit progressive development of iron overload and its clinical manifestations [15].

Other types of hereditary haemochromatosis are rare and occur in all populations. Quite extraordinary is the only autosomal dominant type 4 that differs from other types of hereditary haemochromatosis also by its laboratory parameters [16]. A very rare type is neonatal haemochromatosis, the pathophysiology of which is still unknown.

14.3 Diagnosis of Hereditary Haemochromatosis

In clinically suspected haemochromatosis, it is necessary to determine ferritin levels (>300 ng/l) and the value of transferrin saturation (>45 %). Hyperferritinaemia without elevated transferrin saturation is mostly of inflammatory origin. Combination of transferrin saturation and serum ferritin yields good sensitivity and specificity for haemochromatosis, and increase of both these parameters is an indication for analysis of the HFE gene, including determination of C282Y and H63D mutations. Despite increasing availability of the genetic analysis, it is reasonable, particularly from the economic viewpoint, to follow the mentioned sequence of tests [17]. Type 4 hereditary haemochromatosis exhibiting markedly elevated ferritin levels without a simultaneously increased transferrin saturation occurs only exceptionally. The most probable finding in patients with hereditary haemochromatosis is HFE C282Y homozygosity or simultaneous mutation of C282Y and H63D (compound heterozygote). Better availability of genetic testing for HFE gene mutations has significantly reduced the use of diagnostic liver biopsy to determine the hepatic iron index. In addition to laboratory tests of body iron stores, the extent of iron overload may be assessed by non-invasive MRI examination of the liver. A random finding of a mutation without laboratory signs of iron overload results from low penetrance of the mutation and is not indicated for treatment. Examination of other rare mutations of the HJV and HAMP gene is indicted only in case of a suspected juvenile form of the disease.

14.4 Clinical Features of Hereditary Haemochromatosis

Iron deposited in tissues triggers by its toxic action inflammatory changes and gradual destruction of the affected organs. Hepatic fibrosis and cirrhosis (20 % of treated patients) with development of hepatocellular carcinoma and cardiomyopathy (10 % of patients) are late but life-threatening complications of haemochromatosis [11]. As compared to the healthy population, the overall mortality of patients with manifest hereditary haemochromatosis is 2–2.2 times higher [10, 18], the main contributing factors being hepatic cirrhosis (3.4 times higher mortality), hepatocellular carcinoma (0.9 % of patients annually) and cardiomyopathy. Other associated diseases include diabetes mellitus (12–20 % of patients, OR 5.4) and hypogonadism (OR 2.7) that result from destruction of endocrine glands. A typical feature is also bronzing of the skin.

14.5 Treatment and Prognosis of Hereditary Haemochromatosis

The mentioned complications may be prevented or their manifestation resolved by regular phlebotomies. These mobilise iron from the tissues and eliminate it. Although no randomised studies are available, phlebotomies reduce iron stores down to the lower limit of the physiological reference range in the first phase of the treatment (500 ml of blood twice a week for 1 year) and in the second phase (every 3–4 months for the rest of life) prevent further accumulation of iron in the organism [11]. This approach effectively prevents life-threatening complications and consequently decreases mortality. The advantages of this treatment are its efficacy, simplicity and inexpensiveness. In addition, it

has been recognised that patients with hereditary haemochromatosis constitute a safe source of blood for transfusion [19]. A prerequisite for a successful treatment is, however, its early commencement. Alternatively, chelation therapy may be considered. Patients are recommended to avoid the use of high doses of iron preparations and vitamin C.

14.6 Hereditary Haemochromatosis Arthropathy: Clinical Features

Clinical features of hereditary haemochromatosis typically include, apart from the already mentioned complications, also arthropathy [20]. Although it is clinically and radiologically similar to osteoarthritis, it is characterised by specific features of the affected joints. The dominant clinical symptoms include pain and symmetrical swelling of second and third metacarpophalangeal (MCP) joints, which occurs in up to 60 % of patients with manifest haemochromatosis and is rare in primary osteoarthritis of hands [21].

Although involvement of other joints of hands is less frequent, polyarthritis of fingers in males should be considered as a warning signal in terms of potential haemochromatosis. However, the incidence of bilateral osteoarthritis of the hip [22] and arthritic changes of knee and ankle joints are frequent. Up to 5 % of patients requiring ankle arthroplasty are diagnosed with haemochromatosis [23]. The most common symptom is thickening of the affected joints (66 %), followed by tenderness (47 %) and swelling (14 %).

Although the symptoms of haemochromatosis arthropathy do not significantly differ from arthritic complaints (mild swelling, pain, stiffness, inability to flex fully MCP joints), some patients report intermittent or acute inflammatory changes of the affected joints with pain and swelling, not unlike in synovitis. These episodes are probably attacks of pseudogout resulting from early calcium pyrophosphate dihydrate (CPPD) crystal deposition (chondrocalcinosis) [24].

14.7 Pathophysiology of Arthropathy

The pathophysiology of joint involvement in haemochromatosis remains unclear. A serum ferritin level exceeding 1000 ng/ml at the time of diagnosis is associated with haemochromatosis arthropathy [25, 26] and also with a higher risk of joint failure requiring joint replacement [27]. In 37 % of patients with haemochromatosis, iron deposition was found in synovial resection samples [22]. Although our findings confirm significantly higher haemosiderin deposition in the affected joints of patients with haemochromatosis [28], these findings are not specific for this disease and are common also in other inflammatory rheumatic diseases [29].

As compared to the healthy population, serum ferritin levels are elevated also in males with osteoarthritis of the knee and are associated with a more severe degree of radiological changes [30]. Higher iron levels were detected also in joints affected by osteoarthritis [31], and the heterozygous H63D mutation is more common in patients with primary osteoarthritis of talocrural joints who do not exhibit other manifestations of iron overload [32]. Also, precipitation of CPPD crystals is promoted by iron and thus iron might be directly responsible for the higher occurrence of chondrocalcinosis in patients with haemochromatosis. Therefore, it seems that iron may play a certain role in the development of pathological changes of joints in haemochromatosis, as well as in other arthropathies.

In vitro, iron impairs the synthesis of proteoglycans, induces lipid peroxidation by production of free radicals, thus impairing chondrocyte metabolism, and also negatively affects osteoblasts [33, 34]. In enchondral ossification, an important role is played by hypoxia-inducible factor 2α (HIF2α), the expression of which increases in conditions of elevated iron levels [35]. HIF2α levels are higher in the cartilage of both mice and humans with osteoarthritis, and it is generally known that it induces catabolic enzymes (metalloproteinase, aggrecanase-1, NO-synthetase-2 and cyclooxygenase 2) in chondrocytes [36]. HIF2α could thus serve as a mediator of the adverse effects of iron upon joints.

At tissue level, we have demonstrated that synovial tissue in patients with haemochromatosis resembles by cell infiltrate composition osteoarthritis rather than rheumatoid arthritis [28], except for a significantly increased number of granulocytes that are more typical of rheumatoid or psoriatic arthritis. At the same time, ferritin is able to induce directly the synthesis of pro-inflammatory cytokine IL1 [37], which damages chondrocytes and osteoblasts. Although the relevance of these findings is not clear yet, they may support the use of targeted therapy blocking mechanisms of innate immunity [38]. The role of adhesive molecules in the pathophysiology of arthropathy is not known, either, but VCAM-1 levels correlated well with the presence and severity of arthropathy in patients with haemochromatosis and may serve as a biomarker in its assessment [39].

At the same time, patients with haemochromatosis often develop osteoporosis which belongs to the clinical spectrum of iron overload manifestations. However, also hepatic cirrhosis and hypogonadism may contribute to the development of osteoporosis.

14.8 Epidemiology of Arthropathy

The first studies dealing with hereditary haemochromatosis arthropathy reported a 50–60 % prevalence of joint symptoms in patients [40]. According to our findings, joint pain is reported by up to 70 % of patients with haemochromatosis (at the age of 56 years) [41]. Arthropathy is thus the most common clinical manifestation of hereditary haemochromatosis. Certain studies have not confirmed an increased incidence of arthropathy (defined as painful MCP2 and MCP3 joints) in patients with hereditary haemochromatosis. However, in our group of patients ($n = 199$), the dominant manifestation of arthropathy was not pain but swelling of MCP joints [41]. This may explain the absence of an increased occurrence of arthropathy (defined as painful swelling) in some cohorts. The informative value of the studies published so far is limited also by the small number of included homozygotes and the lack of a complete rheumatologic examination of each patient.

It is remarkable that clinical manifestations of arthropathy are not only a frequent but also an early symptom of iron overload [12, 41]. According to our findings, even today they precede the diagnosis of haemochromatosis by more than 6 years. As a result, up to 50 % of patients exhibit manifestations of arthropathy at the time when they are diagnosed with haemochromatosis, and its treatment is started. Thus, correct interpretation of clinical symptoms, radiological changes and laboratory parameters may contribute to earlier diagnosis of the underlying disease and a timely prevention of other potentially life-threatening complications of haemochromatosis.

14.9 Radiological Changes

Similarly as in osteoarthritis, radiological changes in haemochromatosis arthropathy include narrowing of the joint space, formation of osteophytes, development of cysts and erosive changes [42], as well as sclerotic changes and deformity of the joint [43] (Fig. 14.1). It is characterised by beak-like osteophytes located on the radial aspect of MCP joints. In our group of 170 patients, the most common radiological findings were osteophytes in MCP2 and MCP3 joints (45 %) and narrowing of joint space (48 %) followed by erosive changes (28 %). Using a validated score specific for haemochromatosis arthropathy, we have confirmed the general clinical finding that arthropathy involves most frequently MCP2 and MCP3 joints [43] (Fig. 14.2). At the same time, we have found, in agreement with clinical data published in other studies [23], that radiological changes are not confined only to MCP joints, but are relatively frequent and severe also in other joints (talocrural, radiocarpal). Unlike other authors, we have not found more severe involvement of the dominant right hand [43] (Fig. 14.2). Chondrocalcinosis is identified in 11–33 % of patients, most often in the knee and radiocarpal joints [24] (Fig. 14.3). Some studies also report the relatively rare occurrence of femoral head necrosis in patients with haemochromatosis.

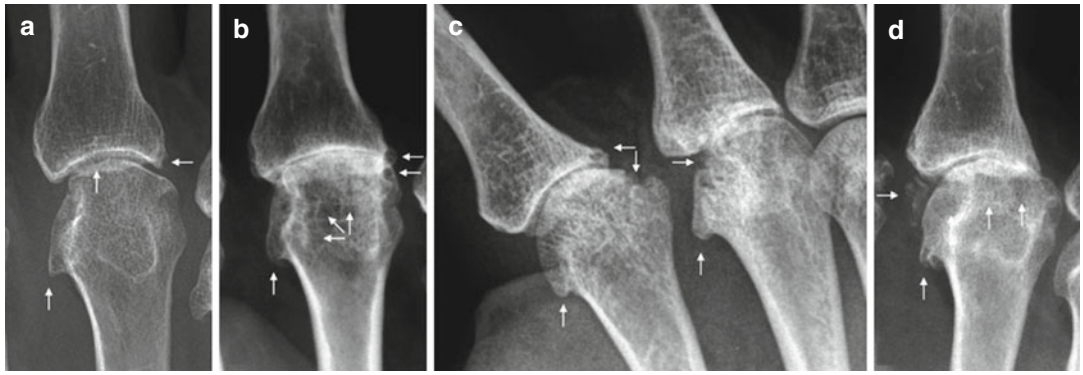

Fig. 14.1 Characteristic radiological changes in metacarpophalangeal joints of patients with hereditary haemochromatosis: (**a**) narrowed joint space, proximal osteophyte, minor distal osteophyte, erosive changes on the proximal articular surface, (**b**) completely absent joint space, sclerotic changes, proximal beak-like osteophyte, cystic changes both proximally and distally, deformity of the head of the metacarpal bone, (**c**) second and third metacarpophalangeal joints with narrowing of the joint space and marked erosive changes and osteophytes proximally, (**d**) severe lesion with marked narrowing of joint space, sclerotic changes, cysts, typical beak-like osteophyte proximally, joint deformity and chondrocalcinosis [43]

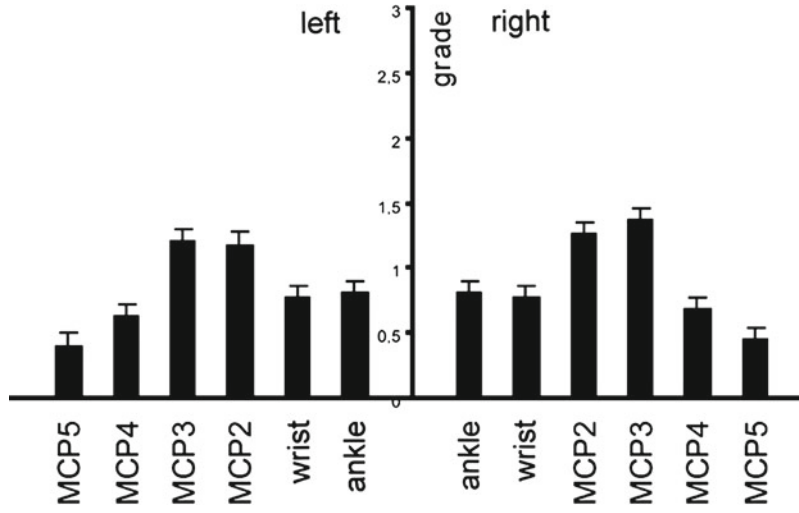

Fig. 14.2 Radiological severity (grade 0–3) of involvement of selected joints in patients ($n=170$) with hereditary haemochromatosis, using validated radiological scoring [43]

14.10 Prognosis of Arthropathy

Most important, in terms of rheumatology, is the fact that involvement of joints, although not affecting patients' survival, has by far the worst prognosis as to the patients' quality of life and the possibility of its reversal by phlebotomy treatment. More than 60 % of patients in our cohort were unsatisfied or highly unsatisfied with the condition of their joints, and only 15 % of them reported resolution of joint complaints after commencement of phlebotomy therapy [41]. In the remaining patients, the joint complaints remained the same, and in 16 % of them, the disease progressed further despite treatment [41]. This correlates with the results of other studies showing that arthropathy is the only complication associated with haemochromatosis that is unresponsive to causal treatment [44].

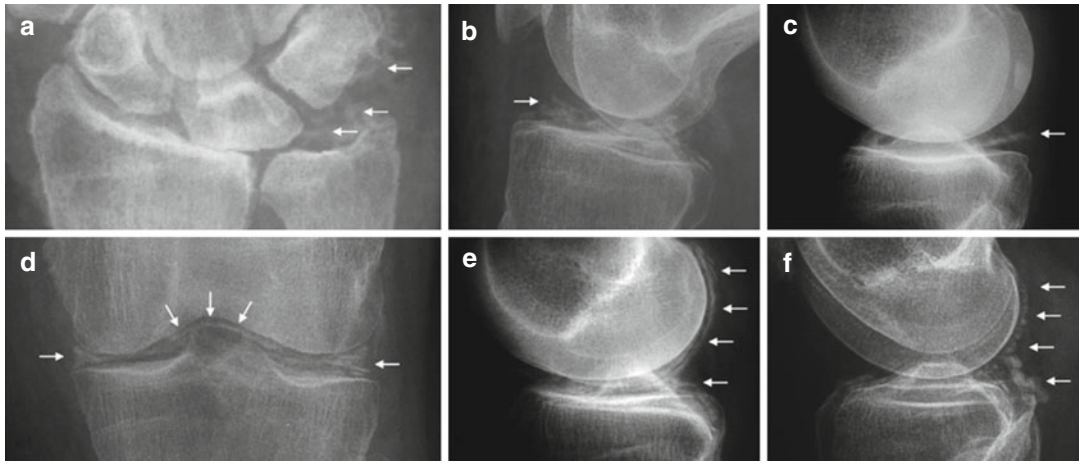

Fig. 14.3 Typical findings of chondrocalcinosis in wrist (**a**) and knee (**b**–**f**) joints in patients with hereditary haemochromatosis [43]

As a result, arthropathy progresses to a severe lesion of the joint requiring its replacement. As compared to the healthy population, the risk of total joint replacement was up to nine times higher in patients with haemochromatosis [45]. This corresponds also with the early need for the first endoprosthesis (58.3 vs 72.1 years) and the increased risk of multiple joint replacements (8.5 % vs 0.3 %) [45]. Most frequent are replacements of hip joints (>80 %), followed by knee and ankle joints. A high incidence of endoprostheses (31 % vs 1 % by the age of 70 years) was reported also in another cohort of patients with haemochromatosis [27]. Higher risk of joint failure requiring total arthroplasty (relative risk 2.14–2.77 for the knee and hip, respectively) was confirmed in a Swedish population study comparing patients with haemochromatosis with their first-degree relatives. As expected, the risk was highest in the youngest patients (HR 6.35) and for endoprosthesis or arthrodesis of the talocrural joint (HR 10.54) [46]. Interestingly, heterozygotes without clinical signs of haemochromatosis (many of them first-degree relatives of patients with haemochromatosis) are exposed to a higher risk of primary osteoarthritis [47]. This may be, in addition to errors resulting from small cohort size, another potential explanation of the higher relative risk found in small cohorts as compared to the healthy population [45]. In summary, despite its seemingly benign nature, arthropathy is the most common and in terms of patients' quality of life the most severe complication of hereditary haemochromatosis [41, 45].

14.11 Diagnosis of Arthropathy

Currently, it cannot be excluded that some patients requiring early arthroplasty for early-onset osteoarthritis actually suffer from undiagnosed haemochromatosis. This hypothesis is supported by the high prevalence of joint replacements in patients with haemochromatosis and by the fact that arthropathy is a frequent and despite significant iron overload often the only clinical manifestation of haemochromatosis.

In practice, the following clinical scenarios are of particular relevance to rheumatologists: (a) a patient with undiagnosed haemochromatosis who presents with joint complaints and (b) a patient with diagnosed haemochromatosis who presents with joint complaints. In the first case, male gender, inadequately young age in terms of degenerative joint disease, involvement of MCP2 and MCP3 joints and severe, early and bilateral involvement of the hip [48] and ankle joints without a history of trauma, requiring joint replacement, should always be warning signals of hereditary haemochromatosis as the underlying cause of arthropathy [46].

A finding of early-onset chondrocalcinosis even without clinical symptoms of pseudogout should always prompt evaluation for hereditary haemochromatosis. Due to the fact that symptoms of arthropathy precede establishment of diagnosis of haemochromatosis by almost 6 years, the latter scenario is probable only in individuals identified by selective screening of relatives of patients with manifest haemochromatosis. In this case, it is desirable to monitor development of iron overload and to commence timely phlebotomy therapy, possibly before manifestation of arthropathy.

14.12 Screening

Hereditary haemochromatosis is a common disorder, clinical symptoms develop over decades, early intervention prevents development of severe complications and its treatment is readily available and inexpensive. In spite of this, population genetic screening is currently not recommended due to low penetrance of the disease and the good therapeutic effect of phlebotomies on life-threatening complications (cardiomyopathy, hepatopathy with cirrhosis and risk of hepatocellular carcinoma), even with therapy onset at an advanced age.

Therefore, selective screening is applied in population groups at risk (men, Caucasian race) in the following clinical situations: (i) first-degree relatives of patients with confirmed hereditary haemochromatosis, (ii) asymptomatic patients with laboratory findings of iron overload, (iii) patients with unclear hepatopathy, cryptogenic liver cirrhosis, type 2 diabetes mellitus and concomitant hepatomegaly or unclear arthropathy and laboratory findings of iron overload. However, even such a selective approach had a low diagnostic yield (22.8 %) in the Slovak population [8]. It seems reasonable to examine also patients reporting haemochromatosis or iron overload in their relatives (sensitivity depending on the respective complication 18.4 %–81.4 %, specificity >94 %) [30].

These recommendations do not reflect the latest findings concerning the severity of arthropathy in haemochromatosis. Although it has been repeatedly demonstrated that phlebotomy therapy cannot reverse the progress of arthropathy [44], this may be due to the fact that at the time of commencement of this therapy (usually 6 years after the onset of first clinical symptoms), accumulation of iron in the synovium or changes in joints are already irreversible. Thus, the question to be answered yet is whether genetic screening and earlier treatment could prevent joint manifestations and thus significantly improve the quality of life of patients with haemochromatosis.

14.13 Treatment of Arthropathy

Phlebotomy therapy that is started in the phase of established arthropathy does not provide the desirable effect and is considered to be insufficiently effective [41, 44]. Unlike in other organs, reduction of total iron stores by phlebotomies does not remove iron from joints which is proved also by the finding of ferritin in the synovium of treated patients [12, 28] and its higher levels in synovial fluid than in serum [26]. Specific, pathogenetic and at the same time effective treatment of arthropathy in haemochromatosis is currently not available. As a result, therapy does not differ from treatment of osteoarthritis and includes administration of analgesics-antiphlogistics, ergotherapy, physical therapy and surgical treatment in case of joint failure. In case of involvement of talocrural joints, recent data indicate more favourable outcomes of total arthroplasty as compared to classic arthrodesis in terms of pain relief and preservation of joint function [49]. Several studies have reported treatment of pseudogout attacks with low-dose colchicine (1 mg/day). In two patients with severe arthropathy in haemochromatosis, a favourable effect of targeted treatment with IL-1 receptor antagonist (anakinra) has been reported [38]. It cannot be excluded that despite the current experimental nature of this approach, it may be a promising

therapy as it influences multiple known pathophysiological mechanisms of arthropathy in hereditary haemochromatosis.

Conclusion

Hereditary haemochromatosis is one of the most frequent monogenic diseases. Arthropathy is not only its earliest manifestation but, in terms of quality of life, also its most severe complication. It is associated with a high risk of severe joint damage requiring its replacement. Unusually severe arthropathy requiring early total arthroplasty (<60 years) should be, particularly in males and in case of preferential involvement of MCP2 and MCP3 joints a warning signal of hereditary haemochromatosis. The finding of elevated ferritin levels and transferrin saturation confirms iron overload and at the same time warrants examination of HFE gene mutations. Apart from the treatment of iron overload with phlebotomies, the standard treatment of haemochromatotic arthropathy currently does not differ from treatment of osteoarthritis. Although there is still no evidence for the efficacy of phlebotomies on halting the progression of arthropathy, early commencement of treatment might prevent irreversible damage and requires further study.

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Diabetic Charcot Neurogenic Osteoarthropathy

15

Renáta Palmajová and Juraj Palmaj

Diabetes mellitus (DM) is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Diabetes is one of the major threats to human health throughout the world. It decreases the quality of life and reduces life expectancy. The necessary long-term comprehensive healthcare provided to diabetic patients is also associated with a heavy socioeconomic burden.

DM is complicated by a number and complexity of the involved etiopathogenetic mechanisms that result in one of the major defects:

1. Inadequate insulin secretion, particularly autoimmune destruction of the pancreatic beta cells that produce insulin
2. Diminished peripheral tissue responses to insulin by development of resistance to insulin action at a postreceptor level

These two key factors characterise two basic DM types:

- Type 1 diabetes, an organ-specific autoimmune disease
- Type 2 diabetes, consisting of resistance to insulin action with a relatively and functionally inadequate insulin secretion [56, 94, 101]

These two mechanisms may coexist in various combinations even in the same patient [94]. DM is an endocrine, metabolic disorder that leads in the long-term run to irreversible changes damaging individual tissue systems of the organism (arthropathy, neuropathy, angiopathy, nephropathy, retinopathy, dermopathy, myopathy) through a pathological change in the carbohydrate, protein and fat metabolism. The time interval of clinical manifestation of these disorders ranges between 8 and 16 years of establishment of DM diagnosis, which in type 2 DM means that they most often affect the middle-age and elderly patients. As the severest disorders involve the nerve and connective tissues, the most frequent chronic complications of diabetes [56, 63, 94, 120] in these age categories include changes in the musculoskeletal system.

The most common complication of diabetes is a diabetic foot. It is a neuropathic and angiopathic involvement of lower extremities, the most severe form of which is the diabetic neuropathic

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Charcot osteoarthropathy (CHOA) with or without secondary infection caused by internal or external factors.

CHOA is manifested by a destructive involvement of the bones and joints of the foot, resulting from neuropathy. In our geographical region, it is most commonly manifested by a devastating consequence of a long-term history of diabetes mellitus complicated by polyneuropathy. It is a progressive disease usually with only little or no pain that affects uni- or bilaterally the musculoskeletal system of the foot, posing diagnostic difficulties mainly in the early phases of the disease.

All types of neuropathy participate in its development. They result from nerve damage during long-term hyperglycaemia, caused by diabetic pseudohypoxia through the sorbitol pathway, non-enzymatic glycation and oxidative stress. Causes of CHOA development include also angiopathy, LJM (limited joint mobility syndrome), type 1 collagen deficiency and trauma (often minor but repeated). It affects predominantly subtalar structures of the foot, involving one or more frequently multiple joints and bones.

15.1 Historical Background

The first to describe arthropathy was William Musgrave in 1703, and its neuropathy origin was suggested by John K. Mitchell in the mid-eighteenth century [34, 67, 81]. The first detailed description of the neuropathic aspect of this disease as a complication of syphilis was given by Jean-Martin Charcot in 1868 [49]; hence, the condition is named after him. As late as in 1936, William R. Jordan [58] linked the Charcot arthropathy to diabetes [67, 77, 81, 85]. Diabetes mellitus is now considered to be the most common aetiology of neuropathic Charcot osteoarthropathy [32, 41, 56, 61, 63, 88], which was pointed out already in 1955 by Miller and Lichtman.

15.2 Epidemiology

In Slovakia, about 250,000 diabetic patients were registered in 2000, which accounts for 3.5–4.7 % of the total population [56, 63, 76, 82]. In 2007, their number increased to 320,000, which follows the global trend of rise in lifestyle diseases and represents a marked increase within our population, reaching the parameters of diabetes epidemic [75]. This number is actually even higher, as not all cases are identified due to inadequate diagnosing, screening and monitoring mainly of type 2 diabetes which affects primarily the older population and is often diagnosed by chance, within comprehensive examinations of other diseases [76].

Neuropathy of lower extremities affects 30–50 % of diabetic patients of which it clearly manifests itself in about 15 % [85, 121, 130]. Important factors are not hyperglycaemia values but rather the age and the history of diabetes, as a rule longer than 10 years [6, 81, 85, 111, 121].

Diabetic Charcot neuropathic osteoarthropathy (CHOA) clinically manifests itself in the acute form in 0.1–2.5 % [85] and in the chronic form in about 8–16 % of cases of diabetic neuropathy of lower extremities [3, 11], which represents in the group registered in the Czech Republic of more than 700 continuously followed-up patients. This most severe complication of diabetes on the lower extremities develops on average after a 10–15-year history of diabetes. Involvement of both extremities is reported in individual groups in 6–40 % of patients affected by CHOA [15, 23, 67, 88, 94, 96]. The most important factors are not hyperglycaemia values (it occurs also in cases of "floating hyperglycaemia" with intermittent increases) but the length of history of DM with pathological metabolism and diabetes-related complications, as mentioned above. The incidence of neuro-osteoarthropathy is increased in coexistence with retinopathy [6, 67]. Based on the length of diabetes history from the

initial phase until CHOA manifestation reported in the literature, the average age of patients ranges between 57 and 68 years [67, 94, 100] regardless of gender [65, 67, 85, 90].

15.3 Etiopathogenesis

Carbohydrate mechanism disorders are among the most severe metabolic disorders damaging tissues via several pathways:

1. *Non-enzymatic glycation*. Increased long-term (several years) offer of glucose in the extracellular and intracellular space is the key to pathological changes in tissue systems of the organism. It increases the incidence rate of pathological links mainly with proteins. In the mesenchymal tissue, it is primarily collagen. These protein fixations last throughout the life of the protein and exhibit altered physical–chemical properties causing damage to individual tissues of the organism, e.g. pathological links to macrophage receptors stimulating cytokine production [63, 88].
2. *Sorbitol pathway*. Increased offer of glucose may induce alternative processing in insulin-independent cells (nerve cells, capillary pericytes). The enzyme aldose reductase converts glucose to sorbitol which is subsequently converted to fructose by glucitol dehydrogenase. These products increase the intracellular volume through a change in the osmotic gradient and damage cells. Accumulation of sorbitol has a direct toxic effect on myosin metabolism of the peripheral and autonomous nervous system [88].
3. *Oxidative stress*. Carbohydrate metabolism disorder with glucose linked to proteins facilitates generation of oxygen and hydroxyl radicals, which leads to oxidative stress, with continuously increasing formation of reactive oxygen radicals and decreased performance of inhibitors and scavenger system [32, 88].

These carbohydrate metabolism disorders cause structural changes at the cellular level of metabolism of all tissues of the organism (dermopathy, retinopathy, nephropathy, neuropathy, angiopathy, osteoarthropathy) but predominantly in the peripheral nerve system and tissues of mesenchymal origin. Neurogenic tissues are affected by lesions and loss of anterior horn cells and axon cylinders (axonopathy) and abnormalities of cells and Schwann sheaths (myelopathy [25, 27]). In the mesenchymal tissue, it is mainly a case of physical–chemical changes of collagen jointly referred to as cheiroarthropathy. These changes are manifested by increased glycation and higher resistance to enzymatic digestion – resistance to degradation and increase in collagen cross-linking, decreased solubility and elasticity and increased thermal stability and mechanical strength. Joint capsules, fascia and tendon sheaths get thicker and sclerotic and lose the ability of physiological extensibility and elasticity. On the one hand, this causes contractures and on the other hand laxity of the structures under load [39].

The diabetic foot syndrome, affecting predominantly the peripheral part of lower extremities, has according to Harrelson [65] several causes – dysvascular, neuropathic and neuroarthropathic – with several forms of clinical symptoms:

1. Ischemic foot
2. Neuropathic foot, including neuropathic swelling, neuropathic ulcerations with digital necrosis and neurovascular gangrene
3. Neuro-osteoarthropathy

Oakley differentiated between the following diabetic lesions of the foot (Fig. 15.1):

- Septic
- Neuropathic
- Ischemic
- Combined [81]

Diabetic Charcot neuroarthropathy is the most severe form of the diabetic foot, which differs in certain pathogenetic and clinical aspects from diabetic and metabolic neuropathy.

In terms of historical development of findings and opinions, there are two theories of CHOA pathogenesis:

1. "The French theory" – neurovascular – was based on the concept of disorder of nutrition of the bones and joints of the foot caused by impairment of the nervous system, particularly the axons and Schwann myelin sheaths, and by higher bone resorption due to increased blood flow [2, 5, 63].
2. "The German theory" – neurotraumatic – rather emphasised the share of external traumatic factors in impaired sensitivity of lower extremities and reduced motor function of muscles [3–5].

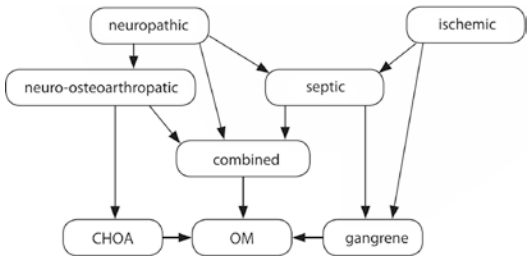


Fig. 15.1 Scheme of diabetic lesions of the foot

Although these theories are still generally accepted, it has been demonstrated that also other etiological factors participating in CHOA development and manifestation have to be taken into account.

Currently there dominate opinions suggesting multifactor etiopathogenesis (Fig. 15.2) of the neuropathic foot and its most severe phase – the diabetic neuropathic Charcot osteoarthropathy, although there are still many unclear issues mainly as concerns its acute clinical manifestation [83].

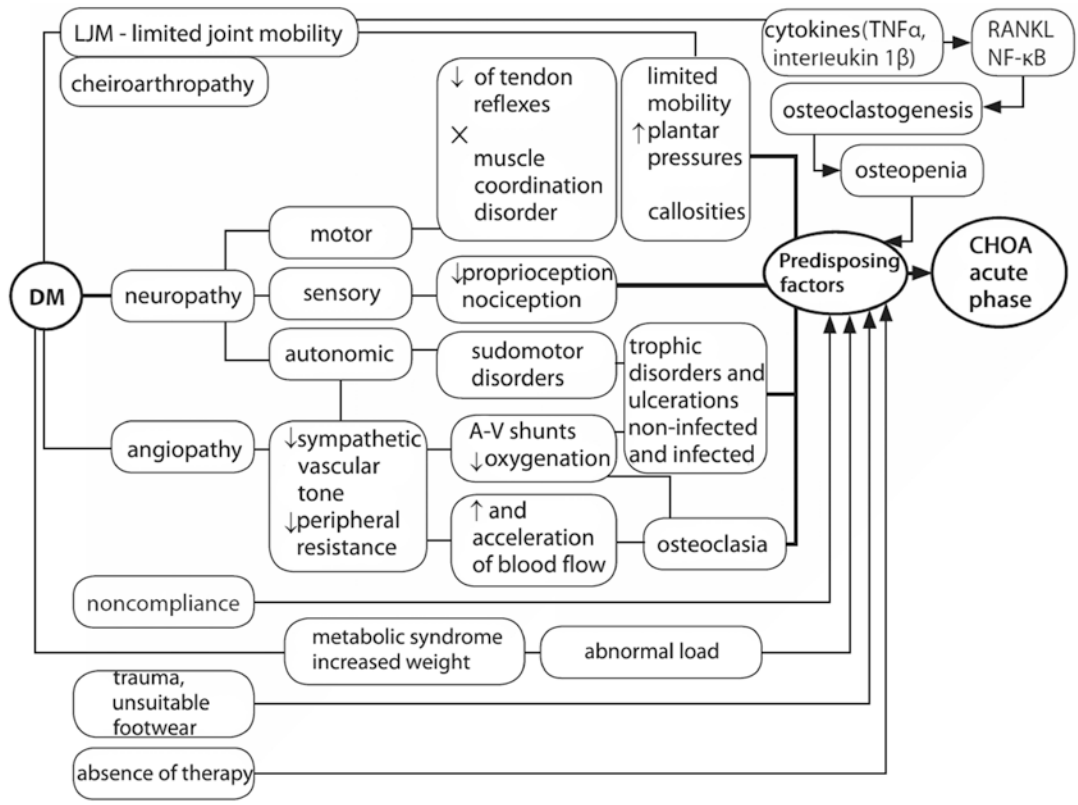


Fig. 15.2 CHOA etiopathogenesis

According to these opinions, responsible for CHOA development are both endogenous and exogenous factors.

15.3.1 Endogenous Factors

- *Peripheral somatic neuropathy* with loss of proprioception and nociception usually of "sock-like" transverse type. Muscle action in normal gait requires a sensory input to modify the movement stereotype of the foot. The sensory perception comes from the visual and vestibular systems, and the proprioceptive input is provided predominantly by lower extremities. Disorders of this complex of systems lead to disorders of gait dynamics with limited plantar flexion and dorsiflexion and reduced gait speed [24, 48, 112].
- *Motor peripheral neuropathy* with muscle imbalance resulting from impaired innervation of muscles and tendons, first of the peroneal muscles, with decrease in muscle mass of extensors, later of the tibialis posterior and the triceps surae, causing typical foot deformities (pes cavus varus excavatus et digiti hamati) with a varus tilt of the talus and subsequently with increase of excessive forefoot plantar pressure and decrease of the plantar ground contact due to predominance of flexors [74, 100], with a simultaneous hypotrophy of the interosseous muscles mainly those of the forefoot. Due to limited mobility of the ankle and foot, adaptation "hip strategy" is used to compensate in gait for weak hip muscle. The limb is driven forward by the hip rather than being propelled by forward thrust of the foot [42].
- *Autonomic neuropathy*. Sympathetic vascular denervation increases blood flow and leads to development of arteriovenous shunting and increased osteoclasia [19, 46, 54, 111] and sudomotor (sweating) abnormalities causing hypotrophic dry skin susceptible to injuries with a secondary infection and loss of distal leg hair.
- *Angiopathy*. Autonomic neuropathy, particularly involvement of C-fibres responsible for reduction of microvascular reserve, causes microcirculation dysfunctions in the form of decrease in endothelium-dependent and endothelium-independent vasodilatation with impaired hyperaemic response to stress situations, mainly heat, in the initial stages of the disease and contributes to development of ulcerations, but not CHOA. Damaged vascular walls they enable beginning of arteriovenous shunts, which may lead to up to five times increase of blood flow [67, 119, 126] with the increase of the arterial and venous pressure and partial oxygen pressure in the venous bed. This increase in capillary pressure causes microvascular sclerosis which together with steal phenomenon of AV shunts reduces patency of terminal capillaries and leads to tissue ischemia.

The limb seems to be well vascularised, with venous dilatation mainly on the dorsum of the foot. However, the damaged cholinergic fibres cause disorders of vascular autoregulation or even paradoxical reactions (auto sympathectomy). These symptoms rather lead to development of microangiopathy, macroangiopathy and medial calcinosis, and their involvement in CHOA development is less than what was initially supposed, unlike ulcerogenic defects. A frequent finding in CHOA is mediocalcinosis caused by smooth muscle atrophy of the tunica media vascular bed and subsequent deposition of calcium salts in this layer. However, its direct participation in the CHOA development cannot be clearly demonstrated [126]. Vascular calcification (Mönckeberg's sclerosis), one of the prominent manifestations of diabetic neuropathy, is extremely frequent in CHOA (90% of patients). It is hypothesised that calcification of arterial smooth muscle cells is triggered by the cytokine system. It seems that RANKL expression is increased in diabetes, being potentiated by free radical formation, hyperlipidaemia, locally increased blood sugar and advanced glycation end products [54].

Diabetic patients are more susceptible to development of generalised atherosclerosis with arterial occlusions below the knee. Capillary basement membrane thickening causes atrophy of the skin and soft tissues and may be involved in the development of the

ischemic foot, but it has no direct impact on CHOA development [28, 32]:

- *Cheiroarthropathy* – LJM syndrome (limited joint mobility) – the presence of abnormal degraded collagen, primarily of type I (which is found in bones, cartilage, capsules and tendons), its glycation, decreased degradation and hyperproduction with a subsequent change in elasticity limits in the first phase the range of motion of pedal joints and later causes due to increased vulnerability the joint instability. This results in loss of the protective buffering effect against mechanical stress.
- *Metabolic causes* are associated with non-enzymatic glycation of proteins of bones and soft connective tissues, diabetic nephropathy, osteopenia, glucocorticoid-induced osteoporosis, dysproteinaemia, hypercholesterolemia and dyslipidaemia [84].
- *Inflammation* results from minor injuries and ligamentous laxity for the above-mentioned causes. It may trigger a cascade of pro-inflammatory changes through increased production of pro-inflammatory cytokines, including TNF-α and IL-1β, leading to a marked osteoclastogenesis through increased expression of pro-inflammatory factor NF-kB (Fig. 15.3).

It is obvious that a significant role in the pathogenesis of the Charcot osteoarthropathy is played by OPG/RANKL (osteoprotegerin/receptor activator of nuclear factor-k ligand) signalling pathway, which is further influenced by many cytokines, such as TNF-α, IGF and TGF [7, 50]. Activation of this transcription factor increases together with other factors secretion of osteoprotegerin and receptor activator of nuclear factor (RANK) [45, 46].

These causes probably contribute to the clinical manifestation of acute CHOA through RANKL–NF-kB signalling pathway. Inadequate control of this system participating in bone formation activates bone resorption which then prevails over the new bone formation, resulting ultimately in osteoarthropathy. It has been proved that neuropathy leads to increased RANKL secretion as a result of depletion of neuropeptides known for the cytokine system antagonistic effect, including calcitonin gene-related peptides. Impairment of circulating peptides, such as leptin and amylin, may also affect the cytokine system in diabetes [45, 46, 51, 52]; endocrine causes IGF-1 disorder (insulin growth factor, known as C somatomedin, stimulating proliferation of cartilage and new bone formation) caused by insulin deficiency that may impair growth and integrity of the foot skeleton.

15.3.2 Exogenous Factors

- *Trauma* may be single, inadequate in terms of consequences and scope or repeated, caused by loss of proprioception and nociception in sensitive neuropathy and instability due to

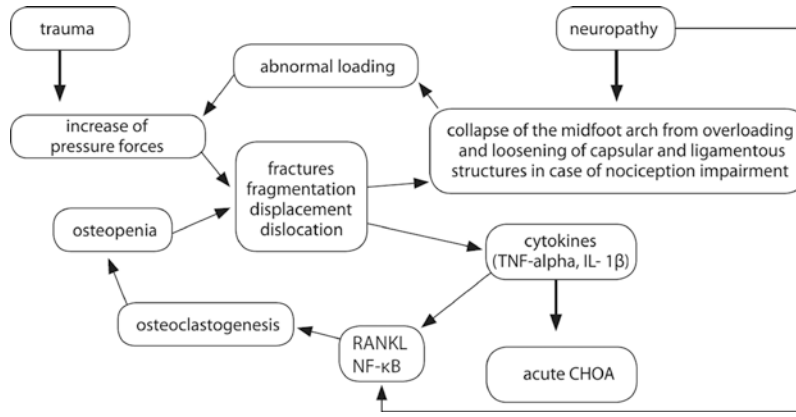


Fig. 15.3 Adverse cytokine effect on acute CHOA manifestation

motor neuropathy. This leads to mechanical stresses at the site of excessive loading of the neuropathic foot. Repeated overloading and injuries cause intra-articular effusions, laxity of joint capsules and periarticular ligaments, as well as subsequent joint instability resulting in damage to bone structures and cartilage of articular facets (subchondral sclerosis, fibril splitting and sequestration of cartilage, marginal avulsion and abruption) [24, 28, 82].

One of the causes of the disease may be considered also improper footwear with chronic excessive pressure at the sites of bone contact with shoes, resulting in defects of the trophic skin with sudomotor dysfunction.

- *Infection* caused by bacterial or mycotic contamination of skin defects and minor injuries with minimal or protracted healing that may affect also soft or osteoarticular structures and complicate by inflammation CHOA diagnosis and treatment.

Neuropathic foot causes changes in normal foot configuration, when the predominance of shortening flexors elevates the medial longitudinal arch, forming excavation or varus deformity of the foot, with hammer toes (Fig. 15.4). During gradual foot excavation, distribution of pressures is changing, with plantar pressures of the hypotrophic foot increasing typically under distal heads of metatarsals, mainly the first ray, less the fifth and the second rays. These excessive pressures of more than 65 N/1 cm^2 with subsequent formation of plantar callosities are a high risk factor in terms of development of skin defects and ulcerations. Armstrong [2] has proved that in patients with CHOA and neuropathic ulcerations, the incidence of excessive plantar pressures is markedly higher than in patients with neuropathy without ulcerations or ischemic disorders (Figs. 15.5 and 15.6). It is not clear why in patients with a unilateral acute CHOA there are no similar increased plantar pressures on the contralateral (intact) side [3, 11, 71, 74, 103].

Despite frequent disorders of the gait mechanism due to loss of proprioception and nociception, as well as muscle weakness, and despite limited mobility and impaired foot configuration, walking on flat, level ground is only slightly altered, while walking on uneven ground is difficult [74].

Where neuroarthropathy has developed from long-term polyneuropathic changes triggered by external injuries, capsular cheiroarthropathy and osteoclasia of bone and joint structures, the midfoot arch will be falling, with a gradual change of the foot configuration from excavation to calcaneo-planovalgus deformity.

For this reason lesions causing the most severe forms of disintegration of the foot arch, particularly of the medial arch responsible for development of the rocker bottom foot deformity, occur as a rule in the Lisfranc joint and the subtalar region [3, 5, 13, 68, 71, 74, 103].

Schon´s classification system of CHOA [104] is based on four types of deformities, with three subtypes each, divided by individual deformity patterns caused by disorders of the foot arch and

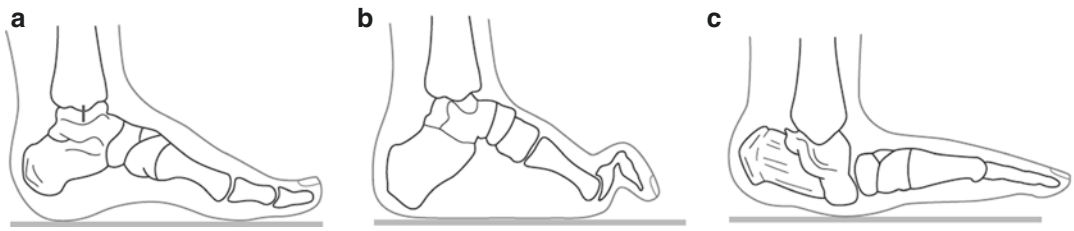


Fig. 15.4 Progression of neuropathic diabetic foot to neuro-osteoarthropathic foot. (**a**) Physiological arch of a healthy foot; (**b**) neuropathic foot (pes cavus varus excavatus et digiti hamati); (**c**) Charcot rocker bottom foot deformity

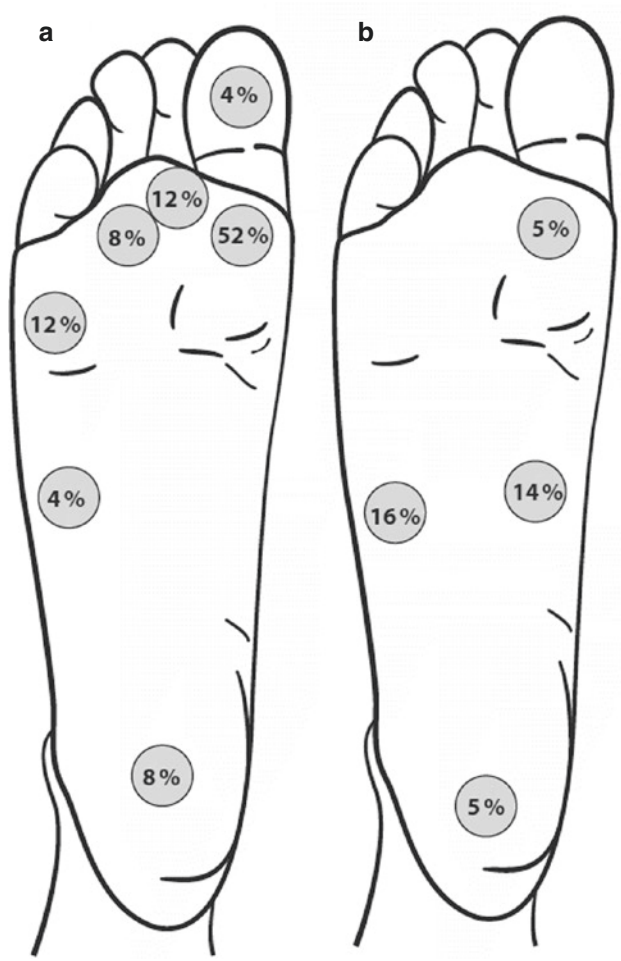


Fig. 15.5 Differences in weight distribution in neuropathic (**a**) and osteoarthropathic diabetic foot (**b**)

osteoclasis associated with necrosis, fragmentation or loosening of soft tissue structures in individual parts of the foot:

I. Lisfranc deformity
II. Naviculocuneiform deformity
III. Perinavicular deformity
IV. Transverse tarsal deformity

The outcomes of treatment of the involvement of the proximal foot with a collapse of the medial or lateral longitudinal arch are considered to be the worst, regardless of whether they were treated conservatively or operatively.

Type I involvement tends to result in valgus deformity, widening of the foot with symptomatic bony prominences and skin breakdown. Medial arch collapse and development of rocker bottom foot deformity prevails in types II–IV of the Schon's classification.

A more precise and currently the most commonly used classification is the scheme developed by Sanders and Frydberg [101] (Fig. 15.7) which differentiates between all locations of the involvement of the fore-, mid- and hindfoot.

If there develops osteoclasia, ligamentous and capsular structures become lax with the following disruption and minor or larger hematomas and hemarthrosis. Bone mass loss, bone matrix in particular, causes trabecular microfractures in the subchondral bone with osteoclast–osteoblast imbalance.

Fragmentation and avulsions can be seen mainly along the edges of articular facets. Their healing reduces elasticity and increases stiffness of the bone [67]. The initial changes in the form

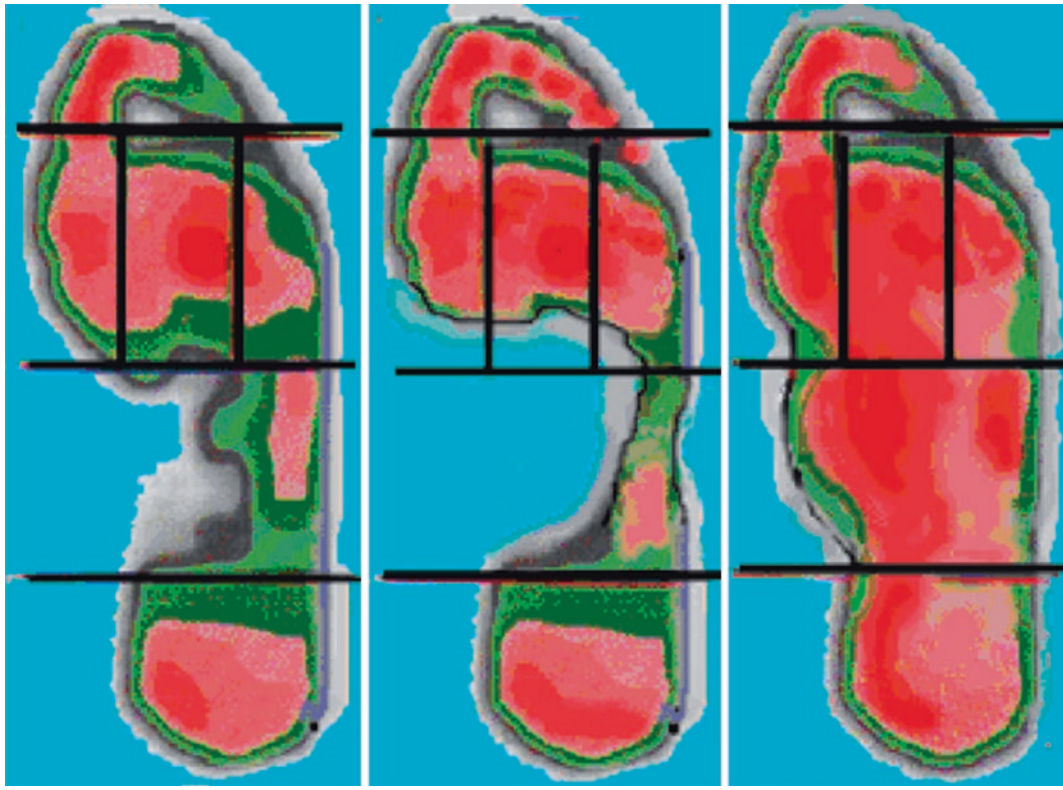


Fig. 15.6 The plantar sole is divided to the parts – toes forefoot, midfoot and heel

of fragmentation occur at the site of maximum action of static and dynamic forces, particularly on the distraction, less on the compression side, which is the first site to exhibit sclerosis of articular facets, destruction of edges, usuration, osteolysis, with formation of osteophytes and later also with fragmentation. Flattening of the arch of the neuropathic foot (pes excavatus) in the subtalar region and Chopart joint leads to posterior fragmentation of this and the talonavicular joints, resulting in a progressive collapse of the arch by subluxation of tarsus downwards. This is followed by decrease of excessive pressures of distal heads of metatarsals and toes on the planta, causing osteopenia or even osteolysis of these heads, and of the stress that was responsible for fractures of metatarsal shafts. Valgus deformity of the midfoot will increase pressure in the distal part of the first metatarsal and distal phalanx of the great toe contributing to another pattern of distribution of skin defects and ulcerations in CHOA, as compared to the neuropathic foot.

15.4 Diagnosis

Early diagnosis is of key importance to a successful treatment. Within the current European medicine approach which puts emphasis primarily on the location of pathological processes, CHOA is considered to be merely a marginal issue of internal diabetology, neurology, orthopaedics, podiatry, rheumatology and dermatology, despite the severity of this disease and its prognosis and in spite of the fact that its treatment is not always successful and may lead to repeated amputations [62, 63, 94, 124].

Diagnosis is established on the basis of the patient´s medical history, clinical and radiographic examination and laboratory tests.

The patient's medical history should be checked for family history of diabetes mellitus of both types and other metabolic disorders. Examination of the medical history of a diabetic patient should focus also on initial lower extremity neuropathic disorders of all types, both sensorimotor and autonomous, including sudomotor

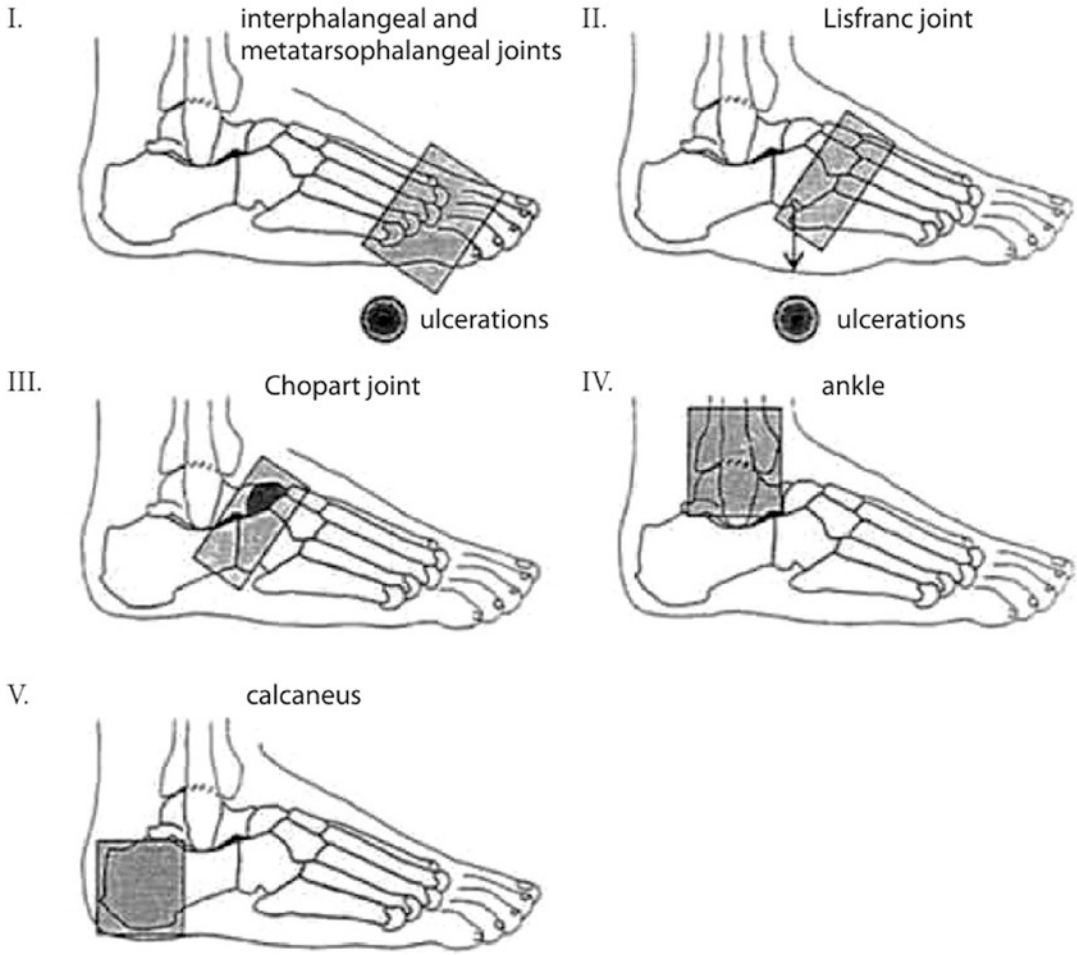


Fig. 15.7 Sanders–Frykberg anatomic classification for Charcot osteoarthropathy

(sweating) disorders, local hyperthermia, swellings, mobility and balance problems and rapid changes in foot configuration while differentiating between static age-related deformities and CHOA. CHOA is markedly more frequent if other diabetic complications are identified, nephropathy and retinopathy in particular [24, 94].

In case of the patient's subjective complaints, attention should be paid to proprioception and nociception disorders, taking into account that in CHOA sensitivity to heat may persist for a longer time, while sensitivity to cold disappears quite soon, as well as to all signs of muscle weakness and limited mobility. It is necessary to follow up any common injury in the region of the ankle and foot (sprain, capsular lesion with a periarticular hematoma, contusion or fracture) in order to eliminate it as a cause of CHOA onset and progression, even if the patient does not report any clinical manifestations indicating the presence of polyneuropathy.

Both clinical and radiographic findings may mimic mainly inflammatory diseases. In a diabetic patient with trophic defects and ulcerations, distinction between the two conditions is complicated particularly in case of deep infection defects and gangrenes, with a potential of development of cellulitis, abscess and continuous osteomyelitis by propagation of the infected defect. Of great help in the diagnosis may be assessment of the blood supply as an ischemic and neuroischemic foot only rarely progresses to a neuroarthropathic foot [50]. On the contrary, a relatively well preserved or even exaggerated arterial blood flow in the foot on the dorsum of the foot indicates a potential presence of CHOA and causes local hyperthermia, as compared to

the contralateral foot or intact parts of the symptomatic foot, with a temperature differential of more than 2 °C [24, 66]. This temperature differential indicates a pathological activity of the process, mainly osteoclasia, and after its decline or resolution, CHOA may be reclassified into the coalescence and remodelling stage [24, 67, 100].

Clinical examination should include examination of peripheral sensomotor and autonomic neuropathy. The preserved sensitivity to touch (filaments) and heat, with a rapid loss of sensitivity to cold in the early stages, indicates a special type of sensitive neuropathy in the first stage of CHOA. In later stages, sensitivity gets impaired in general [67].

In radiographic examination, detection of initial changes is determined by the resolution capacity of plain radiographs. In addition, given the average age of patients with CHOA, the changes may be overlapped by structural changes of degenerative, osteoporotic and rheumatoid nature corresponding to the patient's age, gender and habitus [43, 109, 111]. Computer tomography and magnetic resonance imaging have a much higher sensitivity and specificity, although they are less available. Hyperaemia may be confirmed by three-phase bone scan based on 99mTc-labelled methylene diphosphonate; however, it is impossible to clearly differentiate between osteomyelitis and increased resorption metabolic activity. Similarly, also gallium bone scan is usually positive both in case of infection and noninfected neuropathic bone lesion. The best resolution capacity is provided by the combined technetium bone scintigraphy (99mTe) with indium-labelled leucocytes [24, 34, 67, 100]. A negative scan excludes the incidence of acute CHOA in the phase of rapid bone resorption [3, 5, 6, 9, 10].

In *laboratory tests*, diagnosis of the chronic form of CHOA is associated mainly with markedly elevated alkaline phosphatase level – the bone metabolism marker. These tests relate particularly to calcification, although they may not always reflect synthesis of bone matrix and collagen [24]. Concentration of carboxy-terminal telopeptide of type 1 collagen (1CTP) as the marker of osteoclastic bone resorption is markedly elevated in the venous system of the dorsum of the foot affected by acute CHOA as compared to its chronic form, while there are no significant differences in concentration of carboxy-terminal propeptide of type 1 procollagen (P1CP) as the indicator of osteoblastic bone formation in both forms, which proves excessive osteoclastic activity in the acute phase without the concomitant increase of osteoblastic activity [24]. On the basis of these differences, Gough [37] has demonstrated a disorder of physiological balance between the physiological osteoclasia and osteoplasia, ensuring the skeletal integrity under normal conditions, in diabetic patients with CHOA, where excessive bone matrix resorption through increased osteoclastic activity is not accompanied by increased osteoplastic synthetic activity. If we accept the opinion of Jeffcoat [51] and Hoffbauer [45, 46] on the role of pro-inflammatory cytokines in CHOA onset and progression, laboratory tests of serum activity may be helpful in diagnosis. The diagnostic value in differentiation of inflammatory parameters, especially in case of ulcerations, has however a limited value also with regard to other diseases, particularly myoskeletal tuberculosis, that may exhibit medium- and lower-level inflammatory serum activity, or seroactivity may be absent [60].

Complete blood count and erythrocyte sedimentation rate should be part of the initial routine examination in order to eliminate inflammation. However, it has to be taken into account that deep infection and CHOA may occur simultaneously in the same patient [4, 34].

15.5 Clinical Features

According to Eichenholtz, CHOA is clinically manifested in three basic forms:

- Acute, with acute symptoms indicating CHOA onset and progress (Fig. 15.8)
- Subacute, when certain symptoms of the acute form subside, with decreasing differences in temperature, subsidence of swelling and osteoclastic changes and fragmentation typical of the acute phase stabilised
- Chronic, with subsidence of subacute symptoms and manifestation of destructions and subsequent skeletal disintegration associated with signs of fragmentation healing through hyperostotic changes, decreasing differences in temperature, persistence of mild swelling and sometimes with formation of callosities and defects at the sites of excessive overload

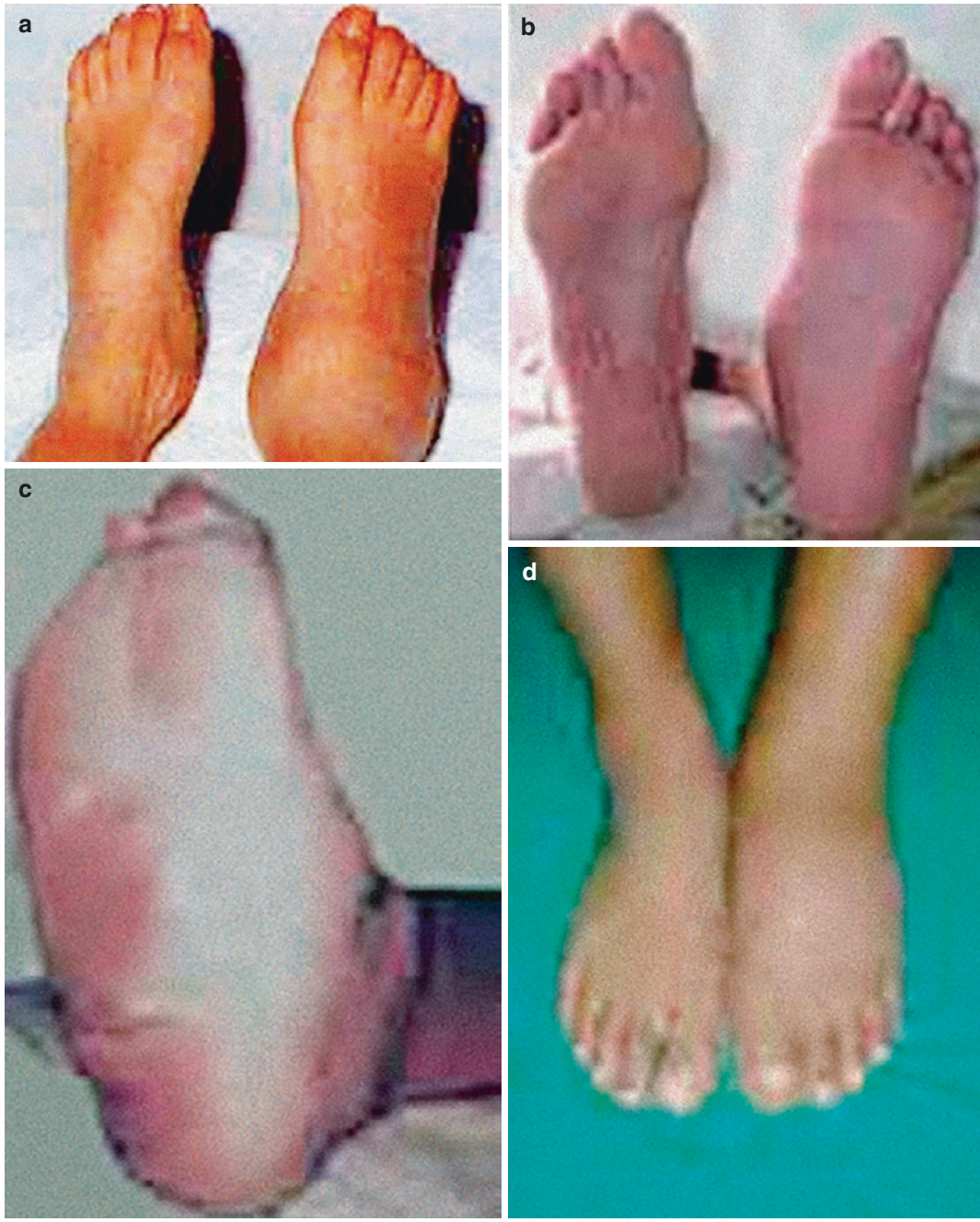


Fig. 15.8 Foot in the CHOA acute stage. (**a**) Acute CHOA in the region of the ankle with a marked swelling of soft structures; (**b**) involvement of the left foot with swelling and subsequent fall of the elevated neuropathic longitudinal arch progressing to planovalgus deformity; (**c**) massive swelling of the midfoot with the longitudinal arch progressed to planovalgus deformity or even rocker bottom deformity foot; (**d**) swelling of soft tissues of the dorsum of the midfoot

Chronic stage may progress to the phase of healing or, more often, the pathological process after latent periods exacerbates probably due to the adverse effects of external factors [43, 44]. This is why other authors divide the CHOA course into two stages, namely, the acute and post-acute ones [3, 13].

Table 15.1 Acute CHOA symptoms

Changes			
Vascular	Neuropathic	Bone–joint	Skin
Preserved pulsation in feet, erythema, swelling, hyperthermia	Lack/reduction of: Nociception, proprioception, deep tendon reflexes, anhidrosis	Hypermobility, rocker bottom foot deformity, medial tarsal subluxation, subluxation of toes, equinovarus hindfoot deformity	Hyperkeratosis, fissures, dry Cutaneous and subcutaneous hypotrophy, neuropathic defect, infection

Criteria of acute CHOA (Table 15.1) include a typical presentation of a swollen and erythematous foot with marked temperature differences (2–7 °C) between the affected and intact locations and the contralateral foot [24, 81], without general fibrillation. It is associated with laxity of capsular and ligamentous structures, bone hyperaemia and bone resorption and destruction.

Mild pain may be caused by fragmentation and incongruence of the joint, although reduction or loss of nociception keeps it below the level experienced by nondiabetic patients after an injury [81]. Within 2–3 weeks there occur fragmentations, subluxations in small joints [5, 24] with symptoms of instability and impairment of joint functions [81]. Examination of passive range of motion may reveal loss of the joint configuration and congruency. Ulcerations may develop in typical locations. The patient´s medical history often contains information about injury shortly before the onset of the disease, indicating the triggering mechanism of acute CHOA.

Swelling associated later with foot deformities, mainly progression to planovalgus deformity, with mild pain without fluctuations are the main clinical features of the acute phase of CHOA. Absence of infected defects indicates absence of inflammatory bone changes.

The patient´s medical history should be checked for family history of diabetes mellitus of both types and other metabolic disorders. Examination of the medical history of a diabetic patient should focus also on initial lower extremity neuropathic disorders of all types, both sensorimotor and autonomous, including sudomotor (sweating) disorders [120], local hyperthermia, swellings, mobility and balance problems and rapid changes in foot configuration while differentiating between static age-related deformities and CHOA [12].

Mild periarticular swellings with no obvious seroactivity are usually caused by cheiroarthropathy, resulting from type I collagen-type disorder, particularly in the insidious onset of the disease. They decrease elasticity of ligaments, causing their subsequent fragility and laxity of joint and ligamentous structures. Acute forms with marked swelling are often associated with inflammatory changes resulting from minor injuries and ligament laxity for the above-mentioned causes. They may trigger a cascade of pre-inflammatory changes through increased production of inflammatory cytokines, including TNF-α and IL-1β, leading to a marked osteoclastogenesis through increased expression of pro-inflammatory factor NF-kB. Its activation increases secretion of osteoprotegerin and receptor activator of nuclear factor (RANK [46, 51, 52]). These causes probably participate in clinical manifestation of acute CHOA through RANKL–NF-kB pathway. External factors include mainly injury, both single and repeated [12].

Criteria of chronic CHOA include the presence of characteristic radiological changes, such as bone destruction, fragmentation, osteolysis and disorganisation of bone–joint structures and hypertrophic changes in bone tissue undergoing the process of reparation, proliferation, sclerotisation and bone fusion. The clinical condition is assessed as a chronic form when radiography does not show substantial changes for more than 6 months; the foot is without swelling and local temperature differences [5, 32].

The chronic form of the diabetic CHOA foot (Fig. 15.9) develops also when the florid form progressed subclinically and gradually, being overlapped by angiopathic ischaemic or even ulcerative changes with swelling, and going

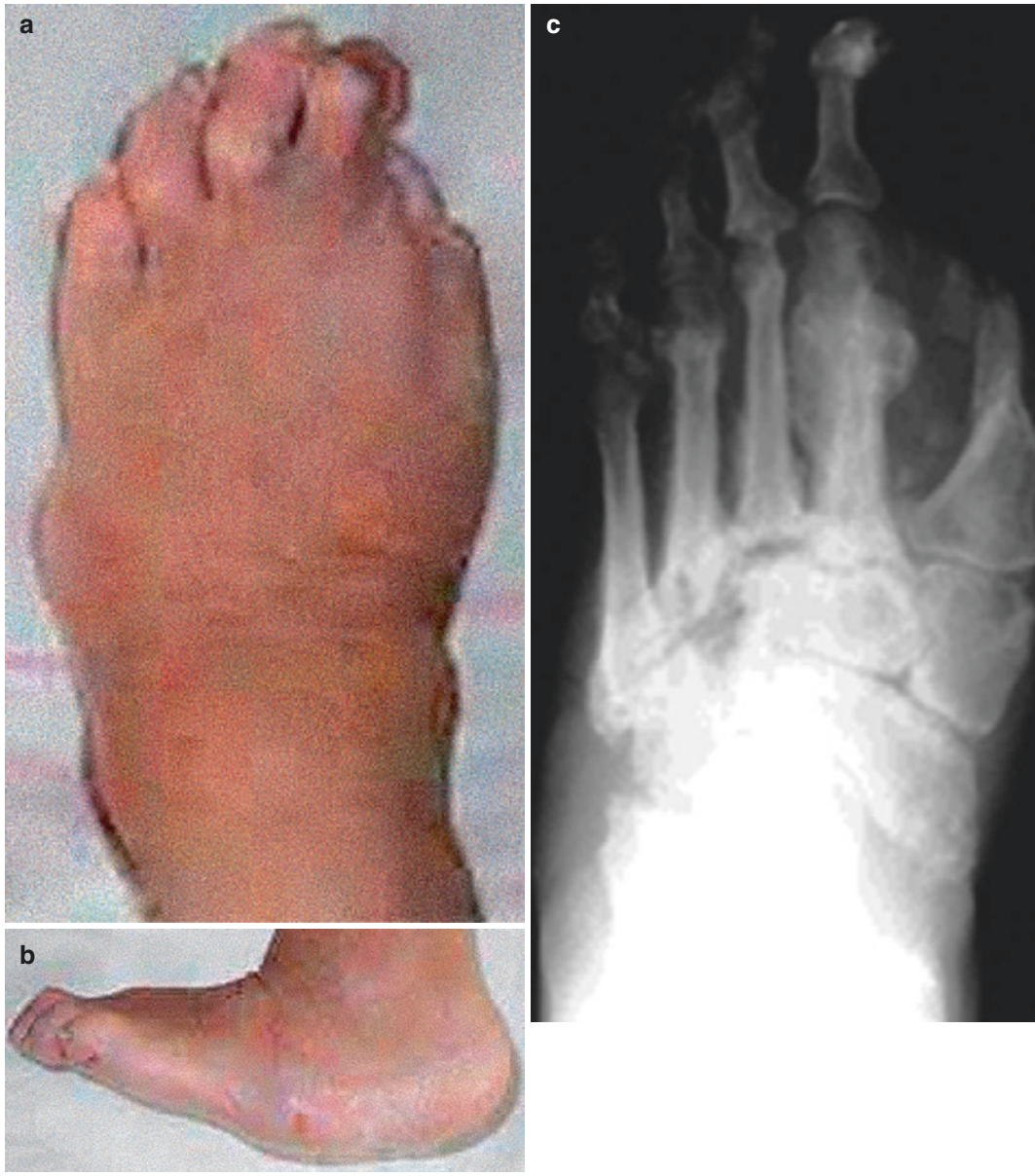


Fig. 15.9 CHOA neurovascular lesion associated with gangrene and osteomyelitis in the advanced stage of healing and reparative changes. (**a**–**c**) Difference between healthy and affected foot

almost unnoticed due to reduced nociception. CHOA diagnosis is confirmed only after obtaining radiological evidence of fragmentation and destruction, exhibiting typical osteoclastic changes with development of planovalgus or rocker bottom foot deformity [13, 16], sometimes even without clinical manifestation of acute form of CHOA, only with slowly developing features typical of stage I or II according to Eichenholtz that is in the extended Eichenholtz´s scheme classified as stage IV. It is characterised by "6 D" changes: density, destruction, debris, distension, dislocation and disorganisation.

The sign of subsidence of osteoclastic activity and progressive reparation (Eichenholtz stage III) is a complete reversal of the negative development of

Table 15.2 Proposed modification of Eichenholtz classification

Stage	Features	Treatment[a]
Stage 0 – clinical manifestation without radiological changes	Reddening, swelling, increased temperature of the foot	Limited weight bearing (where appropriate, NCS or PPB), follow-up
Stage 1 - fragmentation	Periarticular fractures, joint dislocation, instability, foot deformity	NCS, without weight bearing
Stage 2 – coalescence	Reabsorption of bone debris	NCS later RLB
Stage 3 – reparation	Stable plantigrade foot	Anti-stress diabetic shoes[b] with custom-moulded "footprint" insole
Stage 4 – insidious form only with radiological changes	Subclinical stage with slow development of typical radiological changes	Anti-stress prophylactic orthopaedic diabetic shoes with custom-moulded plantar support

NCS non-reinforced circular plaster cast, *RLB* ROM limiting walking brace, *PPB* prefabricated pneumatic walking brace

[a]Orthotic devices

[b]Extra depths shoes and plantar pressure relieving orthoses

structural changes, rounding of the bone ends, presence of advanced reparation with sclerotic changes in sharp edges, synostoses with callus formation and fusions of residual osteoarticular structures.

Although the CHOA symptoms may be preceded by symptoms of polyneuropathy with ischemic changes, in other cases only the acute CHOA form may be the first evident clinical symptomatology. Polyneuropathy, mainly in elderly patients, may have a subclinical form, and certain evident disorders may be attributed to the general age-related habitus, primarily in patients with undiagnosed type 2 diabetes mellitus.

As the so far used Eichenholtz classification into three stages (Table 15.2) does not include the additional two possible forms of the complete range of features (clinical and radiological), the delay of identification of radiological changes caused by certain limitations of imaging by plain radiographs as compared to other substantially more sensitive imaging (CT, MRI, PET) may lead in initial acute symptomatology to a negative radiographic finding. Therefore, authors recommend addition of stage 0 defining this CHOA form. Based on our experience in long-term follow-up of patients with various forms of CHOA, we recommend to add also stage IV for insidious form of slow radiological development of typical structural changes, including the osteoarticular ones, typical of CHOA without a primary clinical manifestation of the acute form.

15.6 Radiology

Radiological presentation mainly of the early acute stage is unspecified and changes according to the location of involvement.

Some authors [118] distinguish between two forms of CHOA radiological manifestation:

- *Destructive* (pseudotabetic), with prevalence of destruction and disintegration of osteoarticular structure and with manifestations of hypertrophy and sclerotic changes in stages II and III according to Eichenholtz
- *Mutilating* (atrophic, resorption, pseudogout) with marked osteoclasia and evident loss of bone–joint structure

There is no sharp dividing line between these two forms; they may turn into each other or occur concomitantly. The underlying factor in both of them is osteoclasia with loss of bone matrix and of bone structure with residual fragments.

In 1986, Wagner described five types of bone changes in CHOA [128]:

1. *Osteopenia* (osteoporosis) develops as a rule as the initial unspecified radiological symptom on the foot. It may occur as part of generalised osteoporosis. Joint space, particularly of the Lisfranc and Chopart joint, are widened; their bones, edges in particular, are

shown as unclear osteoporotic structures. It is painless unless there occur fragmentation and swelling of feet.

2. *Osteolysis* is characterised by virtual loss of bone–joint structures with diaphyseal narrowing and fragmentation, including pencil-in-cup deformity of distal metatarsal heads (osteoclasia). Bones exhibit translucent cystoid changes similar to those in Sudeck's osteoporosis, fragmentation along the edges of articular surfaces and usurations, joint disintegration and disorders of longitudinal and transverse arches of the foot.
3. *Hyperostosis* develops around the affected Charcot joints and at the sites of healing fragmentations, especially metatarsal shafts. Exostoses can be observed at the sites of excessive pressure. Hyperostosis is less frequent in CHOA associated with infected ulcerations.
4. *Spontaneous subluxation and dislocation* are linked to ligamentous destruction, atrophy of small intercostal muscles and marginal joint fragmentations. They are characterised by claw and hammer toes, valgus deformity of big toe and rapidly progressing valgus deformity of the foot (also in case of initial neuropathic excavation). The midfoot arch, mainly in the subtalar region, collapses, resulting in a typical arthropathic rocker bottom foot deformity.
5. *Complete destruction* and *disintegration* of the affected osteoarticular structure with shortening and widening of the foot, changes in its configuration and collapse of the entire arch, loss of bone structures of the mid- and forefoot or their parts and its valgus deformity, with the incidence of atypical prominences. According to Young [127], osteopenia may develop already in the early stage of CHOA, and it has been demonstrated that although density of the axial skeleton bones may be well preserved, the lower limbs exhibit a significant reduction of bone density, which is more marked in the affected limb in case of asymmetrical CHOA involvement [16].

Decrease in bone density may lead to decrease of the bone strength as structural bone density is the main factor of its strength [16, 17] and the risk rate of its fragmentation [92].

Classification of radiological changes of the skeleton of the ankle and the foot affected by CHOA into three stages [1, 14, 15, 27, 31, 43, 62] respects the original Eichenholtz´s scheme:

- Stage I – development of the disease (acute, florid), with development of osteoclasia, bone–joint destruction, fragmentation, laxity of the affected joint structures and disintegration of the foot
- Stage II – coalescence, with the incidence of hyperostotic and periosteal calluses and beginning bone fusions of larger bone fragments, resorption of minor debris and small avulsions
- Stage III – reconstruction (healing), with remodelling and fusion of the residual bone and joint architecture and rounding of the non-fused fragments, bone and fibrous ankylosis of the residual skeleton with hyperostosis and sclerotic changes and structural fixation of configuration disorder

In terms of clinical and radiological development of the disease and its treatment, we propose a more accurate differentiation (Table 15.5).

The time interval between individual stages is variable. The process is often discontinued in the first or second stage and may continue even after several years [21] or exacerbate [43].

Radiography is the basic diagnostic method, although interpretation of radiographs may be problematic, particularly in the early stage of CHOA, as there may occur negative findings or doubts concerning differentiation between early CHOA symptoms and common age-related degenerative static changes. Atrophic and hypertrophic changes may develop simultaneously and are sometimes difficult to be differentiated from the age-related, hypoestrogenic osteoporosis, post-trauma Sudeck´s syndrome and inflammatory changes [26, 37, 61, 100, 102].

According to Armstrong [2, 3], osteoarthropathic changes occur most frequently in the region of the Lisfranc (48 %) and Chopart (34 %) joints and then in the ankle and subtalar region (13 %), in the forefoot (3 %) and in the calcaneus

(2 %). Other authors [5, 6, 11, 13] report different percentage based on evaluation of their groups of patients. Philip [88] reports their incidence in midfoot in 20–50 %, at the level of Lisfranc joint in 15–45 %, Chopart joint in 30 %, in the ankle in 3–10 % and calcaneus in 1 % of cases. The most commonly used Sanders and Frykberg classification [101] into five patterns presents the following distribution of involvement:

1. Forefoot, including interphalangeal joints, phalanges, metatarsophalangeal joints and distal metatarsals in 26–68 % cases, usually in association with distal plantar ulceration.
2. Tarsometatarsal (Lisfranc) joint, most often in the second metatarsal base and middle cuneiform (leading to a rapid collapse of the longitudinal and transverse arch with valgus deformity) in 15–43 % of cases.
3. Naviculocuneiform, talonavicular and calcaneocuboid joints leading to fracture dislocations of the Chopart joint and flattening of the medial longitudinal arch and medial ulcerations under the navicular and first cuneiform bones approximately in 32 % of cases.
4. Ankle joint (tibiofibular and tibiotalar articulation). Although it accounts only for 3–10 % of all cases, it causes the most severe deformities with functional instability. It often occurs after minor injuries (ankle sprain) in patients at risk, but structural changes and disintegration of the ankle progress rapidly and result in rocker bottom foot deformity requiring reconstruction, fusion or amputation.
5. Calcaneus – osteopenia, fractures of the posterior third of the calcaneus and avulsions of the posterior tubercle in conjunction with shortening of the Achilles tendon occur only rarely and may be bilateral.

Radiological abnormalities observed in CHOA may be divided into:

- *Bone related*: osteopenia, pencil-in-cup osteolysis mainly of distal metatarsal heads, "hourglassing" when thinning of the diaphyseal cortex, mainly small tubular bones of toes, reduces the diameter of the shaft to the hourglass shape, and cystoid deposit form of the type of Sudeck´s speckled osteoporosis with cortical thinning or even defects. Fragmentation and fractures of metatarsal shafts can be observed, such as stress fractures, erosion, destruction, in the coalescence stage periostitis, exostoses and mainly juxta-articular; spread of infection to deeply located structures may contribute to development of osteomyelitis.
- *Joint related*: Charcot joints with widened joint space, in the subchondral region with sclerosis, osteophytes, subluxations and dislocations, marginal fragmentation most often of edges of the articular facets and osteolytic usuration [1, 14–16, 62, 116, 128, 129].

15.7 Imaging Techniques

Quality images are an indispensable part of the basic examination within differential diagnosis (Figs. 15.10, 15.11 and 15.12). In the early phase of the disease, radiography may cause certain diagnostic doubts due to its limited differentiation capacity. Detection of initial changes is determined by the resolution capacity of plain radiographs. In addition, the changes may be overlapped by structural changes of degenerative, osteoporotic and rheumatoid nature corresponding to the patient´s age, gender and habitus [15, 16, 62, 86].

Radiological image, particularly of the early acute CHOA stage, is unspecific; at the beginning it may be negative and changes in relation to location of the involvement.

15.7.1 Computer Tomography

Indication of computer tomography is quite rare in differential diagnosis, as the examination has a high sensitivity to structural changes but lower specificity than MRI. It does not provide adequate information about the share and changes of soft tissue structures around the structural bone changes. It is helpful in identification of minor fragmentations and periarticular debris, joint changes, endochondral in particular and assessment of individual stages of the disease and osteopathology in the already diagnosed CHOA

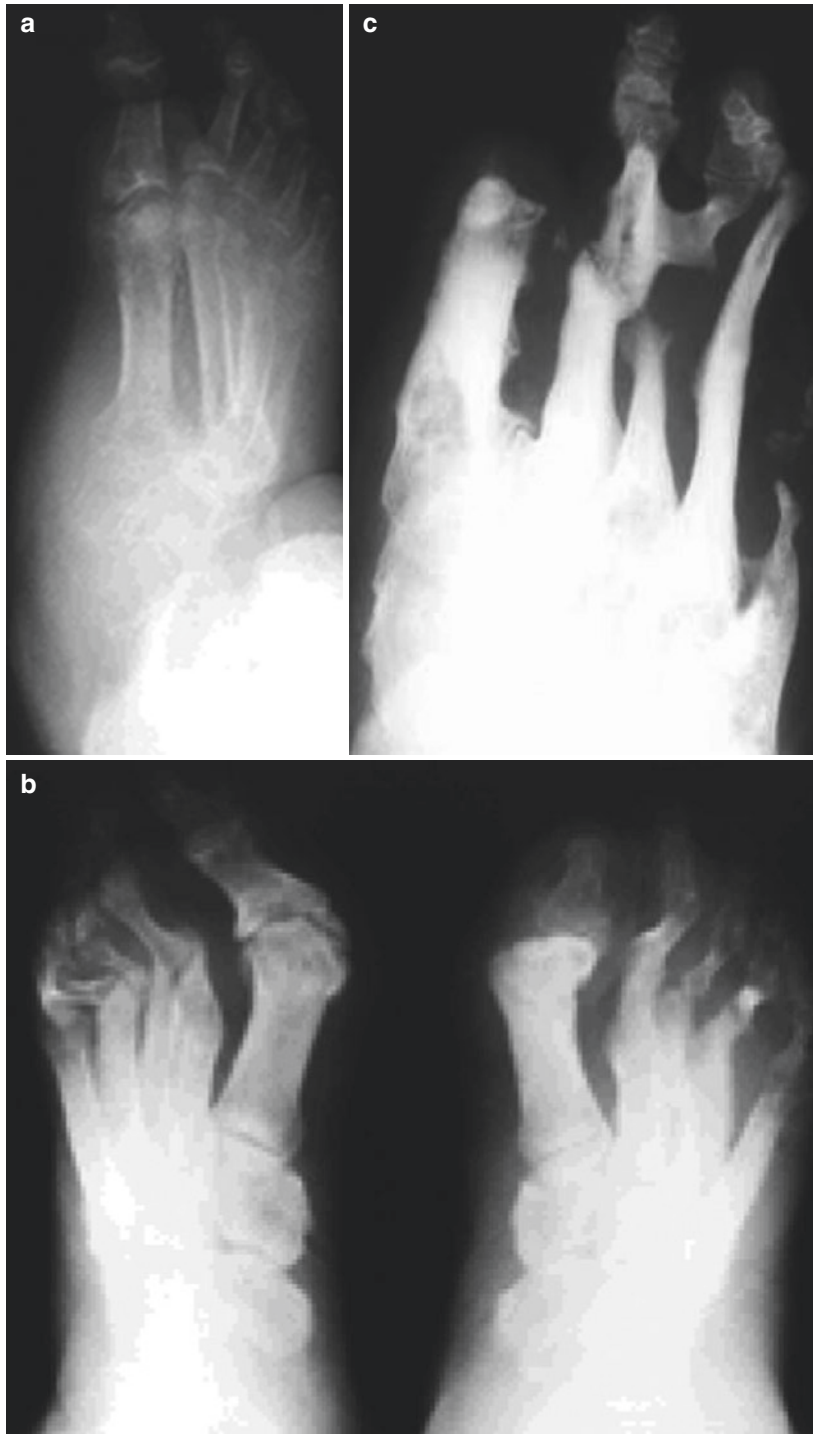


Fig. 15.10 Radiological changes of the foot in CHOA I. (**a**) Eichenholtz CHOA stage I with development of rocker bottom foot deformity due to collapse of tarsus in the Chopart and displacements in the Lisfranc joint. Osteoclastic fragmentations of the entire forefoot, medial calcinosis; (**b**) progressive reparation (Eichenholtz stage III) of bilateral CHOA of the forefoot with deformities of MTP joints and their posterior dislocations, pencil-in-cup deformities, periostitis, MTP I arthritis after marginal fragmentations, synostoses and sclerotic changes. Widening of the forefoot due to collapse of transverse arch; (**c**) synostoses of residuals after CHOA mutilation form

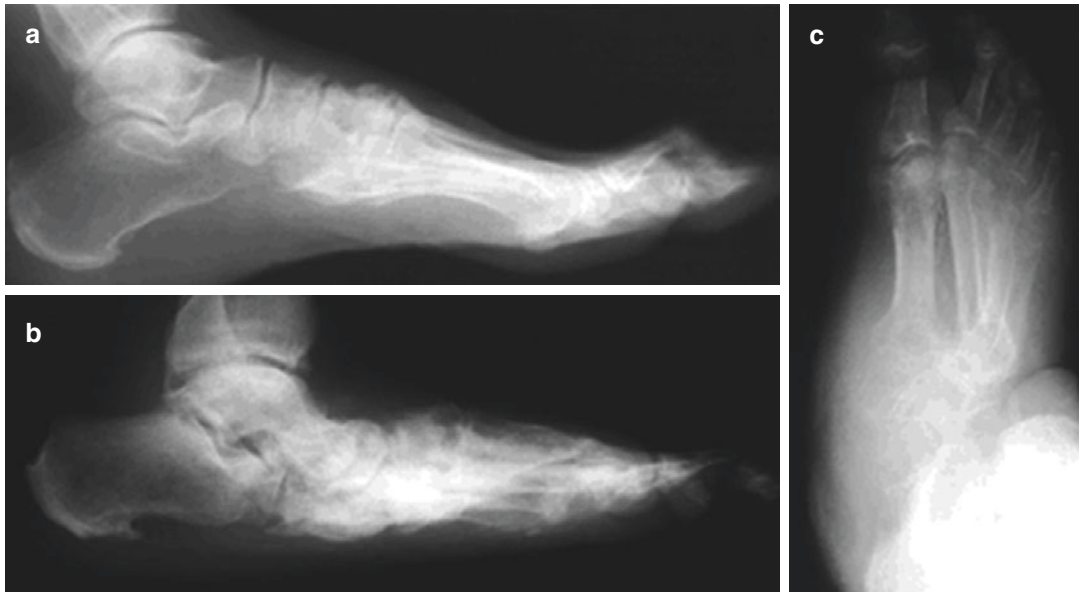


Fig. 15.11 Radiological changes of the foot in CHOA II. Disintegration of the midfoot arch with gradual cheiroarthropathy-induced laxity of joint capsules, marginal fragmentation and collapse into planovalgus deformity. Overloading of the plantar fascia with shortening of the triceps surae leads to calcar calcanei inferiorly and later also posteriorly. (**a**–**c**) Difference between healthy and affected foot

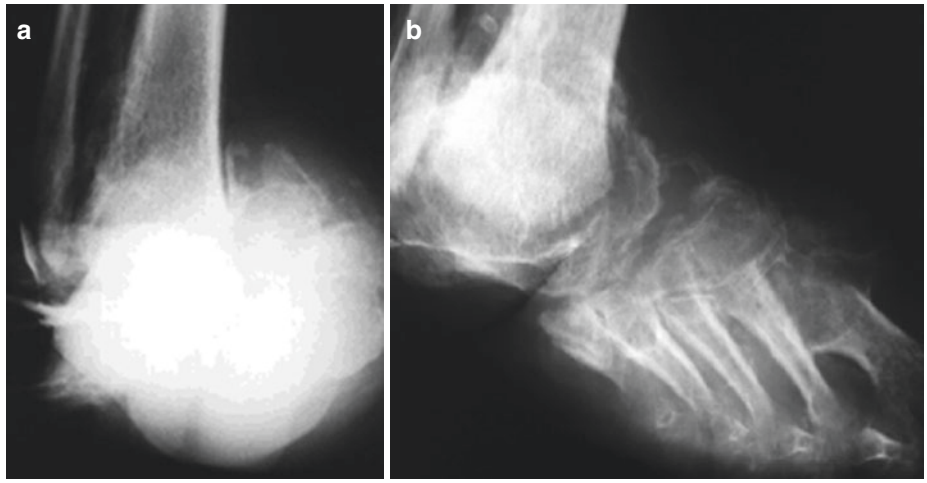


Fig. 15.12 Radiological changes of the foot in CHOA III. Severe calcaneovalgus dislocations associated with osteoclastic fragmentation of malleoli in TC joint and osteoclasis up to osteolysis of the distal tibia and subtalar region. Disintegration of the Chopart joint in the coalescence stage (Eichenholtz II). (**a**) Desintegration of the ankle joint with sequesters dislocated medialy; (**b**) The same foot with oblique projection

for the needs of therapeutic procedures (Fig. 15.13). According to the latest reports [6], new possibilities in differentiation of osteomyelitis (OM) and infection of soft tissues, or neuroischemic forms overlapping CHOA, are provided by 18 F-FDG proton emission tomography [59, 77].

15.7.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is used to differentiate acute or chronic CHOA and osteomyelitis, as well as the coincident form of both diseases (Table 15.3). This differentiation may be

a key to differential diagnosis of OM versus CHOA [1, 9, 14, 23, 26, 35, 69, 73, 78, 128]:

(a) In acute CHOA, a diffuse oedema of soft tissue structures with joint effusions and tear of the Lisfranc ligament between the medial cuneiform bone and the proximal head of the second metatarsal is a manifestation of cheiroarthropathy, with subsequent widening of the joint space. Lesion of this ligament is a key contributing factor for collapse of the stability of the midfoot arch, leading to planovalgus or rocker bottom foot deformity.

The intensity of bone marrow signals may be similar to OM – low signal intensity on T1-weighted and high signal intensity on T2-weighted images. In addition, joint destructions and fragmentation, cystoid formations, osteoclasia and widening of the medullary cavity can be observed in progressive cases [1, 5, 69, 73, 106, 116].

(b) Chronic insidious CHOA without evident acute clinical manifestation (Eichenholtz I) is characterised by "6 D" changes.

Widening and oedema are less clear on MR images or maybe even absent in the reparation stage. Subchondral cysts and erosions are characterised by low signal intensity on T1-weighted and high signal intensity on T2-weighted images. The images show joint deformities with marginal debris, subluxations or dislocations and bone proliferation. A typical chronic form is characterised by lower signal intensity on all sequences regardless of pulse frequencies [8, 69, 106, 116, 128].

15.7.3 Isotope Examination

The use of gammagraphy with technetium in differential diagnosis is relatively expensive and generally insufficiently specific, mainly in differential diagnosis of acute CHOA versus OM (Table 15.4). The presence of hyperaemia may be confirmed by three-phase skeletal scintigraphy by means of 99mTc-labelled methylene diphosphonate, although it is impossible to clearly differentiate between osteomyelitis and increased resorption

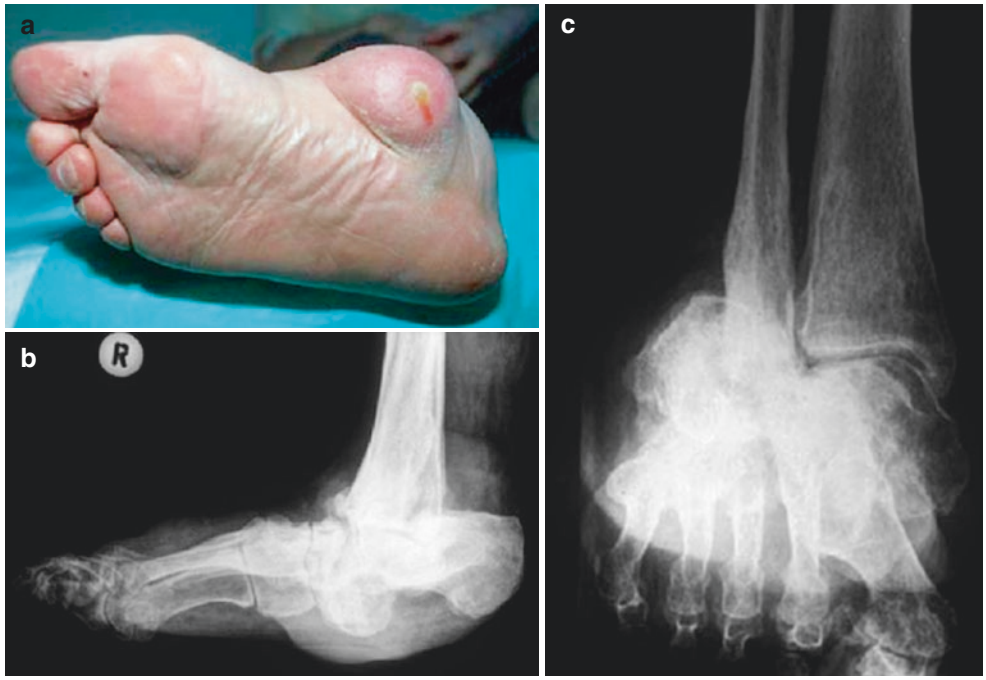


Fig. 15.13 The use of imaging methods in CHOA diagnosis. (**a**) Clinical manifestation of rocker bottom foot deformity; (**b**, **c**) images in two projections; (**d**) 3D CT scan of the same foot; (**e**) MR image of the collapse of the Chopart joint

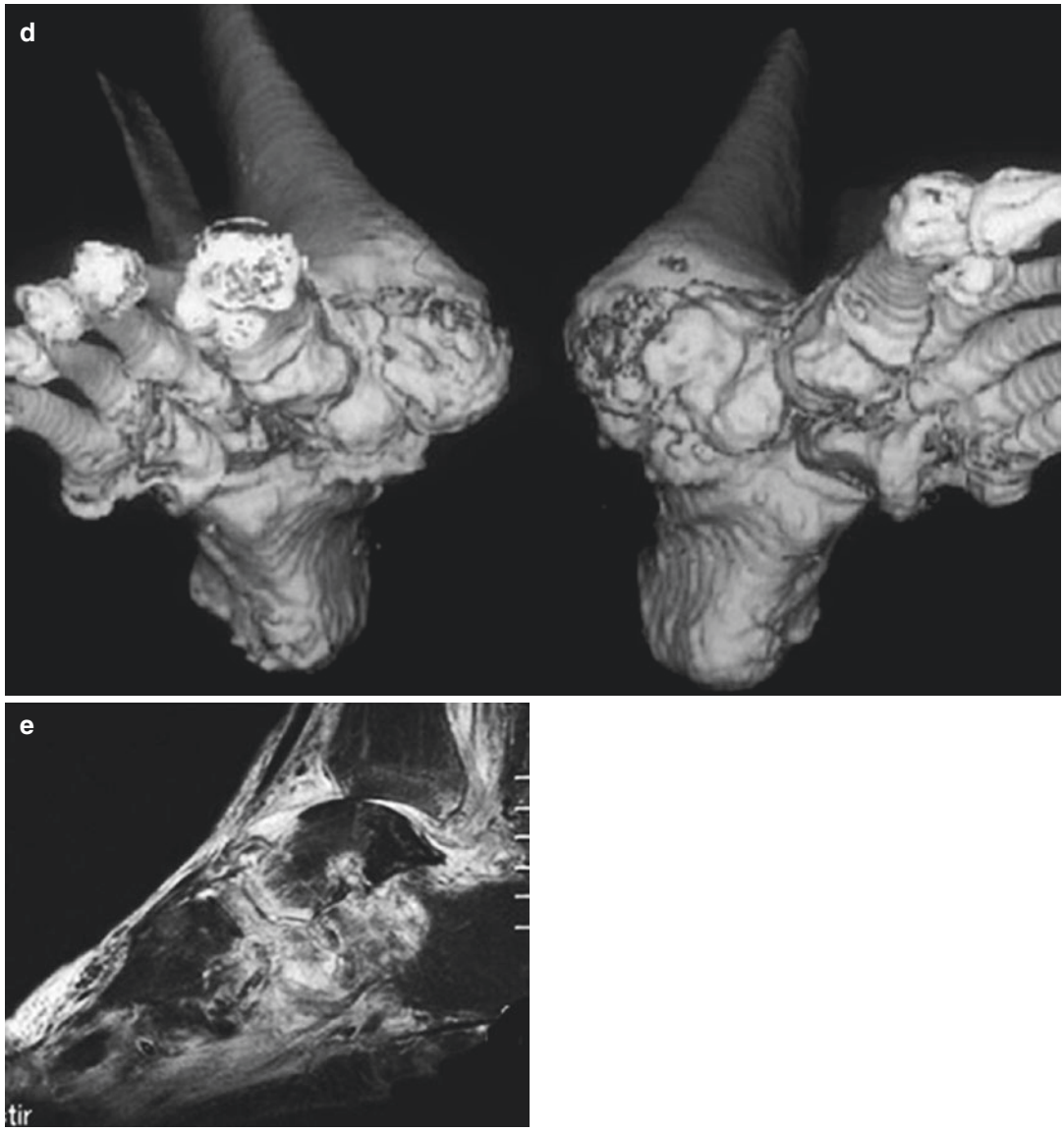


Fig. 15.13 (continued)

Table 15.3 MRI changes in CHOA differential diagnosis

MRI changes (bone marrow oedema)		
T1-weighted image	T1-weighted image	Differential diagnosis
Low signal	Low signal	Chronic CHOA
Low signal	High signal	Acute CHOA
Low signal	High signal	OM?, tumour?

According to Lee et al. [70]

Table 15.4 Diagnostic possibilities of scintigraphy

Tc 99 bone scan	HMPAO-labelled Le	Differential diagnosis
+	–	(+) CHOA (–) OM
–	+	(–) OM (+) infection of soft tissue structures
+	+	(+) OM and/or CHOA

According to Lee et al. [70]

metabolic activity. Similarly, also gallium bone scan is usually positive both in case of infection and noninfected neuropathic bone lesion. Scanning with the use of indium is more specific but due to high costs it is applied only rarely. The best resolution capacity is offered by the combined technetium bone scintigraphy (99mTe) with indium-labelled leucocytes which is reported to be the most suitable by recent studies.

The latest studies have shown that the most suitable method is scintigraphy using Tc-HMPAO-labelled leucocytes, providing a relatively good specificity and sensibility allowing to distinguish soft tissue infections from bone infections [10, 23].

15.7.4 Biochemical Examination

Biochemical examination plays an important role in differentiating acute CHOA from OM in case the results of examination are not altered, e.g. by infected superficial defect. In addition, it has been demonstrated that in chronic diabetic patients with a disorder of immunological condition, certain changes of laboratory parameters may be caused by inflammatory changes of other structures and organ involvement. Leucocytosis with left shift in the differential diagnosis is typical of acute osteomyelitis. Erythrocyte sedimentation rate responding to any inflammatory process in the organism is too non-specific to serve as a determining differential diagnosis factor. Marked elevation of alkaline phosphatase concentration – the bone metabolism marker – is linked rather to the diagnosis of chronic CHOA [87]. Elevation of CRP and inflammatory seromarkers should be considered with caution due to the above-mentioned problems mainly in polymorbid diabetic patients and patients with skin defects of neuropathic or neuroischemic origin, even if with superficial infection only [12]. They may be part of the screening examination for CHOA [58].

15.8 Interventional Diagnosis

Interventional diagnosis includes probatory biopsy of the affected bone structure and the surrounding tissue for histological and microbiological examination consisting of microscopic, cultivation (NSF, BK) and genetic tests (PCR, MTD) or where appropriate BACTEC and ELISA for detection of living microorganisms. Diagnostician´s experience, localisation of the bone disorder, its accessibility, general condition of the affected foot, the presence of defects and superficial infection are the determining factors for application of less aggressive needle or open biopsy. However, the needle biopsy finding may be sometimes misdiagnosed due to problems with targeting of the sampling site by the needle. Open biopsy, if necessary with a subsequent disinfection of the focus of infection after collection of the material, is usually more valuable in terms of diagnosis also because it allows sampling of more locations. The highest risk of open biopsy is potential secondary infection of the surrounding structures and bone; a lower risk is associated with damage to circulation already altered by the disease. Therefore, preoperative analysis of the approach, patient preparation, a nonaggressive surgical intervention and special postoperative care are key factors of a smooth interventional diagnostic procedure [12].

15.9 Differential Diagnosis

Success of various therapies used to treat individual disorders of the diabetic foot directly depends on an early exact diagnosis, before the florid stage of both diseases has caused irreversible structural changes and exacerbation of the foot function. The range of clinical and structural manifestations of both diseases in their early stage is quite broad, with little differences. Therefore only a whole complex of diagnostic methods may provide a sufficiently plausible diagnostic answer.

The complex of differential diagnosis consists of assessment of the local clinical features and the general condition of the patient, radiological examination, laboratory biochemical tests and histopathologic and microbiological examination. Sometimes interventional diagnosis by needle or open biopsy is also required for final differentiation of the diseases.

The aim of CHOA differential diagnosis is to differentiate it from other diabetic foot forms, the polyneuropathy itself and, in the acute phase, from inflammatory diseases (osteomyelitis and infection of soft tissue structures of the diabetic foot), mainly in case when the foot is already affected by skin defect, or infected ulcerations, as well as from foot disorders of diabetic patients, other than diabetic foot.

15.9.1 Differential Diagnosis Between Neuropathic and Ischemic Involvement of the Foot

Proper differential diagnosis between vasculopathy and CHOA in diabetic foot in patients with a long-term history of type 2 DM is often critical for the fate of the patient´s foot, particularly in case of neuroischemic form of the disease, due to a substantially different treatment approach. Of no less importance is detection of inflammatory changes of osteoarticular and soft tissue structures. Hesitation and delayed well-targeted disease often ultimately lead to amputation of the affected foot. Additional disorders of the foot causing in diabetic patients changes similar to CHOA may include in addition to osteomyelitis, also septic arthritis, myoskeletal tuberculosis, rheumatoid arthritis, gout, osteoarthritis and tumour [3].

Differential diagnosis must be comprehensive and requires certain experience in interpreting radiographic findings, mainly in cases when the clinical and radiological features of CHOA in the florid Eichenholtz stage I on a foot with defect of skin and OM in the neighbourhood of a bacterial contaminated defect may be similar on plain radiographs. CT and particularly MRI have a much higher diagnostic value in terms of sensitivity and specificity; the same applies to scintigraphy which, however, is not always readily available.

Differentiation between CHOA and osteitis or osteomyelitis in the diabetic foot is one of the fundamental tasks of differential diagnosis (Fig. 15.14). It requires an active approach with the use of a whole complex of available diagnostic methods for establishment of an early and correct diagnosis of the disease.

Despite a relatively small number of diabetic patients exhibiting clinical CHOA symptoms (at present about 600 patients in Slovakia), chronic subclinical forms with a slow progress and minimal or no symptoms are much more common in elderly diabetic patients, mainly those with a more than 10-year history of type 2 DM. It manifests itself as a rule after an accidental trauma (that may be the triggering factor of the subsequent clinical manifestation) and is usually revealed by radiographs obtained for other reasons.

Most doubts are associated with the neuroischemic form with skin defects of neuropathic type and sometimes slightly infected base, with a concomitant subclinical or secondary bacterially contaminated CHOA with a subsequent osteitis or osteomyelitis of structures affected by osteoclasia close to the skin defect. MRI is able to differentiate more accurately the initial discrete changes that cannot be always detected by standard radiography [12, 15, 16, 72, 130, 132] (Fig. 15.15).

Differential diagnosis of CHOA and OM must take into account also distribution of the affected locations (Table 15.5). OM affects most frequently the toes, metatarsal heads, calcaneus and malleoli, while CHOA predominantly involves the joints of the forefoot, Lisfranc and Chopart joints as well as TC joint [69].

Differentiation between CHOA with infected and noninfected structures, particularly in stages I and II according to Eichenholtz, is sometimes very difficult due to untypical features (Table 15.6). Progressive swelling of soft tissue periarticular structures, shift of fatty tissues and formation of abscess shown by repeated examinations with increased and extended marrow signal suggest osteomyelitis overlapping with CHOA symptoms.

Establishment of diagnosis during the first-degree examination by a specialist is based on assessment of clinical features, regular screening of diabetic patients mainly those with a long-term history of type 2 diabetes mellitus and regular preventive checks of feet and recording of

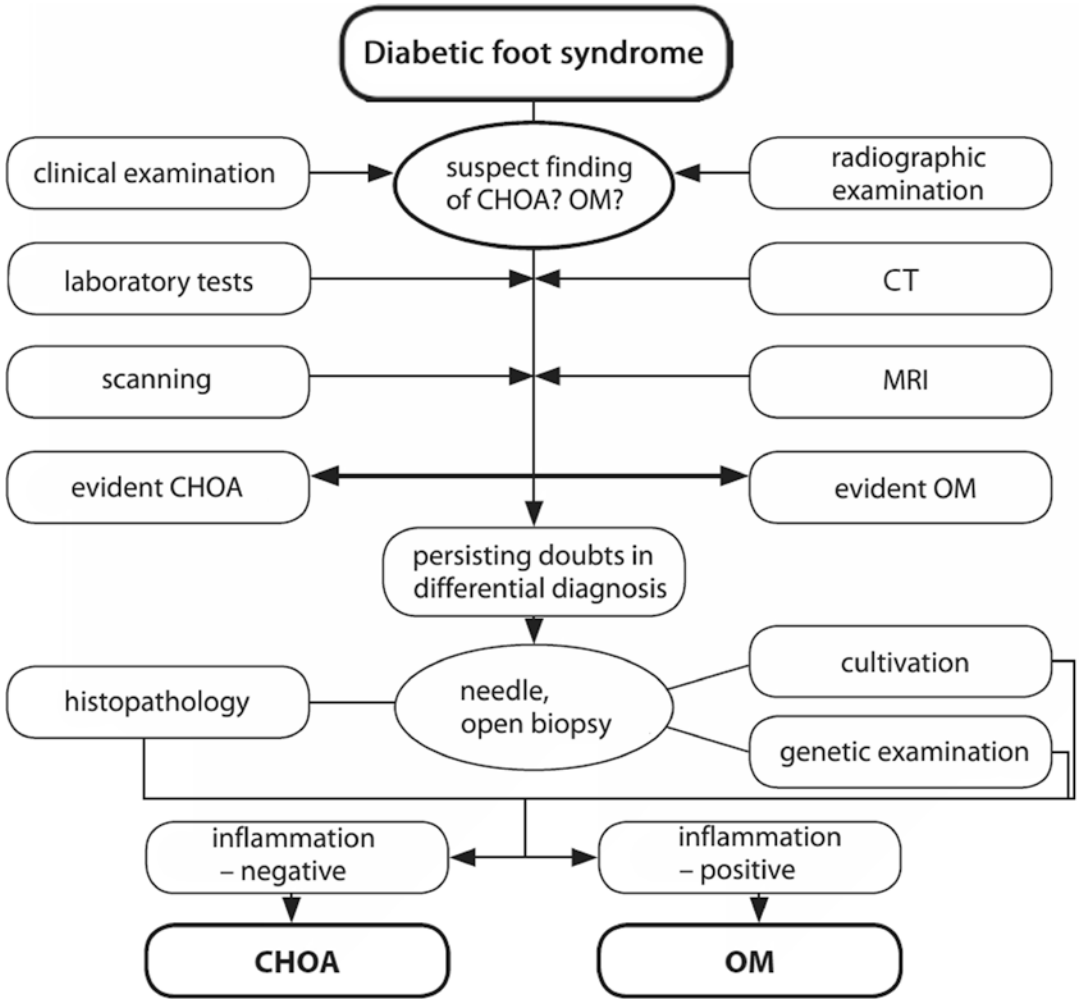


Fig. 15.14 Algorithm of diabetic foot differential diagnosis

changes, if any. Collaboration of diabeticians with orthopedists and rheumatologists allows differentiating between static deformities with functional decompensation, rheumatoid arthritis and other causes of changes in the diabetic foot.

Another significant group in terms of differential diagnosis includes infective inflammatory diseases of different aetiology, such as erysipelas, pyogenic osteomyelitis and arthritis of other etiopathology than diabetic osteoarthropathy and osteomyelitis, caused by penetration of infection through neuroischemic ulcerations. It may include also defects and rare inflammations with low metabolic activity, such as osteoarticular tuberculosis, atypical mycobacteriosis, mycotic and viral disease and leprosy.

Basic differential diagnosis of other diseases:

(a) Rheumatoid arthritis
(b) Congenital and acquired foot deformities
    - Congenital disorders
    - Pes calcaneo-planovalgus
    - Pes excavatus
    - Pes equinovarus
    - Morton´s syndrome
    - Post-fatigue fractures conditions
(c) Osteoarticular tuberculosis
(d) NBF (nerve blood flow) infections of foot structures
(e) Other foot disorders
    - Neurogenic
    - Oncogenic

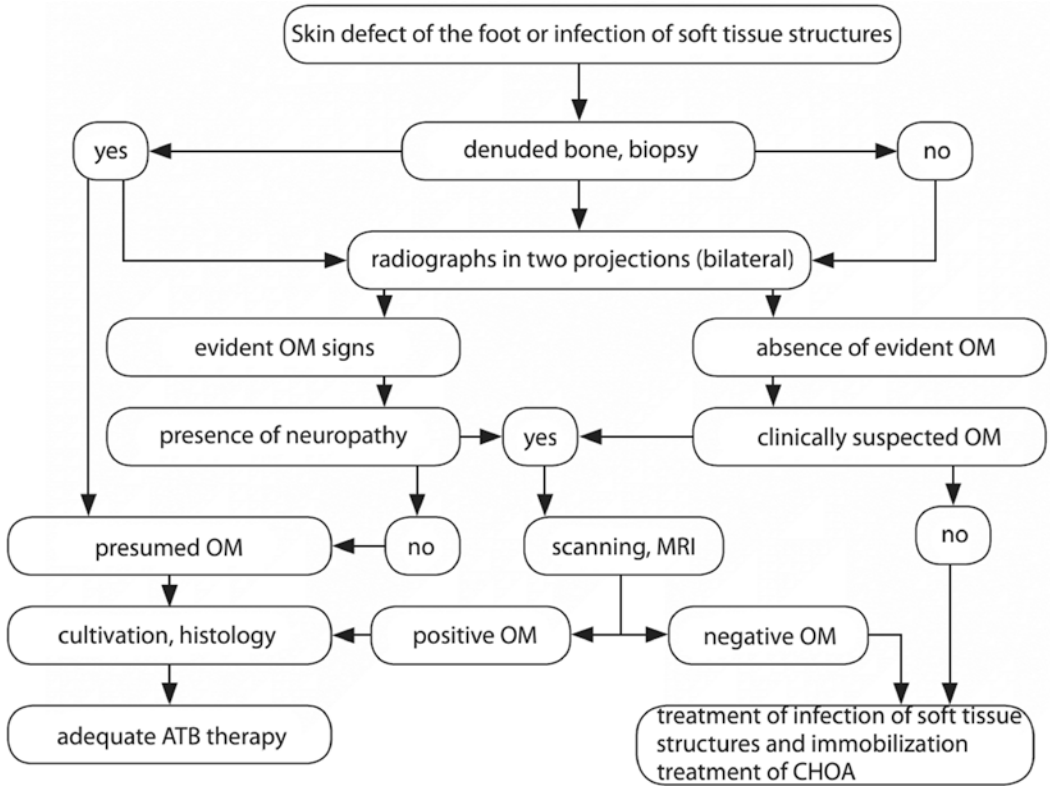


Fig. 15.15 MRI differentiation of infected and noninfected soft tissue structures in CHOA

Table 15.5 Differential diagnosis of osteomyelitis and CHOA

Differentiation of osteomyelitis versus diabetic Charcot osteoarthropathy		
	OM	CHOA
Typical location	Toes (tips, dorsum)	Lisfranc and Chopart joints, metatarsal heads (mainly first and fifth), malleoli, calcaneus
Distribution	Focal, local centripetal spread	Multiple involvement of joints of the foot
MRI of oedema (enhancement deformity)	Dominant involvement of one bone, unusual (unless there is underlying neuropathic disorder)	Epicentre in the joint and subchondral bone, usual (rocker bottom foot deformity
Soft tissues	Adjacent ulcer, cellulitis, fistulation	Enhancement limited to juxta-articular soft tissue structures, skin and subcutaneous tissue are intact

Modified according to Morrison and Lederman [78]
Note: Diffuse subcutaneous oedema is typical of ischemic diabetic foot

Table 15.6 Differential diagnosis of noninfected and secondarily infected CHOA

Noninfected	Infected
Without periarticular fluid collection	Abscess cavity with collection and course of fistulation
Presence of subchondral cysts	Absence of subchondral cysts
Bone marrow abnormalities of subchondral bone	Diffuse or extensive bone marrow abnormalities (mainly widening)
Absence of periarticular swelling	Shift of soft tissue fatty structures, subcutaneous and periarticular swelling
Intact cortex	Bone erosion

Modified according to Morrison and Lederman [78]

Certain radiological changes, particularly in the early stage of other diseases, may mimic abnormalities described in CHOA in the preceding chapter, such as stress fractures of second metatarsal with hyperostotic healing and arthritic changes in the intermetatarsal, intercuneiform and metatarsocuneiform areas and on the dorsum of the foot in the Morton´s syndrome of shortened first metatarsal with instability of the medial Lisfranc joint. Minor marginal fragmentations and massive exostoses in the talonavicular region on the dorsum of the foot may be caused by chronic functional overloading due to limited mobility in the subtalar region. In addition, there may occur aseptic avascular necrobiosis (Freiberg's, Köhler's, Haglund's disease, etc.), unusual accessory bones mimicking fragmentations (os intermetatarseum, intercuneiformium, talonaviculare dorsale, os vesalianum, trigonum, os naviculare accessorium, etc.), often with perifocal periosteal and hyperostotic and arthritic abnormalities caused by a change in structural configuration, Sudeck´s post-traumatic reflex sympathetic dystrophy, glucocorticoid-induced osteopenia and extenso-progressive arthritis and static foot deformity based on congenital predispositions and hypermobility syndrome (pedes calcaneoplanovalgi, halluces valgi gravis with metatarsi primi vari and metatarsi quinti valgi in pedes transver soplanovalgi), talocalcaneal coalition and changes in chronic nephropathy with signs of failure and post-transplantation changes (immunosuppression-induced bone metabolism disorders). Differential diagnosis should take into account potential metabolic arthropathy (gout, psoriasis, chronic alcoholism, drug, industrial chemical and metallic intoxication), inflammatory arthritis (rheumatoid, borreliosis, erysipelas, Hansen´s arthritis, syphilis), villonodular synovitis, sarcoidosis, Paget´s disease, bone cysts, pseudohyperparathyroidism, hyperthyroidism and hypothyroidism, acromegaly, haemophilia and certain benign tumours (enchondroma, giant cell tumour of bone (GCT), osteoblastoma, chondroblastoma, bone fibroma, chondromyxoid fibroma, polyostotic fibrous dysplasia) and malignant tumours (sarcoma, metastatic carcinoma, mainly bronchogenic and prostate, multiple myeloma, leukaemia). In addition, differential diagnosis should be focused on the whole complex of neuropathies, primarily hereditary idiopathic motor–sensory neuropathy, poliomyelitis, spinocerebellar degeneration and lesions, myelodysplasia, myelomeningocele, syringomyelia, hereditary sensory neuropathy, Riley–Day syndrome (congenital insensitivity to pain), Charcot–Marie–Tooth disease – familial or hereditary neuropathy with peroneal muscular atrophy, CNS lesions, Friedreich ataxia [15, 22, 39] as well as diabetic amyotrophy.

OM diagnosis is based on identification of bone marrow changes [78]. Infection of the marrow compartment results in loss of the normal fatty marrow signal on T1-weighted image, with hyperintensive signal on T2-weighted image. It affects predominantly one bone, sometimes also adjacent bones. Such a finding outside the subchondral bone signals the incidence of OM, although also other diseases may alter the marrow signal in a similar way (tumour, contusion, fracture, arthritis [8, 9, 11, 14, 15, 18]).

As about 90 % of OM cases result in the diabetic foot from spread of infection from infected skin defects, a high number of these involvements are associated with combinations of ulcerations of the adjacent skin and subcutaneous tissue, with abscesses and fistulations of soft tissue structures. These alterations are secondary signs and may increase specificity of MRI examination. OM occurs most frequently on the plantar side of the first and fifth metatarsals and in the distal phalanx of the great toe [5]. Chronic OM and Garre's sclerosing osteomyelitis are low-activity inflammations that may be manifested by low signals on both weighted images. Peripheral neuro-osteoarthropathy and angiopathy overlapped by inflammatory process usually modifies the features of the present OM.

In case of ischemic foot, the retarded bone resorption, periosteal new bone formation and healing processes may lead to lack of contrast enhancement on MRI scan [5].

15.10 Therapy

The complex of CHOA treatment includes:

- General treatment
- Local therapy
- Conservative treatment of the acute stage
- Conservative treatment in the stage of coalescence and reparation
- Prosthetic treatment
- Operative treatment
- Physical therapy and rehabilitation
- Continuous diabetologic and orthopaedic care

CHOA treatment is predominantly conservative [80, 95, 96, 113]. The complex of CHOA therapy consists of addressing the florid stage of the disease (Eichenholtz stages I and II) and operative treatment or reconstruction of structural destructions and configuration alterations in the late stages II and III [30].

Conservative treatment is either general or local.

General treatment includes:

(a) Compensation of diabetes: diet, medicaments (PAD, insulin)
(b) Treatment of neuropathy: antioxidants – derivatives of α-lipoic acid, γ-linolenic acid
(c) Treatment of angiopathy – vasodilator and hemorheological
(d) Treatment of infection – antibiotic sensitivity-based treatment [72]
(e) CHOA treatment:
    - Bisphosphonates [107], strontium ranelate, raloxifene
    - Analgesics – salicylates, NSAIDs (COX-1, COX-2)
    - Benzodiazepines
    - Antidepressants
    - Hormonal preparations – calcitonin [8]
    - Supplements – calcium, vitamins (scavengers (vitamins C and E))
    - Neurotropic vitamins of the B group (B1, B6)
    - Steroids – short-term administration of anti-inflammatory doses of prednisone (the treatment is currently under debate: its effect has not been clearly proved by EBM analyses [52])

Of key importance in optimising diabetes compensation is intensive control aimed at reduction of HbA1c below 7.5 %, with insulin therapy being preferred [19].

Local therapy includes:

(a) Treatment of skin defects. It depends on etiopathogenesis, size, depth and causes of the defect and activity of infectious inflammatory changes. It consists of surgical treatment of defect – debridement of necrotic tissue with application of sterile dressing, using wet antiseptic or hydrogel or hydropolymeric material, where necessary with activated charcoal and silver, a super absorbent polyacrylate material (e.g. TenderWet) ensuring atraumatic contact with the defect base, with the Ringer´s solution continuously wetting and rinsing the wound. Application of local antibiotics, mainly in the powder form, is unsuitable [64, 72, 82, 93].
(b) Immobilisation by plaster of Paris cast or brace (Fig. 15.16). Stabilisation of the affected foot in the acute phase with swelling is most frequently addressed by immobilisation by plaster of Paris cast, without weight bearing and with changing of the cast as the initially marked swelling gradually subsides. The procedure reflects the scope of CHOA involvement of bones and joints in individual locations and presence of infection [117, 124].

    Principles: limb elevation to reduce swelling, stabilisation, elimination of infection, pharmacological therapy, prosthetic treatment to reduce plantar pressures, patient education or, where necessary, surgical treatment
(c) Physical therapy and rehabilitation.
(d) Radiographic therapy (which is currently largely debated and the opinions on it are controversial).

General consensus has been reached as concerns pharmacological compensation of DM. Lately, the significance has been pointed out of supporting hormone therapy of CHOA

(calcitonin) and calcium supplements [8]. Opinions on the role of vitamin therapy to support scavenger system and nerve metabolism vary. Its effects should not be overestimated as they are partially still hypothetical due to lack of comprehensive studies of its share in the therapeutic outcome. Nevertheless they may be part of the comprehensive treatment [14]. With the emergence of new hypotheses on the share of inflammation in CHOA development [45, 47, 51, 52], debates have currently focussed on possibilities of short-term use of steroids to suppress the inflammatory component. These discussions are still under way and no consensus has been reached in this respect, yet. The same applies to suitability and indications of radiotherapy [5, 63, 80, 104].

Immediate immobilisation of the affected extremity with a long-term limitation of weight bearing is inevitable in CHOA, in order to prevent a rapid development of foot deformity due to laxity and to reduce extensive oedema in the acute phase of the disease, namely, by circular cast with a moulded medial arch in the acute phase, and its changing at the intervals of several days or weeks, depending on oedema subsiding. In Eichenholtz stage II, stabilisation devices may be used, including two-plate laminate, thermoplastic splints with soft lining and stabilisation shoes of various types, shape and material combined with immobilisation of the tibia [21, 30, 43, 44, 113] (Fig. 15.17).

Diabetic patients require about twice as long immobilisation period as compared to nondiabetic patients, in case of fragmentation and osteoclasia; subsequent stabilisation by brace or plate depends on the phase of coalescence and healing (4–8 months). Opinions on the duration of strict non-weight bearing of the affected limb and its gradual weight bearing largely vary [6, 13, 18, 19, 21, 26, 38, 39, 44, 46, 49, 53, 55]; it is recommended to follow the clinical and radiological findings during healing. CHOA heals faster in the forefoot than in the mid- and hindfoot or ankle [21, 82]. Continuous non-weight bearing with the use of a walking aid during walking or standing is suitable and decreases the risk of CHOA exacerbation or recurrence.

Bisphosphonates have a marked inhibition effect on bone resorption and reduction of the acute phase of the disease [21, 45]. Regardless of the potential need of later surgical intervention, a targeted antibiotic, or antimycotic therapy, is necessary, both local and general, in all types of infected defects of the diabetic foot.

The role of radiotherapy in CHOA treatment is still largely debated. Reported opinions [29, 63, 70, 129] are relatively controversial. In our

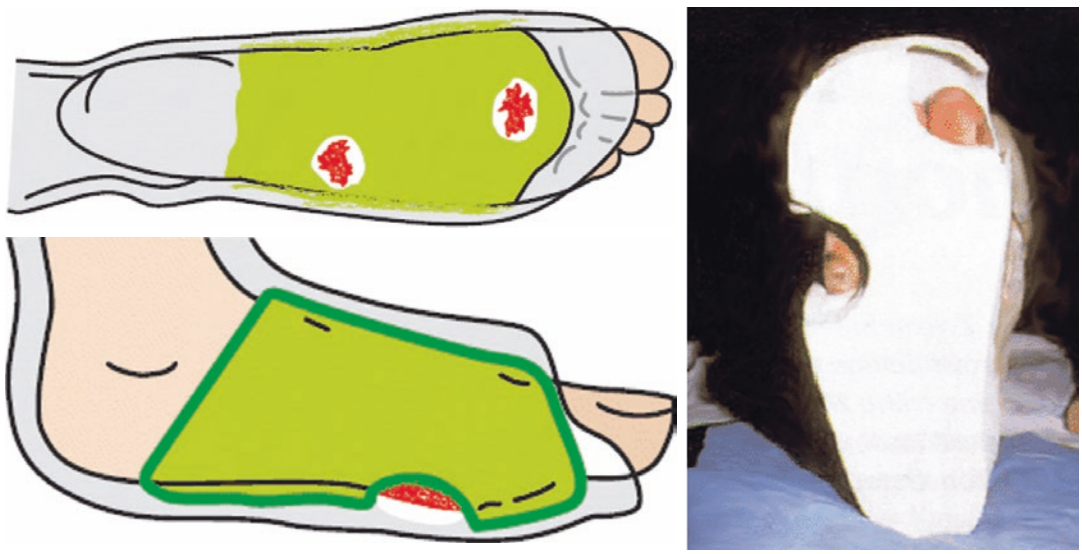


Fig. 15.16 Principles of cast stabilisation of the foot affected by acute CHOA with neuropathic defects. Skin defects must be covered with a sterile hydrophilic dressing, sometimes in combination with ATB antiseptic solution. Application of a cast with a free access to defects, changed every 2–4 days

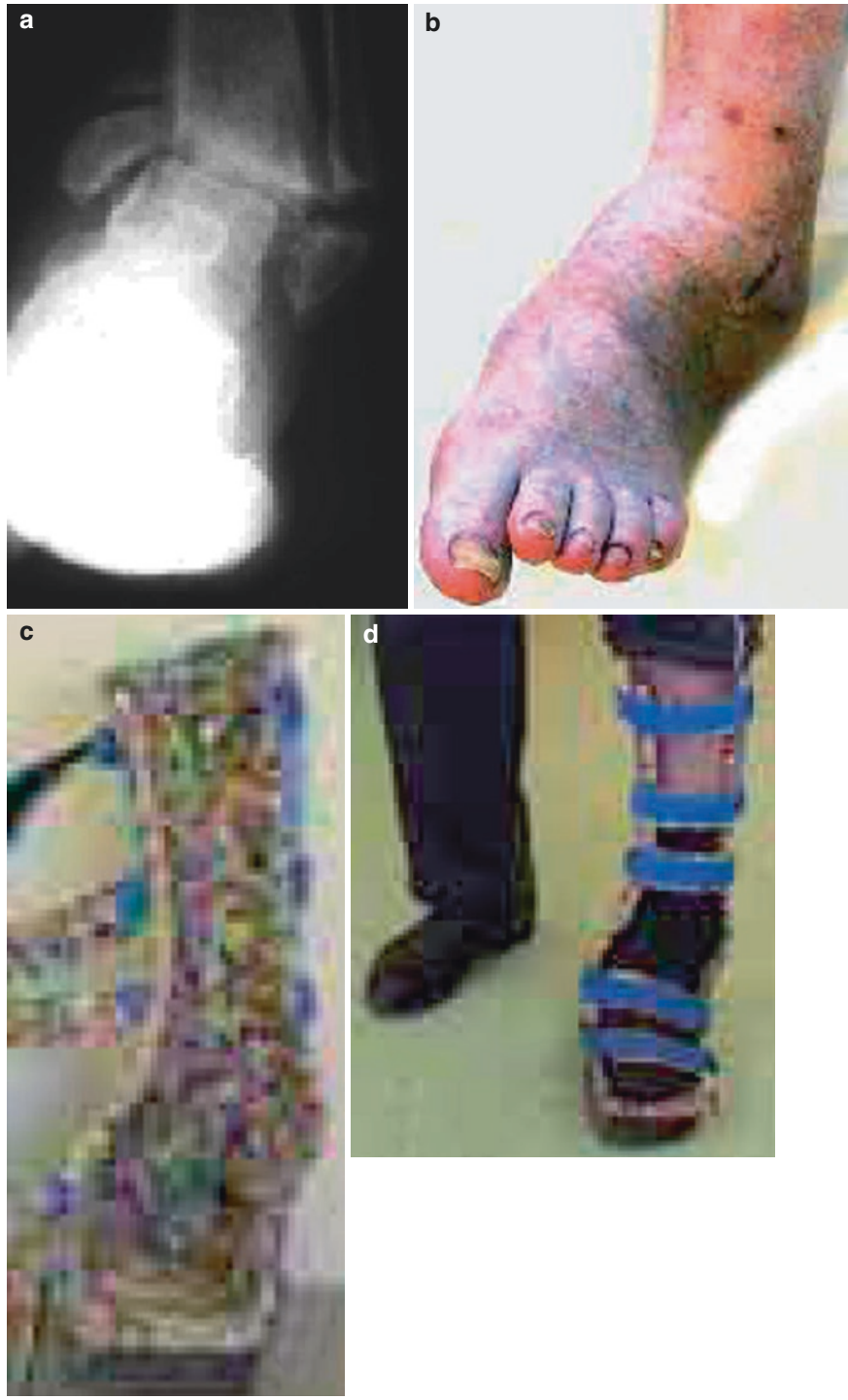
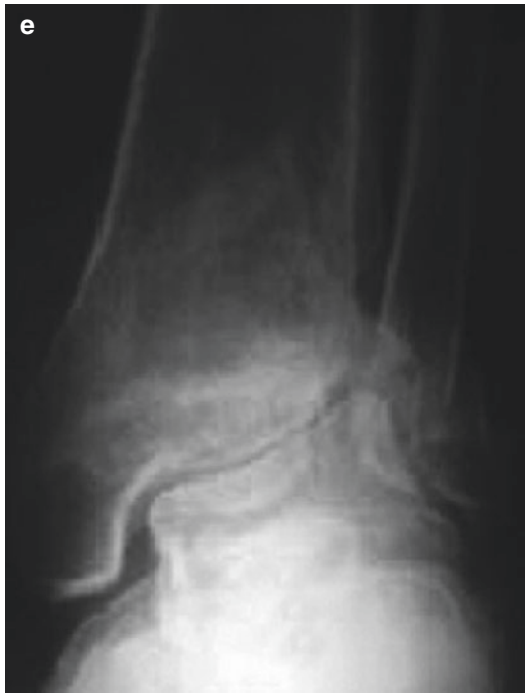
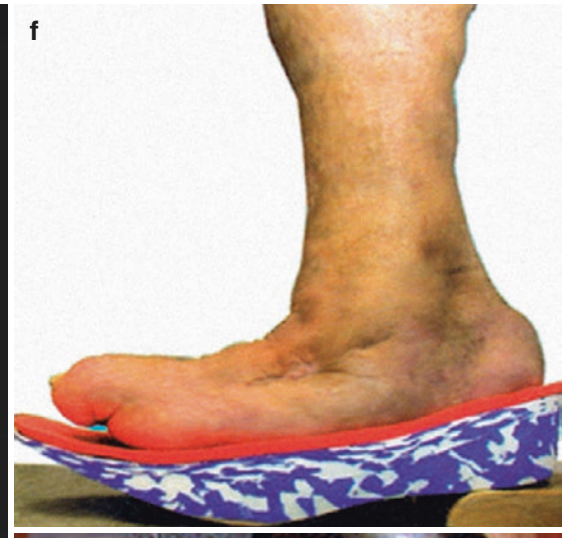
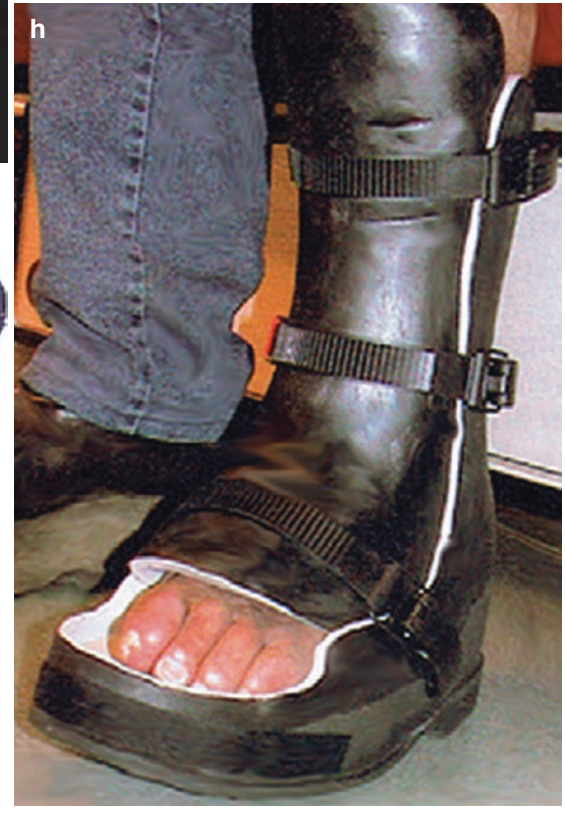


Fig. 15.17 Other orthotic options of CHOA foot stabilisation. (**a**–**d**) Thermoplastic custom-made stabilisation splint for CHOA in TC joint with inveterate bimalleolar fracture–dislocation after partial reduction of fragments (the patient rejected surgical treatment with internal fixation); (**e**) radiograph of ankle in Eichenholtz stage III. Osteoclasia of the lateral tibia resulted in bayonet deformity of TC joint. The patient uses permanently a custom-made thermoplastic stabiliser; (**f**) orthotic device for rocker bottom foot deformity with a stable custom-made insole and anti-stress features; (**g**) OPTIMA DIAB stabilisation brace with the possibility to insert insole; (**h**–**i**) other types of braces; (**j**) orthotic footwear for Eichenholtz stage II and postoperative use; (**k**) types of modified footwear with various distribution of weight bearing. *ZP* weight-bearing area







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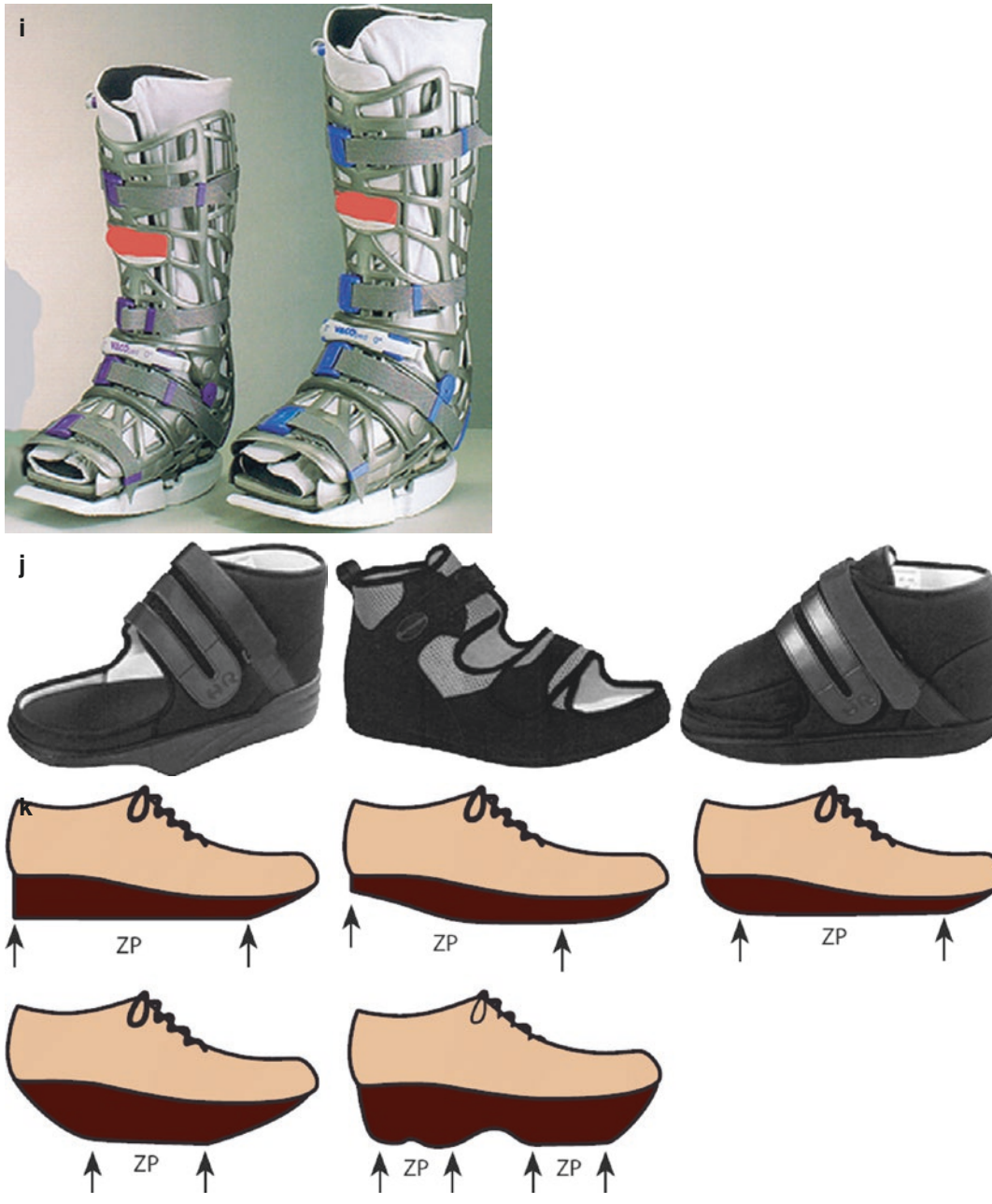

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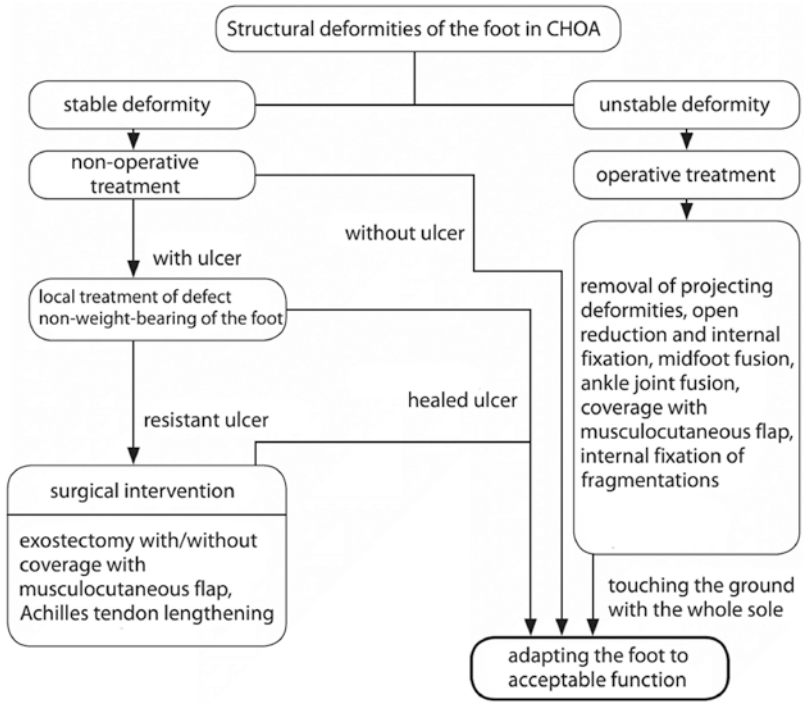

Fig. 15.18 Structural deformities in CHOA

view it is not suitable for use, except for individual cases of periostosis, enthesopathy and osteoplastic changes in Eichenholtz stage III.

15.10.1 Operative Treatment

Despite early commencement, complex conservative treatment is reported to fail [46] in about 21 % of patients. In about 10.3 % of them, there persists malunion and non-union of fragments in Eichenholtz stage III, requiring operative treatment (Fig. 15.18). Mortality of patients with infected foot defects associated with CHOA amounts to 1.3–3.65 % of cases and concerns mainly patients with other DM-related complications, such as nephropathy, autonomic neuropathy with organ involvement and angiopathy [40].

Indications of CHOA operative treatment include:

1. Foot deformities unsuitable for plate stabilisation (rocker bottom foot deformity, toe deformity, forefoot and midfoot deformities extending to planta or laterally, etc.), deformities that cannot be addressed by orthotic devices [90, 92]
2. Newly developing or resistant ulcerations caused by excessive pressures resulting from deformity or instability or both
3. CHOA unresponsive to any method of conservative therapy [28, 44]
4. Marked instability of mid- and hindfoot requiring arthrodesis [60, 80, 123]
5. Gangrenes

Operative treatment consists of:

1. Treatment of infected and noninfected defects:
   (a) Debridement of defects, necrectomy, sequestrectomy
   (b) Skin plasty and transplantation
2. Stabilisation and reconstruction of bone–joint structures [7, 91, 114, 123, 125]
3. Amputation at different levels – partial, total [81, 83]

Except for treatment of infected defects penetrating into deeper structures and subsequent

gangrene or osteomyelitis, sequestration or abscess, where pus release and evacuation, and removal of gangrenous tissue are the basic requirements of anti-inflammatory treatment, it is recommended not to perform surgical interventions in the acute phase of the disease [115]. In spite of this, certain acute traumatic conditions with a marked prevailing deformity require radical intervention in the florid phase (Eichenholtz stage I) with internal stabilisation due to an increased risk of potential complications [7, 39, 80, 89, 91]. Surgeries performed routinely during the acute stage may fail due to complications associated with the progressing osteolysis around fixation devices and may accelerate osteoclastic activities through promoting inflammatory mechanisms by the cytokine system [65, 68, 70]. External fixation is reserved for cases requiring stabilisation with persisting infection in situ and is a suitable alternative in one-step correction in a freshly healed or not healed but not infected defect close to the surgical site, unless the method of choice is excision of the defect with subsequent suturing or coverage with musculocutaneous flap [44]. It is also used for revision and salvage of a previously unsuccessfully reconstructed foot and in acute treatment of insufficiency fracture in diabetic patients with severe peripheral neuropathy, with or without supporting internal fixation.

Persisting plantar defects called according to Hansen malum perforans [15, 50] heal after changing of pressure on the sole by corrective osteotomy or, where necessary, arthrodesis, regulating the inner pressures of incorrectly positioned bones and joints. Prior to surgical reconstruction, the defect base and edges must be debrided, including elimination of infection. If the underlying disease is osteomyelitis, it has to be managed or addressed prior to arthrodesis. External fixation may be considered as a method of choice [29, 32, 44]. Due to the neuropathic site sometimes affected also by angiopathy, antibiotic treatment, even if targeted, is reported to take twice as long period to eliminate infection and heal ulcers [36, 65, 66]. More extensive infections of soft tissue structures and bones, gangrenes require partial amputation. CHOA without infected or noninfected ulcerative defects has a much better prognosis although some of these patients, mainly in case of repeated attacks, also end up with amputation [46, 50]. CHOA itself is not an indication for amputation. Amputation should be considered only after failure of treatment of deep infection or gangrene complications (which are rare in CHOA). Extensive infections of soft tissue structures and bones, gangrenes require partial or even total amputation [36, 40].

Continuous monitoring of Eichenholtz stage III may reveal signs of bone healing. Well-defined cortical defects start to resolve through new bone formation, minor fragmentations are resorbed and larger fragments fuse and form bone blocks. However, disintegration of configuration persists, as well as subluxations and dislocations, sometimes also with extensive deformities with hyperostotic and exostotic prominences, but islets of defective bone are replaced by new bone formed obviously by functionally intact osteoblasts [49]. For this reason it is necessary to wait with the radical solution only after conservative or reconstruction treatment has failed.

Corrective tendinoplasty and tendon transfer to improve mobility and imbalance problems do not have a long-term effect due to the neuropathic cause of the disorder, even if certain authors consider them sufficient in the early stages of nondiabetic neuropathy of the lower limb [50]. An exception is lengthening of the shortened Achilles tendon in equinus deformity of the ankle, where the shortening prevents development of plantigrade foot and may pose problems during arthrodesis of mid- and hindfoot [35, 54].

In CHOA stages II and III, it is possible to use metal components for internal fixation (plates, screws, nails, etc.) in reconstruction and stabilisation procedures. Strategy and the method of choice of operative stabilisation and reconstruction treatment of CHOA are given by the size and location of the neuro-osteoarthropathic lesion.

Recently the CHOA anatomical classification according to Brodský and Rouse [46] has become to be used for the choice of therapeutic method and its duration, describing three types of involve-

ment, although the division does not define position of forefoot:

1. Primary involvement of midfoot, including metatarsocuneiform and naviculocuneiform joints. This type of foot deformity often leads to medial bone prominences and development of ulcers in this region. Long-term immobilisation and stabilisation by plaster of Paris cast and later by braces until the period of late coalescence (according to Eichenholtz) may be associated with the need for arthrodesis and exostectomy or resection and osteotomy of bone prominences with subsequent fusion in satisfactory position.
2. Primary involvement of hindfoot, including subtalar joint complex, talonavicular, calcaneocuboid and talocalcaneal articulations. This type results in extensive rocker bottom foot deformities with a substantial or complete disintegration of both foot arches. Stabilisation arthrodesis but also partial amputation may be the method of choice.

3a. Primary involvement of the ankle, including tibiofibular joint. This type of CHOA lesion, often in conjunction with structural and axial disintegration in talocrural joint, is indicated for arthrodesis of TC joint.

3b. Fracture of the tubercle of calcaneus may be the indication for osteotomy of calcaneus and fragment stabilisation.

Persisting plantar defects called according to Hansen malum perforans [15, 50] heal after changing of pressure on the sole by corrective osteotomy or, where necessary, arthrodesis, regulating the inner pressures of incorrectly positioned bones and joints. CHOA without infected or noninfected ulcerative defects has a much better prognosis although some of these patients, mainly in case of repeated attacks, also end up with amputation [46, 50]. CHOA itself is not an indication for amputation. Amputation should be considered only in case of severe deformities with loss of plantigrade foot that cannot be managed by orthotic devices and after failure of treatment of deep infection or gangrene complications (which are rare in CHOA).

The aim of corrective operative treatment of CHOA is to establish a stable plantigrade foot with acceptable biomechanics [66, 67].

Amputation in CHOA is considered to be the ultimate solution of failed CHOA treatment (Fig. 15.19). The causes of failure include:

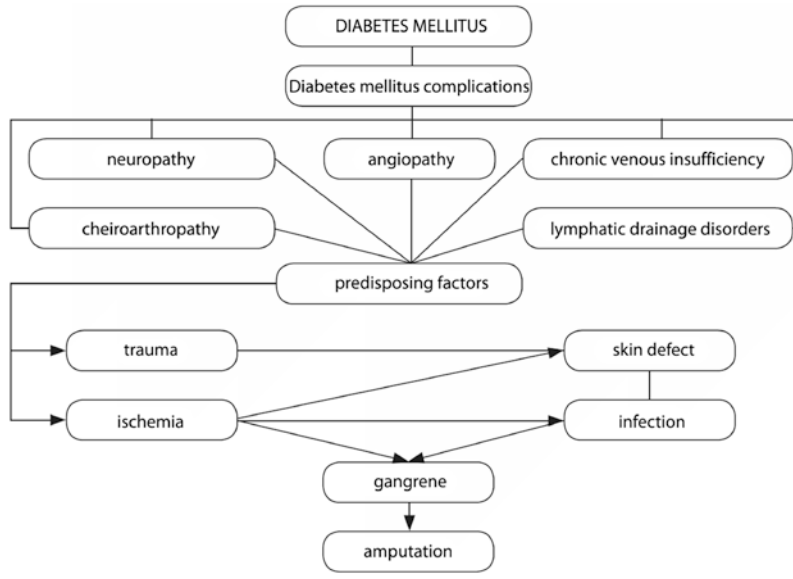

Fig. 15.19 Cascades of causes leading to amputation

- Late diagnosis of type 2 DM
- Absence of patient education or their lack of cooperation in the treatment
- Improper choice and manner of comprehensive therapy
- Patient´s poor general health and immunological condition
- Infection by resistant bacterial strains [81, 84]

It may be used also as a secondary solution in unmanageable mutilating forms, sometimes with persisting, non-healing defects of soft tissue structures. Amputation at various levels is required in about 6.6 % of cases [20, 40, 122, 131].

Early diagnosis is essential for successful treatment of CHOA. St Vincent Declaration has set the goal to develop a comprehensive strategy of DM treatment in order to reduce diabetes mellitus-related complications to 30–50 % and of the treatment of neuropathic foot including CHOA to reduce the numbers of limb amputations by 50 % [31, 132] (Fig. 15.20).

15.10.2 Comprehensive Rehabilitation Treatment

Orthotic therapy is part of lifelong treatment of diabetic patients even after resolution of the disease when it is used to address residual conditions, while the key role in the reparative phase of CHOA and follow-up care is played by physical therapy and rehabilitation.

Regulated and controlled increase of physical activity is an important part of prevention of CHOA development in patients with a long-term history of diabetes. The basic factors of rehabilitation include monitoring of blood glucose during exercises, prevention of potential hypoglycaemia and sufficient supply of liquids. It is necessary to adjust the physical activity to the age, physical and psychical fitness and individual abilities and possibilities. Patients should avoid lifting heavy objects, races and contact sports associated with a risk of injury and sports with feet hitting the ground hard [18, 81].

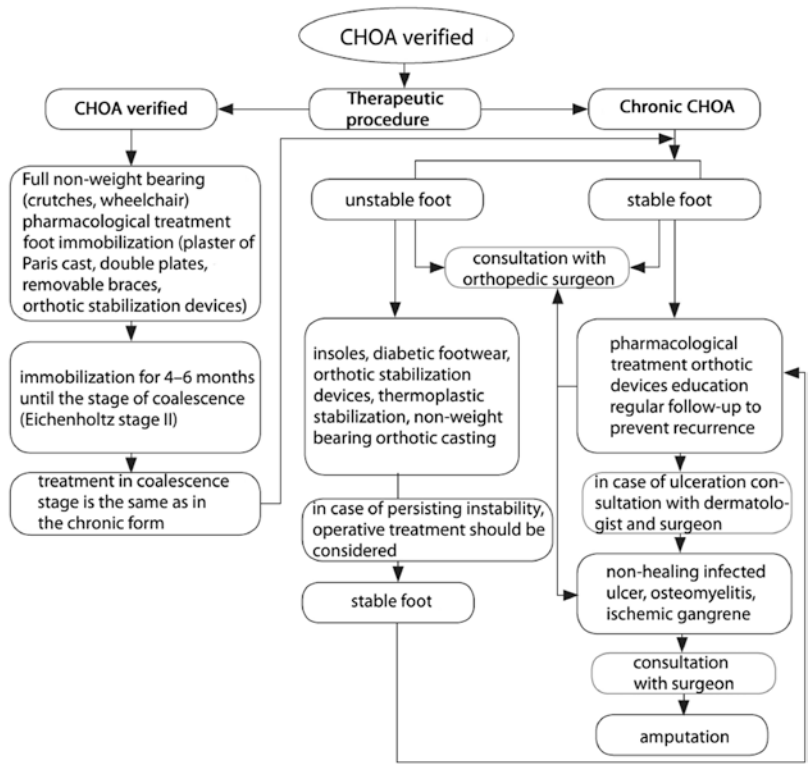

Fig. 15.20 Algorithm of CHOA comprehensive treatment

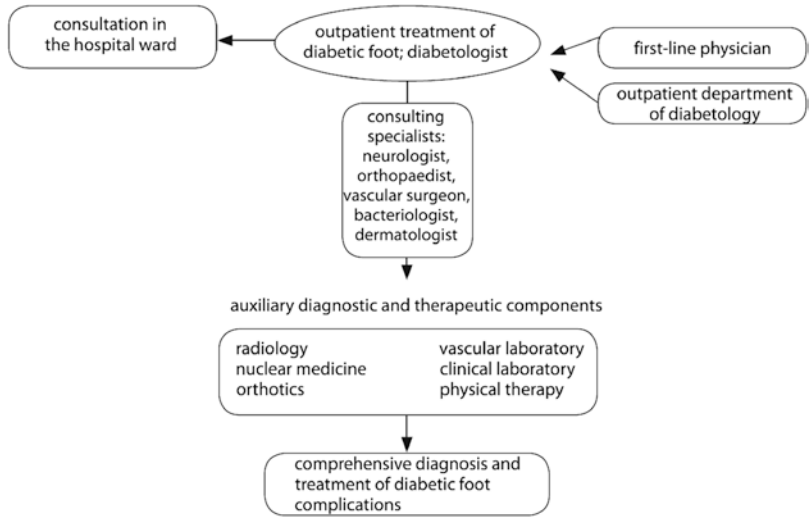

Fig. 15.21 Recommended scheme of comprehensive multidisciplinary care in diabetic foot treatment

Where CHOA has already developed, physical rehabilitation with weight bearing and exercise of the affected foot is not recommended. The method of choice should be physical therapy stimulating bone growth through promotion of osteoblastic processes. This therapy uses pulsed electromagnetic field, where appropriate with an implanted electrode as a supplement of operative treatment of non-healing fractures and fragmentations. There exist several options of physical therapy consisting of mechanical or electrical stimulation to promote bone growth, such as direct current, combined electromagnetic field and low-intensity pulsed ultrasound, which are used to reverse bone changes in individual CHOA stages, although the experience with their application in the acute stage is still limited, and their use in the subsequent reparation stage is questionable [18].

15.11 Continuous Diabetologic and Orthopaedic Care

The above-mentioned facts related to CHOA etiopathogenesis, diagnosis and treatment show that the diagnostic and therapeutic approach may be successful only if it is comprehensive and multidisciplinary, as treatment of this severe disease developing on a multifactorial basis involves several medical disciplines (Fig. 15.21). However, it should be noted in this respect that due to its professional and economic demands, as well as long-term and sometimes also unsuccessful therapy, it remains only a marginal issue for some medical disciplines. Global increase of DM incidence, particularly its type 2, highlights the need for a comprehensive approach within which diabetic patients remain in the primary preventive and therapeutic care of diabetologists, and if necessary, they receive diagnostic and therapeutic care of other specialists. Establishment of specialised centres for diabetic foot treatment, such as the National Institute of Endocrinology and Diabetes in Lubochňa, Slovakia, and also in other regions, could make a valuable contribution in this respect.

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Changes of the Musculoskeletal System in the Metabolic Syndrome

16

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Metabolism – intake and processing of energy by living tissues – is one the most fundamental manifestations and needs of all forms of life. In case of disorder of metabolic processes, the differentiated organism has to use substitute mechanisms to survive and ensure the necessary supply of energy. Absence of these mechanisms has fatal consequences, while if developed, they may have a negative impact on other structures.

Physiology of the mesenchymal tissue must be adapted to adequate compensation for the mismatch of the supply and demand of energy needed to survive. Such adaptation requires sufficient capacity of the use of fat and carbohydrates as fuel and their transient interrelations. This relationship is called metabolic flexibility. Its disorders lead to dysfunctions referred to as the metabolic syndrome [49].

Metabolic syndrome (MS) is a conglomeration of various metabolic abnormalities. The most severe and most frequent are carbohydrate and lipid metabolism disorders, particularly type 2 diabetes mellitus (DM). Metabolic syndrome, which was described in 1988 by Reaven, is known as Reaven syndrome X. However, it has not been exactly defined, yet. Various authors added other disorders to it, and therefore it is not considered as a diagnostic entity but rather a cluster of risk factors (EASD 2005 conclusions). These factors contribute to various extents to the general condition and clinical manifestation of MS and form a mosaic of consequences of metabolic disorders of the organism, including involvement of the mesenchymal structures forming the musculoskeletal system.

There are several definitions of MS, but the most commonly used is that developed by WHO:

- Central obesity, i.e. waist/hip ratio (WHR) >0.9 in men and >0.85 in women and/or body mass index (BMI) >30 kg/m^2
- Triacylglycerol levels >150 mmol/l
- HDL cholesterol <1.0 mmol/l
- Fasting plasma glucose >6.1 mmol/l
- Blood pressure >140/90 mm Hg
- Microalbuminuria >20 μg/min or albumin/creatinine ratio >30 mg/g

Mesenchymal connective tissue is omnipresent and as such it is exposed to changes in extracellular matrix of blood vessels and tissues leading to long-term complications in metabolic diseases.

The prevalent factor affecting the musculoskeletal system is type 2 DM and is often associated

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with lipid metabolism disorders within the MS-related quartet:

- Type 2 DM
- Dyslipoproteinaemia
- Arterial hypertension
- Central obesity

Dyslipoproteinaemia is in this context characterised by elevated LDL and lower HDL cholesterol levels. All these conditions are characterised by altered end products of their substitute metabolism. With DM being one of the most frequent factors of the metabolic syndrome, they include primarily glycation disorder resulting in non-enzymatic glucose reactions with proteins, causing changes in osteoarticular and connective soft tissue structures [42].

Long-term metabolic abnormalities affect all types of connective tissue, mainly through impaired production and degradation of collagen I, noninflammatory and non-dystrophic metaplasia with the development of ossification nuclei in these structures and atypical arthritis, even avascular necrosis of articulation surfaces. It is also assumed that the development of cheiroarthropathy, osteoarthritis or joint necrobiosis is triggered by tissue ischaemia in combination with inflammation, peripheral angioneuropathy, collagen I disorders, excessive accumulation of abdominal fat with increased production of cytokines and by obesity as an external factor. Overweight and obesity significantly conduce to MS development [5]. And vice versa, loss of weight contributes considerably to decrease of MS-associated symptoms. As low as 7–10 % overweight can cause increase in abdominal obesity, dyslipidaemia, triacylglycerol level elevation, decrease in HDL cholesterol and increased plasma glucose [15].

16.1 Etiopathogenesis of Structural Changes of Musculoskeletal System in Metabolic Syndrome

Biological function of bone and joint tissue includes the system's responsiveness to inflammatory impulses of various nature, degenerative processes, trauma, mainly repeated, and metabolic effects [55]. Similar behaviour can be seen also in other mesenchymal structures of the organism responsible for locomotion: muscles, ligaments, bursae, joint capsules and osteocartilaginous structures. Metabolic abnormalities affecting the organism in the long run cause structural changes in the musculoskeletal system [4]. As hyperglycaemia is the most common component of the metabolic syndrome, the incidence of structural changes in the skeleton of diabetic patients is increased, mainly in type 2 DM (82–85 %) [33]. Trophic disorders of osteoarticular structures in conjunction with insulin resistance of tissues affect predominantly patients with type 2 DM and is often associated with other MS manifestations. Insulin resistance is the underlying factor for MS development.

Disorders of glucose tolerance, dyslipidaemia, hypercholesterolaemia, hyperuricaemia, obesity and hypertension are the fundamental prerequisites of MS development.

Abnormal fatty acid metabolism and ectopic fat accumulation are typical manifestations in the relationship between elevated intramyocellular lipid (IMCL) levels and whole body insulin resistance [37, 51]. Trophic disorder of osteoarticular structures in conjunction with insulin resistance of tissues affects primarily patients with type 2 DM which occurs mainly in older population.

16.2 Stimulation Factors Leading to Mesenchymal Tissue Damage

Carbohydrate metabolism abnormalities, particularly in type 2 DM, are often associated with lipid metabolism disorder. Classification of DM with later onset is often problematic, and about 12–16 % of patients are categorised as type 2 DM, despite their serological markers indicating the presence of autoimmune insulitis, which means that they may have in fact a modified type 1 DM. This slow progressing form of type 1 DM is in the literature referred to as latent autoimmune DM in adults (LADA). Patients with LADA are more frequently obese, have higher

C-peptide concentrations, lower tendency to ketoacidosis and more marked manifestations of the metabolic syndrome risk factors (hypertension, hyperlipoproteinaemia, insulin resistance and obesity, mainly the abdominal one).

Relations between DM and its supposed structural manifestations in the mesenchymal tissue may be divided into four categories:

- Consequences of diabetic complications
- Consequences of DM-related metabolic disorders
- Syndromes participating in aetiology of these changes with microangiopathy
- Their probable interaction [3]

Fatty tissue disorders are associated with the metabolic syndrome of obesity type. However, it is not quite clear whether fatty tissue inflammation causes primarily the local and then systemic insulin resistance or whether systemic insulin resistance leads to fatty tissue inflammation which subsequently increases insulin resistance. The expected shift of fatty tissue accumulation towards changes of its function has significant diagnostic and therapeutic implications, although not always straightforward [24]. Insulin resistance is the underlying factor for the development of MS as well as of many other diseases in the elderly [20]. Glucose tolerance disorders, dyslipidaemia, hypercholesterolaemia, hyperuricaemia, obesity and hypertension are the basic prerequisites of MS development. Abnormal fatty acid metabolism and ectopic fat accumulation are typical manifestations in the relationship between elevated intramyocellular lipid (IMCL) concentrations and whole body insulin resistance [37].

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a new marker of inflammation associated with metabolic syndrome and type 2 diabetes mellitus. Noto et al. [31] have demonstrated that Lp-PLA2 potentially facilitates the overall estimate of MS incidence in patients with type 2 DM. Lp-PLA2 is significantly increased in patients with MS. Insulin resistance is associated with many protease inhibitors, as well as with the presence of lipodystrophy, and participates in progressive increase of fasting blood glucose levels in DM monitoring. Insulin resistance increases lipolysis and, as a result, also the amount of free fatty acids further inhibiting glucose oxidation, which results in secondary exacerbation of hyperglycaemia [11, 13, 20]. Insulin has a similar structure as the growth hormone somatomedin, and with increased plasma levels, it may have a similar effect on fibroblasts, inducing osteoproductive changes. Other growth factors affected by metabolic abnormalities may also have an impact on the development and growth of articular cartilage: TGF-β stimulates production of collagen I and fibronectin, TGF-α influences cartilage degradation, BMP-3 (bone morphogenetic protein 3) induces osteogenesis in the collagen matrix and IL-1 promotes collagen I synthesis and significantly increases cartilage degradation [6, 13]. Altered glucocorticoid hormone action contributes to the MS aetiology. In addition, raised skeletal muscle cell expression of GR-α and 11β-HSD1-mediated regulation of intracellular cortisol may play a fundamental role in mechanisms contributing to the MS pathogenesis [53].

Hyperinsulinaemia coinciding with insulin resistance stimulates fibroblasts and has a hypertrophic effect on vascular smooth muscle cells, contributing to the decrease of fibrinolytic activity and increase of fibrinogen levels [2]. Collagen I disorders are caused by oxidative stress with hyperglycation, reduced degradation and excessive production of the degraded collagen. This leads to its accumulation in the region of joint capsules, muscle insertions and origins, ligaments, synovial membranes and impairment of their optimal function. Subsequently, there develops noninflammatory and non-dystrophic metaplasia of fibromatous tissue at sites exposed to maximum load with the development of ossification foci, turning into diffuse and, in the last phase, continuous ossification [54, 55]. These changes occur first and most frequently in ligaments and muscle tendons, particularly in their insertions and joint capsules, less frequently in bursae. Subsequently there develops nodal pericapsular and enthesopathic ossification forming gradually continuous ossification, sometimes

even of bone-like structure [36, 42, 47, 54, 55]. The triggering mechanism of ossification is considered to be macromolecular aggregation state of collagen proteins with a disorder of mucopolysaccharide protective barrier of collagen I fibres. Depolymerisation of protective proteoglycans opens this barrier for diffusion of water and inorganic ions towards collagen fibrils. It is possible that, namely, proteoglycans suppress crystallisation on collagen fibres by competitive balancing of calcium ions [19]. The impetus for ossification and calcification is according to Connor and Hamilton [10] the presence of crystals of hydroxyapatite or pyrophosphate dihydrate in pericapsular, peritendinous or ligamentous structures.

Other authors suggest the triggering mechanism to be the presence of capillary bed in the extracellular matrix of these structures, where calcified deposits precipitate, while elastic and collagen fibres serve as mineralisation conductors [27, 28]. Calcification consists in amorphous deposition of hydroxyapatite in the mesenchymal structures. The pattern of deposition in the protein matrix during ossification is similar to bone structure. Collagen I degradation resulting in ossification is manifested histopathologically at the cellular level by swelling of collagen fibres with focal mucoid separation, subsequently by their hyalinisation and fragmentation, followed by cell proliferation, depolymerisation and even metachromasia. The process is associated with progressing sclerosis of perifocal arterioles. Later there occur nodal mineralised deposits with a subsequent development of calcification, initially diffuse and, in the final stage, continuous ossification [43, 54–56]. LJM syndrome (Limited Joint Mobility syndrome) is associated with the incidence of abnormal collagen, mainly of type I (which can be found in bone, cartilage and tendon structures), with altered glycation combined with its hyperproduction and altered tissue elasticity. This decreases the normal range of motion of the affected joints. The result is excessive production of lower quality collagen and its decreased degradation. This pathological process is called cheiroarthropathy (formerly called diabetes collagenase). Degradation of excessive collagen causes loss of elasticity and thickening of soft tissue structures with limited joint mobility during performing activities of daily living, chronic vulnerability, scarring and secondary instability [1]. The entire process leads to increasing laxity and finally to instability of joint capsules and periarticular ligaments. There occur disorders of fine motor congruence in the joint caused by shear mechanisms, with ossification of nuclei in the hypertrophic structures. The protective buffering effect of the ligament and muscle system against mechanical stress is gradually disappearing, and the intensity of adverse shear stress mechanisms is growing in the affected joints. This results in microtrauma structural changes of capsular, ligamentous and cartilaginous joint structures with washout of acid radicals, followed by progression of degenerative osteoarthritic changes. Disorders of proprioception and nociception increase vulnerability of joint capsules, periarticular ligaments and muscles, with the subsequent unfavourable combination of their rigid and unstable structures results in the development of cheiroarthropathy. Association of LJM syndrome and retinopathy indicates association between LJM and both microalbuminuria and macroalbuminuria. It has been hypothesised that the occurrence of LJM requires a genetic predisposition that could influence the formation of advanced glycation end products that are thought to be responsible for the increased cross-linking and stiffness of collagen in diabetic patients. Genetic predispositions seem to be responsible also for the susceptibility to LJM and other diabetic complications and should be linked especially to the male sex, perhaps because of different biochemical or hormonal pathways.

The relatively increased joint flexibility in women may mask the influence of other factors. It seems that the function of LJM as an indicator of microvascular disease is linked to the male sex only, while in women, LJM rather shows an association with macrovascular disease [19]. The swelling of collagen fibres at the cellular level with focal mucoid separation results in their fragmentation and hyalinisation. The presence of immunogenetic inflammatory disorders contributes to cell proliferation with depolymerisation and metachromasia. Metabolic microangiopathy

is associated with progressive sclerosis of arterioles which may trigger ischaemic changes and subsequently the production of nodal mineralised deposits that are initially diffused and later form continuous calcification or even ossification of the affected capsular and pericapsular structures.

Pathological findings in LJM – increased collagen deposition, cross striation and glycosylation – cause rough and tight skin of the peripheral parts of the body in the affected individuals. The thickened skin and bowed fingers in cheiroarthropathy are remarkably similar to the appearance of the skin and fingers of individuals with early systemic sclerosis, where the development of bowed fingers appears to be secondary to collagen proliferation in the skin, subcutaneous tissues and muscle [16].

Neuroangiopathy with endothelial dysfunction, macroangiopathy and microangiopathy and medial calcinosis with atherosclerosis exacerbate vascular supply by chronic ischaemia [26, 38]. Visceral fat, typically accumulated in metabolic syndrome, is the source of inflammatory cytokines and, due to the disorders of the acid radical scavenger mechanism formed by groups of vitamins C and E, leads to an increased amount of free oxygen radicals and the development of inflammatory activities. Accumulation of abdominal fat in metabolic syndrome together with reduced mobility contributes to the weakening of the anterior abdominal wall. Patients with metabolic syndrome suffer quite frequently from umbilical hernia. The harmful effect of free radicals is presented, among other things, by lipid disorders at the DNA level, the development of atherosclerosis and diabetes. During the process of ageing, lipid composition is getting worse, cholesterol levels are increasing, blood supply gets impaired, levels of fibrins and their degradation products are elevated, erythrocyte rigidity and thrombocyte aggregation as well as plasma viscosity are increasing. All this exacerbates circulation and oxidation of all tissue structures [26].

A typical finding in familial hypercholesterolaemia (FH) is isolated increase in cholesterol levels (total cholesterol and LDL cholesterol in plasma with a normal or only marginally elevated triacylglycerol concentration). FH may be associated with the development of tendon xanthomatosis (at the sites of most frequent enthesopathies, e.g. above the Achilles tendon or above elbow extensors). Hypertriacylglycerolaemia and apolipoprotein abnormalities result in decreased HDL cholesterol levels. Treatment of certain components of metabolic syndrome may also have secondary effects on the musculoskeletal system.

The positive effect of statins on bone formation in the treatment of hypercholesterolaemia through stimulation of osteoblasts and inhibition of osteoclasts is used also in the treatment of hyperlipidaemia. In type 2 DM, they contribute to increase of BMD [22].

Neuropathy occurs also in chronic liver disorders. Chronic liver disease which is not caused by alcoholism may be associated with asymptomatic or slightly sensitive-motor demyelinating polyneuropathy. Peripheral neuropathy is often reported in conjunction with primary biliary cirrhosis and after acute viral hepatitis.

Acute motor neuropathy resembling the Guillain-Barré syndrome may also occur in association with dyslipidaemia [12].

Other factors leading to similar changes of the musculoskeletal system include hyperuricaemia, rheumatoid arthritis, Strümpell-Pierre Marie-Bekhterev disease, psoriasis, acromegaly, trauma (mainly chronic), metachromasia and hyperparathyroidism [33, 50].

16.3 Metabolic Syndrome-Related Osteoarticular Changes

Metabolic-diabetic cheiroarthropathy, which is associated with collagen I disorders, is a significant underlying factor for acceleration of degenerative osteoarticular changes of joint structures. These changes may be characterised qualitatively by decreased elasticity and reduced physiological retractability and quantitatively by reduced degradation and increased production of collagen that lead to thickening of articular and periarticular structures. Joint capsules, fascia

and tendon sheaths get thicker, fibrotic or sclerotic and lose the ability of physiological extensibility and elasticity and, consequently, also the buffering effect of absorption of stress mechanisms. Changes in joint capsules limit the range of motion of joints (LJM syndrome); permanent decrease of elastic properties results in their subsequent functional instability and, ultimately, in rigid and unstable structures [39, 47]. Such unfavourable combination increases vulnerability also during common physical load. Natural degenerative changes typical of diabetic patients and elderly patients with metabolic syndrome accelerate, with a higher involvement of weight bearing joints and joints with high functional demands, such as small joints of hands. Contributing to this acceleration is neuromicroangiopathy with insufficient blood supply and nutrition of joint structures. Etiopathology and pathogenesis of osteoarthritis are multifactorial, including genetic predetermination, various traumas resulting mainly from excessive load, as well as metabolic and inflammatory cause or dietary habits.

Remodelling of the bone may be associated with changes in calcium, phosphorus, phosphatase and osteomarker serum levels. During the process of ageing, the lipid composition is getting worse, cholesterol levels are increasing, blood supply is impaired, levels of fibrins and their degradation products are elevated, and erythrocyte rigidity and thrombocyte aggregation as well as plasma viscosity is growing.

This exacerbates circulation and oxidation in all structures [26]. Mild seroactivity can also be observed, due to increased release of deoxidants in case of scavenger mechanism disorder [55] (Fig. 16.1).

Osteopenia or osteoporosis commonly found in older population is usually more marked if associated with MS; however, with concomitant osteochondrosis or sclerosis of joints, discs and

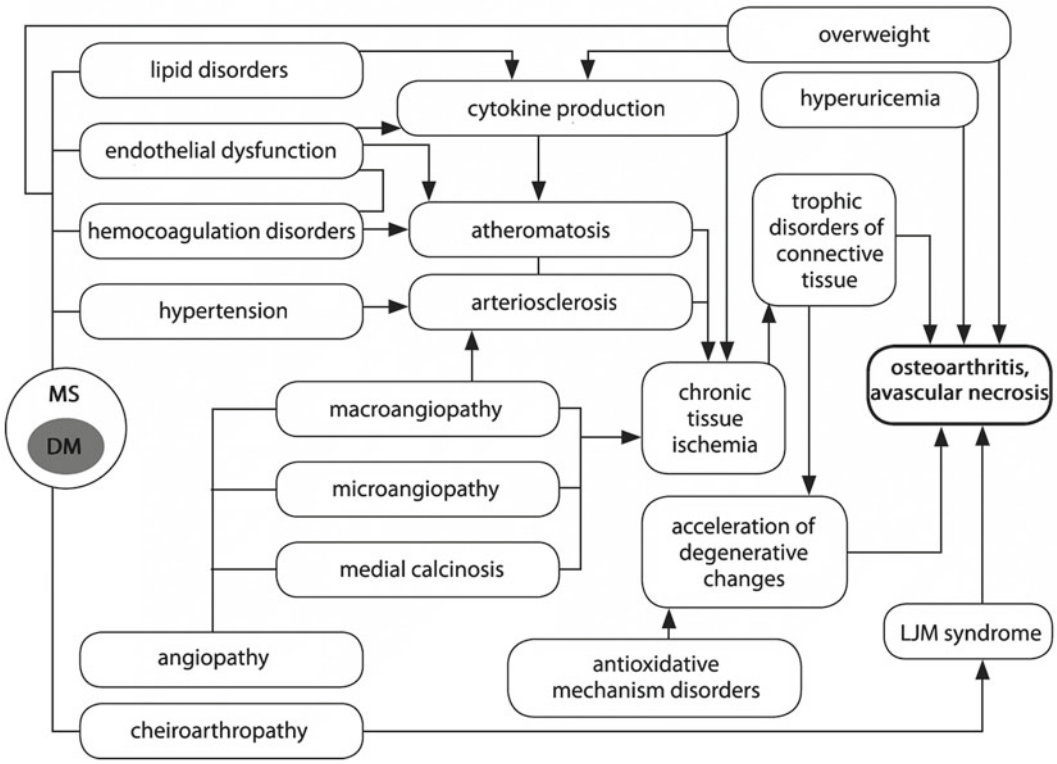

Fig. 16.1 Predisposing factors of metabolic arthritis and avascular necrosis

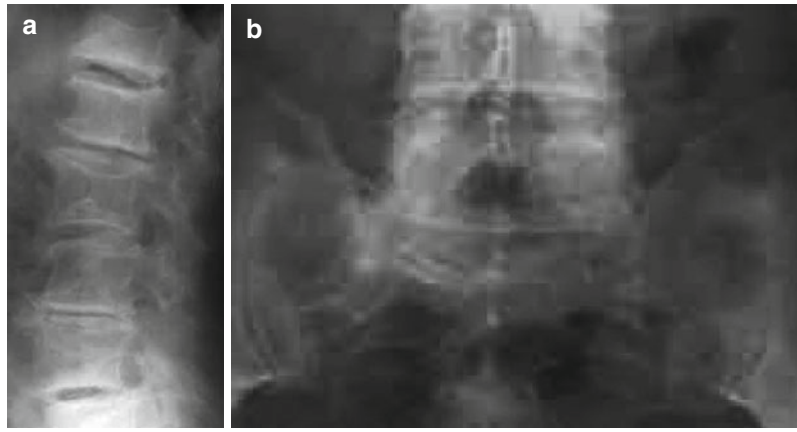

Fig. 16.2 Radiograph of metabolic Charcot spondyloarthropathy. Female diabetic patient (58 years) with type 2 DM and MS with 12-year history and 6D syndrome of Charcot spondyloarthropathy. (**a**) LL view (**b**) AP view

enthesopathy (periostosis) shown on radiographs, it is difficult to assess. They manifest themselves particularly in diabetic patients in the form of diabetic Charcot spondyloarthropathy (Fig. 16.2), protrusion of the acetabulum due to supraacetabular demineralisation. Old-age hypoestrogenic demineralisation in patients with type 2 DM is not provably significantly higher, although diabetic osteopenia induced by metabolic disorders remains classified among manifestations of MS associated with DM.

Due to the complex neuropathic, angiopathic and collagenous involvement, osteoarthritis caused by metabolic disturbances may have slightly different radiological features than other forms of osteoarthritis [9]. There develop joint deformities associated similarly as in rheumatoid arthritis with clinical and radiological features of fragmentation of edges of articular surfaces, resulting from laxity of capsular structures with subsequent joint instability.

Findings frequently include protrusion of acetabulum and impact sequestration of hip joints, cheiroarthropathy and rhizarthrosis of peripheral regions similar to RA, osteochondritis dissecans with marginal hyperplasia of articular cartilage [43]. Concomitant hypovascular trophic disorders sometimes even result in sequestration (most often impact) and avascular necrosis of the epiphyses, primarily of the femoral or humeral heads.

16.4 Metabolic Syndrome-Related Ligamentous Changes

Acidic environment induces local reactive tenosynovial physical-chemical inflammatory changes with proliferation of the mesenchymal tissue, subsequent retraction and tenosynoviosclerosis. Such changes develop also in conjunction with inflammatory processes of joints, their capsules and periarticular structures, as well as metabolic disturbances associated with collagen I disorder. Mechanical negative factors arising from functional impairment of muscles and ligaments contribute to structural changes, mainly in their attachments. Long-term retraction, subsequent loss of elasticity and protracted increased tension in attachments induce enthesopathic ossification. Metabolic enthesopathies constitute a heterogeneous group of enthesopathies occurring in various metabolic diseases [56] (Fig. 16.3).

16.5 Metabolic Syndrome-Related Muscle Changes

It is believed that insulin resistance is the underlying condition of metabolic syndrome and that accumulation of ectopic fat has an impact on whole body metabolism of carbohydrates and

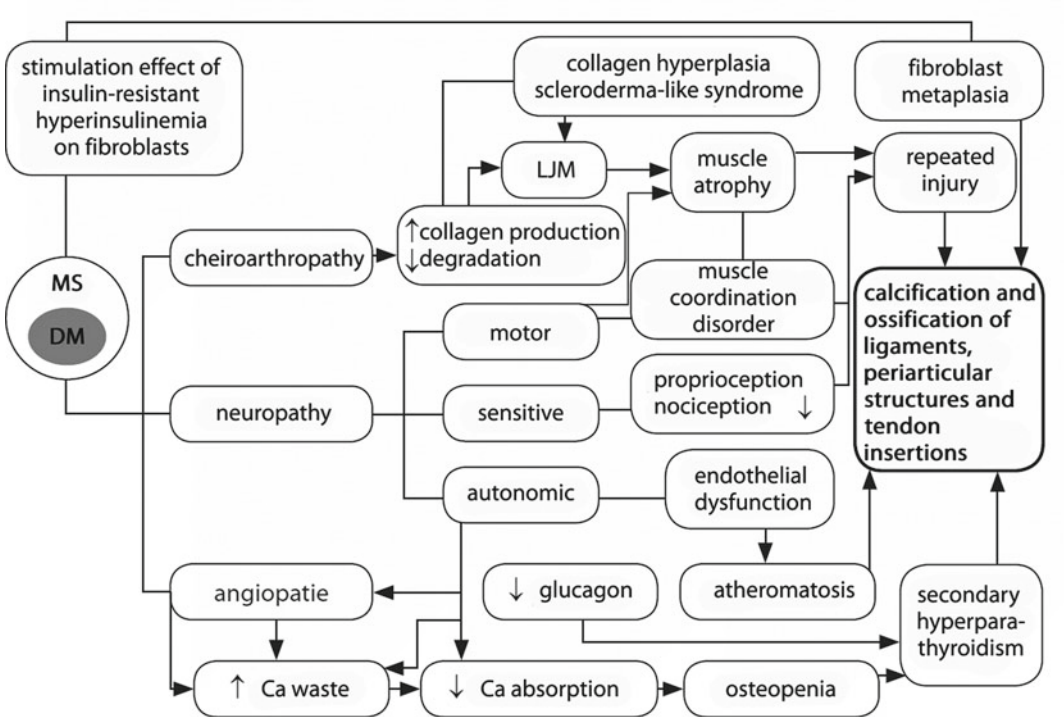

Fig. 16.3 Predisposing factors leading to pericapsular and ligamentous ossification

on pathogenesis of insulin resistance in the muscle tissue.

The flow of muscle fatty acids as the source of oxidative energy probably plays a key role in the onset and development of muscle abnormalities and in the whole body metabolism and is potentially involved in pathogenesis of obesity, MS and type 2 DM. Impaired metabolic flexibility of carbohydrate and lipid metabolism contributes to failure of skeletal muscle to appropriately move between the use of lipid in the fasting state and use of carbohydrate in the insulin-stimulated prandial state. This inflexibility results in reduced mitochondrial size and density, which is typical of MS, mainly in obese and diabetic individuals.

Peripheral neuropathy resulting from metabolic disorders causes regulation changes in motor, sensitive and autonomic innervation of muscles. Loss of nociception and proprioception, mainly in elderly patients with a long history of type 2 diabetes, neuromicroangiopathy with perfusion disturbances, trophic changes in the skin, muscle weakness and lower speed of muscle action, arising from microangiopathy-related endothelial neuropathy of muscles with impaired neuroregulation and with collagen degradation and limitation of functional qualities of the muscular tissue by decreased oxidation constitute the complex causes of muscle changes in MS.

16.6 Diabetic Muscle Infarction

The first to describe diabetic muscle infarction were Angervall and Stener in 1965 [3]. It is one of the late complications in elderly individuals with type 2 diabetes affected also by other systemic disorders, mainly retinopathy and nephropathy and in patients requiring dialysis.

The dominant factor in etiopathogenesis is neurogenic microangiopathy with subsequent disorder of tissue vascularisation. It has been hypothesised that chronic reductions in nitric oxide bioavailability contribute to a loss of skeletal muscle microcirculation, leading to impaired muscle perfusion with elevated metabolic demand [17].

Recent investigations demonstrate abnormalities in fatty acid metabolism and accumulation of ectopic fat in the skeletal muscles. The findings support a hypothesis about strong relationship between elevated intramuscular lipid levels and insulin resistance of all tissues in the body [51]. Peroxisome proliferator-activated receptors (PPARs) delta are transcription factors involved in both developmental and metabolic functions. These are activated by fatty acids, fatty acid metabolites and synthetic compounds marketed for their lipid-lowering and antidiabetic actions. Activation of PPARs – fat burning sensors – induces fatty acid beta-oxidation in striated skeletal muscle and attenuates metabolic syndrome. Nuclear receptors play a central role in the control of fatty acid burning in adipose and skeletal muscle tissues [21, 44, 52].

Diabetic muscle infarction is characterised by acute atraumatic painful swelling occurring most frequently in thigh or tibia muscles. The disease is not diffuse, but local, with occasional recurrences. Muscle tissue is exposed to local necrosis, healing with a scar.

The laboratory finding shows elevated erythrocyte sedimentation rate and most often normal or threshold leukocyte and creatinine phosphokinase levels. The most accurate diagnosis is provided by MRI.

16.7 Bruns-Garland Syndrome

A relatively rare form of muscle disease is the Bruns-Garland syndrome – diabetic muscle amyotrophy. It is an infrequent type of neuropathy that markedly affects the patient´s mobility. It occurs usually in patients with type 2 diabetes. It is clinically manifested by muscle pain in proximal lower limbs and their increasing weakness arising from perineural microangiopathy with chronically developing ischaemia of peripheral nerve fibres. The current opinions on etiopathogenesis prefer the theory that the disease results from inflammatory response of the walls of perineural capillary bed, induced by immunologic disorders. It is a clearly neuropathic disease despite the fact that its clinical manifestations in the early stages may be of myopathic nature.

Diabetic amyotrophy begins as a rule with unilateral pain in the thigh, hip, gluteal muscle or tibia. Occasionally it may occur in the acute form in both thighs, sometimes with predominance of one side, with the development of muscle weakness and later with atrophy of thigh muscles that can be first observed in quadriceps, but after several months, it progresses into adjacent muscle groups. It typically has subacute course with muscle pain and asymmetrical weakness up to hypotrophy of muscles of the hip. Occasionally the disease may involve muscles of the tibia and foot or rarely also upper limb muscles. This type of neuropathy affects predominantly elderly patients with type 2 DM. The associated lower limb weakness makes transition from sitting to standing impossible without assistance [34].

16.8 Reflex Sympathetic Dystrophy Syndrome

Reflex sympathetic dystrophy syndrome is also known as algodystrophic syndrome, Sudeck's atrophy and type 1 complex regional pain syndrome. It is characterised by localised or diffuse pain usually in conjunction with swelling, trophic and vasomotor changes [41] and movement disorders. It may occur spontaneously, after trivial injury of soft tissue structures, fracture, distortion, or after surgical intervention in loco. Predisposing factors include diabetes mellitus, hyperthyroidism, hyperparathyroidism and type IV hyperlipidaemia [8].

16.9 Clinical Manifestations of the Musculoskeletal System Changes in Metabolic Syndrome

Involvement of the musculoskeletal system in metabolic syndrome is general or local, with structural changes at predilection sites.

According to the nature of the affected structure, it is possible to distinguish between joint changes resulting from osteoarthritis and avascular necrosis of joint structures, capsular and pericapsular

changes arising from calcification or ossification of various degree and chronic adhesions of joint capsules and muscle-tendon changes in the form of ossifying enthesopathies and tenosynoviosclerosis, muscle hypotrophy and infarction. Thecal structures – bursae – are affected less frequently.

Clinical findings include limited mobility of the spine or altered joint with different degree of pain, enthesopathic pain of tendon insertions and of hands, with digital flexor contractures and compression of the carpal tunnel structures, later loss of axial alignment, trophic changes and joint deformities partially resembling RA, mobility disorders and muscle weakness.

16.10 Osteopenic Structural Changes in the Spine

Generalised osteoporosis frequently accompanies metabolic disturbances, which may potentiate age-related disorders of calcium metabolism (hypoestrogenic, malabsorption) or induced osteoporosis.

A rare form is neuropathic Charcot diabetic spondyloarthropathy, a less frequent variant of neurogenic Charcot diabetic osteoarthropathy, often confused with degenerative spondylitic, osteochondrotic and spondylarthritic changes.

Charcot diabetic spondyloarthropathy (CHDS) develops after a long history of metabolic disorders, most often in type 2 DM.

Multifactorial etiopathogenesis of diabetic neuropathic CHDS includes the following contributing factors:

(a) Peripheral neuropathy.
   - Sensory – with loss of proprioception and nociception. Disorders of this systemic complex impair mobility in terms of dynamics and coordination.
   - Motor – with muscle imbalance resulting from impairment of muscle and tendon innervation, first of postural muscles, with loss of muscle mass. The role of ligaments as proprioceptive receptors responsible for postural fixation is decreasing, which leads to adverse shear stress mechanisms in spine movement, mainly at the junctions of individual spinal segments, and subsequently to progressive damage of osteoarticular structures, their fragmentation, structural disorganisation and osteolysis.
   - Autonomic – with disturbed sympathetic vascular innervation leading to impaired regulation of blood flow, its increase, mainly in the region of the Batson´s plexus, the development of arteriovenous shunts and increased osteoclasia.

(b) Angiopathy with features of microangiopathy, macroangiopathy and mediocalcinosis, with the development of atheromatosis associated with calcification, resulting from blood vessel wall sympathetic denervation as well as chronic tissue ischaemia.

(c) Cheiroarthropathy – with abnormality of collagen I (which is part of bone, cartilage and tendon structures) causing limited mobility of joint and the respective ligaments and their subsequent ossification.

(d) Overweight – associated with increased loss of muscle mass, leading to excessive overloading mainly at the thoracolumbar and lumbosacral junctions with progression of degenerative processes. Abdominal fat accelerates rheumatoid inflammatory changes associated with demineralisation and chronic arthritis syndrome.

(e) Trauma – as an external factor, it may be a single (inadequate in terms of consequences and scope) or repeated injury, caused by loss of proprioception and nociception in case of sensitive neuropathy and instability resulting from motor neuropathy. This induces mechanical stress at the sites of excessive loading of neuropathic spine. Repeated overloading and traumas damage disc structures, contributing to intradiscal haematoma and Knuttsen vacuum phenomena, capsular laxity and effusions of facet joints and paravertebral ligaments. The resulting segmental instability is responsible for damaging bone structures and vertebral cartilage and edges of the articular surface of facet joints, with features of bone disorganisation, fragmentation and debris. This disorder has a radiological presentation of 6D-syndrome [35] (Table 16.1).

Table 16.1 6D syndrome

Bone structure disorganisation
Density – osteopenia, osteoclasia
Debris – bone particles along the edges of discs and articular facets
Distension – changes in intervertebral space, Knutson's vacuum phenomena
Destruction – articular facet fragmentation, isthmic osteolysis, erosion of end plate edges
Dislocation – listhesis

16.11 Osteoproductive Structural Changes in the Spine

A specific form of involvement of both the spine and periphery is diffuse idiopathic skeletal hyperostosis (DISH), also known as Forestier's hyperostotic spondylosis, where ossification of the spine, the long ligaments in particular, is associated with ossification in the periphery, mainly in the region of the shoulder and pelvic ligaments and manifestation of tenosynoviosclerosis and cheiroarthropathy.

DISH is characterised by new bone formation in the spine, calcification and ossification of vertebral ligaments and, in the periphery, by enthesopathy associated with periosteal as well as endosteal ossification [29, 35, 40, 55]. DISH is manifested by direct localised metaplastic calcification or ossification of the matrix in the thin mesenchymal tissue between the longitudinal ligament and vertebral body (most often polysegmental anterior longitudinal ligament) and secondary involvement of the ligament, as well as enthesopathies [29, 40, 55]. Metaplastic ossification may be direct, where false bone in tendon insertions is formed from mature fibrous structures through hyaline dystrophy and calcification of matrix and indirect which is preceded by the formation of granulation tissue with formation of osteoblasts. Dystrophic calcification is accompanied by calcification of matrix [55].

DISH exhibits features of flowing ossifications of vertebral bodies, fragmented ossifications, hyperostotic osteophytes and syndesmophytes of shapes typical of this manifestation of metabolic disorders (Fig. 16.4).

Osteophytic changes have a specific radiographic manifestation of various modifications typical of DISH (Fig. 16.5).

Criteria for DISH development and diagnosis are based on the Fornasier's classification:

- Type I – initial focal ossification
- Type II – bridging ossification of one segment
- Type III – bridging ossification of multiple segments

or Utsinger's classification:

- Type I – flowing ossification along the anterolateral aspect of at least four contiguous vertebral bodies, primarily in the thoracolumbar spine, with the absence of osteochondrosis, vacuum phenomenon and facet-joint ankylosis
- Type II – flowing ossification of two corners of contiguous vertebral bodies
- Type III – symmetrical peripheral enthesopathies of posterior heel, patella and olecranon

Possible DISH is diagnosed if criterion II or III is fulfilled (osteophytes must be in all locations).

Probable DISH is diagnosed if criterion II and III are fulfilled.

Definite DISH is diagnosed if criterion I is fulfilled.

Hyperostosis is bone tissue hyperplasia, mostly generalised.

This disease can be seen in persons over the age of 40, with obesity of metabolic-endocrine nature, with male predominance (male-female ratio of 2:1) [55]. Except for spinal stiffness, it does not always have marked clinical symptoms, unless it compresses medullary and radicular structures. In the advanced stage, it affects whole segments of the spine. Patients may develop secondary, trauma-induced localised hyperostosis. DISH is often associated with enthesopathies, most frequently in the pelvic ring, shoulders, weight bearing joints, and tenosynoviosclerosis of hand, less frequently of the foot, flexor tendons [38, 56].

Fig. 16.4 Types of osteophytes. (**a**) Bywater-Dixon osteophyte, (**b**) flowing ossification with "umbrella" phenomenon, (**c**) "duck beak" hyperostotic osteophyte, (**d**) "Schallknoten" fragmented osteophyte, (**e**) "claw" osteophyte, (**f**) "flamme de bougie" (candle flame) osteophyte, (**g**) "parrot beak"

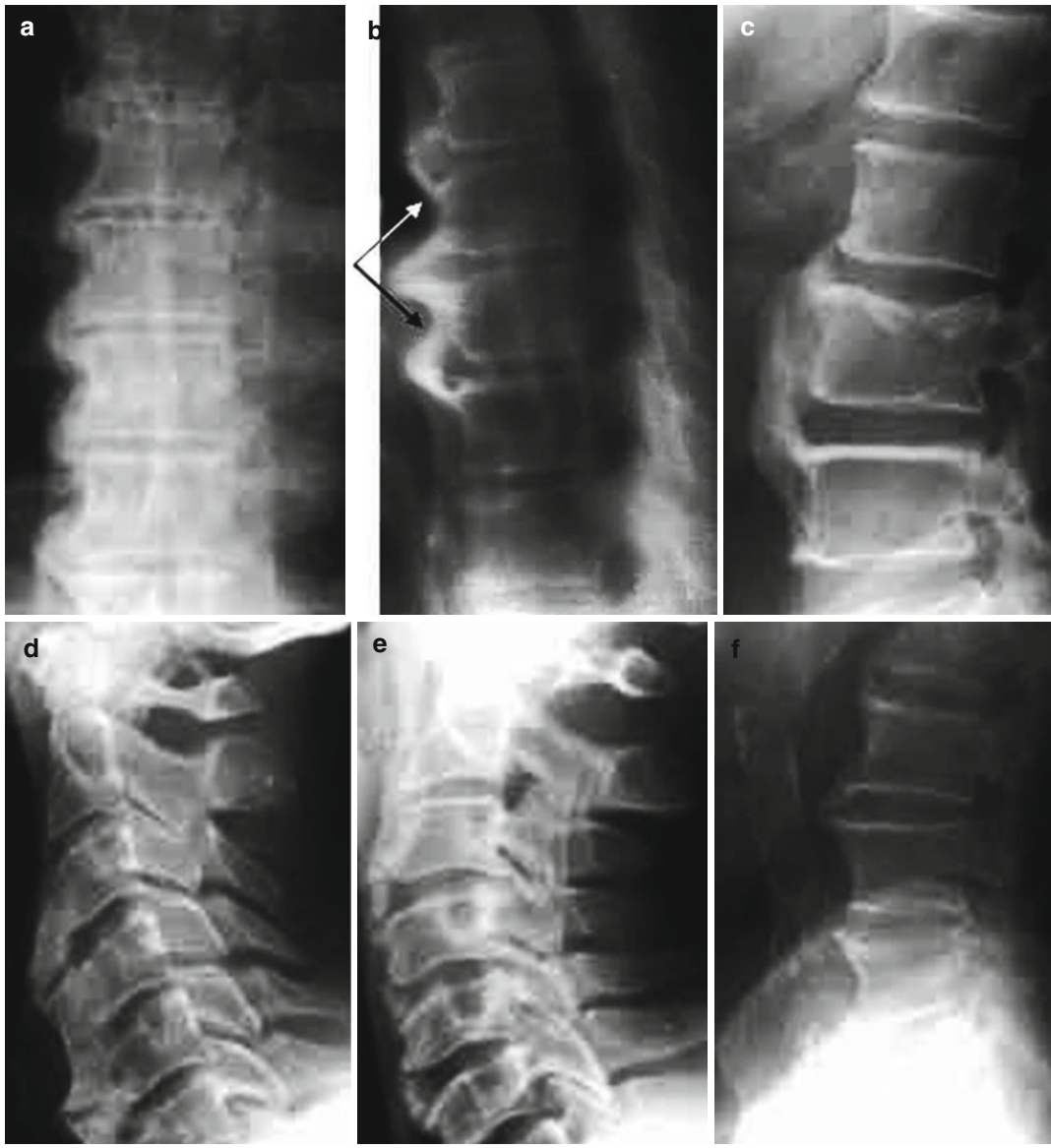

Fig. 16.5 Radiography of DISH. (**a**) Hyperostotic osteophytes or even bridging of DISH type, but similar to certain forms of seronegative rheumatoid, or psoriatic spondylitis; (**b**) Bywaters-Dixon osteophytes with a tendency to bridging, "Umbrella" phenomena; (**c**) bisegmental stabilisation after impression of vertebral end plate (Schmorl node) with subsequent instability due to massive bridging extending as far as the adjacent superior vertebra in a patient with MS; (**d**) massive bridging extending from C3 distally by calcification of anterior longitudinal ligament in DISH; (**e**) "Schallknote" type of cervical spine ossification in DISH; (**f**) Bywaters-Dixon osteophytes. Marked atherosclerosis of the abdominal aorta

16.12 Structural Changes in the Region of the Pelvis and Hip Joints

These changes include:

- Ossification of pelvic ligaments – the most pronounced ossifications can be found mainly in iliolumbar ligaments, anchoring the spine to the pelvic ring. Ossifications of sacrospinous and sacrotuberous ligaments are less frequent [7] (Fig. 16.6).
- Periosteal appositions – sometimes even spicular ossifications along edges of iliac wings, often overlapping with enthesopathic osteophytes in muscle attachments, particularly of gluteal muscles on the iliac wing and greater trochanter, and ossifications, often symmetrical, of capsular and pericapsular structures of hip joints (Fig. 16.7).
- Arthropathy of hip joints – with features of periarticular demineralisation associated with acetabular protrusion, sometimes even osteochondritis dissecans, with a marked OA of the hip with geodes and disconfiguration or even

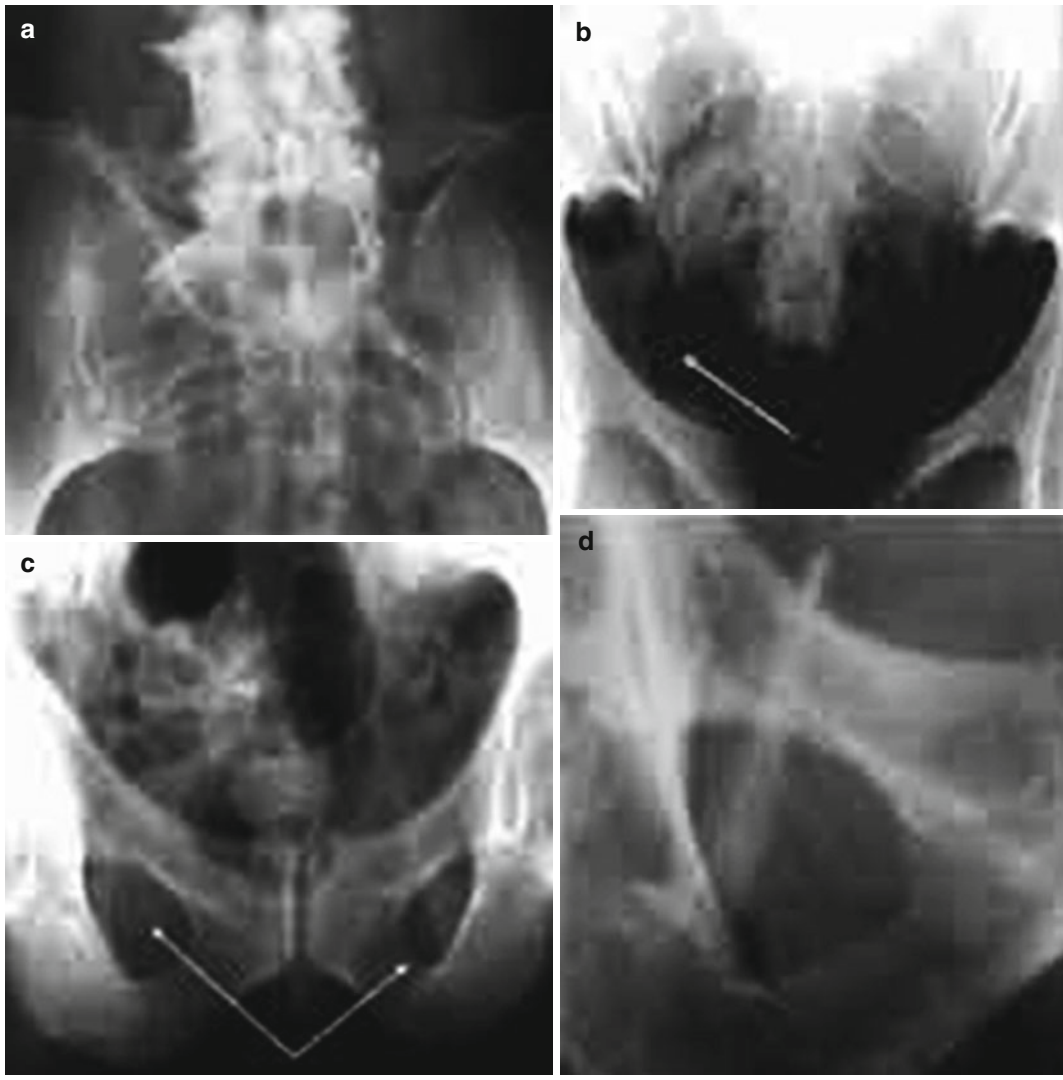

Fig. 16.6 Ossification of iliolumbar, sacrospinous and sacrotuberous ligaments. (**a**) ossification of iliolumbar ligaments in 67-year-old female patient. Osteitis condensans ilii as a manifestation of chronic instability of the pelvic ring; (**b**) ossification of the sacrospinous ligament (*arrow*); (**c**) ossification of the sacrotuberous ligament (*arrows*); (**d**) spicular ossification of the sacrotuberous ligament

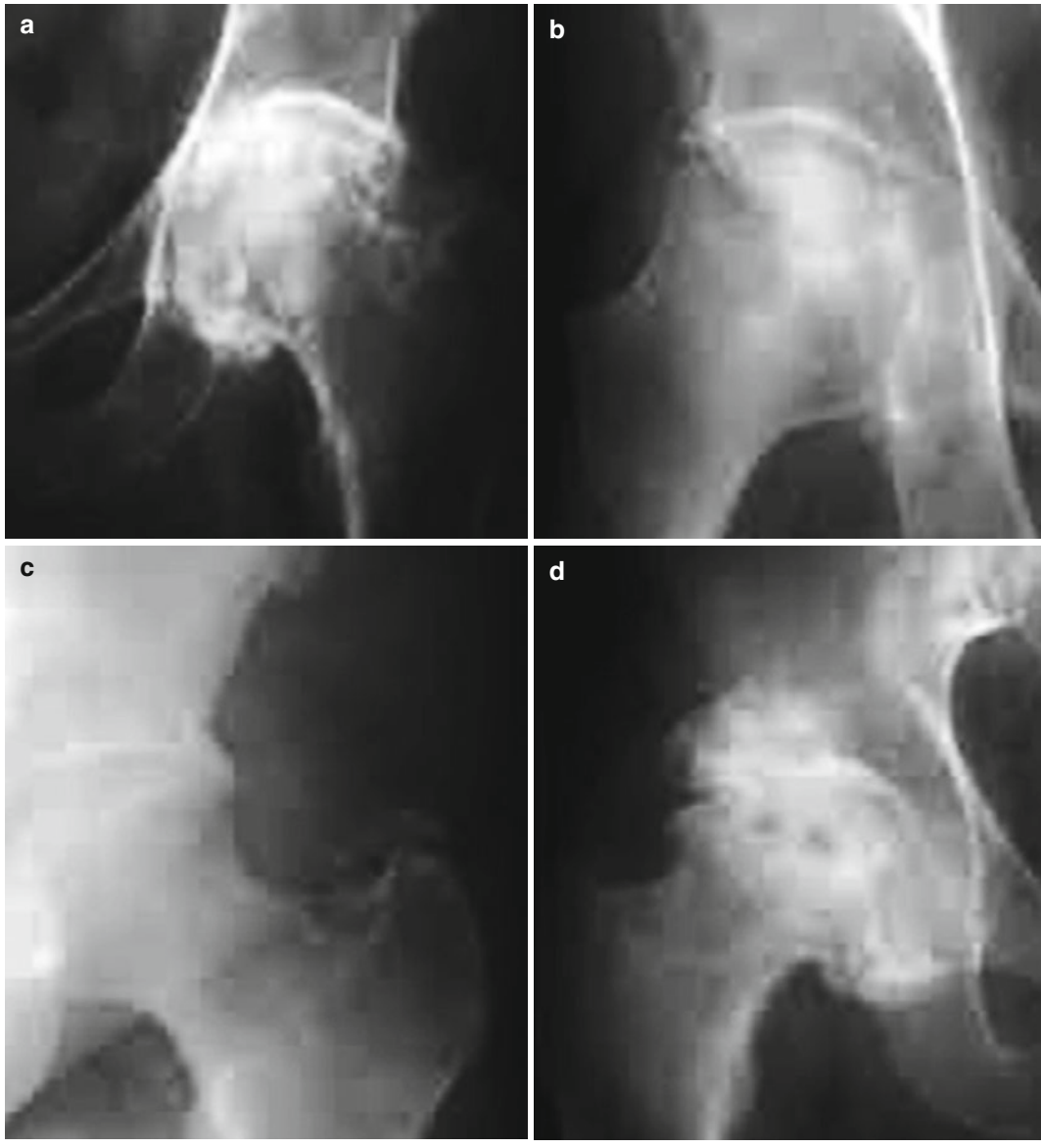

Fig. 16.7 Supra-acetabular ossification. (**a**) Acetabular protrusion with avascular necrosis of the femoral head, with migration of the femoral neck into the fragmented femoral head; (**b**) impaction sequester of the proximal pole of the femoral head; (**c**) enthesopathic ossification in the region of greater trochanter in gluteal muscle attachments; (**d**) acetabular protrusion with supraacetabular capsular ossification

avascular necrosis of the femoral head. Femoral head necrosis is a specific form of aseptic hypovascular bone necrosis, as it develops at the site of high loading of the hip joint. The exact incidence is not known.

A typical macroscopic finding shows delamination of cartilage at the site of femoral head loading beneath the subchondral bone, well-defined necrosis of cancellous bone and osteocytes, collapsed cancellous bone, sometimes with fragmentation of edges, sequestration and gradual loss of the round shape of the femoral head. The cause of the disease is impaired blood supply of the femoral head. It often occurs in conjunction with MS with steroid-induced lipid metabolism disturbances, sickle-cell anaemia and chronic alcoholism and after femoral

neck fractures. As type 2 DM is a common part of the metabolic syndrome, avascular necrosis of the femoral head can be found more frequently in elderly diabetic patients. The underlying factor of these changes is microangiopathic disorder with deteriorating vascularisation, particularly in cancellous bone structures [14].

16.13 Structural Changes in the Region of the Knee Joint

Structural changes in the region of the knee joint (Fig. 16.8) include:

- OA of the knee – with prominent hyperplastic enthesopathic spurs of the eminence and along the articular edges, sometimes also with dissecates and with calcification of menisci, patellofemoral arthritis with bone spurs and osteochondritis of the patella.
- Ossification of capsular and pericapsular structures – exostotic, similar to Pellegrini-Stieda syndrome, but also isolated focal ossifications along the edges of condyles.
- Enthesopathic ossification around the patellar tendon, as well as in the quadriceps tendon insertion to the tibial tuberosity (Fig. 16.9).
- Tenosynoviosclerosis of the rectus femoris tendon at its transition anterior to the patella into the patellar tendon is shown as spicular periostosis with signs of ossification.

16.14 Structural Changes in the Region of the Ankle and Foot

The following structural changes can be observed in the region of the ankle and foot (Fig. 16.10):

- Limited joint mobility (LJM) with involvement of the forefoot manifested in the first stage by elevated medial arch, sometimes accentuated by predominance of flexors in the presence of peripheral neuropathy with excessive load on metatarso-phalangeal joints, often also with posterior subluxation.

The symptoms include rigid hammer toes with callosities on the dorsal aspect of distal phalanges and under metatarsal heads and intermetatarsal rigidity, later associated with toe deviation. Diabetic patients develop symptoms of neuropathic foot with excavation and hammer toes due to predominance of flexors in neuropathic dysregulation. Excessive pressure of metatarsal heads on the planta causes plantar calluses or even skin defects and callosities on the dorsal aspect of flexed interphalangeal joints. In the second stage, ligamentous and capsular structures of the midfoot get lax; there occurs flattening of longitudinal arch of the foot, arthritis (sometimes dissecting) in the Chopart, or Lisfranc joint, with the development of posterior osteophytes:

- Enthesopathic osteophytes that can be found most often on the calcaneus as spurs at the insertion of the plantar fascia as well as Achilles tendon, caused by chronic plantar fasciitis with retraction and increased tension in the tendon due to tenosynoviosclerosis
- Tendinous xanthomatosis that may occur at the site of calcaneal tendon insertion in familial hypercholesterolaemia
- Diabetic neurogenic Charcot osteoarthropathy

Structural changes in MS are characterised by different features, course and prognosis than neurogenic diabetic Charcot osteoarthropathy (CHOA), which is the most severe destructive, even mutilating neuropathic form of the diabetic foot. It is given by the predominating carbohydrate metabolism disorders in the MS complex, marked neuropathic effect of all forms of peripheral regulation and a significant impact of both micro- and macroangiopathy on the lower limb structures, with formation of arteriovenous shunts. Neuroangiopathic changes in the lower limb in diabetic patients, contributing to the development of ulcers, gangrenes or manifestation of Charcot osteoarthropathy of the foot are not so frequent and significant in metabolic disorders, if DM is not a marked predominating and long-term pathological factor within MS [32]. Therefore CHOA is dealt with in a separate section.

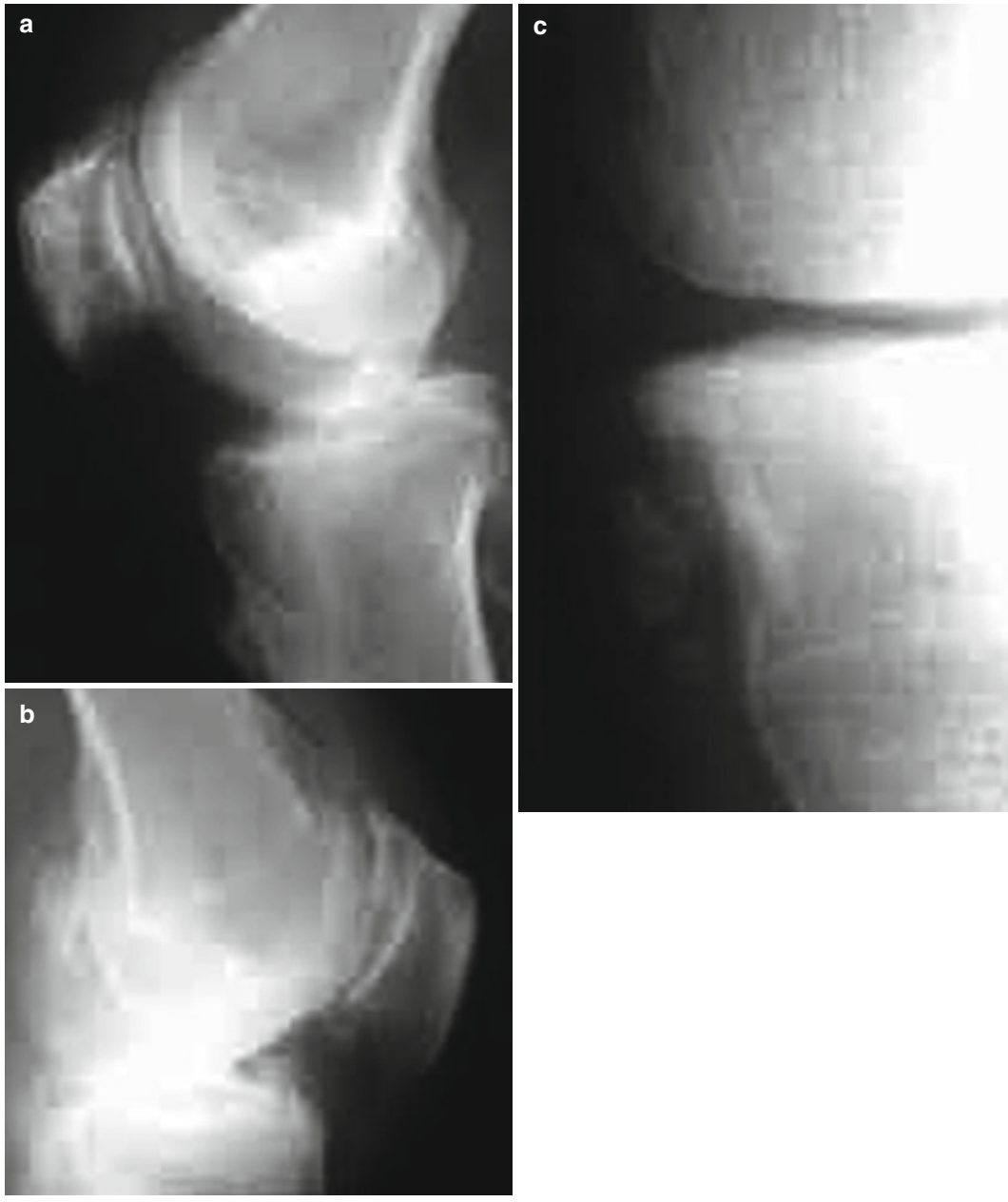

Fig. 16.8 Changes in the region of the knee joint. (**a**) Enthesopathic spicular appositions in the proximal part of the patella, with osteophytic spurs of the superior pole of patella and the tibial tuberosity at the attachment of the patellar tendon; (**b**) Para-articular ossification in the posterior supracondylar region and along posterior edge of the tibia, enthesopathic ossifications of intercondylar eminence, massive osteophytes on both poles of patella and suprapatellar enthesopathic ossifications in the quadriceps tendon insertion; (**c**) extracapsular periarticular ossifications of the medial tibial plateau with cortical impression (calcified bursa?, ossified capsule?, pes anserinus enthesopathy?)

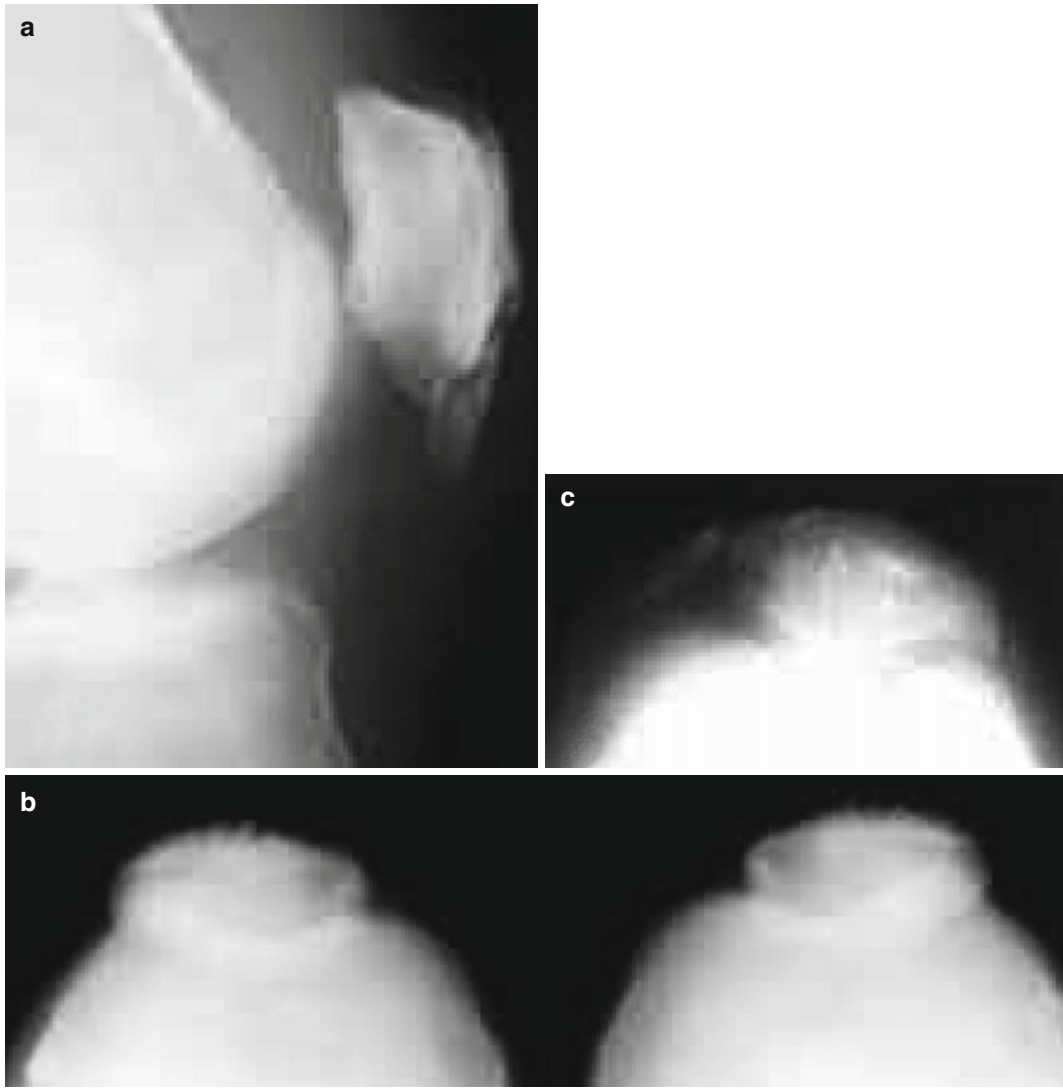

Fig. 16.9 Changes in the region of patella. (**a**, **b**) Parapatellar ossifications in MS with signs of patellofemoral osteoarthritis and enthesopathy of pattelar tendon; (**c**) spicular periostoses and tendinopathy of the intermedius a rectus femoris tendons

16.15 Structural Changes in the Region of the Shoulder

In the region of the shoulder (Figs. 16.11 and 16.12), MS is associated with the following conditions:

- Avascular necrosis of the humeral head resulting from avascular trophic disorder caused by microangiopathy

Characteristic features include slow disintegration and deconfiguration of the humeral head with irregular well-defined osteoclasia alternating with sclerotic lesions:

- Calcific periarthritis, exhibiting calcifications and ossifications in rotator cuff, capsular and pericapsular structures due to their previous loss of elasticity and subsequent functional overload, sometimes of the nature of enthesopathic calcification and ossification.

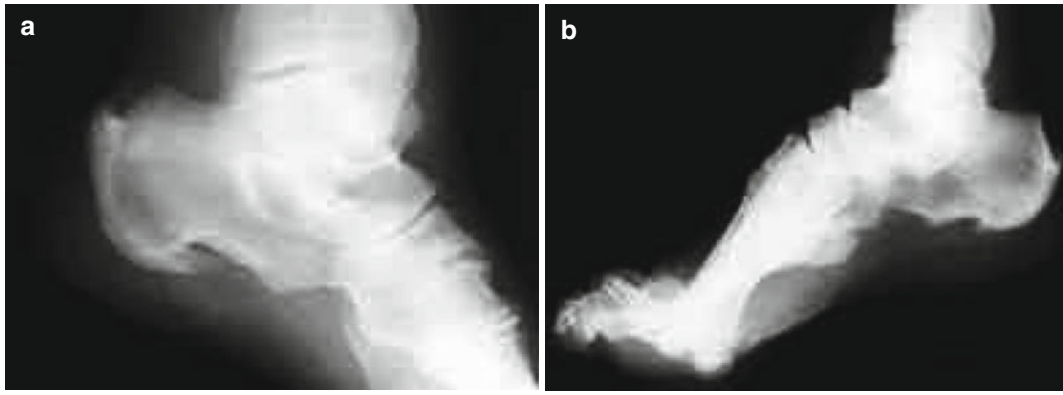

Fig. 16.10 Structural changes associated with MS in the region of the foot. (**a**) Massive calcaneal appositions in Achilles tendon insertion and plantar fascia, with signs of developing fibrotisation. Arthritic osteophytic spurs on the dorsal aspect of midfoot, without evident fragmentation; (**b**) enthesopathic ossification on the foot skeleton in Achilles tendon insertion and plantar fascia – calcar calcanei inferior and posterior. Pes excavatus resulting from neuropathic foot without symptoms of osteoclasia and demineralisation

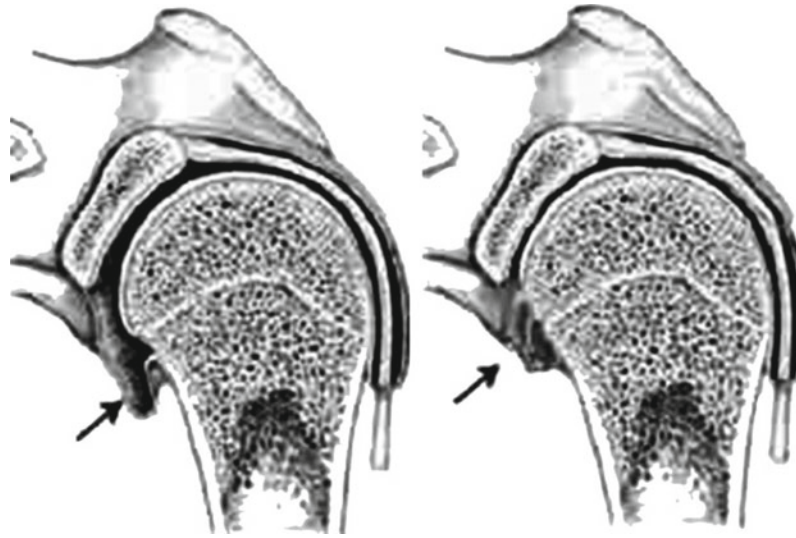

Fig. 16.11 Adhesive capsulitis. Axillary plica of the shoulder joint capsule (*left*) and adhesive capsulitis (*right)*, with rough synovialis and subsynovial capsular layers, that are glued together and adhered to the edge of the humeral head (Modified according to Neviaser)

- Rotator cuff tenosynovitis with thickened and rough tendon sheaths, their hypotrophy and increased vulnerability. Increased incidence of ossification.
- Cheiroarthropathy-induced LJM syndrome – leads to multiplication of degraded collagen, its hypertrophy, loss of elasticity, increased vulnerability, later followed by joint laxity and instability, with subsequent osteophytic arthritis of both the glenohumeral and acromioclavicular joints.
- Adhesive capsulitis (frozen shoulder syndrome) with painful retraction and stiffness of the capsule, with periarticular adhesions, mainly in the axillary region, and a subacromial migration of the humeral head [30, 41].
- Calcareous bursitis (with radiographic contrast paste with small hydroxyapatite crystals

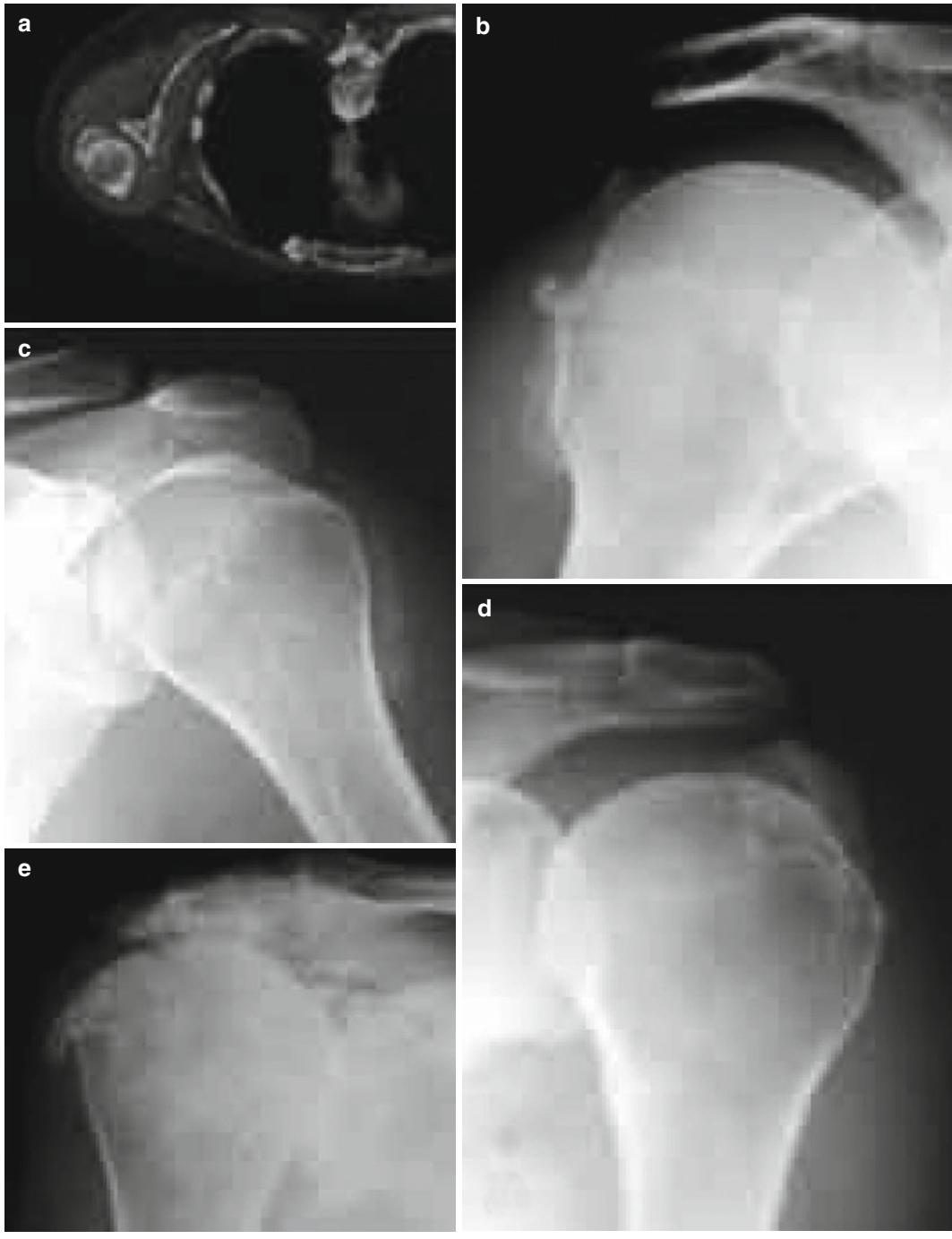

Fig. 16.12 Structural changes in the region of the shoulder in MS. (**a**–**c**) Periarticular ossification of the shoulder; (**d**) bursitis calcarea subdeltoidea; (**e**) avascular necrosis of the humeral head with chronic retractile capsulitis and acromioclavicular joint arthritis

developed by precipitation in the intrathecal region, which later calcifies) – caused less frequently by metabolic disorders.
- Reflex dystrophy with hypotrophy of the shoulder girdle and radiological manifestation of focal demineralisation of the Sudeck's type.
- Involvement in conjunction with DISH, characterised first of all by enthesopathic appositions and calcification of periarticular structures [29, 55, 56].

16.16 Structural Changes in the Region of the Elbow

Structural changes in the region of the elbow (Fig. 16.13) are rare and take mainly the form of enthesopathic appositions in insertions of the biceps and triceps and muscles of the forearm on epicondyles. They can be seen also in the form of heterotopic para-articular ossifications.

16.17 Structural Changes in the Region of the Hand

These changes are manifested by the development of cheiroatropathy with limited joint motion (LJM) and peripheral joint deformities resembling extenso-progressive arthritis, sometimes also with slight seropositivity. They most commonly affect carpometacarpal and metacarpophalangeal joints of the thumb [48]. The disorder typically begins with an extension deficit at the fifth finger on each hand and spreads radially, involving metacarpophalangeal and interphalangeal joints. LJM of the hand may serve as a clinical barometer of collagen alteration analogous to long-term glycosylated haemoglobin determination. LJM can be found in about 55 % of patients with insulin-dependent diabetes mellitus (IDDM) and in more than 75 % patients with non-insulin-dependent diabetes mellitus (NIDDM). It is significantly related to duration of diabetes. The skin exhibits increased amount of degraded collagen [19]. The presence of peripheral neuropathy increases LJM incidence to 70 % of diabetic patients [50]. The inability of digital extension, usually painless and not disabling, is secondary to thickening of the subcutaneous tissue, the flexor tendon sheaths and sometimes the periarticular skin [19].

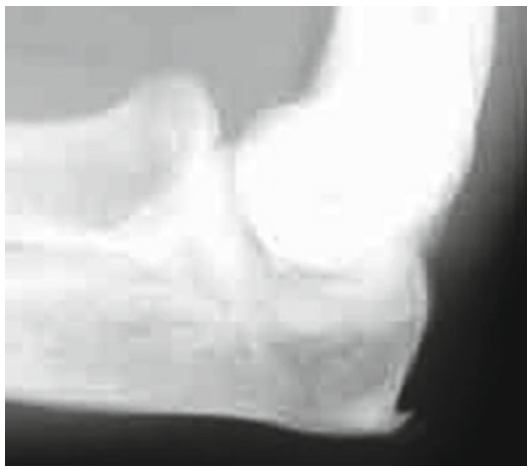

Fig. 16.13 Enthesopathy in the region of the elbow, in the presence of MS. Enthesopathy at the insertion of the triceps brachii on the olecranon of the ulna

Limited joint mobility is classified according to the Rosenbloom's criteria. Mild limitation is considered to be limitation of one of PIP or MCP joints. Moderate limitation refers to involvement of both PIP and MCP joints. Severe limitation is an obvious hand deformity, including also involvement of larger joints [16, 42].

The development of rheumatic lesion in the presence of MS remains unclear, and it has been hypothesised that MS is rather its result. Limited joint mobility with the underlying metabolic abnormality is such a manifestation which characterises MS.

Association of cheiroarthropathy with a high frequency of angiopathy and insulin therapy suggests that this condition is also a valid indicator of DM severity. The underlying cause of diabetic cheiroarthropathy is unquestionably multifactorial.

Factors that may lead to impaired mobility include alterations of the structures in the hand [16]:

- Involvement of small joints of the hand, a clinical manifestation of extenso-progressive arthritis, sometimes also with Heberden's

nodes, cheiroarthropathic hyperplasia of joint capsules with deviation of digits and dominant involvement of the first radial ray in the form of radiocarpal rhizarthrosis.

- Diabetic scleroderma is caused by collagen I disorder I (scleroderma-like-syndrome), particularly in peripheral regions. Combination of collagen-related defect of the skin and other mesenchymal structures with the metabolic syndrome is clinically most commonly manifested on hands.
- Carpal tunnel syndrome is more common in patients with metabolic syndrome, where other aetiologic factors (trauma, overload, etc.) are combined with collagenase and osteofibrotic changes of the retinaculum and ligament. The positive Tinel's and Phalen's signs and "table desk sign", the stiff hand syndrome, are associated with tenosynoviosclerosis of flexor tendons in the palmar region. Both hands are usually affected more or less symmetrically, more often on the ulnar side, with clinical manifestation of a painful trigger finger (digitus saltans) progressing into flexion contracture of the finger with a positive "prayer sign" (Fig. 16.14), sometimes resulting in Dupuytren's contracture [18, 22, 23, 45].
- Tenosynoviosclerosis with chronic retraction synovitis, mainly of digital flexor tendons, is manifested by "trigger fingers" (digitus recellens, digitus saltans) and later by the development of Dupuytren's chronic stenosing synovitis [18, 46] (Fig. 16.15).

Fig. 16.14 Stiff hand syndrome "prayer sign"

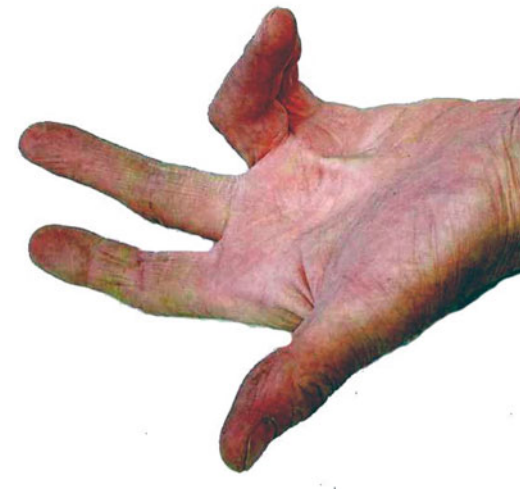

Fig. 16.15 Dupuytren's contracture of 4th digit resulting from stenosing tenosynovitis

16.18 Treatment of Metabolic Syndrome-Related Musculoskeletal Disorders

Due to its multifactorial etiopathogenesis and change in all tissue structures of the human body with a wide range of clinical manifestations, metabolic syndrome requires a comprehensive treatment. Energy demands put on the musculoskeletal system have certain specific features. In order to survive, immediate energy-intensive functional response is sometimes needed, with adequate metabolic flexibility between the lipid and carbohydrate metabolic systems. These principles are often impaired by the metabolic syndrome and require adequate treatment.

While a substantial part of metabolic disturbances are treated by pharmacological therapy with the support of intervention treatment, the

musculoskeletal system by virtue of its function requires a higher share of intervention procedures. Therefore a comprehensive MS treatment is multidisciplinary, but quite often marginal from the viewpoint of participating disciplines.

The mainstay of the therapeutic complex remains pharmacological treatment of various MS components, including changes in the mesenchymal musculoskeletal system [51]. Intervention treatment consists of local steroid and anaesthetic injections, where account has to be taken of temporary hyperglycaemia after steroid application and loss of soft tissues following repeated administration of local anaesthetics that are cytotoxic and cause atrophy of the treated site. Other intervention procedures include release of nerve and tendon structures, osteotomy, arthroplasty, joint replacement, stabilisation and amputation, most often diabetes-related. The need for amputation should always be seen as a failure of treatment. An important part of the complex of therapeutic procedures to treat metabolic disorders of the musculoskeletal system is orthotic treatment and rehabilitation and physical therapy.

Active rehabilitation is essential not only in diabetic patients but also in patients with MS manifestation. Muscular strength was inversely associated with metabolic syndrome incidence, independent of age and body size. Potential benefits of greater muscular strength presumably through resistance exercise training should be considered in primary prevention of metabolic syndrome, as well as in its treatment [25, 53].

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Clinical Syndromology of Gouty Arthritis

17

Jozef Rovenský, Marián Kovalančík, Karol Bošmanský, Emília Rovenská, and Jana Sedláková

Diagnosis of gouty arthritis in the elderly may be complicated due to its different clinical course as compared to younger age groups. Clinical observation of gout in elderly patients has revealed the following differentiating signs:

- The onset in the elderly patients may be insidious, with pain or swelling not so intensive as in the classic gout [1].
- More frequent polyarticular incidence of gout.
- The disease develops most often after the age of 65; in older age it is more common in women due to their predominance in population. In younger age groups, gouty arthritis prevails in men; in the elderly patients, its overall incidence has a more equal gender distribution.
- Involvement of small joints of the hand is more frequent.
- Often atypically localized incidence of tophi.
- Typically a small number of acute episodes, if any, with a typical development of tophi [2].
- Fever and delirium may occur in the elderly patients with gout, but urate renal stones are less frequent.
- The underlying cause of gout in the elderly is often renal insufficiency and use of diuretics, mainly in women [3]. Alcoholism contributes less frequently to the development of gout in the elderly [4].

17.1 Polyarticular Gout

Patients with polyarticular gout are as a rule older than those with monoarticular form [5–7]. In a group of 36 patients with the onset of gouty arthritis after the age of 60, the polyarticular form in the early stage (Fig. 17.1) was found in 18 patients (50 %), which is a marked difference as compared to the middle-aged patients who developed this condition [1].

Frequency of polyarticular involvement in the elderly is probably the result of multiple factors.

Chronic hyperuricemia may be induced by cardiovascular and renal diseases, as well as continuous treatment with low doses of aspirin and diuretics.

The clinical course with low intensity of the inflammatory component may cause difficulties in distinguishing between rheumatoid arthritis and polyarticular gout.

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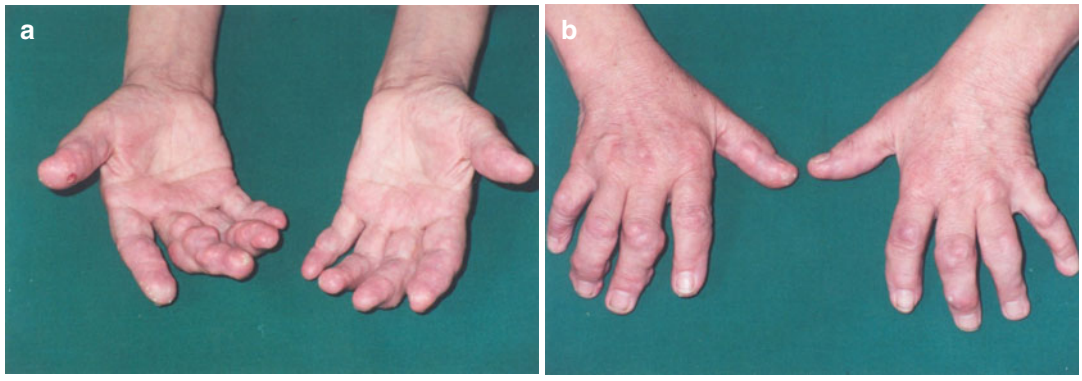

Fig. 17.1 Polyarticular tophaceous gout. (**a**) Palmar view. (**b**) Dorsal view

Table 17.1 Clinical symptoms of gout: typical gout vs late-onset gout

Characteristics	Typical gout	Late-onset gout
Age at the onset of the disease	The highest incidence in the middle of fourth age decade	Older than 65 years
Gender distribution	Men > women	Men = women
Manifestations	Acute monoarthritis Lower limb (podagra 60 %)	Often polyarticular onset; more frequent involvement of upper limb
Tophi	After multi-year history of attacks	More frequent involvement of fingers; may occur in the early stage without a history of previous attacks
Associated characteristics	Elbows > fingers Obesity Hyperlipidemia Hypertension Intensive alcohol consumption	Possibility of frequent involvement of fingers Renal insufficiency Use of diuretics mainly in women Occasional alcohol consumption

Modified After Wise [4]

Elderly women exhibited increased incidence of gout particularly when they developed gouty arthritis in advanced age (Table 17.1). In up to 85 % of women, gouty arthritis was diagnosed after menopause. Puig et al. [8] and Park et al. [9] described in 75 % of Korean women the first symptomatic episode of gout after the onset of the menopause. On the other hand, the group of women who developed gout prior to menopause usually had renal insufficiency or were taking cyclosporin after renal transplantation. Female patients in this group were on average by 7–10 years older than men, with a shorter duration of this disorder [8, 10].

Studies published by MacFarlane and Dieppe [3], Fam et al. [11], and Lally et al. [12] have shown that in 50–60 % of women, gout developed after the age of 60; at the age over 80, gouty arthritis was found only in women.

17.2 Clinical Features of Involvement of Small Joints

In recent years, arthritis of small joints of the fingers has been more frequently noted in conjunction with gout in the elderly patients. Osteoarthritis of distal and proximal interphalangeal joints is a common feature in elderly patients, women in particular.

A typical feature is inflammatory exacerbation caused by basic hydroxyapatite crystals or other factors. In 1983, Simkin et al. suggested a potential share of gout in the inflammatory process in DIP during osteoarthritis. In a group of five patients (four women and one man at the age of 67–77 years), acute inflammation attacks were observed in joints affected by osteoarthritis, with the presence of sodium urate crystals in the involved joints.

Medical history of most patients showed a previous gouty attack. The affected joints and other sites exhibited the presence of gouty tophi. Gradually also other studies have confirmed involvement of small joints of the hand in elderly patients with gout, mainly in women. Ter Borg and Rasker [1] have pointed out the fact that elderly patients with late-onset gout had initial symptoms of the disease in fingers of hands, with the incidence in 25 % of women and their absence in men. Another study [8] has demonstrated that of all women who had gouty arthritis of upper limbs, small joints of hands are affected in about 30 % of cases.

In other studies Fam et al. [13] and Lally et al. [12] demonstrated in large groups of patients involvement of PIP and DIP joints in late-onset gouty arthritis; the mean age of women was 70 years, but involvement of DIP joints was more frequent than that of PIP joints. It should be noted that typical erosive changes in erosive osteoarthritis were sometimes hard to distinguish radiologically, but the presence of density associated with sodium urate crystal deposition in soft tissues, large intra-articular and non-marginal erosion, and osteolysis supported the diagnosis of gouty arthritis (Figs. 17.2 and 17.3). In patients with IP joint involvement and gouty arthritis, high frequency of use of diuretics was observed.

17.3 Early Atypical Tophaceous Gout

Initial development of tophi at atypical sites was described in elderly patients with gouty arthritis, women in particular. The incidence of tophi is higher in women (44 %) as compared to men (8 %) despite a shorter duration of the disease and less attacks. MacFarlene and Dieppe [3] found in a group of elderly women three patients who had tophi in fingers without a previous gouty attack. This tendency to tophi development without previous gouty attacks was confirmed also by other authors. In four elderly women, the incidence of tophi was described at an atypical site – in the finger pads [14]. These unusual findings occurred also in a larger group of elderly women [15]. Puig et al. [8] found in 27 % of women, mostly after menopause, tophi that were in 90 % of cases located in fingers and none above the elbow. Ter Bork and Rasker [1] analyzed the incidence of tophi in a group of elderly patients including 22 women and 18 men with gout and found no difference in the incidence of tophi in fingers between women and men. The relation between gender and the incidence of tophi in finger pads was not confirmed by Holland et al., either [16]. The cause of predisposition to atypical incidence of tophi in elderly patients is unknown.

17.4 Incidence of Gouty Arthritis in Diuretic Treatment

A high association between diuretic treatment and renal insufficiency was observed in elderly patients with gout. Use of diuretics was confirmed in 75 % of patients with late-onset gout, mainly in women (95–100 % of female patients).

Continuous use of diuretics was proved in multiple groups of patients with atypical condition of finger (toe) joints or tophaceous deposits (Figs. 17.4 and 17.5) [12–14, 17]. Retrospective studies revealed an almost twice as high risk for the initiation of anti-gout therapy in hypertensive patients treated with thiazide diuretics during the period of 2 years of commencement of hypertension treatment as compared to patients without thiazide diuretic therapy [18]. Consumption of alcohol in elderly patients with gout is not very frequent, mainly in women. A certain degree of renal insufficiency is a regular phenomenon in

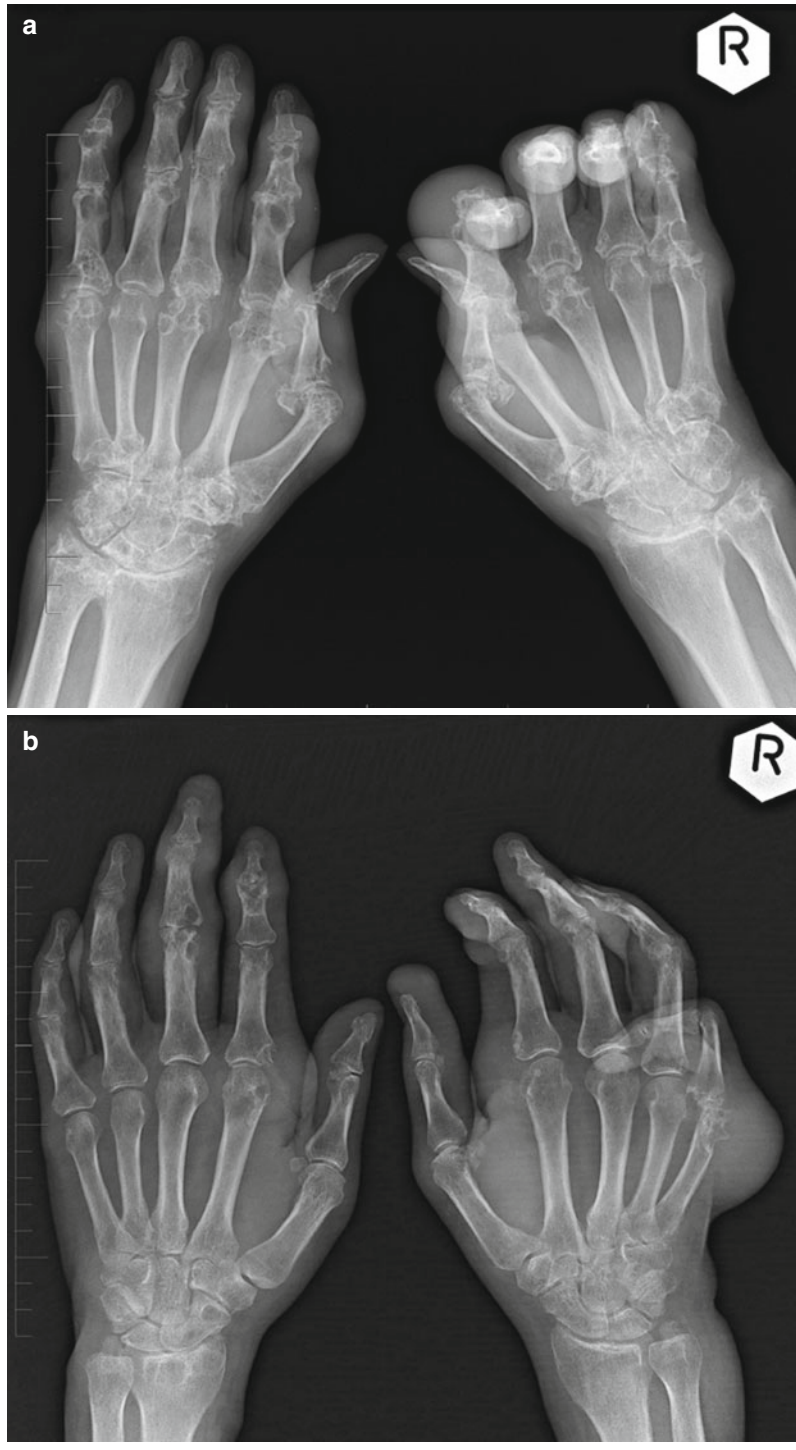

Fig. 17.2 Hands. (**a**) Sharply contoured multiple large defects in the finger skeleton of both hands, slightly deformed edges of articular surfaces with the presence of minor cystoid subchondral defects in MCP joints and both wrists; (**b**) multiple asymmetrical widening of the shadow of soft tissues in both hands and forearms, multiple round well-defined hyperlucencies of the skeleton, partially also with interrupted contours, with maximum in MCP5 on the right, PIP3 and DIP2 on the left

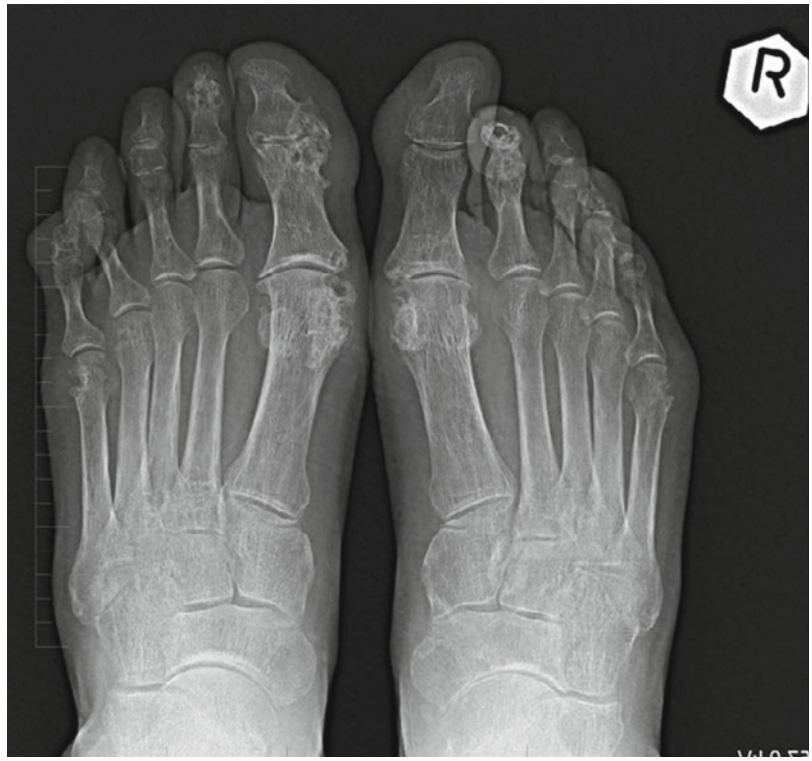

Fig. 17.3 Feet. Minor skeletal lesions, predominantly marginal in the form of usurations, but also pseudocystic hyperlucencies, with maximum in the left great toe joints and in DIP5 bilaterally

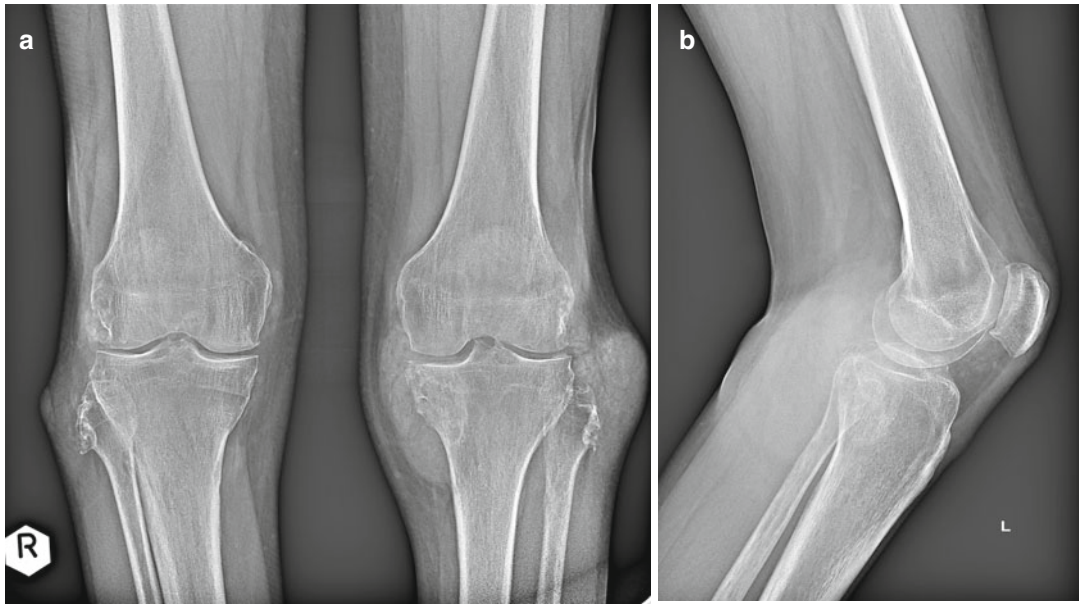

Fig. 17.4 Knee joints. Arthritic narrowing of joint space in both knee joints, markedly dense tophaceous deposits in soft tissue structures of the left knee, primarily fibular, extending deep into the popliteal fossa; on the right – less dense shadow in the soft tissue structures around the fibular head, cystic hyperlucency in the medial condyle of the tibia, and the fibular head on the left side. (**a**) AP anteroposterior view. (**b**) Laterolateral LL view

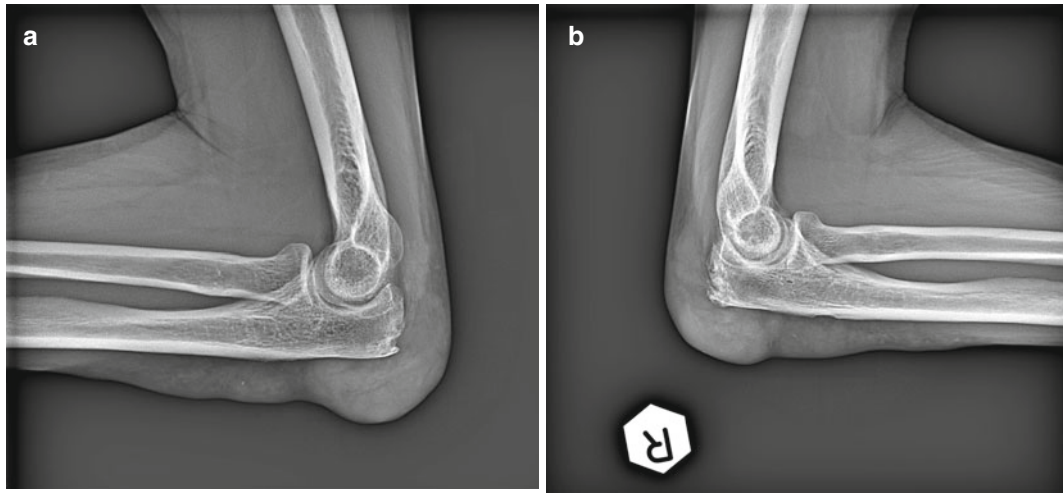

Fig. 17.5 Elbows. Deposits in soft tissue structures of various density, with maximum in the region of olecranon of both elbows, enthesopathic ossification of olecranon bilaterally. (**a**) Laterolateral LL view of the *right* elbow. (**b**) Laterolateral LL view of the *left* elbow

elderly patients with gout. As there is no available comparison with other groups of elderly patients, it is not clear to what extent decreased renal function is associated with gout or is typical of elderly population in general.

17.5 Gout Therapy in Elderly Patients

Gout therapy in elderly patients differs from that of middle-aged population. The priority is to ensure the quality of life and to prevent potentially serious drug toxicity. The patients are often polymorbid and take multiple medications, and medical drug interactions are quite common in them. First it is necessary to verify acute gout by aspiration of synovial fluid in the affected joint and identification of monosodium urate microcrystals, to determine the value of hyperuricemia and blood count parameters, and to examine renal functions.

In addition it is necessary to detect any predisposing factors (e.g., diuretics, alcohol, etc.) and eliminate them, where possible [19–21].

In the next step, decision has to be made if the therapy is inevitable. The patients' complaints are often insignificant and acute gout attacks infrequent. On the other hand, tophi may be painful and/or destructive, and hyperuricemia may induce further renal damage. In such case the disorder must be appropriately treated. Painful gout inflammation is best treated with low doses of colchicine (0.5 mg twice a day), which usually does not pose any problems in this amount. More caution is certainly required in NSAID treatment, as they are potentially dangerous in terms of the patients´ age, mainly in simultaneous renal insufficiency and diuretic therapy, not only for their low efficacy and adverse gastrointestinal and neurological effects, but also for their potential nephrotoxicity and fluid retention [21]. Caution is necessary also in allopurinol therapy which is indicated only in inevitable cases at low doses up to 100 mg daily, where necessary, with reduction of the dose according to the degree of renal insufficiency. Allopurinol toxicity increases with increasing age and is also potentiated by renal insufficiency and diuretics [22]. Rash and hypersensitivity may occur in conjunction with vasculitis, hepatitis, cytopenia, acute interstitial nephritis, and toxic epidermal necrolysis. Treatment of gout in elderly patients must be carefully monitored (Table 17.2).

Table 17.2 Therapeutic procedures in gouty arthritis treatment in elderly patients

Acute attack treatment	
Nonsteroidal anti-inflammatory drugs (NSAIDs) (indomethacin and others)	Cautious administration, low doses, limited period, normal renal functions; use of COX-2 inhibitors should be considered
Glucocorticoids (intra-articular, oral, parental)	Preferably in patients with comorbidities, caution is required in patients with diabetes
Corticotropin (ACTH)	Similar as in glucocorticoids
Colchicine (oral, intravenous)	Highly cautious administration, low doses, in patients without comorbidities
Short-term prophylaxis	
Low doses of colchicine	Cautious administration, very low doses; renal insufficiency must be excluded
Low doses of NSAID	Cautious administration, low doses; renal diseases and peptic ulcers must be excluded; use of selective COX-2 inhibitors
Long-term hypouricemia therapy	
Uricosurics	Rarely efficient in elderly patients due to renal diseases
Allopurinol	In repeated attacks; decrease of the dose according to creatinine clearance

Modified after Agudelo and Wise [23]

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Radiology and Ultrasonography Findings in Chondrocalcinosis

18

Mária Krátka and Jozef Rovenský

Clinical manifestation of chondrocalcinosis is nonspecific, and therefore one of the decisive roles in establishment of diagnosis is played by classic skiagraphy. Radiological evidence of calcification of the superficial layer of articular cartilage is at the same time considered as the basic criterion specific for this condition.

A typical manifestation of calcification of articular cartilage and intervertebral discs in classic skiagraphs is caused by deposits of calcium pyrophosphate dehydrate that can be found in intra-articular (fibrous and hyaline cartilage, synovium), para-articular (joint capsule) and extra-articular (tendons, mainly at the site of their insertions, ligaments, bursae and soft tissue) structures. Calcifications develop slowly but progressively, with varying distribution and size. Total calcification is characterised by continuous stripes that are less visible in partial calcification. It affects predominantly fibrous cartilage (knee menisci, fibrocartilaginous disc of symphysis and articular discs of radiocarpal joints). Calcification occurs inside the fibrous cartilage, is diffuse and has a granular pattern. Hyaline cartilage in large joints (elbow, knee, shoulder and hip) are affected less often and even more rarely in small joints (intercarpal, radiocarpal, talocrural, metacarpophalangeal, metatarsophalangeal, tarsal, sternoclavicular, proximal and distal interphalangeal joints). Calcifications can be found in the superficial layer of the cartilage oriented to the synovial cavity. Chondrocalcinosis accelerates onset of secondary arthritis, the first osteoarthritic changes involve weight-bearing joints and their development depends on the functional load and duration of the disease. The resulting generalised osteoarthritis with typical gradual narrowing of the joint space mimics minor intra-articular calcifications [1].

The course of arthropathy is more progressive in case of early onset of the disease – in the third age decade – and therefore the hereditary polyarticular type is associated with a significant inflammation. The sooner the first signs appear, the more severe and the more extensive they are.

In case of late onset of the disease – in the fifth or sixth age decade – the changes affect predominantly fibrous cartilage; the course is rather stationary and mild and leads to a latent oligoarticular type of chondrocalcinosis, which can be clinically best distinguished. Arthritis episodes are less severe and radiograph shows mostly only partial calcifications. Oligoarticular

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asymmetrical involvement predominates. Sporadic chondrocalcinosis is manifested in patients in the fifth to seventh age decade [2, 3].

18.1 Knees

One of the first radiological signs, as a rule at the very beginning of the disease, is a symmetrical bilateral calcification of knee menisci that can be found in almost all patients with polyarticular hereditary form of chondrocalcinosis. It is shown on radiograph as granular or flowing speckled dense shadow along the medial and lateral borders of the joint space (Fig. 18.1). Often, in more than 50 % of cases, it is associated also with superficial calcification of the hyaline cartilage of condyles of both the femur and the tibia that can be better seen in the lateral projection as a dense calcification line paralleling the contour of the condyles (Fig. 18.2). Sometimes also para-articular ossifications are present in the joint capsule and extra-articular calcifications in the insertions of adjacent tendons, particularly the quadriceps femoris tendon [4, 5].

The first changes appear usually in the third age decade in the form of discrete calcifications. In case of polyarticular involvement, the changes come slightly earlier. Calcifications get more pronounced and are gradually accompanied by signs of secondary knee osteoarthritis (Fig. 18.3) that is already well developed in the fifth age decade.

In addition to calcifications, skiagraphs show also narrowing of the joint space, sclerotised articular surfaces, subchondral geodes and marginal osteophytes. In the advanced stage (Fig. 18.4), the changes are more intensive, with a massive hyperplastic osteophyte lining, which may sometimes result even in bone ankylosis.

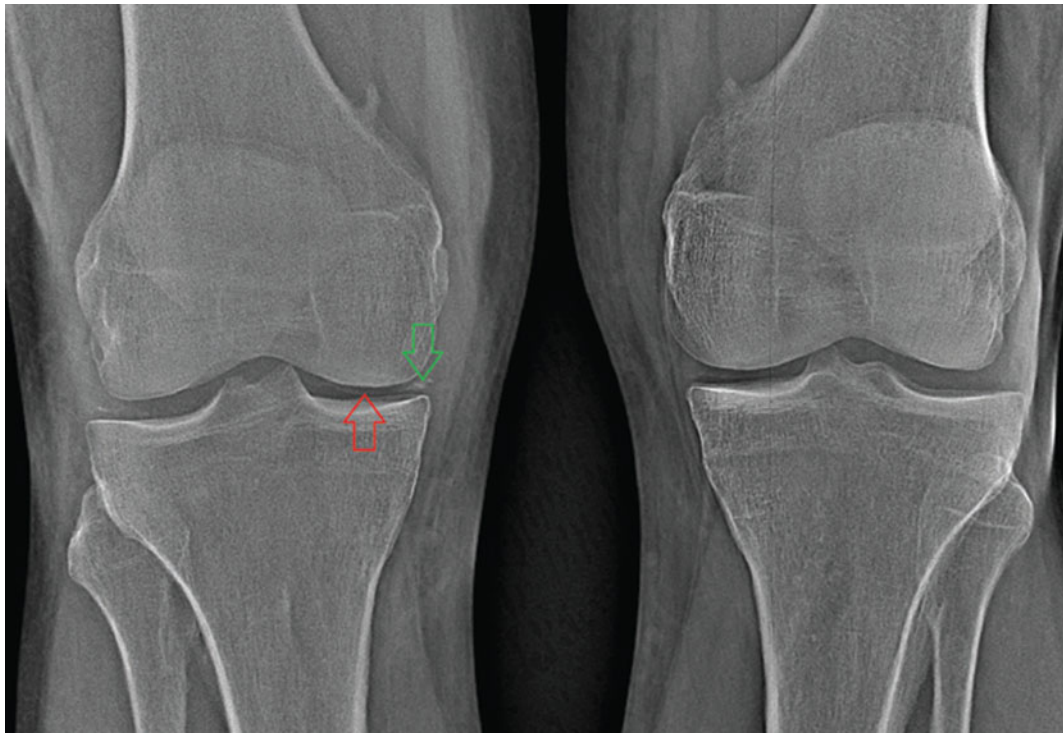


Fig. 18.1 Knees – AP – early signs of chondrocalcinosis, fine linear shadow in the central part of the tibiofemoral joint space in both knees, calcification of hyaline cartilage (*red arrow*) and speckled shadow medially; on the right side, calcification of the right medial meniscus (*green arrow*)

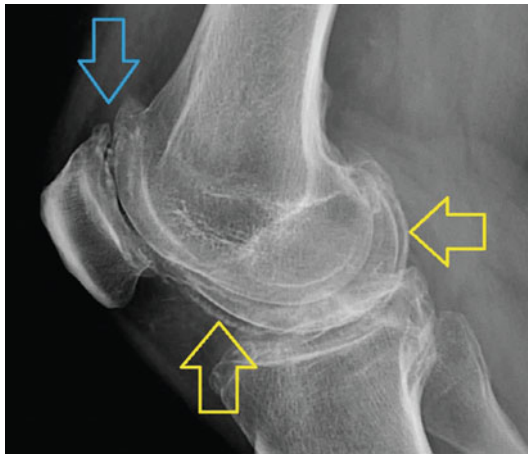


Fig. 18.2 Right knee – LL – calcification of hyaline cartilage lining the contour of epiphyses (*yellow arrows*), hyperplastic patellofemoral OA of the knee (*blue arrow*)

Oligoarticular involvement is characterised by calcifications in the meniscus, especially the lateral one, gradual development of secondary OA of the knee, often also isolated patellofemoral, calcified cruciate ligaments and the quadriceps tendon, intra-articular loose bodies and "Charcot knee" [2].

18.2 Pelvis

One of the most frequently affected sites in the early stage of chondrocalcinosis, both its hereditary and solitary form, is the fibrocartilaginous disc (lamina interpubica) of symphysis. Calcifications are shown as granular shadows, the density of which and subchondral sclerosis of the edges of the symphysis get more intensive with the progress of the disease [4, 5].

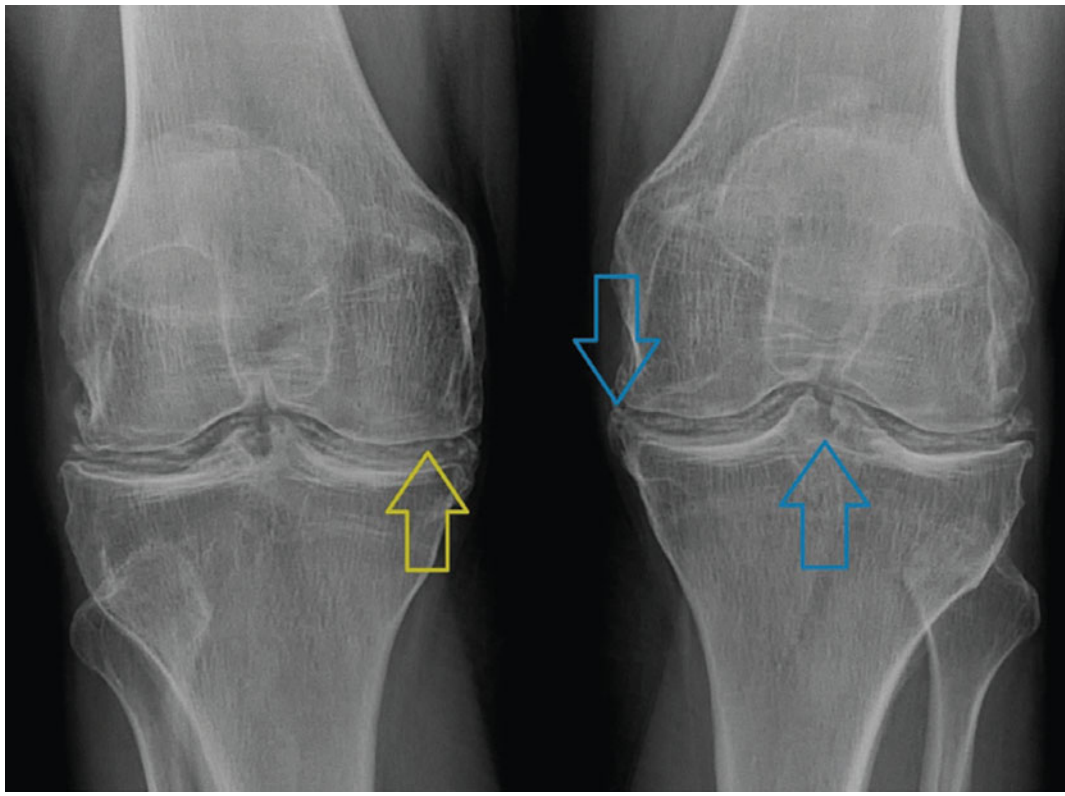


Fig. 18.3 Knees – AP – advanced chondrocalcinosis; dense granular or flowing shadows in the joint space (*yellow arrow*) are accompanied by marked osteoplastic changes along the edges of articular surfaces and intercondylar eminences in bilateral secondary OA of the knee (*blue arrows*)

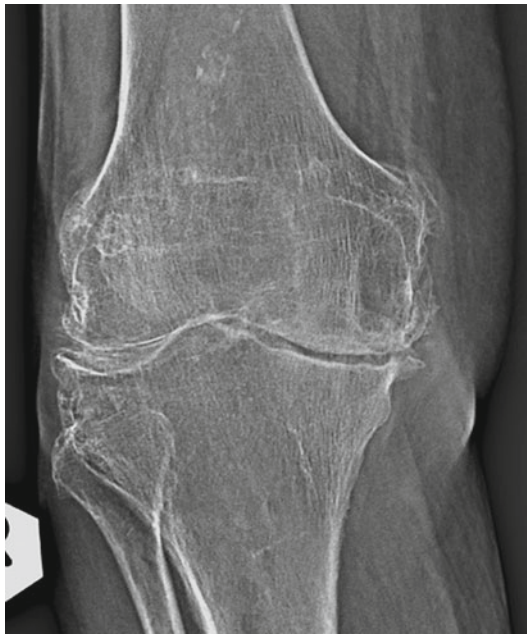


Fig. 18.4 Right knee – AP – severe destructive changes and varus deformity in secondary OA of the knee with impression of the medial condyle; calcification in the joint space is less pronounced

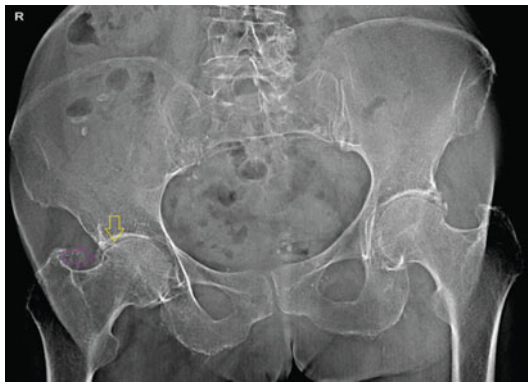


Fig. 18.5 Pelvis – AP – linear fine shadow in the central part of the joint space of both hip joints, calcifications of hyaline cartilage (*yellow arrow*); on the right side also para-articular calcification in the joint capsule (*violet arrow*)

Involvement of sacroiliac synchondrosis is also quite common and is presented in the skiagraphs by discrete granular shadows in the joint space and subchondral sclerosis of the bone. Some patients exhibit late reactive hyperplastic changes of SI joints, most frequently unilateral ankylosis [4, 5].

In the polyarticular form of chondrocalcinosis, skiagraphs show approximately from the fourth age decade calcifications of the hyaline cartilage of hip joints (Fig. 18.5) that are by their nature similar to those in shoulders. Calcifications get gradually more intensive and are accompanied by development of secondary hip osteoarthritis that reaches after about 10 years of the disease its advanced stage and is characterised mainly by central narrowing of the joint space, subchondral geodes and osteophytic lining along edges of articular surfaces [2, 3].

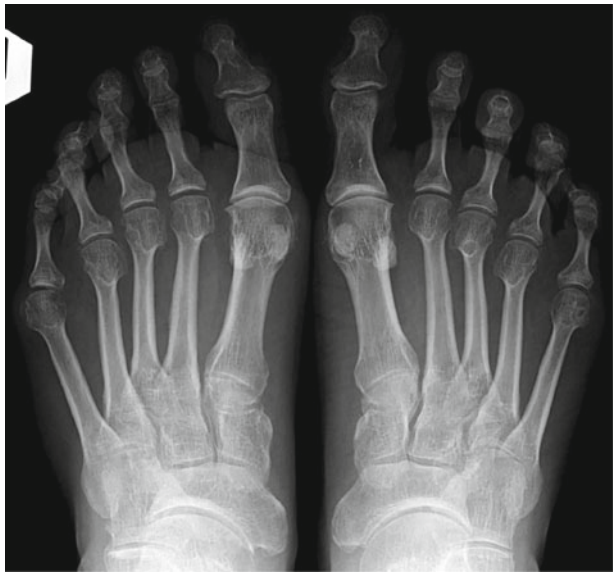
Late onset of hip joint involvement (approximately in the sixth age decade) has skiagraphic signs of the initial stage of early polyarticular form with a slow progress. Sometimes hip joint involvement may be associated with extra-articular calcification of tendons and their insertions mainly in the region of the ischial tuberosity. Rare cases of "coxa profunda" as a secondary response to capsular calcification deposits were also reported [6].

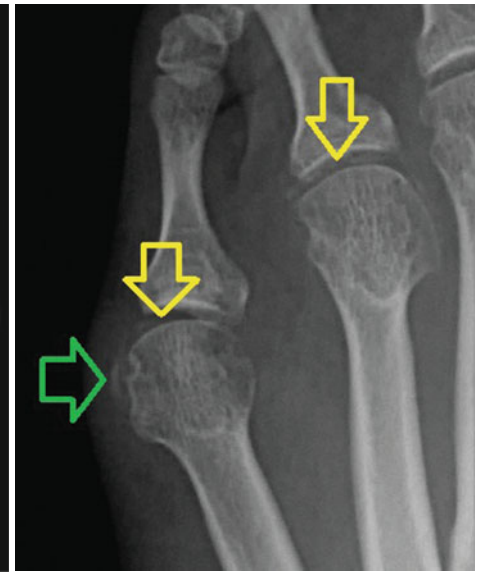
18.3 Ankles and Feet

The initial lesions of talocrural and tarsal joints in polyarticular chondrocalcinosis can be noted as a rule in the fourth age decade and is usually associated with gradual development of secondary arthritic changes.

Tarsometatarsal and intertarsal joints are affected only rarely [4, 5].

Approximately in the fourth decade, skiagraphy of the polyarticular form of chondrocalcinosis may confirm intra-articular calcifications shown as linear shadows in both the central parts of the joint space and the metatarsophalangeal joints (Figs. 18.6 and 18.7). In the early stage, they are accompanied also by para-articular calcification deposits in joint capsules and early onset of secondary osteoarthritis, with later





Figs. 18.6 and 18.7 Feet and fourth and fifth MTPs on the right side – AP – calcification of hyaline cartilage in all tarsal joints, thin linear shadow in the middle part of the joint space of both the fourth and fifth MTP joints of the right foot (*yellow arrow*), extra-articular calcification in the joint capsule of the fifth MTP joint in the region of fibula (*green arrow*)

severe deformities, mainly valgus deviations of great toes [4, 5].

Intra-articular calcifications in the proximal and distal joints of toes are extremely sporadic.

In some patients there dominates extra-articular involvement – progressive calcification of the Achilles tendon and plantar fascia [6].

18.4 Shoulders, Elbows and Sternoclavicular Joints

The first signs of calcification of the hyaline cartilage of the shoulder joint may be proved in case of polyarticular hereditary chondrocalcinosis as early as in the third decade. It is manifested as a narrow dense striped shadow along the humeral head (Fig. 18.8) which doubles at the site of its contact with the glenoid fossa. During the following 10 years, the cartilage becomes completely calcified. Later there develop also signs of para-articular calcification at the site of rotator

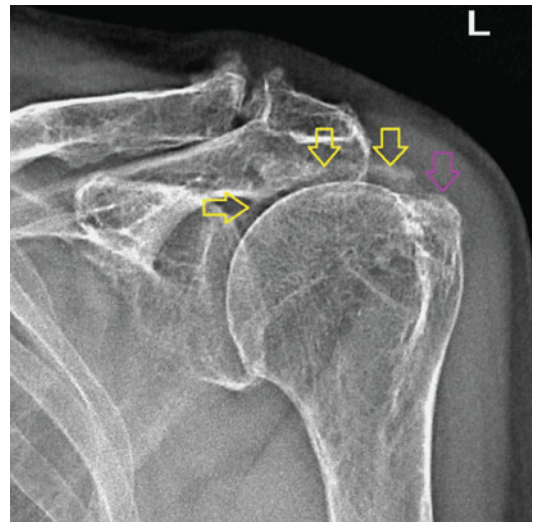


Fig. 18.8 Left shoulder – AP – linear calcification in hyaline cartilage copying articular surfaces (*yellow arrows*), incipient enthesopathic ossification at the site of insertion of the supraspinatus onto greater tubercle of the humerus (*violet arrow*), fine-speckled calcifications also in articular cartilage and joint capsule of the acromioclavicular joint

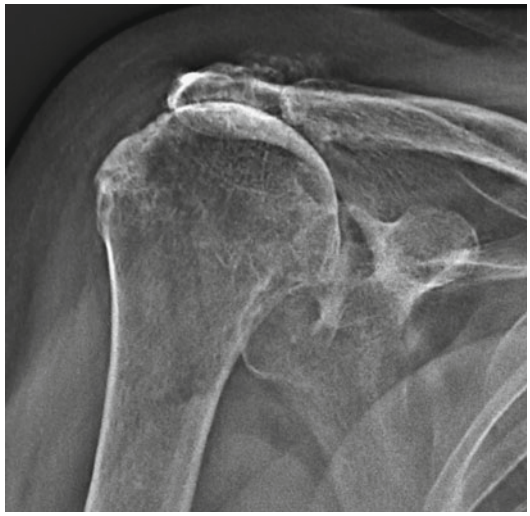


Fig. 18.9 Right shoulder – AP – severe destructive changes in advanced chondrocalcinosis with secondary omarthritis, subacromial retraction; cartilage calcifications are almost invisible

cuff tendon insertions, mainly the tendon of the supraspinatus and subdeltoid bursa [4, 5].

Gradually there develops secondary omarthritis (Fig. 18.9), particularly in the region of the inferior pole of the glenoid. Signs of joint calcification become less noticeable with gradual reduction of cartilage and narrowing of the joint space. Hyperplastic changes become more intensive and the subchondral bone structure is remodelling. Late onset of the shoulder involvement (approximately in the sixth decade) has skiagraphic signs of the initial stage of early polyarticular form with a slow development. Infrequent cases have been reported also of calcification of cartilage of the acromioclavicular joint [2, 3].

The first discrete signs of deposition of pyrophosphate microcrystals in elbows can be detected in skiagraphs in the third decade. It is displayed as a narrow doubled stripe in the central part of the joint space, which can be better seen in AP projection. During the following 10 years, the cartilage becomes completely calcified symmetrically and exhibits incipient signs of secondary osteoarthritis. Gradual progression of hyperplastic changes, subchondral bone remodelling and mainly narrowing of the joint space result in reduction of signs of cartilage calcification. After about 20–30 years of the disease, arthritic changes in the elbow are highly significant and may be of osteonecrotic nature. In case of late onset of chondrocalcinosis, there dominates extra-articular involvement of tendon insertion and joint capsules; intra-articular involvement is not so pronounced and has a granular pattern. If oligoarticular chondrocalcinosis develops as late as in the seventh or eighth decade, cartilage calcification may be completely absent [2, 3].

Hyaline cartilage of sternoclavicular joints is involved in the fourth decade at the earliest, in polyarticular chondrocalcinosis. Later it is accompanied by development of secondary arthritic changes.

18.5 Wrists and Hands

A typical image of a lesion of the fibrous cartilage of the articular disc of the radiocarpal joint is granular and amorphous. It is the third most frequently affected site in the polyarticular hereditary form and the second in sporadic oligoarticular form of chondrocalcinosis.

Calcification of hyaline cartilage of the radiocarpal, intercarpal, carpometacarpal and intermetacarpal joints is less often; it occurs typically in early-onset polyarticular hereditary chondrocalcinosis. Radiologically it shows as a fine striped shadow in the central part of the joint space (Fig. 18.10). In about 10 years of the onset of the disease, there develop secondary arthritic changes.

Involvement of metacarpophalangeal joints is rare in the third decade; however, gradually the number of intra-articular deposits is growing and is associated with unequal development of para-articular calcifications of joint capsules that are often quite extensive and accompanied by development of atypical more pronounced or even bizarre osteophytes [2, 3] (Fig. 18.11).

Intra-articular involvement of proximal and distal interphalangeal joints is rare. Starting from the fifth decade, para-articular calcifications in the polyarticular hereditary form can be occasionally observed in some proximal interphalangeal joints, together with secondary arthritic changes.

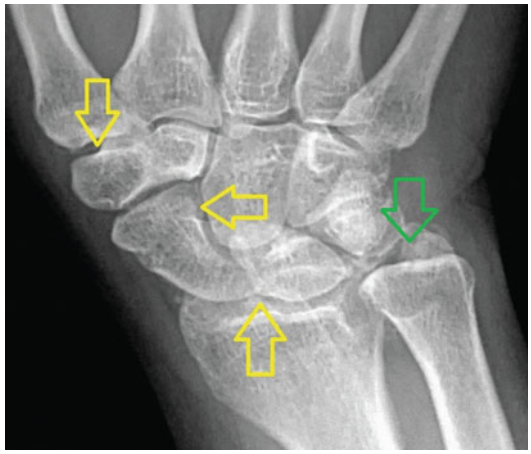


Fig. 18.10 Left wrist – AP – linear shadow in the region of hyaline cartilage of radiocarpal, intercarpal and carpometacarpal joints (*yellow arrows*), fine-speckled flowing shadows also in the region of the articular disc of the ulna (*green arrow*)

18.6 Spine

Calcifications in the region of intervertebral discs are usually observed as late as in the advanced stage of chondrocalcinosis. Deposits of pyrophosphate microcrystals in intervertebral discs are shown by skiagraphy as cloud-like to granular shadows, primarily in the central part of the intervertebral space and at its anterior edge. The most frequently and most significantly affected sites include the cervical and lumbar spine, in some patients also the proximal part of the thoracic spine and coccyx [4, 5].

The initial signs of involvement of intervertebral discs in the form of discrete cloud-like shadows in the central part of the intervertebral space are shown by skiagraphy in the fourth decade, when the involvement of peripheral joints is already fully developed. A concomitant

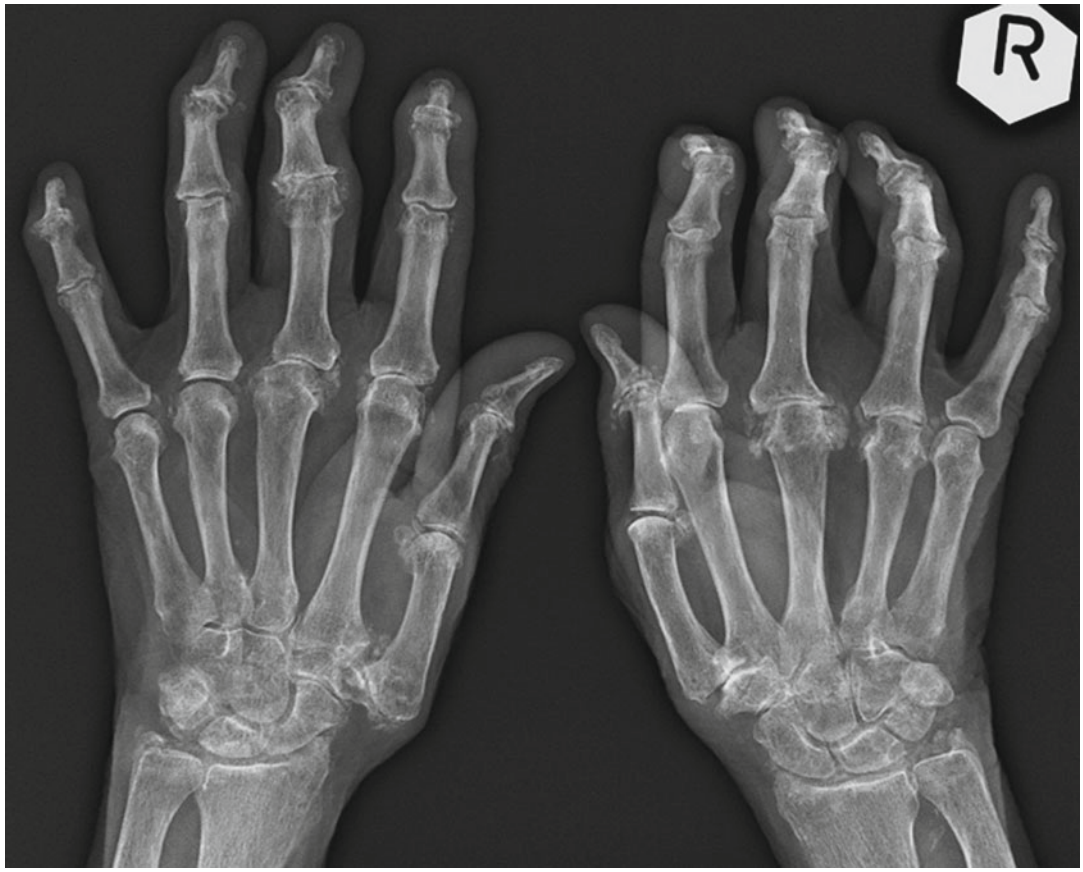


Fig. 18.11 Hands – AP –progressive features of chondrocalcinosis in the region of radiocarpal, intercarpal and carpometacarpal joints of both wrists and massive speckled ossifications in joint capsules of metacarpophalangeal and proximal interphalangeal joints also with progressive secondary arthritic changes

feature may be also straightening of the cervical and lumbar lordosis and signs of early-onset spondylosis, primarily in the affected inferior segments. During the following 10 years, calcifications in the intervertebral space get more intensive, shadows become noticeably granular and speckled and the structure becomes denser in the anterior area (Fig. 18.12) [2, 3].

Simultaneously with progression of the disease, end plates of vertebral bodies get more sclerotic and osteophytes along the edges become larger, resulting in degeneration of the affected discs and subsequent narrowing of the intervertebral space (Fig. 18.13). Late onset of the involvement of the spine – from the sixth age decade – has skiagraphic signs of the initial stage of early polyarticular form with a slow progress. Mainly in oligoarticular form of chondrocalcinosis, there develop in elderly patients also well-defined hyperostotic ossifications in the anterior longitudinal ligament (Fig. 18.14), similarly as in diffuse idiopathic skeletal hyperostosis, quite often associated with deformities of vertebral bodies, however, never resulting in ankylosis [6].

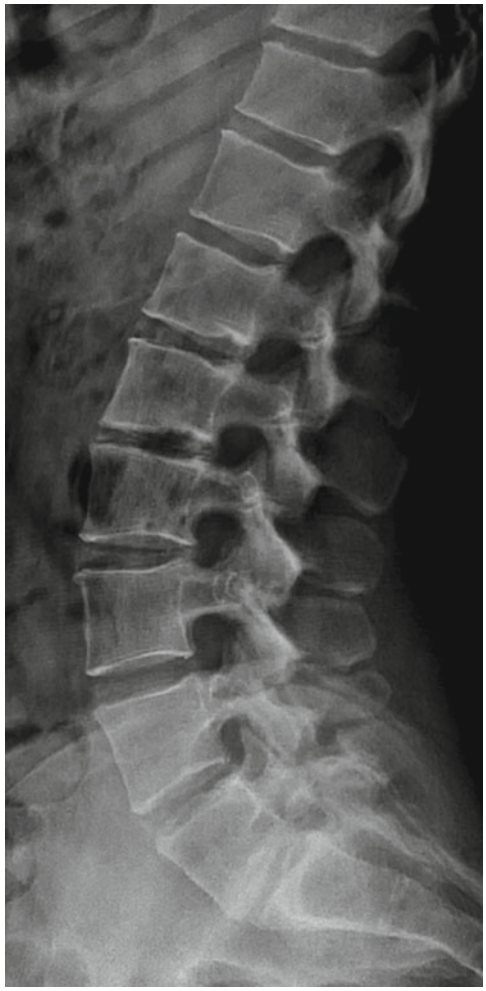


Fig. 18.12 LS spine – LL – central cloud-like calcifications with increased density in the anterior part of all intervertebral spaces, hyperlordosis

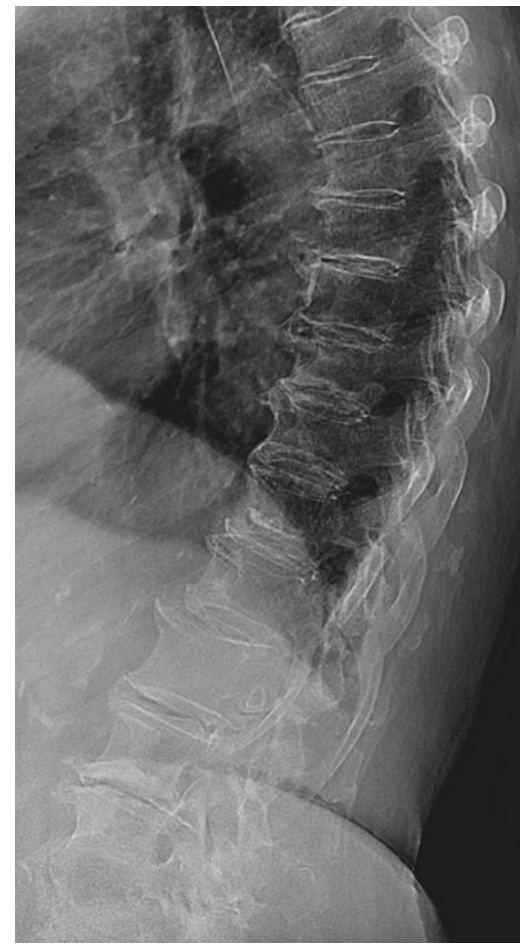


Fig. 18.13 Th–L spine – LL – calcifications in intervertebral spaces, polydiscopathy of the type of severe osteochondrosis, hyperostotic changes along anterior edges of vertebral bodies

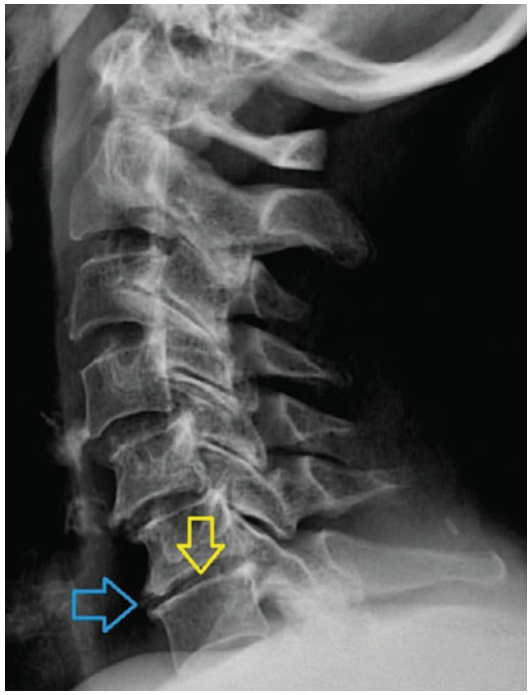


Fig. 18.14 C spine – LL – central calcifications in C4–C7 intervertebral spaces (*yellow arrow*), narrow intervertebral spaces and anterior osteophytes in these segments: osteochondrosis (*blue arrow*)

18.7 Ultrasonography

High-frequency ultrasonography with high-resolution capacity is a sensitive and specific method, which reliably reveals calcifications in the soft tissue, sometimes also those that cannot be visualised by classic skiagraphy, either because of their location or limitations of this method. Magnetic resonance imaging is not considered to be efficient in detection of calcifications probably due to lack of mobile protons in calcifications [7, 8].

Calcium pyrophosphate deposits are displayed by ultrasonography as hyper-echoes that usually exhibit shadowing only after they are larger than 10 mm. Calcifications of another origin exhibit acoustic shadowing already with the size of 2–3 mm [7, 8].

Hyperechogenic calcium pyrophosphate formations in soft tissue may be of various nature, according to the type of the affected tissue:

Hyaline cartilage – hyaline cartilage calcifications may have a punctiform or linear morphology. Thanks to its high-resolution capacity (formations of more than 0.1 mm), ultrasonography can visualise also very small isolated hyperechogenic points or their larger deposits involving a greater part of the cartilage. Linear calcifications on the surface of the hyaline cartilage of the most frequently affected condyles of the femur do not exhibit acoustic shadowing and allow imaging of the parallel bone line of the condyles. Such lesions can be observed also in the hyaline cartilage of metacarpal heads.

Fibrous cartilage – calcifications in the fibrous cartilage are usually round but amorphous; certain sites are difficult to examine; calcifications can be well observed in the region of the medial and lateral meniscus of the knee and in the triangular fibrocartilage disc of the wrist.

Synovial fluid – dynamic examination of joints may reveal round or oval well-defined hyperechoes floating in the synovial fluid. A similar finding can be sometimes observed also in bursae.

Extra-articular soft tissue – calcifications are of various shape, size and location; they are most often visualised as rather extensive linear hyper-echoes in the fibrous structure of the tendon that may exhibit acoustic shadowing [7, 8].

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Alkaptonuria and Ochronosis

19

Jozef Rovenský, Richard Imrich, Tibor Urbánek, and Vladimir Bošák

Alkaptonuria (AKU) is an inherited disorder of metabolism of aromatic amino acids phenylalanine and tyrosine that is caused due to the lack of activity of the enzyme homogentisate 1,2-dioxygenase (HGD). The homogentisic acid is not metabolised; it accumulates in the body and is excreted into urine.

19.1 Clinical Signs

Alkaptonuria is characterised by:

- Homogentisic acid accumulation in the body
- Presence of homogentisic acid in urine
- Visible, functionally benign symptoms of the eyes and ears
- Debilitating changes in the musculoskeletal system

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19.2 Historical Background

Scientists found alkaptonuria in the Egyptian mummy Harwa dated to around 1500 BC. The term alkaptonuria (AKU) was first used in 1859 in a patient whose urine contained a reducing compound (alkapton) later identified as the homogentisic acid. In 1902, Garrod postulated a hypothesis that alkaptonuria is an inherited metabolic disease and that deficiency of the enzyme that metabolises homogentisic acid is a result of a defective gene. This concept was later proved correct. His article about alkaptonuria, the Lancet, was published in 1902 [1]. At that time, it was a daring statement, taking into account how little was known of enzymes, human genetics and intermediary metabolism. His knowledge was summarised in the book Inborn Errors of Metabolism [2]. In 1958, the study by La Du et al. [3] provided a biochemical evidence of the defect in alkaptonuria. They demonstrated the absence of homogentisic acid metabolising enzyme activity in liver homogenates from a patient with alkaptonuria. They found that the defect is related to one enzyme – 1,2-dioxygenase of the homogentisic acid. They suggested that the people affected do not synthesise the enzyme. The gene responsible for alkaptonuria was identified in 1993 by Pollak et al. [4], and it was localised to chromosome 3q2. In alkaptonuria, the homogentisic acid is not broken down due to the lack of enzyme activity that metabolises

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the homogentisic acid; it accumulates in the body and is excreted in the urine.

The homogentisic acid builds an oxidised polymer in the body, which is stored in the form of blue-black deposits in tissues (ochronosis).

19.3 Aetiology and Pathogenesis

Phenylalanine and tyrosine are the simplest aromatic amino acids derived from alanine. Phenylalanine is an essential amino acid that cannot be synthesised by our body. This is not true for tyrosine. The body can synthesise tyrosine, but only if there is sufficient amount of phenylalanine – a precursor of tyrosine and the enzyme involved in the conversion of phenylalanine to tyrosine. Phenylalanine and tyrosine are closely related; phenylalanine is converted to tyrosine in the liver and to phenylpyruvate in the kidneys. Aromatic amino acids have a common intermediary metabolism. The conversion of phenylalanine to tyrosine and further metabolism are controlled by a complex enzymatic system. The failure to convert phenylalanine to tyrosine is known as phenylketonuria – one of the most common recessive inborn diseases (approximately 1 affected in 10,000 newborns). Phenylketonuria is caused by the lack of the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine or its cofactor tetrahydrobiopterin. Alkaptonuria arises as a result of the lack of another enzyme – 1,2-dioxygenase of the homogentisic acid (homogentisate 1,2-dioxygenase; HGD). This enzyme is part of the degradation pathway of aromatic amino acids phenylalanine and tyrosine. Homogentisate excreted in the urine is then oxidised by oxygen in the air to brownish-black pigment – alkapton. Other symptoms later in life include ochronosis – pigmentation of the connective tissue (cartilage). The mechanism of ochronosis is the oxidation of homogentisate polyphenoloxidase resulting in the production of benzoquinone acetate, which polymerises and binds to macromolecules of the connective tissue.

19.4 Epidemiology and Genetic Aspects

The observation of alkaptonuria inheritance described by Garrod was studied closely by Hogben et al. [5], who, in 1932, confirmed that alkaptonuria is inherited in an autosomal recessive manner. They found that about half of the affected individuals came from kin marriages.

The list of scientists who significantly contributed to the knowledge of the clinical manifestations of alkaptonuria and ochronosis includes Siťaj, Červeňansky, Urbánek, Hüttl and others [6–11].

In 1947, Siťaj [6] diagnosed and described the first case of alkaptonuria. Till 1953, Siťaj and his team collected a sample of 102 patients – members of 15 families – while at that time approximately 100 cases were described in the whole world, mostly isolated case reports. Between 1956 and 1960 [28], they registered additional affected families, and the total number of patients with alkaptonuria increased to 182, of whom 43 had ochronosis. Slovakia and the Dominican Republic became known in the literature as the countries where the highest incidence of alkaptonuria (1 in 19,000 inhabitants) was found. The world prevalence is one case in 250,000–1,000,000 inhabitants. Increased prevalence in Slovakia is explained by the fact that patients come from mountainous areas where the population evolved as genetic isolates with frequent marriages of parents related to each other. However, it should be noted that the active way of looking for patients, which has been a tradition in Slovakia for more than 50 years and dates back to the first case described by Siťaj, also contributed to the sample.

Siťaj, Červeňansky and Urbánek [6–10] described ochronosis, its development in patients with AKU and the detailed clinical features, as well as manifestations in the joints. They published the results in a monograph titled Alkaptonuria and Ochronosis (1956), which was the first in the world literature [7]. Their pioneering work is still being cited. Sršeň et al. [12–15] from the Research Laboratory of Clinical Genetics in Martin followed up on their

epidemiological studies and continued in the genetic analysis of patients with AKU in Slovakia. Institutions participating in the molecular characterisation of mutations in the Slovak population include the Institute of Molecular Physiology and Genetics of Slovak Academy of Sciences in Bratislava and Faculty of Natural Sciences of Comenius University in Bratislava [16–18]. Most of the observed families came from sites in Slovakia studied by Siťaj et al. [6–10]. Later work was continued by Rovenský and co-workers and the genetic aspects by Bošák in cooperation with laboratories in Bratislava [19–21].

In 1958, La Du with co-workers [3] found that the biochemical essence of AKU is the lack of biological activity of the enzyme homogentisate 1,2-dioxygenase (HGD) in the liver, thus confirming the original assumption of Garrod that it is a metabolic disorder. HGD is an enzyme that is involved in the catabolism of phenylalanine and tyrosine. It has a molecular weight of 50 kDa and consists of 445 amino acids. It is specific for homogentisic acid and does not oxidise related substances such as gentisic acid and phenylacetic acid. The gene that encodes the HGD enzyme was cloned in 1996 [22], thereby opening the era of molecular genetics of alkaptonuria. Today we know that the HGD gene consists of 14 exons (coding parts of the gene) and 13 introns (non-coding parts of the gene). HGD gene has a tissue-specific expression, particularly in the liver, kidneys, small and large intestines, prostate and brain [23]. Increased activity in the liver and kidneys has been attributed to the metabolic activity of these organs. In the brain, HGD probably participates in the degradation of amino acids derived from neurotransmitters, which often contain aromatic amino acids. The HGD gene was localised on the long arm of chromosome number 3 in humans (3q) [4, 24].

In the following years, its location on the third chromosome has been further specified to the locus 3q21-23 using the technique of polymerase chain reaction (PCR) and fluorescent in situ hybridisation – FISH [25].

Molecular genetic studies of alkaptonuria yielded a surprising finding that the defect of the HGD enzyme is not caused by a single mutation, as originally expected, but by several mutations in coding and non-coding sequences of the HGD gene. By 2000, more than 40 different mutations that cause alkaptonuria were identified in more than 100 patients from several countries around the world [16, 26]. Currently, there are at least 67 known mutations. Most mutations change the sense of the genetic information (missense), which involves changing one nucleotide in the DNA molecule. The most common mutation in Europe, which represents about 20% of all mutations, is Met368Val (substitution of methionine instead of valine at position 368); in the Dominican Republic, it is Cys120Trp; and in Slovakia, it is IVS5 + 1G → A [25].

19.5 Clinical Features

The first signs of alkaptonuria can be seen in the newborns. Their urine darkens when exposed to the air and leaves brownish-black spots on their diapers. The spots are highlighted and cannot be washed away when alkaline soap is used. The dark earwax is also a characteristic that can be seen after birth. Dark urine and ear wax remained the only clinical symptoms of alkaptonuria for many years. In the meantime, a much more serious process takes place in the organism affected by this metabolic disorder. The ochronotic pigment is produced by oxidative polymerisation of the homogentisic acid; it accumulates in bradytrophic tissues and stains them dark brown. In principle, it is a benign process, which goes on unnoticed for a long time.

The first signs of deposition of the ochronotic pigment can be detected accidentally during specialised examination of the anterior segment of the eye. The ochronotic pigmentation of the ocular structures is present in approximately 70 % of patients. In addition to the sclera, lumps of the ochronotic pigment can be found in the conjunctiva and cornea. Since similar pigmentation of the cornea is not present in other medical conditions, this finding is regarded as pathognomonic for alkaptonuric ochronosis. Skinsnes [27] described a patient who underwent enucleation of his only

eye (the other one was lost due to injury) due to a pigment stain in the sclera deemed as melanosarcoma. After an unrelated death of the patient, however, the autopsy revealed that this was an alkaptonuric ochronosis with ocular pigmentation. Pigment spots on the sclera are mostly visible. They appear usually in the third decade of life in two-thirds of patients with alkaptonuric ochronosis. In the advanced stage, they can be seen with the naked eye (Fig. 19.1) [1]. When found, chronic poisoning with phenolic substances, arsenic and lead, Addison's disease and blue sclerae in osteopsathyrosis should be excluded.

The diagnosis of alkaptonuria is based on the characteristic findings in urine. Alkaptonuria patients do not seek medical help due to difficulties with viewing these spots – they are without subjective complaints.

In parallel with the ocular manifestations, ochronotic changes can be found in the hearing organ. Colour changes of the auricle are visible in the 10th to 15th year of life.

Detailed histological examination of the temporal bone performed by Brunner [28] revealed accumulation of the ochronotic pigment in the bone and its membranous parts. The changes taking place in the ears are slow, and patients are alerted to the blue-grey colour of the ear by their relatives. On the cartilage, painless, hard, rough lumps can be seen firmly connected with the basis and shining through the delicate skin as dark-blue-violet colour. The first rough ridges appear on the lower arm of the anthelix and later throughout the anthelix, in the fossa triangularis, cavum conchae, cymbal and the tragus.

In advanced cases, sometimes auricle deformation can be found (Fig. 19.2). The external auditory canal is without changes; earwax is dark brown; and drum is dark, dull, often inverted, with an atypical reflex, with bluish tint, and in most cases, calcium incrustations are present. Patients may also suffer from hearing loss type hypoacusis mixta with a stronger involvement of the perceptive apparatus. Symptoms of alkaptonuria hearing organ are specific and often lead to the diagnosis of this disease.

Also, changes in the skin typical of alkaptonuric ochronosis include mainly brownish or bluish pigmentation of the skin under the arm; in the face, neck and hands; and rarely on the nails. Given their visibility, they may be relevant for the early diagnosis of alkaptonuric ochronosis.

Ochronotic pigment is deposited also in the internal organs. In the region of cardiovascular organs, it is the myocardium and blood vessels. Statistically significant myocardial disorders were not found, but earlier atherosclerotic changes in the aorta were observed.

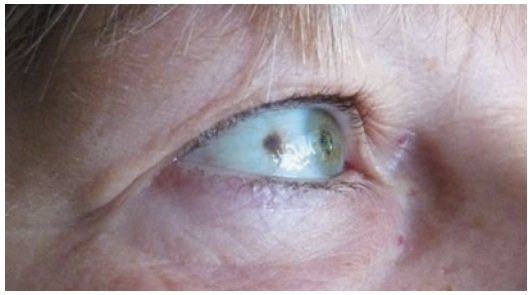

Fig. 19.1 Pigmented patches in the sclera typical of alkaptonuric ochronosis

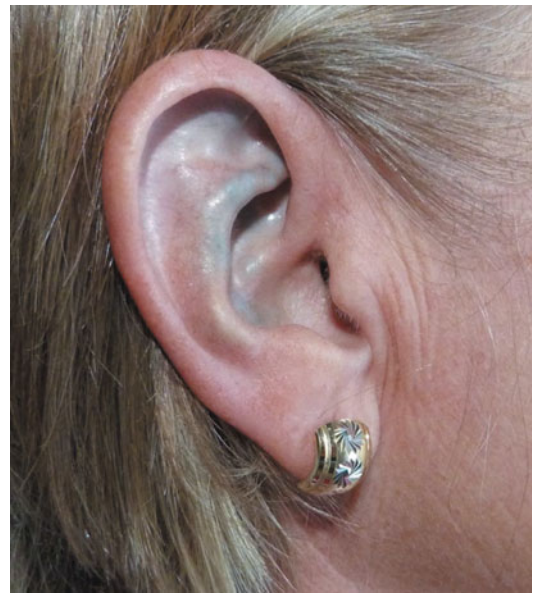

Fig. 19.2 Ochronotic changes in the auricle

Urolithiasis was found in more than half of the patients, and rare cases of nephropathy were seen.

From a clinical point of view, the most serious process takes place in the joints and is called ochronotic arthropathy. Basically, it is a degenerative process with a known genesis and with an increased risk of disability. The basic clinical manifestation of ochronotic arthropathy from the beginning is related to the spine.

The first subjective complaints appear at the end of the third decade of life. Gender is significant with a predominance of men relative to women 2:1. Objective findings include flattening of thoracic kyphosis and lumbar lordosis and mild rigidity with a tendency to deterioration. Later, in an advanced stage, the contours of the spine worsen with irregular spinous processes and complete ankylosis of the entire lumbar and thoracic spine. The spine is rigid and irregular and the contours do not change when bending forward (Figs. 19.3, 19.4 and 19.5). Cervical spine maintains its mobility for a relatively long time despite significant skiagraphic changes. In an advanced stage, dorsal flexing and rotational movements become limited, while the head moves forward. As a result of degenerative changes of the plates in the narrowing intervertebral space, body height decreases up to 8 cm in 20 years.

Radiographic examination may reveal characteristic calcification of intervertebral discs (Fig. 19.6). Osteolytic and hyperplastic changes and secondary reactive bone formation can be found on the vertebral bodies. Osteophytes are created, sometimes even massive bone bridges of the type of ankylosing hyperostosis. Calcification of some peripheral bundles of the connective rings may be similar to pseudosyndesmotic bridges.

Even in the early stages, hollow formations in the plates are formed; this is called the vacuum phenomenon. In the intervertebral joints, the space is narrowed and reactive subchondral sclerosis is present.

Sometimes, calcification is found in the ligaments between the spinous processes. Occasionally, osteoporotic vertebral fractures are found. On the other hand, thickening of bone structure is not unusual. This resembles Paget's osteitis.

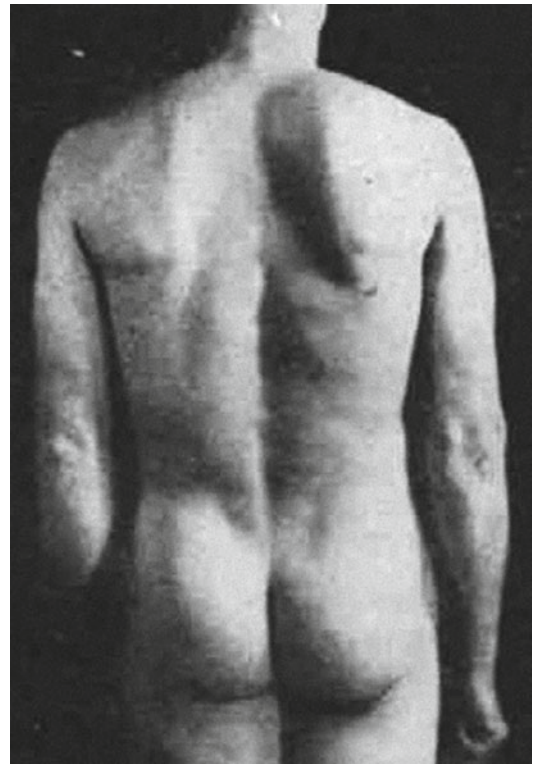

Fig. 19.3 Initial stage of ochronotic changes in the spine. Flattening of physiological spinal curvatures (thoracic kyphosis and lumbar lordosis)

While the spine is involved in all patients with ochronotic arthropathy, peripheral joints are often, but not always, affected. Based on the analysis of 26 patients with ochronotic arthropathy, it may be noted that small joints are spared and large joints are affected in the following order: knee (64 %), shoulders (42.3 %) and hips (34.6 %) [6].

The finding in the knee is basically of arthritic nature. It differs from genuine osteoarthritis by an earlier onset (on average at the age of 39 years), faster progress and larger deformities. Hydrops occurred in 30.4 % of our patients. Based on a series of investigations, Hüttl et al. [11] have found that the synovial effusion is of a noninflammatory, irritating and degenerative nature. The effusion has a yellowish colour that remains unchanged even after prolonged standing in air, suggesting a low concentration of

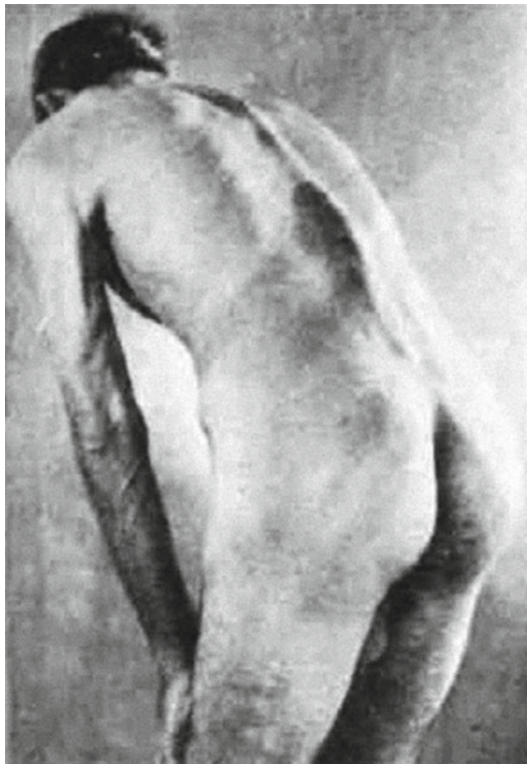

Fig. 19.4 The spine in ochronotic arthropathy is rigid, irregular and contours do not change in bending forward

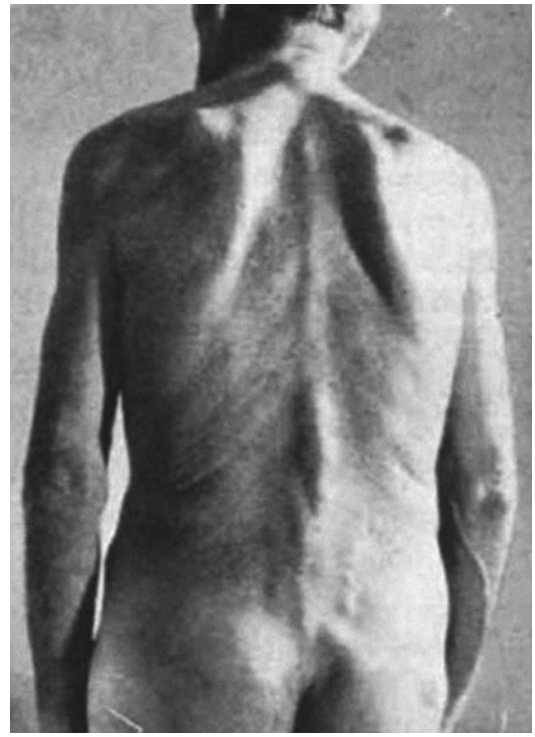

Fig. 19.5 The spine of a patient with advanced stage of ochronotic arthropathy

homogentisic acid. From the nosographic point of view, it is important to find histiocytes with brown-violet and blue-black cytoplasmic inclusions, which can be assumed to be the phagocytosed ochronotic pigment. The finding of histiocytes with pigment inclusions in the cytoplasm was described for the first time in the world literature by Hüttl et al. [11]. Radiographs in ochronotic arthropathy show similar changes as in osteoarthritis, and this is often asymmetrical. The characteristic sign is the formation of free calcified and ossified pea-sized or even larger bodies of a diverse shape. These are signs of ochronotic chondromatosis. Occasionally, narrow strips of calcified soft tissue parts of the extremities are detected that resemble Thiberge–Weissenbach syndrome. The main difference between genuine arthrosis and ochronosis of the knee is in a more rapid progression and in advanced findings in relation to the age of the patient with ochronosis.

In the shoulder joints in the early stages of ochronosis, there are painful episodes of the type of humeroscapular periarthropathy that are probably related to the deposition of pigment and calcium deposits in the rotator tendons. Gradually, the mobility gets limited due to the retraction of the joint capsule, destruction of the cartilage and the adjacent bone structures.

Radiographs of the shoulder joints show even at an early stage signs of ossifying enthesopathy. Based on analysis of 42 patients with ochronosis, Siťaj [7] reports that the calcium deposits in the shoulder rotators are present in more than 25 % of patients. In the next stage, around the 50th year of life, patients develop degenerative changes with exostosis at the inferior edge of the glenoid cavity and later with cystoid translucency, usures and destruction in the humeral head. This finding is completely different from genuine osteoarthritis and pathognomonic for ochronotic arthropathy of the shoulder.

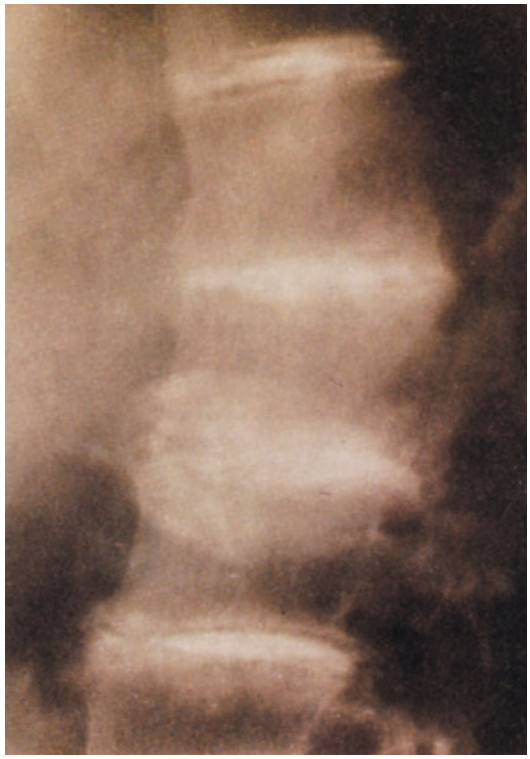

Fig. 19.6 Typical calcification of intervertebral discs in ochronotic arthropathy

Hip joints are affected only in later stages of ochronosis and approximately in a third of patients. The progress is faster than in osteoarthritis (OA) of the hip and results in an almost complete restriction of the mobility.

Radiographs show a severe, in some patients, destructive OA of the hip. Červeňanský et al. [10] describe ochronotic enthesopathy in the hip area and highlight the selective deposition of the ochronotic pigment in the tendons.

19.6 Coincidence of Alkaptonuric Ochronosis with Other Diseases

The metabolic disorders in ochronotic arthropathy of the spine and large joints of the limbs include osteoporosis. It is assumed that this is a secondary form of osteoporosis due to immobilisation of severely affected individuals. Barel et al. [29] describe a family affected by alkaptonuria, phenylketonuria and congenital cataract. Occasionally, alkaptonuria occurs concurrently with psoriasis. In 1955, Urbánek et al. [9] described a unique coincidence of alkaptonuric ochronosis and ankylosing spondylitis in a 51-year-old man. The patient came from a family in which four of five siblings had ochronotic arthropathy. Based on an analysis of clinical and radiographic findings in the spine, it could be assumed that ochronotic arthropathy and ankylosing spondylitis interacted. Our patient exhibited typical ochronotic changes, especially calcifications of the intervertebral discs, less marked in comparison with other patients with ochronosis in the same advanced disease stage. It may be hypothesised that the premature rigidity of the spine due to the ankylosing spondylitis caused in this patient development of ochronotic changes later in life. On the other hand, despite standard ankylosing spondylitis symptoms (affected sacroiliac joints, paraspinal ligament ossification and obliteration of intervertebral joints), the patient had disproportionately low pain throughout the course of the disease. The long-term follow-up of a large number of patients with ochronosis revealed that the relatively mild pain is characteristic for ochronotic arthropathy [7].

Japanese authors Kihara et al. [30] described the coexistence of ochronosis and rheumatoid arthritis in a 64-year-old woman. Magnetic resonance imaging of intervertebral discs revealed typical changes indicative of ochronotic arthropathy.

At the same time, symptoms of rheumatoid wrist arthritis were identified with positive rheumatoid factor and nodules, which were histologically compatible with the diagnosis of RA. The authors concluded that the pre-existing ochronotic arthropathy could mask the manifestation of RA and made it quite difficult to diagnose.

The conclusion of these two case reports is that the process of ochronosis slows down the development of inflammatory symptoms of ankylosing spondylitis and rheumatoid arthritis and makes it more benign.

19.7 Diagnosis

Diagnosis of alkaptonuria is based on the evidence of homogentisic acid in urine which does not occur in healthy population. Laboratory evidence of homogentisic acid is based on its reducing properties. In practise, the test using the Fehling's solution, which is used in diabetes, proved valuable. While diabetic urine with Fehling's solution brings brick-red clot, alkaptonuric urine changes the colour after the addition of the Fehling's solution to grey-black.

For screening, alkalinisation of the urine with 10 % NaOH can be used. After adding NaOH to the tube with the urine, a dark ring is created and then the entire sample of urine darkens.

Earlier quantitative methods for determining homogentisic acid in the urine used the ability of the acid to reduce silver, phosphomolybdic acid or iodine. The drawback of these methods was the fact that they may determine also other reducing compounds present in the urine. This bias appeared in lower concentration of homogentisic acid in the urine of patients with alkaptonuria. Certain marked improvement brought the extraction of homogentisic acid into ether and subsequent iodometric determination. In 1961, Seegmiller et al. [31] developed a spectrophotometric enzymatic determination of homogentisic acid in plasma and urine using the purified homogentisic acid oxygenase, which enabled the authors to specifically determine 1 μg of the acid. The oxidatively produced maleylacetic acid is determined spectrophotometrically at 330 nm. Electrophoretic method of determining homogentisic acid was established by Trnavská [32]. At present, the quantitative determination of the homogentisic acid in urine is based on liquid chromatography and capillary electrophoresis.

The diagnosis of ochronosis is based on finding pigment spots in ocular structures, on the blue-grey discolouration of the auricles and skin in the armpit and on the radiographic findings in the calcified intervertebral discs. In the advanced stage of the disease, irregularly protruding spinous processes of the thoracic and lumbar spine are typical of ochronotic arthropathy, with a specific finding of pigmented inclusions in the cells of the synovial effusion.

19.8 Differential Diagnosis

The fresh urine of a patient with alkaptonuria has a normal pale yellow colour, and after prolonged standing in air or contact with alkali media (soaps, etc.), it turns to dark grey or black. This sign of alkaptonuria is specific, and it will almost always distinguish it from other diseases associated with changes of urine colour. For example, the urine in another hereditary disease, congenital erythropoietic porphyria (m. Günther), which also begins shortly after birth, has a very typical red colour. Similarly, in haematuria or haemoglobinuria urine has a pinkish red colour. The analysis of the urinary sediment is of decisive importance for the diagnosis. In bilirubinuria, the urine has a reddish-brown colour (like black beer) and in melanuria a dark brown colour. Urine is always coloured when it is fresh, with the exception of alkaptonuria, when the urine darkens in contact with the air after several hours or immediately after the addition of alkali.

Ochronosis may be endogenous (on the basis of alkaptonuria) and exogenous, caused by the contact with certain chemicals. Several authors have described yellowish pigmentation of the skin and cartilage caused by carbolic acid (phenol), which was previously used to treat lower leg ulcers and other cases. This exogenous "carbolochronosis" was not associated with spondylosis and arthropathy. More recently, exogenous ochronosis in the skin and sclera associated with myxedema caused by long-term use of resorcinol was reported. Anderson [33] described the pigmentation of the eye conjunctiva and cornea in persons working in the production of hydroquinone. The sclera was dark and spots on the cornea caused blindness. Sugar and Waddel [34] found a pigmentation of the sclera and cartilage similar to ochronosis after long-term use of Atabrine. Skinsnes [27] describes a case of incorrect melanosarcoma diagnosis in a patient with ochronosis that led to a tragic outcome – enucleation of a single eye of the patient (see above).

Decisive for differentiating ochronotic changes in the spine from other spondylopathies is the finding of calcified intervertebral discs, which are pathognomonic for alkaptonuric ochronosis. Spondylopathies in chondrocalcinosis could cause certain problems in differential diagnosis, but this disease is characterised by painful process with episodes of attacks of inflammatory nature, by calcifications of small joints, especially at the wrists, and the spondyloarthropathy has a milder course with no tendency to ankylosis. In rare cases, a distinction from calcified discs in haemochromatosis can be considered. When in doubt, analysis of the urine for the presence of homogentisic acid is decisive, as well as a comprehensive examination of the patient and evaluation of the eye, ear and skin findings.

Alkaptonuric ochronosis has a characteristic polytope symptomatology that usually does not cause greater difficulties in differential diagnosis. Rather, it is necessary to exclude other diseases that may require more urgent intervention before clinical features fully develop.

19.9 Therapy

Since no causal treatment is available for alkaptonuria, therapeutic interventions essentially focus on the following three objectives:

- Reduction of the excretion of homogentisic acid into the urine
- Restriction of the onset of ochronosis
- Therapeutic and preventive interventions to influence ochronotic arthropathy

In recent decades, various dietary interventions have been tried to reduce the formation of homogentisic acid and its excretion into urine including vitamins, hormones and other substances with uncertain and, in some cases only, a transient effect.

In terms of limiting the production of the ochronotic pigment and reducing the risk of ochronosis with its disastrous consequences especially on the musculoskeletal system, a positive effect is attributed to vitamin C [35, 36]. Some studies, however, did not confirm the positive effect of vitamin C, and there is a lack of long-term controlled clinical trials targeting this problem [37]. Therapy has recently focused on direct pharmacological reduction of the homogentisic acid by nitisinone [38], a triketone herbicide that quickly and reversibly inhibits 4-hydroxyphenylpyruvate dioxygenase, which catalyses the formation of homogentisic acid from 4-hydroxyphenylpyruvate. According to the latest outcomes of the SONIA 1 dose-response study, with the participation of our institute, the optimal dose of nitisinone is 8 mg. This dose successfully reduces homogentisic acid levels, with a good tolerance of the drug (report on outcomes in print). Currently SONIA 2 study is underway that should demonstrate a long-term effect of nitisinone on the progress of the disease.

Alkaptonuria as a congenital metabolic disease is now well defined. Gene therapy has moved from the phase of model experiments to the phase of clinical application in humans, and one can hope that prospectively it will be introduced in the therapy of alkaptonuria. The solution would be the replacement of the missing homogentisate dioxygenase, but the application of recombinant homogentisate dioxygenase requires more detailed studies of the distribution of isomerase and other enzymes following the metabolic pathway.

Therapeutic and preventive interventions aimed at influencing ochronotic arthropathy are essentially identical to those used in the treatment of the degenerative disease of the spine and limb joints. These include nonsteroidal antirheumatic drugs, physical therapy, rehabilitation with balneotherapy, prevention of deformities and rheumosurgical interventions if needed.

The follow-up of all newborn children diagnosed with alkaptonuria, their constant monitoring, diet and lifestyle guidance, proper selection of sports and especially a suitable profession are very important.

In this regard, the research and practise of the workgroup of Professor Sršeň at the Faculty of Medicine of the Comenius University in Martin are of particular importance. In children with

alkaptonuria, mild restriction of daily intake of proteins rich in phenylalanine and tyrosine, as well as the application of ascorbic acid supplemented with vitamins E and A and selenium, is recommended. In addition, the recommendations include a daily regimen sparing the predilection sites, i.e., large joints and the spine, with adequate activities of daily living, including the choice of occupation.

The gene therapy is progressing from the phase of experimental models to the stage of clinical application in humans, and one can only hope that treatment for alkaptonuria will be introduced in the near future.

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Metabolic Osteopathy in Late-Onset Celiac Disease

20

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Metabolic osteopathy in adult patients is one of the potential manifestations of celiac sprue (CS), also called gluten-sensitive enteropathy. CS is a lifelong intolerance of prolamin contained in crops (gliadin – gluten fraction in wheat, secalin in rye, hordein in barley, etc.) [1]; CS is a common disease widely distributed worldwide, with a characteristic mucosal lesion of the proximal small intestine, associated with nutrient malabsorption. Mucosal lesions range from the initial lymphocytic infiltration up to total atrophy of the resorption epithelium of the small intestine. Histological changes are assessed by means of the Marsh histological criteria for evaluation of the extent of lymphocytic infiltration, glandular crypts, and small intestinal villi (0–4 scale [2–4]).

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20.1 Case Reports

20.1.1 Case Report 1

A 57-year-old female patient presented with a long-term history of lower limb pain, confirmed osteopenia with elevated levels of parathyroid hormone and alkaline phosphatase. From childhood she was receiving iron supplementation for iron deficiency anemia, the cause of which was not revealed even by repeated examinations of the digestive system and gynecological examination, including ultrasonography of the small pelvis. She has three children and went through menopause at the age of 45, without hormonal substitution. She had rheumatic fever in childhood. There is no history of nutrient intolerance in the family; the patient´s brother has type 2 diabetes mellitus. Several months before admission she started to have diarrhea with stool frequency of 4–7 times a day, without signs of blood and without any apparent dietary association, with weight loss of 10 kg (body weight 61 kg, height 170 cm, BMI 21), progression of iron deficiency anemia, and symmetrical lower limb swellings extending almost as far as the groins.

Physical examination has revealed in the asthenic patient pale skin color without signs of cyanosis or icterus, waddling antalgic gait, and extensive swellings of lower limbs of hypoalbuminemic nature extending as far as the groins and finger clubbing as a secondary finding in upper limbs.

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20.1.1.1 Examination Methods

Laboratory tests showed iron deficiency type of anemia (Ery 3.85* 10^{12} l; Hb 115 g/l; Htc 0.35; MCV 90,1 fl, MCH 29,9 pg/l), decreased levels of serum iron (Fe 7.8 μmol/l), ferritin (4.5 ng/ml), and iron-binding capacity at the upper limit (76 ng/ml). The findings included increased values of alkaline phosphatase and elevation of its bone fraction (ALP 3.06 μkat/l – isoenzymes: intestinal 0.0; bone 2.05; liver 0.6), as well as hypocalcemia (Ca 2.09 mmol/l), hypoalbuminemia 30 g/l, and hypoproteinemia (53.7 g/l).

Coagulation parameters showed decreased prothrombin time (INR 2.5). Serum parathyroid hormone levels were increased (PTH 204 ng/l), and serum vitamin B12 levels (100 ng/l) were low.

Normal values were found in serum levels of Na, K, Cl, P, ALT, AST, GMT, Kr, Ur, LDH, bilirubin, CRP, erythrocyte sedimentation rate, selected laboratory tumor markers, anti-dsDNA, ANA, rheumatoid factor, immunoglobulin levels, and C3 and C4 complement components. Fecal occult blood was not confirmed.

Radiographic examination of heart and lungs did not show pathological findings; however, radiographs of the cervical, thoracic, and lumbar spine revealed an overall porotic structure of the vertebral bodies. Gastroscopic examination found anemic gastric mucosa and flattened duodenal folds suggesting chronic gastritis or malabsorption syndrome.

Bone densitometry dual energy X-ray absorptiometry (DEXA) revealed skeletal demineralization with L-spine BMD value of 0.910 g/cm^2 and T-score −2.4; femoral neck BMD value of 0.819 g/cm^2 and T-score −0.8, and forearm BMD value of 0.358 and T-score −5.3 (Fig. 20.1).

In order to find the cause of osteopathy, iliac crest bone trephine biopsy was performed, and the sample was examined histomorphometrically, confirming osteomalacia (atrophic cancellous bone trabeculae covered with a massive layer of demineralized bone tissue, osteoid; Fig. 20.2).

Abdominal sonography proved marked meteorism that spontaneously subsided. Ultrasonography and CT examination of parathyroid glands has not proved any pathological process in this location.

Histological examination of the intestinal mucosa described a finding typical of celiac disease: total atrophy of resorptive epithelium of small intestine with crypt hyperplasia and increased lymphoplasmacytic cellularization in the lamina propria with dispersion pattern of eosinophilic leukocytes (Fig. 20.3, Table 20.1).

20.1.2 Case Report 2

A 64-year-old female patient presented with progressive persistent pain in the ribs, lumbar spine, and long bones, lasting for about 6 months, associated with the development of anemia and marked elevation of alkaline phosphatase. General practitioner diagnosed suspected metastatic tumor disease of unknown primary location. Skeletal pain developed relatively quickly, without any triggering mechanism; gradually it was getting worse both during activity and at rest and did not respond to common analgesics. The patient complained of unclear digestive difficulties in the form of flatulence and pain after meals, however, without diarrhea or constipation. Thirty years ago she had type A jaundice. No food tolerance was found in the family history. The patient did not take regularly any medications, and she used nonsteroidal antirheumatic drugs only in case of bone pain. She went through menopause early, at the age of 44. She has two children. Physical examination of this asthenic patient (body weight 54 kg, height 158 cm, BMI 21) revealed kyphotic thoracic spine. Dominating signs included tenderness to palpation along the entire spine as well as in the thoracic region, rib cartilage in particular, and waddling gait, of markedly antalgic duck-like pattern.

20.1.2.1 Examination Methods

Laboratory tests showed iron deficiency anemia (Ery 4.76* 10^{12} l; Hb 111 g/l; Htc 0.36 MCV 75.8 fl; MHC 23.3 pg). Low levels were found of serum iron (6.4 μmol/l), ferritine (3.2 ng/l), vitamin B12 (177 ng/l), folate (1.7 μg/l), calcium (Ca 2.18 mmol/l), 1.25 OH vitamin D (33.6 ng/l), high value of alkaline phosphatase (ALP total 14.13 μkat/l, bone fraction 13.43 μkat/l), and

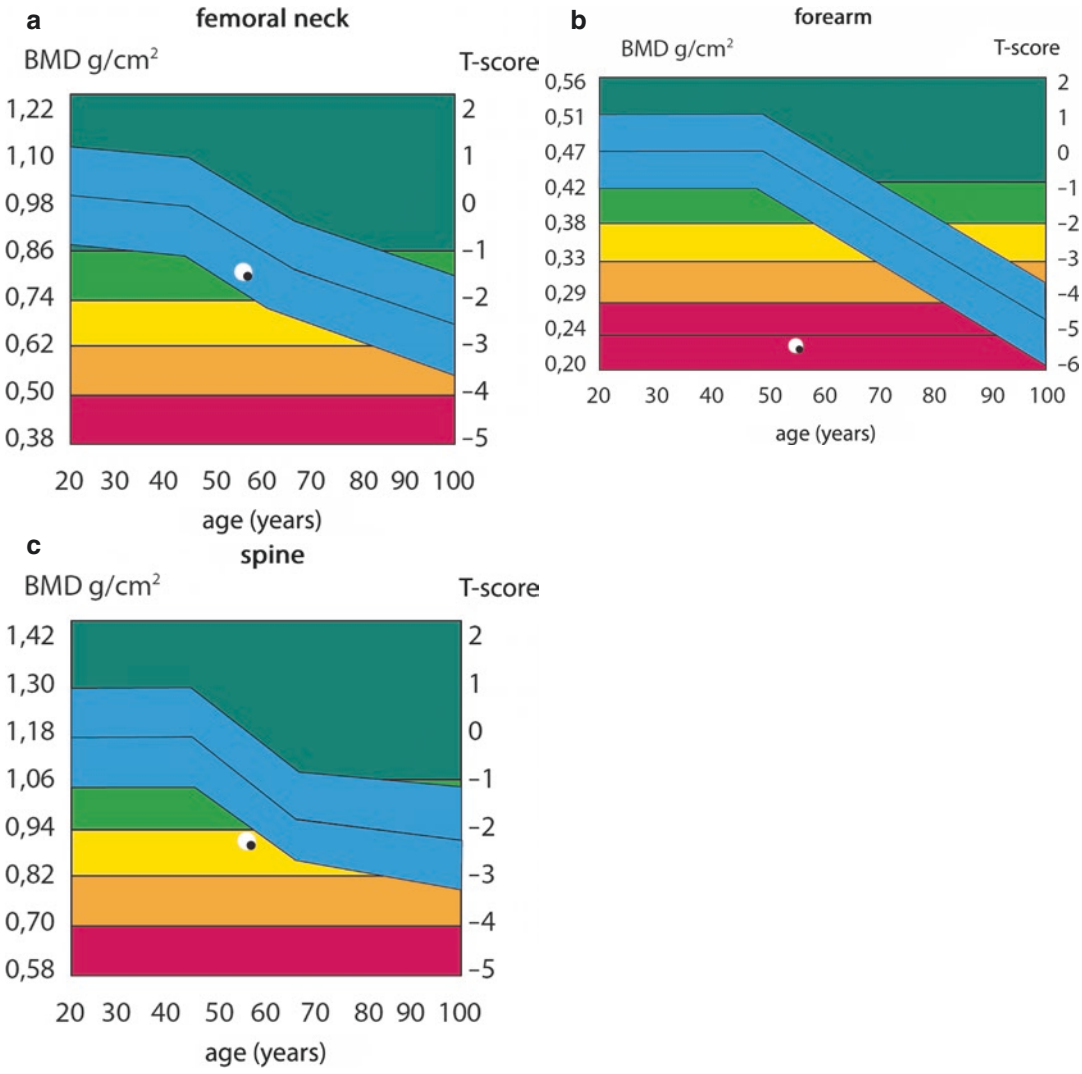

Fig. 20.1 Case study 1. Bone densitometry demonstrates skeletal demineralization with L-spine BMD value of 0.910 g/cm^2 and T-score −2.4, femoral neck BMD value of 0.819 g/cm^2 and T-score −0.8, and forearm T-score −5.3

elevated parathyroid hormone level (PTH 741.1 ng/l).

Laboratory findings within physiological reference ranges were obtained in case of serum levels of Ur, Kr, K, Na, Cl, Ca, ALT, GMT, AST, bilirubin, albumin, total protein, CRP, total iron-binding capacity and prothrombin time, and selected tumor markers.

Radiological examination of the chest showed a heart shadow of threshold size and minor rib fractures. Radiographs of the skull, cervical, thoracic, lumbar spine, sacrum, pelvis, and femurs showed marked diffuse osteoporosis of the displayed skeleton. Primarily the spine exhibited changes corresponding to a marked or even extreme osteoporosis.

Bone densitometry confirmed severe skeletal osteoporosis with lumbar spine BMD value of 0.414 g/cm^2 and extreme T-score −6.7, femoral neck BMD value of 0.484 g/cm^2 and T-score −4.3, and forearm BMD value of 0.313 g/cm^2 and T-score −7.2 (Fig. 20.4).

Scintigraphic examination showed serially located minor lesions in the ribs of the axial

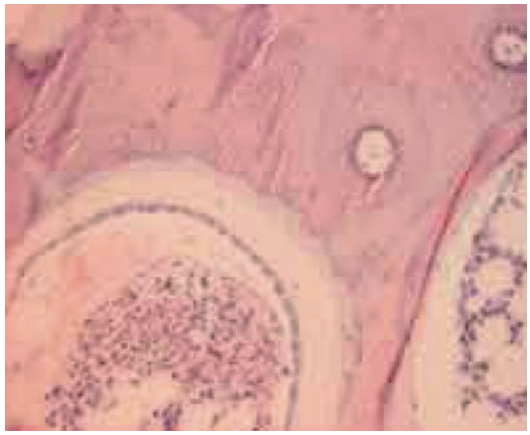

Fig. 20.2 Case report 1. Detail of bone trabecula lined by osteoid with activated osteoblasts on its surface (HE staining). Trabecula (atrophic) of cancellous bone covered with a massive layer of demineralized bone tissue, i.e., osteoid. Proportional hematopoiesis in surrounding chambers (Goldner staining)

skeleton, typical of osteomalacia (Fig. 20.5). Gastroscopic examination revealed axial hiatal hernia and gastroesophageal reflux disease of degree I.

Colonoscopy, gynecological examination, and ultrasonographic and CT examination of parathyroid glands were without a pathological finding.

Histomorphometrical examination and iliac crest bone trephine biopsy confirmed osteomalacia (cancellous bone trabecula with a broad layer of osteoid and intratrabecular demineralization – Fig. 20.6). Antiendomysial antibodies (EmA), antibodies against transglutaminase (atTG 290 U/ml), and antigliadin antibodies of IgA class were positive, while antibodies of IgG class were negative.

Enterobioptic examination using a jejunal capsule did not provide a sufficiently representative sample for histological examination (see Table 20.1).

20.2 Conclusions, Treatment, and Its Outcomes

Celiac disease and active osteomalacia with a high rate of bone turnover were diagnosed in both women. In the first case, the diagnosis was established by a histological evidence of typical intestinal changes; in the other, in the absence of a histological finding, by differential diagnosis based on analysis of the clinical condition and laboratory changes.

Diagnosis of both patients included celiac disease with fully developed malabsorption syndrome, with iron deficiency anemia, low serum levels of vitamins K and B12, and with hypocalcemia and metabolic osteopenia. In addition, the first patient suffered from hypoalbuminemia, while the other had normal serum albumin levels. Strict gluten-free diet was introduced in both patients who excellently cooperated.

A series of vitamin B12 injections was administered (B12 1000 μg once a week for 1 month, then 300 μg once a week for another month), including preparations with vitamin D first in the parenteral (ergocalciferol once a month i. m.) and then oral forms (calcitriol 0.5 μg 1 × 1), vitamin K (phytomenadione 15 drops a day), and calcium and iron preparations. Gluten-free diet and supplementation therapy resulted within about 10 weeks in subsidence of clinical symptoms and improvement of all laboratory values in both patients. Bone densitometry performed after 1 year of therapy and dietary regimen showed in case of patient 2 a marked increase of bone mass, L-spine BMD value of 0.740 g/cm^2 and T-score −3.7, femoral neck BMD value of 0.835 g/cm^2 and T-score −1.4, and distal forearm BMD value of 0.497 g/cm^2 and T-score −4.4 (Fig. 20.4).

These two case reports point out the possibility of a rapid development of osteomalacia in celiac disease also in adults. It is a disease where a relatively simple treatment procedure can ensure a good therapeutic response in a majority of cases.

20.3 Discussion

The prevalence of this disease ranges in Europe between the highest incidence in Ireland (0.3 % of population) and 0.005–0.2 % in other European countries. These figures are, however, rather misleading as many silent forms of celiac disease go unnoticed (Table 20.2) [2, 5].

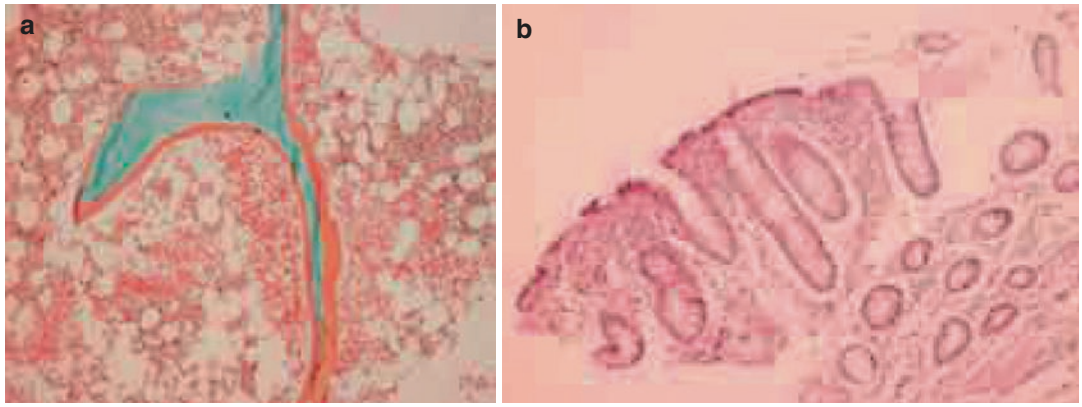

Fig. 20.3 Case report 1. Small intestinal mucosa with total atrophy of resorptive epithelium, crypt hyperplasia, and increased lymphoplasmacytic cellularization in the lamina propria with dispersion pattern of eosinophilic leukocytes (Marsh III.c; hematoxylin-eosin staining)

Celiac sprue occurs typically in early childhood, as a rule between 6th and 18th month of life [1]. However, this disease is not strictly confined to the period of childhood and may develop at any age. The most typical symptoms include frequent diarrhea with signs of steatorrhea, weight loss, general weakness, and anemia. The physical finding may include palpable shortening caused by stasis of intestinal content in dilated loops of the small intestine [2].

In addition to its classical form, CS may have also atypical forms that are not often diagnosed as they overlap with signs of another disease, or CS is not taken into consideration in time, due to a higher age of the patient [5]. The only manifestation may be insidiously developing malabsorption symptoms, the severity of which depends on the extent and intensity of bowel involvement. In adulthood, the triggering mechanism is often intestinal infectious disease, stress situations, pregnancy, or another condition stressful for the organism. Fever and abdominal pain are not usually signs of CS; however, they may be the first manifestation of intestinal lymphoma accompanying CS. CS is often associated with dermatitis herpetiformis or Duhring's disease, autoimmune endocrinopathies, atopic eczema, Down syndrome, rheumatoid arthritis, or nonspecific intestinal inflammations [2, 6].

The risk of development of CS in the patients´ families ranges around 10 % of first-degree relatives where the disease may develop in the form of typical CS or only laboratory abnormalities [2, 6]. Genetic predisposition to this disease should be taken into account. Association has been identified between the presence of CS and incidence of certain HLA-genes on the short arm of chromosome 6. Typical of CS is HLA-DQ2 haplotype which can be found in up to 90 % of patients, but its incidence is high also in healthy population (20–30 %). Other less frequent haplotypes include HLA-B8 and DR3 [3, 6].

Despite unquestionable effect of genetic factors, the exact pathogenesis of the disease has not been fully clarified yet. CS diagnosis is based on clinical manifestations of the disease and the laboratory finding together with enterobiopsy [7]. The cheapest and the most available screening method is determination of antigliadin antibodies (AGA-IgG, AGA-IgA) by the ELISA method. This test, however, is insufficiently specific, and other CS serological markers must be added, such as antibodies against tissue transglutaminase (atTG) and antiendomysial antibodies (EmA). None of the given markers is 100 % specific and sensitive [3]. A positive finding with the respective clinical symptomatology implies indication for enterobiopsy [7]. With the gluten-free diet, the level of antibodies decreases in remission;

Table 20.1 Comparison of laboratory and clinical findings in patients

	Patient 1	Patient 2	Normal laboratory values
Age	57	64	–
Hb	115	111	120–160 g/l
Ery	3.85	4.76	3.8–4.9 · 10^{12}/l
Hct	0.35	0.36	0.37–0.47
MCV	90.1	75.8	82–96 f
Leu	5.73	4.40	4–10 · 10^{9}/l
Thromb	277	302	150–400 · 10^{9}/l
INR	2.5	1.16	0.9–1.25
ALP (total)	3.06	14.13	0–2.1 μkat/l
Bone fraction ALP	2.05	13.43	20–74 %
Fe	7.8	6.4	14.5–26 μmol/l
Fe binding capacity	76	66.6	44.8–71.6 μmol/l
Ferritin	4.5	3.2	20–150 ng/ml
Folate	3.1	1.7	3–12.1 μg/l
Vitamin B12	100	177	179–915 ng/l
Ca	2.09	2.18	2.1–2.9 mmol/l
P	1.31	0.78	0.8–1.6 mmol/l
PTH	204	741.1	10–69 ng/l
CRP	11.6	<1.0	0–12 g/l
Total protein	53.7	69.5	65–85 g/l
Albumin	30	39	43–51 g/l
DEXA L-spine Proximal femur Forearm	BMD 0.910; T=−2.4 BMD 0.819; T=−0.8 BMD 0.358; T=−5.3	BMD 0.740; T=−6.7 BMD 0.835; T=−4.3 BMD 0.497; T=−7.2	T-score above −1,0 Osteopenia −1.0 to −2.5 Osteoporosis above −2.5
Radiography of spine	Osteoporosis	Osteoporosis	–
Bone histomorphometry	Osteomalacia	Osteomalacia	–
Histology of intestinal mucosa	Total atrophy of resorptive epithelium of small intestine	Unevaluable sample	–
Anti-gliadin antibodies: – AGA-A – AGA-G	Positive Positive	Positive Negative	Negative Negative
IgA antiendomysial antibodies (EmA)	Positive	Positive	Negative
Antibodies against transglutaminase	181	290	0–15 U/ml

Antiendomysial antibodies (*EmA*), antibodies against transglutaminase (*atTG* level 181 U/ml,) and antigliadin antibodies in both IgA and IgG classes (*AGA-A*, *AGA-G*) were positive.

therefore, determination of antibodies is used for a long-term follow-up of patients and their adhering to the gluten-free diet. Negative AGA in a positive bioptic finding admits the possibility of CS resistant to gluten-free diet and indicates another bowel disorder. The most feared late CS complication is both intestinal and extraintestinal T lymphomas (10 % of patients), small intestine adenocarcinoma, and esophageal carcinoma [2]. For this reason, CS may be considered to be a precancerous condition.

The mechanism of bone loss in patients with CS should be perceived as a multifactorial process consisting of a complex disorder of absorption of calcium, vitamin D, amino acids, and trace elements, as well as of other factors, such as hormonal impact, for instance, in menopause [8] and overall reduction of physical activity. The

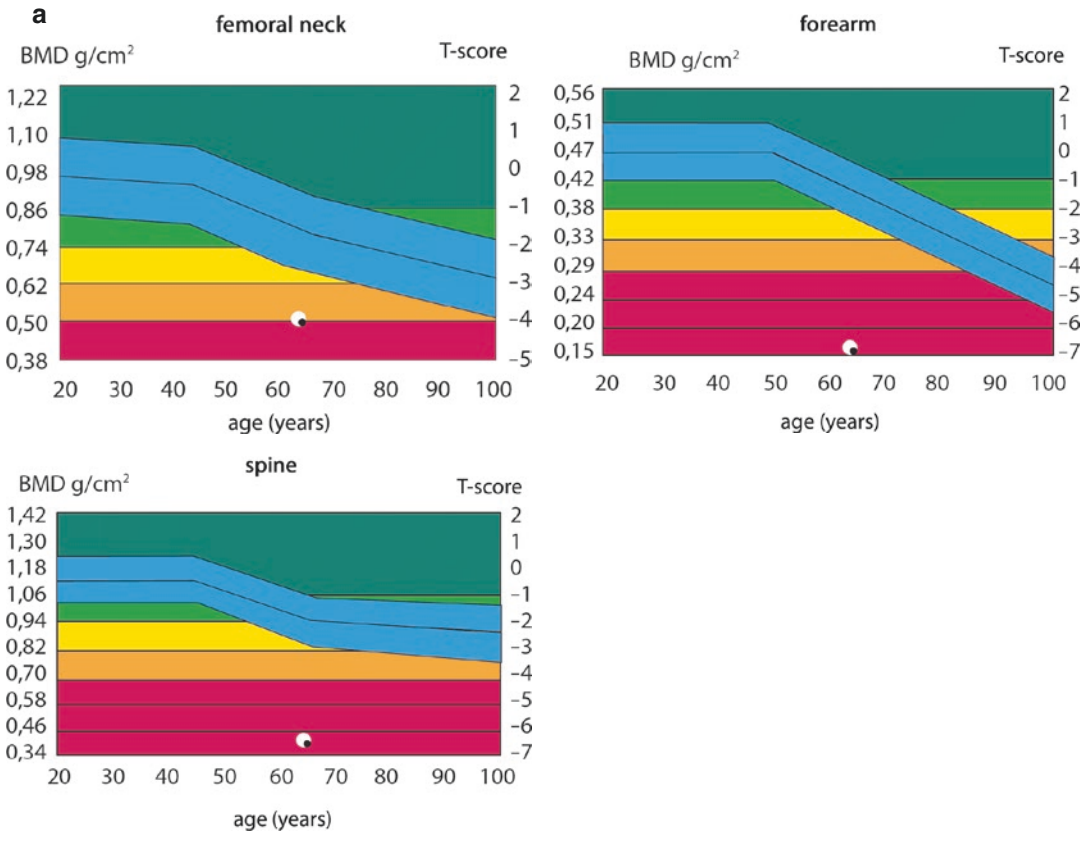

Fig. 20.4 (**a**) Case report 2. Bone densitometry reveals severe skeletal osteoporosis with lumbar spine BMD value of 0.401 g/cm² and T-score −6.7, femoral neck BMD value of 0.315 g/cm² and T-score −4.3, and forearm T-score −7.2. (**b**) Case report 2. Densitometry after 1 year: markedly improved finding, increase of BMD index, L-spine BMD value of 0.740 and T-score −3.7, femoral neck BMD value of 0.835 and T-score −1.4, and distal forearm BMD value of 0.497 and T-score −4.4

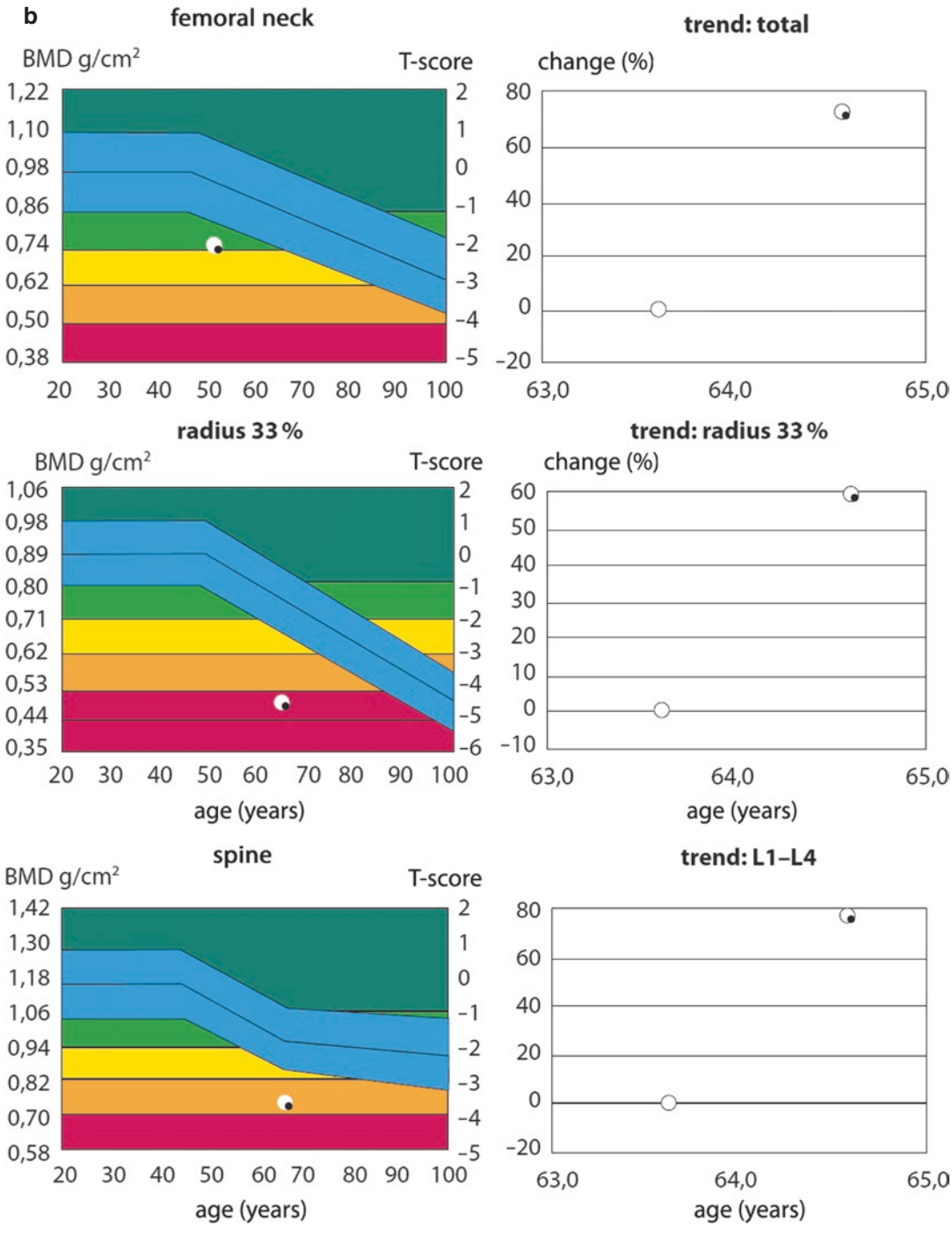

Fig. 20.4 (continued)

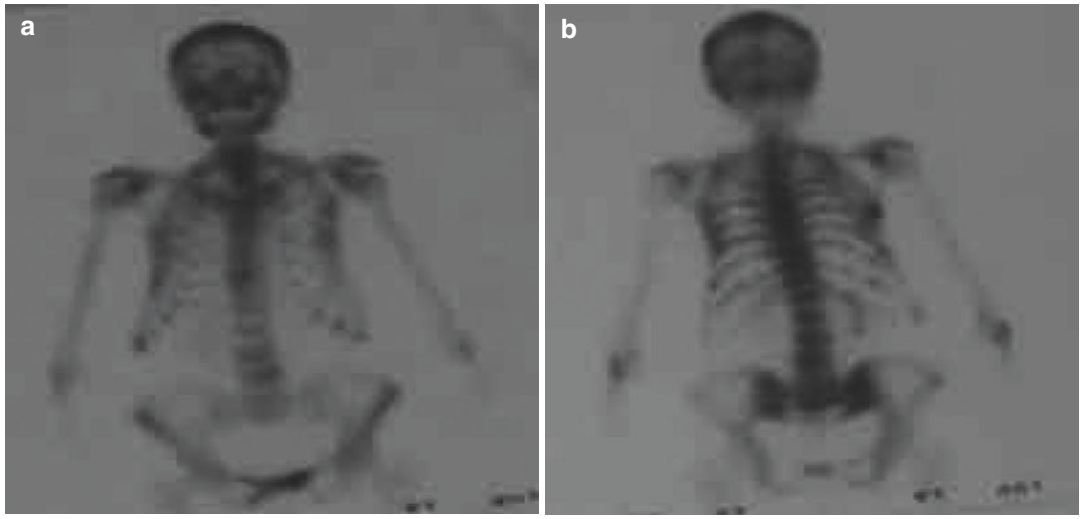

Fig. 20.5 Case report 2. Skeletal scintigraphy: nonhomogeneous distribution of the radiopharmaceutical, minor lesions in the axial skeleton and ribs. It cannot be clearly decided whether it is a metastatic spread of minor deposits or osteomalacia. However, in view of serially located lesions in the posterior ribs, osteomalacia seems to be more probable

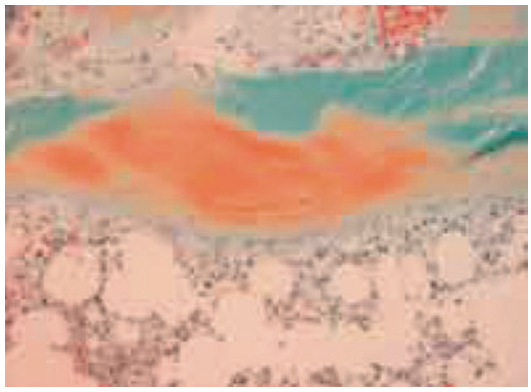

Fig. 20.6 Case report 2. Cancellous bone trabecula with a broad layer of osteoid and intratrabecular demineralization (Goldner staining)

Table 20.2 Celiac sprue (CS) – "tip of the iceberg"

Active CS	Expression of clinical signs of malnutrition, malabsorption, laboratory signs, positive enterobiopsy
Silent CS	Absence of clinical signs, positive enterobiopsy, and laboratory findings
Latent CS	Bioptic finding may be normal, but the patients have a provable history of total or subtotal atrophy of mucosa compensated by dietary modifications and mostly have clinical symptoms
Potential CS	Patients have never had a positive bioptic finding, but their immunological abnormalities are the same as in active CS (primarily first-degree relatives)

According to Maki and Colin [5]

patients exhibit a wide range of findings ranging from mild forms of osteopenia up to severe osteoporosis or osteomalacia, which may be further exacerbated by severely reduced calcium absorption due to the development of secondary hyperparathyroidism, as was the case in the two reported patients. Bone biopsy is one of the methods to prove bone lesions, particularly in case of diagnostic doubts. Of great importance for differential diagnosis is the combination of clinical and laboratory findings. Osteoporosis is characterized by normal serum levels of calcium, phosphorus, alkaline phosphatase, metabolite of vitamin D, and parathyroid hormone, while typical features of osteomalacia include high ALP values and low calcium levels, which may be accompanied by elevation of parathyroid hormone levels. Skeletal pain and fractures are frequent and may be the first symptom that makes patients seek medical care. Skeletal involvement is a symptom that may be encountered in practice also by rheumatologists or osteologists. This diagnostic entity is rightly included in differential

diagnosis of osteopenia or osteoporosis and should be brought to attention of the specialized public. Complications of gluten enteropathy constitute a set of findings that not only reduce the patients' quality of life but may also endanger their lives, mainly in case of a late-diagnosed disease with severe metabolic breakdown in predisposed patients (risk of arrhythmia in hypocalcemia, hypokalemia, etc.) [2, 3].

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Coeliac Disease in Elderly Patients

21

Petr Fojtík, Martin Kliment, and Pavel Novosad

Coeliac sprue is traditionally perceived as a disease related to early age, although young individuals may also suffer from typical bowel symptoms, which belong to the group of active coeliac syndromes. This opinion has been so far generally accepted by the medical public. Full-scale screening performed in the European countries and in the USA, however, has shown that the prevalence of this condition is about 1:100. It means that there are about 40,000–50,000 people affected by coeliac sprue in the Czech Republic, although currently the diagnosis has been established only in 15–20 % of the patients and the greater part of them remains undiagnosed. Thus, a majority of patients affected by coeliac disease are asymptomatic, oligosymptomatic, i.e. without typical intestinal symptoms of coeliac disease, and are therefore included in the category of atypical and silent coeliac disease (Table 21.1). This group comprises most adults without diagnosed coeliac disease. The most frequent atypical manifestation of the disease in adults and in the elderly is osteoporosis which, when combined in women with postmenopausal osteoporosis, may be difficult to treat. Therefore, attention should be paid to elderly patients with osteoporosis, where the incidence of coeliac disease may be expected in at least 3–6 % of patients.

21.1 Definition

Coeliac sprue (CS, coeliac disease, gluten-sensitive enteropathy) is a lifelong genetically conditioned autoimmune disease. It develops in genetically susceptible individuals (association with HLA-DQ2 and HLA-DQ8) after varying periods of consumption of gluten-containing cereals. The delivery of gliadin peptides (fraction of gluten) to HLA-DQ2- and HLA-DQ8-positive cells provokes an excessive immune response in the small intestine mucosa, mediated by T cells [1, 2].

At the same time, a high amount of highly specific antibodies (AtATG – antibodies against tissue transglutaminase) is being generated. Ultimately, reaction to gluten results in damage of the intestinal mucosa (mostly duodenal and jejunal) with a varying degree of atrophy and inflammatory mucosal changes (Fig. 21.1).

21.2 Epidemiology

On average, the prevalence of celiac disease in the Western countries is supposed to be 1:100. It affects more women than men, with the male-to-female ratio of about 1:2. Coeliac disease has a

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Table 21.1 Forms and classification of coeliac disease

CD forms	Classic	Silent	Latent	Potential	Subclinical
Symptoms	+	(+RA)/–	–	Often –	Atypical
Biopsy	+	+	↑IEL	↑IEL/–	+
Serology	+	+	+	±	+

+*RA* positive family history, ↑*IEL* increased intraepithelial lymphocytes

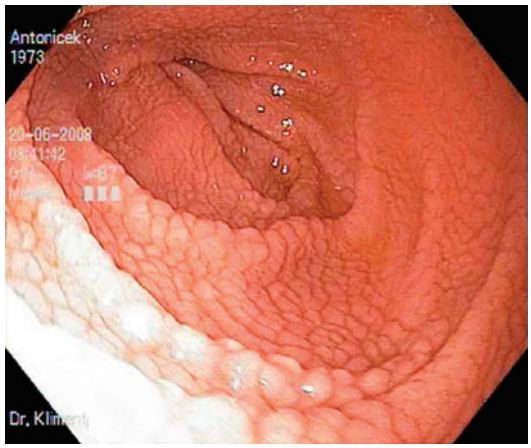

Fig. 21.1 View of the duodenum in D2–3, with atrophic mucosa without villi, with a typical notched appearance

strong hereditary component, with incomplete penetrance. The prevalence of the condition in first-degree relatives is approximately 8–18 %. Concordance in monozygotic twins approaches 70 %. The estimated frequency of coeliac disease in the Czech Republic is 1:200–250, i.e. there are about 40,000–50,000 affected individuals [1, 2].

21.3 Clinical Features

The symptoms and clinical features of coeliac disease largely vary, depending on the patient's age. The course of the disease is also influenced by genetic dispositions, age, duration of gluten exposure and the extent and degree of morphological affection. Coeliac disease is no longer a rare condition affecting mostly small and preschool children and causing only diarrhoea, weight loss and anaemia. With the increasing age at the time of its onset, gastrointestinal symptoms become less intensive and atypical manifestations play a more important role. In adulthood, the disease is mostly detected between the 30th and 40th year of age, later diagnosis is less frequent. After the 60th year of age, coeliac disease is not considered at all, usually due to more frequent and urgent conditions to treat. Manifestation of coeliac disease may be triggered by a stressful situation (infection, surgery, long-term stress). The commonest symptoms observed in adulthood are minor gastrointestinal problems (flatulence, lack of appetite), fatigue syndrome and/or atypical extra-intestinal symptoms, including primarily development of osteoporosis not correlating with age, anaemia, and neurological and psychological disorders. Glossitis, aphthous stomatitis, muscle weakness, alopecia, infertility, amenorrhea and dermatitis herpetiformis occur less frequently.

Osteopenia and osteoporosis are among the most severe atypical manifestations of coeliac disease in adulthood and in the elderly. A total of 18–24 % of coeliac patients suffer from osteopenia; 34 % of postmenopausal female patients have osteoporosis in the lumbar region and 27 % of them in the region of the femoral neck. Bone metabolism is disturbed primarily by malabsorption of nutrients with a subsequent disorder of passive and active Ca transport, by lower levels of regulatory protein of vitamin D, growth hormone (GSF) and the insulin-like growth factor 1 (IGF-1).

21.4 Diagnosis

Diagnosis of coeliac disease in adulthood is based on three factors:

1. Serological markers – AtTGA (antibodies against tissue transglutaminase) with a sensitivity of 90–98 % and specificity of 95–97 %, EMA (antiendomysial antibodies) and AgA

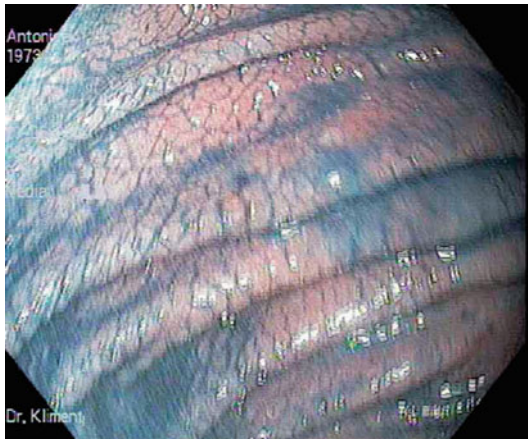

Fig. 21.2 Indigo carmine staining to accentuate the mucosal relief

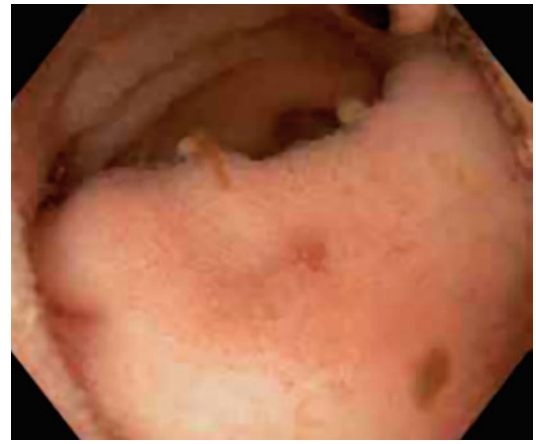

Fig. 21.3 Normal appearance of duodenal villi in water immersion

(antigliadin antibodies). Thanks to its high sensitivity, as well as for favourable cost and availability, AtTgA is the most suitable marker [3].

2. Biopsy of the small intestine mucosa – endoscopically obtained sample of the mucosa of the aboral duodenum. Macroscopically clearly visible atrophy of the duodenal mucosa with cobblestone and notched appearance of Kerckring folds (Fig. 21.1). Since recently, endoscopy may be facilitated by indigo carmine staining (Fig. 21.2) to accentuate mucosal atrophy or a typical white-light image in combination with water immersion to distinguish better between the normal and atrophic mucosa with absence of villi (Figs. 21.3 and 21.4). Microscopically, mucosal damage is evaluated according to the Marsh classification (stages 0–4), where stage 3 (destructive) is the most typical of coeliac disease [2, 4, 5].
3. Clinical symptoms of coeliac disease in adulthood include primarily extra-intestinal disorders, such as development of osteoporosis not correlating with age, anaemia, and neurological and psychological disorders [1, 2, 6].

Glossitis, aphthous stomatitis, muscle weakness, alopecia, infertility, amenorrhea and dermatitis herpetiformis occur less frequently [2, 7].

21.5 Classification: Forms of Coeliac Disease

Due to prevalence of non-specific symptoms of coeliac disease in adulthood, they often go unnoticed. According to the reports, up to 80 % of adult patients with coeliac disease are not diagnosed. This supports the concept of the "tip of the coeliac iceberg" where the smaller part above the surface represents the active forms of the disease and the greater part remains under water and thus undiagnosed. The most frequent form of the disease in adulthood and in the elderly is atypical (extra-intestinal) coeliac disease [2, 8].

CS classic (*typical*) *form* (fully developed) accounts for about 30 % of the patients. Serological and histological markers are present, as well as gastrointestinal symptoms typical of CS.

CS subclinical (*atypical*) *form* (extra-intestinal). Serological and histological findings are positive. Clinical features include atypical extra-intestinal symptoms (anaemia, metabolic osteopathy, neurological and gynaecological symptomatology).

CS silent form. Histological and serological findings are positive. Clinical symptoms are absent; coeliac disease is often in the family history.

CS latent form. Serological findings are positive. Histologically, there is only an increased

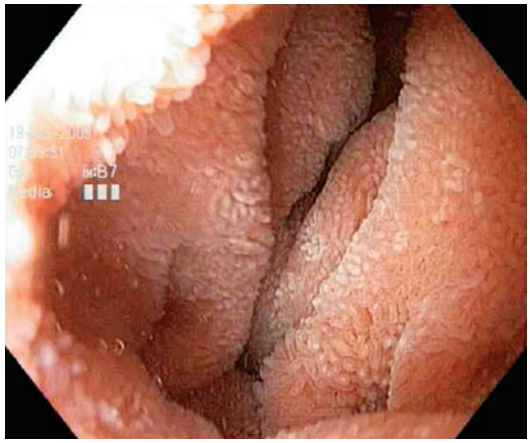

Fig. 21.4 White-light image – normal villi in duodenal mucosa in D2

number of IEA (intraepithelial lymphocytes) without atrophy. Clinical symptoms are absent. This finding is typical of early stages of the disease in patients with the diagnosis of coeliac disease confirmed before, who already are on the respective diet (Table 21.1).

CS potential form. Serological findings are both negative and partially positive; histological finding is negative and/or with increased IEL. Clinical symptoms are absent. Genetic examination (HLA-DQ2 and HLA-DQ8) is recommended. These patients are at risk of developing coeliac disease in the future.

21.6 Complications of Coeliac Disease

The most severe complication of coeliac disease in adulthood and in the elderly is osteoporosis. In female patients, secondary osteoporosis induced by coeliac disease often combines with postmenopausal osteoporosis. In the Czech Republic, osteoporosis affects about 15 % of men and 33 % of women older than 50 years and 39 % of men and 47 % of women older than 70 years. The clinical impact of osteoporosis consists mainly in its consequences and complications, primarily pathological fractures of both axial skeleton and extremities. The most frequent are compressive fractures of vertebral bodies, the proximal femur and radius. These fractures significantly worsen the quality of life and reduce life expectancy. Mortality of women over the age of 50 with a diagnosed fracture of the femoral neck is by 15 % higher than that of the other women. In women older than 65 years, this mortality reaches up to 30 %. For this reason, increased attention is paid to identification of adult and elderly patients with coeliac disease. Other complications in adult patients are less frequent and include anaemia caused by deficiency of iron, folate, pyridoxine, and vitamin B_{12}, gynaecological disorders (infertility, dysmenorrhoea, abortions), psychological disorders (anxiety, depressions) and neurological disorders (peripheral neuropathy, manifest tetany, muscle weakness, lesion of posterior spinal cords, cerebellar atrophy, epileptic seizures). The most severe, although rare, complication is development of a small intestine tumour – intestinal lymphoma (Fig. 21.5),[6, 9, 10].

21.7 Therapy and Follow-Up

The treatment of coeliac disease is simple. The patients have to adhere to a gluten-free diet for life. During the initial 3–6 months, the intestinal mucosa is being restored. This process can be supported by substituting vitamins of B group and trace elements. Once the diagnosis is established, it is recommended to substitute calcium in doses of 1000 mg per day and vitamin D in doses of 1600 IU per day (e.g. 4 drops of Vigantol per day or 20 drops once a week) in the first year of treatment and then to adapt dosage to the results of densitometry [11, 12].

There are no data concerning suitable doses; however, vitamin D seems to play a crucial role. Therefore, administration of active form of vitamin D is also considered.

In children the bone mineral density (BMD) is normalised within 3 years of gluten-free diet. On the contrary, in adulthood BMD usually does not return back to normal, especially in patients with secondary hyperparathyroidism in the initial stage.

Densitometry is advisable prior to commencement of the treatment and then after 1 year of dietary regime and of treatment of osteoporosis.

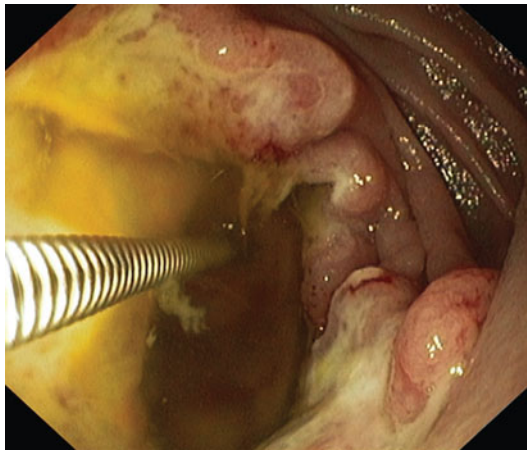

Fig. 21.5 Lymphoma of transition from the jejunum to the ileum – white-light image in enteroscopy

Bisphosphonates are currently considered to be the most suitable medication for the osteoporosis treatment. Promising results have been provided also by strontium preparations.

21.8 Screening of Target Groups of Adult and Elderly Patients

In co-operation with an osteology centre in Zlín, we examined a serological marker of coeliac disease (tTG) in 1409 patients. Thirteen patients were positive, and, subsequently, gastroduodenoscopy confirmed atrophy of the duodenal mucosa of stage III a–b according to the Marsh classification. The total prevalence of coeliac disease in our group was then 1:100. The group was divided into two subgroups: A (patients younger than 55 years) with the prevalence 1:28 and B (patients older than 55 years) with the prevalence 1:100. None of them had typical bowel symptomatology. Five patients complained of intermittent diarrhoea and eight had occasional abdominal distension. We hereby confirmed the high prevalence of coeliac disease in the population of osteoporotic patients in the Czech Republic – 1:100, which is equal or twice as high as in the common population. However, in patients with osteoporosis, older than 55 years, the prevalence is 1:28, i.e. four times higher than in the common population. Therefore, it is recommendable to screen for coeliac disease all osteopenic and osteoporotic patients younger than 55 years. Osteoporotic patients older than 55 years should be screened if they do not respond to the treatment adequately or show even minimal intestinal symptomatology [1, 2, 8].

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Bone and Joint Involvement in Celiac Disease

22

Lenka Franeková and Marie Sedláčková

Celiac disease (celiac sprue, gluten-sensitive enteropathy) is a chronic inflammatory condition that primarily affects the small intestine mucosa and is clinically manifested by bowel symptoms of various severities. However, it may have also a number of extraintestinal manifestations which prevail in adulthood, and as a result the disease goes unnoticed. Celiac disease is an autoimmune condition induced by gliadin fraction of gluten, protein that can be found in grains such as wheat, rye, barley, and oat, in genetically predisposed individuals – HLA DQ2 or DQ8 carriers [3, 11, 17].

Prevalence of celiac disease in Europe is 1:200–250, in USA 1:100 [3, 11]. Celiac disease manifests itself most often between 1st–2nd and between 30th–40th year of life and affects primarily women and relatives of celiac patients [26].

Diagnosis is established on the basis of biopsy, where histology of intestinal mucosa shows a typical jejunal villous atrophy, lymphoplasmocytary infiltration, crypt hyperplasia, and increased number of intraepithelial lymphocytes [17].

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The patients' serum is examined for antigliadin, anti-endomysial, tissue transglutaminase, and anti-reticulin antibodies that are highly specific for this disease and help identify patients with unexpressed intestinal clinical manifestations of the disease. Diagnosis is continuously improved with the ongoing progress in serological screening methods for detection of antibodies [11, 20].

Undiagnosed celiac disease poses multiple risks for patients. One of them is osteoporosis, including osteoporotic fractures, but primarily susceptibility to development of other autoimmune conditions and malignancies of the digestive system (small intestine lymphoma or adenocarcinoma). Also patients with neurological and joint disorders or female patients presenting with infertility are not adequately treated and such noncausal treatment has a less chance to succeed.

The therapy is based on strict gluten-free diet, nutritional care, and compensation for the deficit of minerals and vitamins, initially predominantly in the parenteral form [3]. Recent studies confirmed in patients adhering to gluten-free diet the incidence of autoimmune diseases [7] and GIT malignancies comparable to that of general population [13]. Early detection of celiac disease in infertile female patients with subsequent introduction of gluten-free diet provably restores fertility and reduces the number of complications in pregnancy to the level of healthy female patients [22, 31].

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Gastroenterologists therefore recommend active identification of patients by screening for antibodies in groups of individuals at risk [3].

The aim of the study is to provide rheumatologists with details about manifestations of celiac disease in the musculoskeletal apparatus, facilitating identification of patients with undiagnosed disease, which is an essential prerequisite of a causal and in most cases successful treatment.

22.1 Etiopathogenesis of Celiac Disease

Celiac disease is currently considered to be a clearly autoimmune disorder. It develops in genetically predisposed persons, exclusively the carriers of HLA class II genes known as HLA-DQ2 and HLA-DQ8. In DQ2, but also MYO09B homozygotes, there is a higher incidence of refractory celiac disease and intestinal lymphoma [1, 34]. One of the genetic predispositions is also a higher incidence of celiac disease among relatives of celiac patients (5–15 %) and in monozygotic twins (70–75 %).

Gluten is a protein that can be found in grains such as wheat, rye, barley, and oat. Gliadin, a gluten component, triggers autoimmune response, or its toxic cleavage products gluten peptides deamidated by tissue transglutaminase are presented in conjunction with HLA-DQ2 or DQ8 cell surface antigens by antigen-presenting cells, to CD4 T lymphocytes, resulting in their activation and development of Th1 immune response with production of pro-inflammatory cytokines (mainly IFN-γ) and metalloproteinases.

Two types of immunity are responsible for the propagation of mucosal damage, namely, specific and innate [11, 17], resulting in enterocyte destruction, loss of villous structure, lymphoplasmocytary infiltration, and compensatory deepening of crypta.

Although the exact etiopathogenetic mechanism of this disease is not known, the cause of disruption of mucosal barrier and development of inflammatory process is in certain persons considered to be the history of intestinal infection or surgery [3, 17]. Another proved contributing factor is the time of introduction of cereals into infant diet [16].

An important characteristic feature of this autoimmune disease is production of antibodies. The main autoantigen is considered to be tissue transglutaminase. The exact pathogenetic mechanism of the effect of these antibodies is not known, but their evidence is highly specific and highly sensitive for celiac disease.

Studies reporting high prevalence of neurological disorders, skin or joint manifestations, or infertility in patients with celiac disease and their subsidence or improvement after introduction of gluten-free diet indicate association between celiac disease and these extraintestinal organic manifestations. Pathogenetic mechanisms of these manifestations are still unknown.

It is assumed that both autoimmune mechanisms and malabsorption are involved to varying extents.

Clonal expansion of intraepithelial lymphocytes results in development of lymphoma as a potential complication of celiac disease [5, 11].

Celiac disease is often associated with other autoimmune disorders such as Hashimoto's thyroiditis, type 1 diabetes, psoriasis, as well as systemic connective tissue diseases. The incidence of celiac disease is ten times higher in patients with Sjögren's syndrome as compared to general population, which is probably given by a similar genetic basis – association with HLA DQ2 [23, 30].

22.2 Clinical Manifestations of Celiac Disease

Based on clinical manifestations, there are three main forms of the disease, active, silent, and latent [9]. Active forms include a classic malabsorption syndrome triad with diarrhea (steatorrhea), fatigue, and weight loss, accompanied by deficiency of nutrients, minerals, and vitamins, and are usually easy to diagnose.

Celiac disease goes unnoticed mainly in patients with the silent or latent form of the

disease. Silent forms are manifested only by nonspecific dyspeptic problems (abdominal pain, bloating, lack of appetite, or constipation). Latent forms are not associated with any gastrointestinal manifestations; patients may only feel tired and may have a number of extraintestinal manifestations of this disease, such as neurological (ataxia, polyneuropathy, migraine, epilepsy) [4], joint (arthralgia and arthritis) [12], psychiatric (depression), skin (dermatitis herpetiformis or Duhring's disease), and hepatic disorders [8], cardiomyopathy, or fertility disorders [22, 31] – Fig. 22.1. Underweight is usually not typical of celiac patients, quite the opposite, at the time of diagnosis about one third of patients are overweight.

22.3 Diagnosis of Celiac Disease

Diagnosis is established on the basis of biopsy. In adults biopsy taken from descending duodenum distal to the papilla of Vater within gastroscopy is sufficient. The histological finding of intestinal mucosa includes a varying degree of mucosal atrophy, lymphoplasmocytary infiltration, crypt hypertrophia, and increased number of intraepithelial lymphocytes (Marsh classification I–IIIc). Histochemical examination proves enzymatic disorders [17]. Biopsy is indicated on the basis of evaluation of clinical and laboratory signs of malabsorption and evidence of serum antibodies typical of celiac disease: antigliadin (AGA), anti-endomysial (EMA), tissue transglutaminase

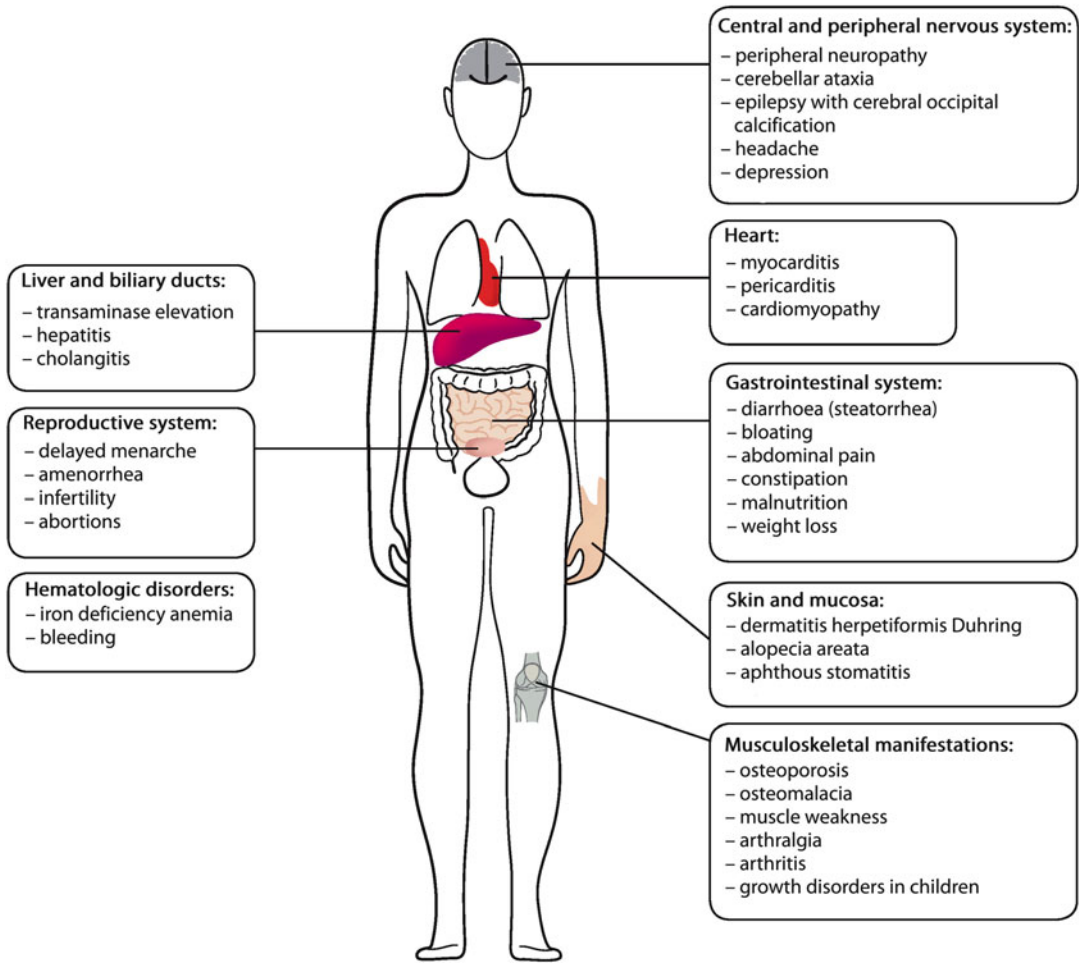

Fig. 22.1 Clinical manifestations of celiac disease

(anti-tTG), and anti-reticulin antibodies (ARA [3, 10, 15]). Antigliadin antibodies are not specific enough for celiac disease. In terms of both specificity and sensitivity, the dominating method is evidence of anti-endomysial antibodies and antibodies against tissue transglutaminase. The most efficient single serologic test for the detection of celiac disease is the IgA tTGA (ELISA). Specificity of these antibodies is more than 95% and sensitivity 90–96%. EMA antibodies (examined by indirect immunofluorescence) have only slightly less sensitivity, but their specificity is also high (99.6%) [3].

In addition to these conventional tests, new kits are available for determination of antigliadin antibodies targeted only against specific epitopes of gliadin peptides. Examination of ARA antibodies is currently used quite rarely, as these antibodies, although highly specific, have a low sensitivity [15].

It has to be taken into account that celiac patients who are, for instance, IgA immunodeficient will not produce IgA anti-tTG recommended in the screening, or only in insignificant amount, and therefore patients with a high suspicion of celiac disease should be examined for IgA immunoglobulin levels even in case of negative IgA AGA [3].

Prevalence of celiac disease in the highest risk groups is shown in Table 22.1.

In 2013, the Czech Gastroenterological Society published a methodological guideline for celiac disease screening, which recommends, in addition to the high-risk groups included in the table, to perform screening by IgA antibodies against tissue transglutaminase and total IgA also in individuals with therapeutically resistant diarrhea associated with the irritable bowel syndrome, polyneuropathy, myopathy and ataxia of unclear etiology; unexplained weight loss, with depression, retarded psychosomatic development, recurrent aphthous stomatitis, and enamel hypoplasia; and associated autoimmune disorders, such as systemic lupus erythematosus, primary sclerosing cholangitis, and IgA nephropathy.

In addition to screening, examination of AGA, EMA, and anti-tTG antibodies is used to observe the therapeutic effect. With a good therapeutic effect of gluten-free diet and the patient's compliance, titers of these antibodies decrease down to the normal values not quite correlating with the histological finding [14]. A sudden evident increase in total IgA levels may signal development of a malignant lymphoma.

If celiac disease is clinically suspected despite negative serologic test results, genetic examination may be useful. Except for DQ2 and DQ8 antigen carriers, celiac disease may be reliably excluded and there is no need for biopsy [3, 10].

Table 22.1 Groups at risk recommended for celiac disease screening – according to the official recommendations of the American Gastroenterological Association

Group at risk	Prevalence of celiac disease in the group (%)
First-degree relatives of celiac patients	10
Second-degree relatives of celiac patients	2.6–5.5
Patients with iron deficiency anemia	3–9
Patients with osteoporosis	0.9–3.4
Patients with type 1 diabetes mellitus	2–5
Patients with transaminase elevation of unclear cause	1,5–9
Patients with autoimmune hepatitis	2.9–6.4
Patients with primary biliary cirrhosis	6
Patients with Down syndrome	3–12
Patients with Turner syndrome	2–10
Patients with autoimmune thyroid diseases	1.5–6.7
Patients with unexplained infertility	2.1–4.1
Patients with Sjögren's syndrome	10

22.4 Metabolic Osteopathy in Celiac Disease

In newly diagnosed patients with celiac disease, osteoporosis is found by densitometry in 28% of cases in the region of the lumbar spine and in 15% of cases in the region of the proximal femur [2].

Studies dealing with prevalence of celiac disease in patients with low BMD report that 0.9 up to 3.4 % of patients with osteoporosis have celiac disease. Screening of celiac disease in children with low BMD proved the diagnosis of this disease in 5 % of cases. In a study of 978 patients with low BMD, performed in the Great Britain, biopsy proved celiac disease in 2.1 % of patients with osteoporosis and in 1.2 % of patients with osteopenia. Where the screening covered only selected patients with decreased BMD and minimal gastrointestinal manifestations or with anemia, prevalence of celiac disease in osteoporotic patients amounted to 3.9 % and in osteopenic patients to 2.6 %.

It is not recommended to perform screening in all patients with osteoporosis; it is more efficient to select those with gastrointestinal disorders and unclear iron deficiency anemia [27].

Pathogenesis of osteoporosis and osteomalacia in patients with celiac disease is associated not only with disorder of intestinal calcium absorption because of reduced resorption surface and steatorrhea with decreased absorption of fat-soluble vitamin D but also other mechanisms, such as low calcium intake due to lactose intolerance, secondary hyperparathyreosis, and impact of pro-inflammatory cytokines activating osteoclasts through increased production of RANKL (receptor activator of nuclear factor kB ligand) by stromal cells and osteoblasts.

In celiac patients, osteoporosis may develop also without diarrhea, skeletal pain, and biochemical abnormalities as well as during a gluten-free diet (in case of lactose intolerance [18]). Decreased BMD can be found mainly in the peripheral skeleton; it is caused by hyperparathyreosis that relatively spares the axial skeleton. Decreased bone density in the peripheral skeleton persists even with good response to treatment of BMD in the spine and its returning back to normal [19, 28].

The basis of treatment of osteoporosis in celiac disease is in addition to gluten-free diet also calcium and vitamin D substitution [2, 19, 24]. After introduction of gluten-free diet, it takes minimally one year (depending on the degree of intestinal mucosa damage) before the structure of intestinal mucosa is restored and intestinal absorption of Ca and vitamin D gets back to normal and at least 2 years before the bone tissue is remineralized. Patients with celiac disease diagnosed and treated since childhood reach the BMD values comparable with the general population [25]. Osteomalacia occurs in celiac patients less frequently.

22.5 Joint Involvement in Celiac Disease

Celiac disease should be considered in examination of patients with joint pain of unclear origin, accompanied by fatigue, muscle weakness, and digestion and neurological disorders (polyneuropathy), particularly in individuals suffering from depression. In the course of several years, arthralgia may progress to arthritis. Special attention should be paid to patients with the primary Sjögren's syndrome, as prevalence of celiac disease in these patients is the highest of all systemic connective tissue diseases [6, 30].

Similarly as Crohn's disease and ulcerative colitis, celiac disease may be the cause of enteropathic arthritis. Enteropathic arthritis is a seronegative, nonerosive condition, although sometimes erosions may occur [12]. This form of arthritis is classified as one of the group of seronegative spondyloarthropathies [35]. Joint involvement in enteropathic arthritis includes typically both peripheral and axial joint disorders – sacroiliitis with or without spondylitis, as well as tendinitis and enthesopathy. Peripheral joint involvement is divided into two types. In HLA-B27-positive patients, it is first of all type 1 – pauciarticular (affecting less than five joints), asymmetrical, affecting mostly lower limbs, acute course associated with intestinal inflammation relapse, and self-limiting (spontaneously resolving within about 10 weeks). Type 2 with polyarticular involvement, developing independently of the activity of bowel inflammation, persists over months or years. The latter type occurs typically in celiac patients. Association with HLA-B27 in this type of involvement has not been proved.

The exact pathogenesis of joint changes in inflammatory bowel diseases remains unclear. A key role is probably played by circulating antigen-specific gut-derived T lymphocytes penetrating the joint synovium. Another contributing factor may be also increased permeability of the intestinal mucosa and colonization of inflammatory lesions by anaerobic bacteria, leading to absorption of pro-inflammatory bacterial components stimulating a pathological immune response, which is proved by the evidence of the presence of bacterial components or DNA in the joint of a patient with enteropathic arthritis [32]. The hypothesis of involvement of immune complexes has proved to be rather improbable as the circulating immune complexes consisting of bacterial antigens and secretory IgA immunoglobulins were not found in the synovium of arthritic joints.

The first to describe association of celiac disease with arthritis was Adelizzi, as late as in 1982. Lubrano et al. examined 200 celiac patients and found arthritis in 26 % of them, of which 19 (36.5 %) patients had peripheral, 15 (28.8 %) axial, and 18 (34 %) a combined involvement. In sacroiliitis, the disorder is mostly unilateral (80 % [21]). Duration of the bowel disease was irrelevant in this respect. Joint manifestations may precede manifestation of bowel inflammation. A number of cases were reported of axial or peripheral arthritis with absence of intestinal disorders that had the form of silent celiac disease [6, 29]. The most common pattern is polyarticular, symmetrical arthritis affecting large joints – the shoulders, hips, and knees [12] – although cases of monoarthritis, oligoarthritis, or arthritis of small joints were also reported. They may be expressed as radiographic or scintigraphic changes indicating enthesopathies. Scintigraphy confirmed sacroiliitis in 63.6 % of celiac patients [33].

The basic therapy of joint involvement in celiac disease is introduction of gluten-free diet, rest, NSAID administration, and intra-articular application of corticoids.

Certain cases require general corticoid treatment. Arthritis remission was recorded in most patients after introduction of gluten-free diet, with only 21 % of patients with persisting joint disorders [21]. Re-exposure to gluten induced relapse of arthritis or sacroiliitis [29].

Conclusion

In differential diagnosis of arthralgia, peripheral arthritis, sacroiliitis, osteoporosis, or osteomalacia, rheumatologists should consider the potential presence of a not yet diagnosed celiac disease also in patients who do not suffer from diarrhea or other digestive disorders.

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Diffuse Idiopathic Skeletal Hyperostosis

23

Andrea Pavelková

23.1 Introduction

Diffuse idiopathic skeletal hyperostosis (DISH), also known as Forestier's disease, is a chronic noninflammatory systemic skeletal disorder of unclear aetiology, the hallmark of which is new bone formation in the region of the spine and peripheral skeleton. This entity was for the first time described by Forestier and Rotés-Querol in 1950, as senile ankylosing hyperostosis of the spine, although reports in the literature of skeletal ossifications are more than 150 years old. In DISH, local metaplastic calcification of matrix occurs in the thin connective tissue between the anterior longitudinal ligament and the vertebral body due to calcification of the longitudinal ligament. Ossification progresses from attachments of tendons, ligaments and joint capsules [1]. Heterotopic bone tissue can be found predominantly in the spine, primarily as flowing ossification of vertebrae. Peripheral involvement includes enthesopathies that occur predominantly in the region of the heels, knees, elbows and pelvis [2]. Diagnosis is based on compliance with Resnick's criteria [3] (Table 23.1) that characterise a typical radiographic finding in the spine, but do not include clinical or laboratory signs.

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DISH affects predominantly middle-aged men (male–female ratio, 2:1) [4]; it is common in middle-aged patients, with only rare incidence before the age of 40. Prevalence of this disease raises with increasing age. In the age group over 70, the prevalence grows in men up to 10.1 % and in women up to 6.8 %.

23.2 DISH Aetiology and Aetiopathogenesis

DISH aetiology is not known. The underlying cause of ossification in DISH is multifactorial, including metabolic, hormonal and genetic factors. Correlation has been described with centripetal obesity and primarily type 2 diabetes mellitus, a hyperinsulinaemia [5] or glucose tolerance disorder [6]. Frequent disorders, of lipid metabolism (hypercholesterolaemia, hypertriacylglycerolemia) and also hyperuricemia have been reported. Prevalence of diabetes in adults and glucose tolerance disorder reaches in patients with DISH 17–60 %, prevalence of DISH in adults with type 2 diabetes mellitus is about 13–50 % [7]. The current findings show that the main contributing factor in aetiopathogenesis of this disease is hyperinsulinaemia, or insulin resistance [8]. No correlation has been found between the degree of hyperglycaemia and bone changes in the skeleton.

Another important factor is hormonal effect particularly the effect of the growth hormone

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Table 23.1 Resnick's DISH diagnosis criteria

Calcification and ossification along the anterolateral aspect of at least four consecutive vertebral bodies
Preservation of the intervertebral disc space
Absence of SI joint ankylosis and SI erosion/sclerosis

(GH). Similar hyperostotic bony bridges as in DISH occur also in acromegaly, which only proves the GH role in this process [9]. Age-related hormonal changes also play a role in GH regulation. It is assumed that decline in gonadotropins, androgens in particular, is responsible for increased production of estrogens as natural growth hormone stimulators. In hyperinsulinaemia, IGF-I secretion is stimulated, which increases osteosynthetic potential. This could explain the correlation between osteoproductive changes and incidence of diabetes mellitus and obesity. The increase rates of obesity in patients with DISH might imply a role of adipokines in the pathogenesis of DISH, as leptins and osteoblast inhibitor Dickkopf -related protein-1 (DKK-1) [10, 11].

An important role in aetiopathogenesis of DISH as well as ossification of the posterior longitudinal ligament (OPLL) is played also by genetic factors, due to familial incidence of DISH is described. Association with the metabolic syndrome. Correlation, however, has not been so far proven within the HLA systems which, as a result, cannot be used yet to distinguish mainly DISH and ankylosing spondylitis. Authors of extensive Slovak studies expressed a hypothesis about DISH autosomal dominant inheritance, which would explain also association between the above-mentioned metabolic disorders and DISH [12].

Based on analysis of bone turnover markers and their impact on bone formation and bone resorption, as well as the findings related to the role of hyperglycaemia and insulin resistance, associated with DISH, these parameters were examined in the patients with DISH treated in the Institute of Rheumatology in Prague. The results were published in details in the journal Česká revmatologie. Another study conducted by the same institute included 64 patients with DISH and focused on bone turnover markers (ALP, osteocalcin, vitamin D, pyridinoline, deoxypyridinoline) and local factors affecting the activity of bone cells (IGF-I, free IGF-I and their binding proteins IGFBP2, IGFBP3). The authors focused on bone metabolism in this group of patients and deviations, if any, either in favour of bone formation or bone resorption or a change in the activity of local factors. Results of the examinations, however, did not reveal any correlation with or a trend to a change in values of bone turnover markers or local growth factors in the bones of the group of patients with DISH [13].

As a result, it seems that the process of heterotopic bone formation in DISH has no impact on the values of bone turnover markers and the changes are rather of local nature.

23.3 Clinical Manifestations of DISH

Sometimes the course of the disease is quite asymptomatic, and the diagnosis is established accidentally, e.g. during chest radiography, or sometimes as late as during autopsy; but often it is a cause of multiple serious disorders. An important clinical symptom is onset of pain after the age of 40, often associated with gradual limitation of mobility of the spine, accompanied by rigidity especially in the mornings and evenings and sometimes resulting from inactivity or weather changes, similarly as in osteoarthritis. A typical feature is segmental involvement of the spine, with only sporadic cases of flowing ossification of all vertebrae in the same extent and with the bamboo-like pattern as seen in ankylosing spondylitis. Some patients report marked pain of the axial skeleton, mainly the cervical and lumbosacral spine, which may lead to development of radicular syndromes, but in general the pain is usually temporary, mild, associated with physical activity and accompanied by gradual limitation of mobility. Quite often, DISH may be combined with enthesopathic pain at the periphery (38%). It affects predominantly heels, knees, shoulders, and elbows, sometimes with palpable bone appositions. Pain in these locations often occurs in combination with inflammatory irritation or overloading. Enthesopathic manifestations in pelvis develop usually in the late phase.

Other clinical manifestations of DISH may include also dysphagia caused by compression of the oesophagus by cervical ossification formations [14], which exacerbates in extension of the spine and gets milder in with its flexion. Pain in the chest may result from ossification of sternocostal and costovertebral articulations, and in elderly patients, it may be confused with heart disorders. A DISH-like process is ossification of the posterior longitudinal ligament (OPLL) in the cervical spine. This entity occurs most often in Asia; its prevalence in Japan is reported at about 1.5 % [15]. OPLL may be responsible for a number of neurological complications, particularly cervical myelopathy, paresthesia, motor disorders and other neurological symptoms.

23.4 Differential Diagnosis

DISH is quite often clinically and radiographically confused with ankylosing spondylitis (AS). DISH has a typical radiographic finding, with absence of SI joint involvement.

The most frequent and one of the first locations of typical radiographic changes is Th spine. The changes are usually asymmetrical, located on the right side, which is explained by pulsation of the aorta on the left side. Initially ossifications are incomplete and only gradually fuse. Intervertebral space is as a rule preserved. Involvement of C and LS spine develops later and is less frequent.

Unlike in DISH, in AS, there develops secondary metaplasia of inflammatory tissues along the anterolateral aspects of vertebrae and ligaments, with gradual ossification of the peripheral part of the fibrous ring of intervertebral discs and the adjacent ligaments. As compared to DISH, it is an inflammatory condition of the spine. AS typically affects apophyseal, costovertebral and sacroiliac joints (sacroiliitis); syndesmophytes can be found in the pelvic region. Patients with AS often have a history of iridocyclitis or arthritis and are HLA-B27 positive (Table 23.2).

DISH diagnosis is also proved by laboratory metabolic abnormalities (hyperglycaemia, hypercholesterolaemia and hyperuricaemia) normal acute phase reactants and the already mentioned age above 40 years.

Osteoarthritis is characterised by osteophytes, sclerotic vertebral bodies and reduced height of vertebral discs that are absent in DISH. Differential diagnosis is facilitated by radiography of the spine, or the affected sites of the peripheral skeleton, as well as metabolic changes revealed by biochemical examination.

Differential diagnosis should take into account also acromegaly, hypoparathyroidism, ochronosis, chondrocalcinosis and other types of seronegative spondylarthritis.

Table 23.2 Differential diagnosis DISH vs AS

	DISH	AS
Age at the time of onset of the disease	Over the age of 40	Younger (under 35 years)
Disease development	Gradual	Progressive
Pain	Max. v Th	LS Th
Rigidity	Up to 30 min	More than 30 min
SI joint involvement (sacroiliitis)	No	Yes
Peripheral arthritis	No	Possible
Iridocyclitis	No	Possible
HLA-B27	No	Frequent
Association with metabolic factors	Yes	No
Acute phase reactants	Normal	Often increased
Inflammatory origin of the disease	No	Yes

23.5 A Case Report of an Elderly Patient with Severe Deforming DISH

A male patient (born in 1920) is with a history of duodenal ulcer disease, stomach resection, diabetes mellitus (treated by oral antidiabetics), cholecystopathy and pancreatopathy. The patient presented with back pain in 2004, when he experienced gradual pain worsening, and had progressive hyperkyphosis of Th spine. He was referred by the general practitioner for marked kyphosis of Th spine and exclusion of ankylosing spondylitis. The patient reported vertebrogenic pain from the age of about 50 years; the pain was

intermittent, with periods of relative relief. He did not tolerate analgesics and NSAIDs for chronic dyspepsia associated with GIT disorders.

During initial examination, he was markedly asthenic, with body weight of 55 kg, with obvious kyphotic deformity of Th spine that could not be compensated and with lumbar lordosis completely missing (Fig. 23.1): fleche, 5 cm; Schober, 3 cm; and Thomayer, 30 cm.

Results of laboratory examination were normal, including acute phase reactants and bone metabolism. HLA-B27 was negative.

Radiographs of both Th and LS spine showed massive flowing ossification along the entire Th spine, with right side predominance; gross osteophytes were found also in the LS spine, its proximal part in particular. Intervertebral space was reduced only slightly. Gross ossifications could be seen also in the C spine; C5 disc height was decreased (Fig. 23.2). Summation radiography showed SI joints without greater abnormalities.

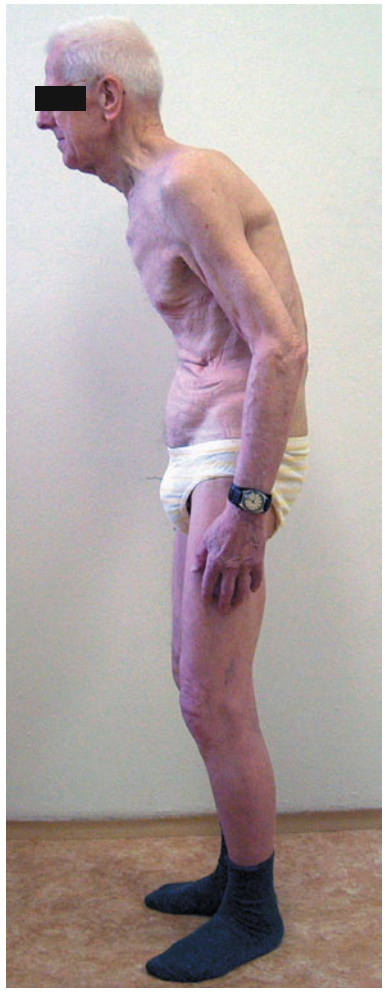

Fig. 23.1 The patient's forward stooped posture

The patient was diagnosed with DISH. Intensive and regular rehabilitation was commenced with a focus on strengthening of paravertebral muscles and keeping upright posture. After rehabilitation, the complaints stabilised. The patient underwent also water therapy and regularly exercised at home according to instructions. However, the deformity gradually progressed, the patient felt forward pull on the spine and was unable to compensate the deformity and keep the upright posture. He received a custom-made back brace fixed over the shoulders (Fig. 23.3). The patient's condition was further complicated by food intake disorder and gradual cachexia that contributed to further weakening of muscles. He started to have pain in hips; radiography showed OA of the hip on the right side of degrees II–III. The patient began to use crutches to increase stability and prevent further deformity of the spine. He continued to exercise at home and underwent further rehabilitation in the Institute of Rheumatology; analgesic therapy was very difficult, partial relief was provided by chondroprotectives. In the spring 2008, the objective parameters included fleche 29 cm, Thomayer 55 cm, and the patient was continuously losing weight (down to 49 kg).

23.6 Discussion of the Case Report

The reported case shows a relatively rare, progressive involvement of the entire spine, significantly deforming the whole axial skeleton and the posture. Due to his age, the patient exhibits also classic degenerative involvement of the spine, indicated by degenerative disease of hips. However, the most severe complications in this patient are flowing ossifications that form a structure quite similar to disorders caused by ankylosing spondylitis. A certain role is played

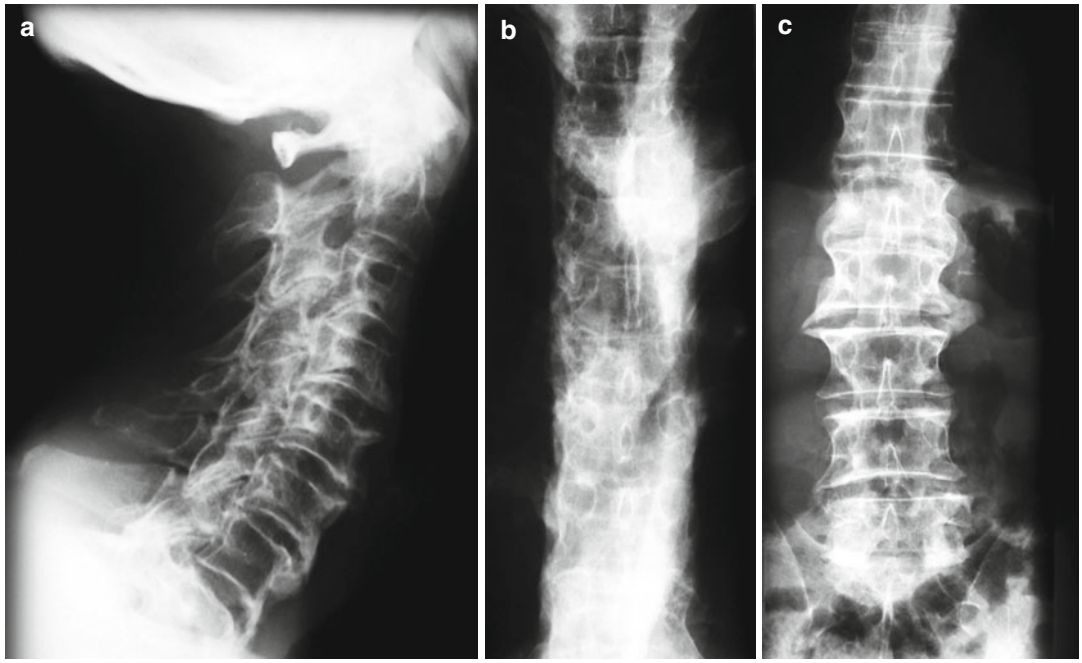

Fig. 23.2 Radiography of C, Th and LS spine – massive flowing ossifications

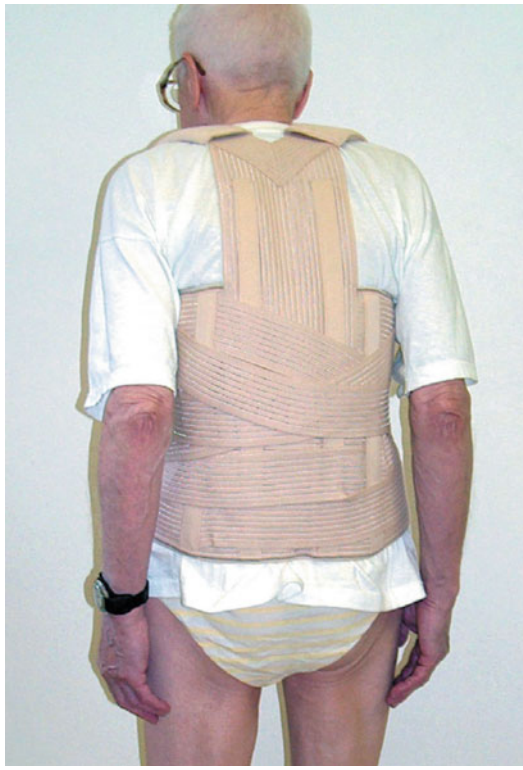

Fig. 23.3 Back brace with fixation over the shoulders

also by the patient's advanced age and the associated fully developed hyperostotic formation. However such advanced form of the disease is rather rare.

23.7 DISH Therapy

Causal treatment of this disease is not known. Due to the nature of the disease, it is very important to prevent obesity, gout and hypertension and adhere to healthy lifestyle. Medications increasing hyperinsulinaemia should be avoided. Type 2 diabetes should be ideally treated with metformin, while ACE inhibitors should be preferred in treatment of hypertension as they meet this requirement.

Analgesics or NSAIDs are symptomatically used to manage pain, while respecting other internal diseases. Pain resulting from peripheral enthesopathies can be managed also by local NSAIDs or short-term use of muscle relaxants; mesocaine or glucocorticoid injections are exceptionally administered to manage pain caused by irritated osteophytes. Heat, hot baths and swimming can

help to relieve rigidity. Additional benefits are offered by ultrasound and electrotherapy; an integral part of the treatment should be exercises focused on improvement of mobility. Despite these therapeutic tools, certain disorders in some patients are difficult to control.

Conclusion

DISH is one of the typical disorders of the musculoskeletal system of elderly patients. Subjective symptoms range from manifestations of mild vertebrogenic complaints up to intensive pain limiting the patient's mobility, as shown by the case report above.

Of great interest is also the frequent DISH association with diabetes mellitus and the metabolic syndrome. Investigations of potential direct effect of hyperglycaemia and hyperinsulinaemia on the development of heterotopic ossifications are under way. Further exploration of the role adipokines play in patients with DISH is required. Preventive measures as well as symptomatic treatment (pharmacotherapy, rehabilitation and physical therapy) are highly important components of the therapy.

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Senile Osteoporosis

24

Petr Broulík

Since 1994, osteoporosis has been defined as a progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

The most severe complication of osteoporosis are femoral neck fractures, requiring hospitalisation, that cause the patient's immobility and lead potentially to 10–20 % increase in patients' mortality during the first year after fracture. The most frequent cause of femoral neck fractures are falls. A total of 80 % of them can be seen in women, and 90 % of them are sustained by individuals older than 50 years. Forearm or wrist fractures are most likely to occur in women over 65 [1].

Bone is highly metabolically active throughout life, controls the calcium level in blood, helps maintain acid–base balance, creates space for bone marrow and has mechanical functions. Bone is a tissue with active metabolic turnover associated with its remodelling [2]. Bone resorption is induced by osteoclasts activated by proteins of the tumour necrosis factor family. Membrane osteoprotegerin ligand produced by stromal cells and osteoblasts binds to specific monocyte receptors (RANK). These activated osteoclast precursors respond by increased production of osteoresorptive cytokines interleukin I and tumour necrosis factor. Antiresorptive protein is osteoprotegerin which inhibits osteoclast maturation and causes their apoptosis. Of special importance are osteocytes, modified osteoblasts, housed in lacunae and connected with each other by canaliculi, as well as with the lining cells on the bone surface [7]. Osteocytes capture bone mass deformities (microcracks) similarly as a spider sensing vibrations of insect caught in its web. As soon as they detect a deformity, it is transferred to the lining cells on the bone surface, which differentiate into osteoblasts of cells responsible for new bone formation. It should be noted in this respect that bone metabolic turnover continues also in advanced age, although at a different level than in youth and adulthood. Pathological intervention in this process leads to metabolic osteopathy.

Aetiopathogenesis of osteoporosis (OP) varies and has multiple causes. In secondary osteoporosis, the causes are known and can be found in the underlying diseases of which secondary OP is a part. These include endocrine diseases (hyperthyroidism, hypercortisolism, hyperparathyroidism, hypogonadism), hereditary diseases (osteogenesis imperfecta, homocystinuria), chronic liver disorder, long-term immobilisation, diabetes mellitus, tumour diseases and iatrogenic osteoporosis.

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The term *primary osteoporosis* classically includes *idiopathic* and *involutional osteoporosis*. Involutional osteoporosis can be divided into postmenopausal and senile variety. In women, the dividing line between these two varieties is not quite clear, as the senile osteoporosis may directly follow the postmenopausal variety [9]. The study below is focused on senile osteoporosis only [10].

Senile osteoporosis (sometimes referred to as involutional) is characterised by patients' age (older than 65 years), gender (male–female ratio of 2:1), type of bone loss (trabecular, cortical), fracture pattern (involvement of both axial and appendicular skeleton, with the latter prevailing; proximal femur fractures are more common), increased serum immunoreactive parathyroid hormone, decrease in intestinal absorption of calcium and lower levels of active metabolites of vitamin D. Age-related factors in aetiopathogenesis of senile osteoporosis include low intake of vitamin D and reduced capacity to synthesise vitamin D in the skin of elderly individuals. At the age of 70, the activity of enzymatic apparatus of the skin synthesising vitamin D is up to ten times lower than in young individuals. With increasing age, hydroxylation of vitamin D slows down, and resistance of target tissue to the active vitamin D metabolite calcitriol increases. Lower levels of active vitamin D metabolite lead to reduced intestinal absorption of calcium and hypocalcemia, stimulating production and release of parathyroid hormone (PTH) by parathyroid glands; the patients' levels of immunoreactive PTH (senile secondary hyperparathyroidism) are increasing. There occurs imbalance in bone remodelling in favour of bone resorption, with marked multiplication of resorption cavities and their inadequate filling with osteoblasts. Lack of vitamin D and its active metabolites also results in reduced muscle strength, up to four times in the quadriceps, and limited neuromuscular coordination. Endocortical resorption in long bones is not compensated by periosteal bone formation.

In the ageing process, bone is also adversely affected by decrease in production of bone anabolic peptides, such as growth hormone, insulin and insulin growth factor I, and adrenal steroids, such as dehydroepiandrosterone and androstenedione.

An important factor with a negative impact on bone mass is immobilisation, even if short term, when due to insufficient stimulation of bone mechanoreceptors, bone resorption prevails over bone formation. Elderly persons have often their joint apparatus damaged by degenerative diseases limiting their mobility, ability to walk and protracting periods of immobility, which are significant risk factors for development of osteoporosis.

Of great interest is the relation between blood circulation and bone metabolism. Ischaemia caused by ligature of the femoral artery in rabbits resulted in cortical thinning and reduction of the mechanical resistance of the bone. Laroche found atherosclerotic changes in interosseous arteries that were similar to those in coronary arteries [5].

Bones receive about 5 % of cardiac output. The size and shape of the completed Haversian system depends on the size and shape of the resorption cavity created by osteoclasts. A limiting factor for centrifugal resorption is most probably the demand of most remote cells for adequate supply of oxygen and amino acids and the possibilities of removing resorption waste. Of great importance for bone cells and their metabolic activity is regional blood flow. A group of women with compression fractures of vertebral bodies exhibited a higher incidence of ischaemic heart disease or ischaemic disease of lower limbs [4]. Calcification of atherosclerotic plaques increases with increasing age of patients. In addition, a group of women with compression fractures showed a higher number of atheroplaques in the aortic arch, visible on radiographs.

Prediction of femoral neck fractures is based on analysis of risk factors. Age is an independent risk factor for fractures. Risk factors for development of senile osteoporosis develop as early as in childhood. Peak bone mass is reached between ages 25 and 30 years. In 70 % it is determined genetically, and therefore it is always necessary to take into account also family history during examination. The remaining 30 % are influenced by the lifestyle in youth, i.e. smoking drug abuse, diet and physical activity. Other factors contributing to OP development include premature or induced menopause, mainly in terms of

protective effect of oestrogen on bone cell metabolism; thin or skinny figure with low muscle mass; low physical activity; sedentary lifestyle, or even immobilisation; chronic pulmonary obstructive disease; glucocorticoid treatment; and severe scoliosis. The cause is unknown, but it may be hypothesised that there is a correlation between connective tissue abnormality and development of both static and dynamic disorders of the spine [6].

24.1 Clinical Features

Clinical features largely vary. In extreme cases, osteoporosis may be quite asymptomatic and is revealed accidentally by radiographic examination. However, most frequently patients seek medical care for back pain, often pulling and nonspecific, which gets more intensive during physical activity, or prolonged sitting or standing and is eased by lying down or resting. Sudden sharp pain can be experienced after a quick movement, most often in the region of the lower and upper lumbar spine, which radiates forward into the abdomen and lower limbs. There may appear also reflex spasm of paravertebral muscles with radicular irritation. Vertebral spinous processes may be tender to palpation. Pain is caused by microfractures and later by compression fractures of vertebral bodies.

These fractures conduce to deformities of vertebral bodies, including depression of superior and inferior endplates of vertebral bodies (fish vertebrae). These changes result in graded thoracic kyphosis, absence of cervical lordosis and increased lumbar lordosis and the patient's height loss.

Osteoporosis often manifests itself as late as after a fracture following minor injury. The most feared fractures are those of the femoral neck, humerus and wrist. In elderly people, femoral neck fractures are a serious life-threatening complication [15]. Almost 20 % of patients die of urosepsis, pressure sores or hypostatic pneumonia. Surgery and the subsequent stay in the hospital are highly demanding in terms of costs, as well as the patient's stamina and rehabilitation. Clinical complaints may be manifested also as pain in prolonged standing, climbing stairs, difficulties with dressing, tying shoelaces and transition from lying to sitting position. In elderly individuals the condition is further complicated by combination of osteoporosis with degenerative changes of the spine, which makes a proper conclusion based on the patient's medical history even more difficult. Therefore it is important to take a detailed medical history, including radiographs of the thoracic and lumbar spine.

24.1.1 Examination of Senile Osteoporosis

The basic examination of patients with suspected OP includes tests for calcaemia, phosphataemia, calciuria, phosphaturia, immunoreactive PTH, TSH, creatinine and ALP with GMT in order to avoid underdiagnosing secondary osteoporosis [3].

Another part of the initial examination is radiography of the thoracic and lumbar spine that may reveal a whole range of degenerative changes in the spine, often explaining the pain syndrome, if present. A typical compression fracture indicates bone mineral density loss by more than 30 % and almost confirms the diagnosis of osteoporosis.

As for specific biochemical indicators of bone resorption, the most important is currently the serum C-telopeptide collagen degradation product. Under the condition of normal renal functions, bone formation indicator is the bone isoenzyme of alkaline phosphatase or osteocalcin. The disadvantage of biochemical parameters is their considerable inter- and intraindividual variability. Where osteoporosis is not clearly shown by radiography or where patients are examined for the effect of antiresorption medications, bone densitometry may be performed using DEXA Lunar or Hologic devices.

BMD decreases with the patient's increasing age, 50 % of women in 70–79-year age group have T-score of bone density in the femoral neck less than –2.0 SD and at the age of 80 years and more their number increases up to 70 %. In patients over 75 years, Z-score rather than T-score should be taken into account. However, experienced osteologists do not focus merely on densitometry that

may be associated with a number of errors (degenerative changes in the spine) especially in the region of the L-spine, but assess all indicators of the disease, including the patient's habitus.

In elderly patients, the predictive value of densitometry assessment of the proximal femur is much higher. BMD measuring of the proximal femur and femoral neck has shown that a higher incidence of fractures in these locations is associated with a lower BMD value. Although there are not many longitudinal studies measuring BMD in the elderly, it seems that in some patients, loss of the cortical, and perhaps also trabecular, bone stops after the age of 70.

Elderly patients with senile osteoporosis should be diagnosed on a case-by-case basis, as in advanced age, a number of severe degenerative changes can be found in the spine concomitantly with osteoporosis that may play a significant role in explaining the patients' complaints [13].

24.1.2 Treatment of Senile Osteoporosis

The treatment of involutional osteoporosis is currently much more effective in prevention of bone loss than in its restoration. Treatment of elderly patients is less effective than in the young individuals. Data on treatment of osteoporosis reported in the literature relate almost exclusively to the population younger than 75 years. It should be noted that the speed of loss of the cortical and trabecular bone changes with increasing age, and its response to treatment varies. Trabecular bone is metabolically more active than cortical bone, and therefore its response to treatment is different [8].

Treatment of senile osteoporosis should be focused on the control of senile secondary hyperparathyroidism by administration of vitamin D and calcium. Patients receive vitamin D3 Vigantol, either in drops (14–20 gtt once a week) or injections of cholecalciferol (vitamin D2) 300,000 IU i.m. once a month that have proved to be more effective as they are more regular and better absorbed. In case of drops, there is a danger of forgetting to take a dose and of worse resorption [11]. The given protocol of administration of vitamin D prevents overdosing because it has been demonstrated that the level of active vitamin D 25(OH)D3 is extremely low in the elderly. The optimum dose of vitamin D3 in the elderly is 800 IU per day. Administration of vitamin D may probably prevent fractures in the elderly. Therefore it is recommended to administer vitamin D to seniors. In addition, it is necessary to ensure the daily intake of calcium, i.e. at least 500–1000 mg of elemental calcium per day. These requirements are met by a number of preparations available in the market. Calcium administered in several doses during the day is better absorbed. Some polymorbid patients may have problems with calcium intake (intolerance, constipation, lack of appetite). This condition may be addressed by food high in calcium, e.g. 500 ml of milk containing about 500 mg of calcium, 100 g of cheese with about 750 mg of calcium and two white yoghurts with about 500 mg of calcium. It is also possible to combine calcium supplements with foods rich in calcium. Calcium carbonicum requires an acidic environment and therefore is administered during meals (caution is necessary in case of administration of blockers of H2 receptor or proton pump!).

Certain cases of severe osteoporosis with pain syndrome were successfully treated with intravenous injections at the dose of five vials of 10 % calcium gluconicum with one vial of Quajacuran or Tramal. The cycle includes up to ten such infusions. Combined administration of 1200 mg of calcium per day with a physiological dose of vitamin D3 significantly decreases the incidence of non-vertebral fractures, including proximal femur fractures, in individuals older than 75 years.

It is also possible to use osteogenon which contains both inorganic (hydroxyapatite) and organic (ossein) components. A similar preparation, made from eggshells, is Biomin H.

The above-mentioned preparations together with specialised rehabilitation, exercises, massage and iontophoresis are essential tools in treatment of senile osteoporosis. Of no less importance is a proper diet with adequate amount of proteins. People with positive protein balance heal much better following surgery, such as total hip replacement.

A high intake of salt increases calciuria values, similarly as excessive intake of proteins. A diet rich in salt and animal proteins may increase the patient's calcium requirement.

A favourable effect of rehabilitation and bone loading exercises is explained by irritation of bone cells responsible for bone formation, namely, by electrical current induced by activation of bone crystals. These crystals are bent and pulled by pressure and pull of muscles during exercises. Another favourable effect of exercises is remodelling of bone trabeculae in the direction of the highest loading. Elderly patients experience especially in the region of an osteoporotic bone affected by microfractures muscle spasms that cause pain syndrome. Therefore exercises are aimed at relieving painful muscle spasms. Cross-sectional and prospective studies demonstrate that physical activity increases bone mass. It is imperative to prevent falls. About 30 % of persons older than 65 years and 50 % of persons older than 80 years fall at least once a year. A total of 90 % of all proximal femur fractures are caused by fall. It is necessary to control factors leading to falls, i.e. gait and stability disorders (arthropathy, peripheral neuropathy, impairment of the ocular or vestibular system), postural hypotension (treatment of hypertension by diuretics), arrhythmia and the use of hypnotics, sedatives, anxiolytics and antidepressants.

Hormone therapy should not be used in senile osteoporosis, as recommended by the recent WHI study. In elderly women there occurs pain in atrophic mammary gland, proliferation of atrophic endometrium with bleeding; the risk of ischaemic heart disease, phlebothrombosis, hypertension and stroke is increasing.

Reasonable doses of anabolics have proved to be beneficial in senile osteoporosis. They considerably strengthen the muscle corset of the axial skeleton, and their androgenic component has a favourable effect on osteoblasts.

A certain role is played also by their euphorising effect. Unfortunately, they are not currently available in the Czech market.

The range of medications that may be used to treat more severe forms of osteoporosis with compression fractures include antiresorptive drugs – bisphosphonates. Currently the market offers second-generation bisphosphonates – alendronate sodium, and third-generation bisphosphonates – ibandronate and zoledronate will be shortly available. These medications have a powerful antiresorptive effect targeted directly at osteoclasts, resulting in marked decrease of bone resorption, increased density and significant reduction of fractures of the axial skeleton, but primarily in the region of the proximal femur. Bisphosphonates are the only antiresorptive preparations; the effect of which on femoral neck fractures was demonstrated by the respective studies. With appropriate administration they have only a minimum of side effects confined to the upper part of GIT [16]. Only rarely there may occur jaw necrosis or pathological fractures in immunocompromised patients. Currently, it is possible to administer bisphosphonates once a week or even once a month, which considerably decreases the incidence of adverse gastrointestinal effects.

In senile osteoporosis with compression fractures, the basic treatment may be combined with administration of these highly effective preparations. However, such a decision requires a good knowledge of the patients in terms of their ability to comply with the prescribed use of medications and of their other comorbidities that should not be so severe to decrease the therapeutic efficacy of bisphosphonates. The approach must be strictly individualised, based on the knowledge of the patient's medical history, social status, possible polymorbidities, hearing and sight abilities and finally the ability to adhere to therapy [14].

Strontium ranelate is an antiosteoporotic drug with an innovative dual mechanism of action combining the osteoanabolic and antiresorptive effect. It increases bone formation with a simultaneous decrease of bone resorption. Up to 30 % of fractures are sustained by a specific population of women older than 80 years. Clinical data available in relation to this group demonstrate antiosteoporotic effect and prevention of both vertebral and non-vertebral fractures provided by strontium ranelate [12].

Another drug that can be used to treat senile osteoporosis is raloxifene. This selective blocker of oestrogen receptors has antiresorptive effect

on bone, reduces the incidence of new fractures in the region of the spine and increases bone density. It decreases low-density lipids, prevents breast cancer and significantly reduces endometrial height. Similarly as estrogens, it may induce phlebothrombosis. The patient's condition should be assessed in order to estimate if the drug may achieve the expected effect.

Intermittent administration of teriparatide, a synthetic recombinant fragment of human parathyroid hormone, increases bone mass. This drug stimulates preferentially osteoblasts and this activity prevails over its stimulation of osteoclasts. It is indicated in postmenopausal women at high risk of fracture and women with a severe osteoporosis with compression fractures, unresponsive to treatment with other medications.

A new successful drug is also denosumab, a monoclonal antibody blocking RANKL-RANK interaction. Its efficacy has been verified by a study focused on treatment of osteoporosis in elderly patients [17].

Another antiresorptive drug is calcitonin. Its administration reduces in the long run the incidence of new fractures of the axial skeleton. The PROOF study demonstrated that calcitonin taken for the period of 2 years reduced the rate of new fractures of vertebral bodies and had analgesic effect. Due to certain adverse effects, it is no longer used to treat osteoporosis.

In addition to the above-mentioned drugs, it is important for the patients to follow the rehabilitation plan, including exercises to strengthen lower limb muscles and to improve gait and postural stability. Elderly patients should be adequately informed about all environmental safety hazards in their homes, particularly in the bathroom, leading to potential falls.

It has to be taken into account that individuals aged 80 and more are highly susceptible to fractures resulting from falls, even if they receive adequate treatment. The risk of fracture of the arm, forearm, femoral neck or vertebral body increases between the age of 45 and 85 years eight times in women and five times in men. Pain caused by both osteoporosis and degenerative changes of the spine or weight-bearing joints should be managed by a reasonable analgesic therapy that should relieve pain without affecting the patients' mobility and sense of orientation.

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Nutrition and Osteoporosis

25

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Nutrition in treatment of osteoporosis is currently in the centre of attention of research activities as it contributes to bone quality throughout the whole life, during bone maturation as well as in adulthood. In addition to common therapeutic procedures consisting in pharmacological interventions, nutrition plays one of the key roles in treatment of advanced osteoporosis.

This issue is paid increased attention because it is one of the three main factors for achieving peak bone mass at the age of about 25 years. Up to 80 % of peak bone mass is determined by the first factor, i.e. genetic predispositions, which cannot be influenced. The second factor is physical activity during growth stage which has an essential impact on bone mass acquisition and bone quality. Bone loading is the main stimulus for bone regeneration. Regular physical activity during all phases of life is beneficial for bone mass accrual and skeletal health. The third factor is a proper nutritional status during the whole life. This factor becomes even more important in advanced age as osteoporosis is one of the common diseases in the elderly population, affecting predominantly the group of postmenopausal women.

Another group where nutrition plays essential role comprises patients who developed osteoporosis in association with another disease which has a negative impact on bone. This is so-called secondary osteoporosis. The underlying causes include drug-induced osteoporosis, mainly after long-term use of corticosteroids, celiac disease and lactose intolerance.

Nutrition serves not only as the basic source of energy, but it is decisive also for other processes and bone quality. The basic components of nutrition that influence bone quality include adequate intake of calcium and vitamin D and a balanced intake of proteins, vitamins and trace elements [1].

25.1 Calcium

Calcium (Ca) is the basic building component of bones, and its daily intake should be about 1000–1500 mg depending on age. Ca absorption rate achieves 75 % in childhood and 30–50 % in adulthood and decreases with ageing. It is promoted by the proper level of hydrochloric acid in the stomach, adequate vitamin D level, lactose in food and the proper Ca/P ratio in the diet. The most common Ca sources include dairy products, the absorption rate of which, however, ranges

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only around 30 %, while in vegetables, such as cauliflower, broccoli, kale, watercress, the absorption rate exceeds 50 % [2].

25.2 Vitamin D

Vitamin D is essential for Ca absorption in the small intestinal loop through active transport mechanism. Adequate absorption of calcium prevents development of secondary hyperparathyroidism and decreases bone resorption. Achievement of optimal vitamin D levels requires sunlight exposure, as vitamin D is activated mainly through skin (80–90 %). In our geographical location zone, two sun exposure units (30 min) weekly are recommended. It has been demonstrated that during autumn, winter and spring most people in our geographical location have low levels of vitamin D. Particularly the housebound elderly have very limited sun exposure, and natural generation of vitamin D is therefore considerably limited. For this reason, supplementation is recommended during winter months (400–800 IU/d), which equals 2 drops of Vigantol per day, or 20 drops once a week. Vitamin D supplementation reduces the risk of fractures from falls and improves the function of lower limbs in the elderly.

Research has recently focused also on extraskeletal effects of vitamin D, such as the proved reduction of incidence of tumours, decreased prevalence and severity of autoimmune diseases (multiple sclerosis, arthritis, juvenile diabetes mellitus) and neuroprotective effect – reduction of the risk of neurodegenerative diseases and blood pressure reduction [2, 3].

Natural foods high in vitamin D include mainly fatty fish and seafood that account for about 20 % of available vitamin D. Vitamin D is currently provided also through food fortification (milk, butter, etc.).

25.3 Proteins

Bone matrix is composed predominantly of proteins, such as osteocalcin and collagen. Recent studies have investigated impact of diet on internal environment in direct association with protein intake and a higher share of animal proteins at the expense of plant proteins. Foods can be categorized by the potential renal acid loads (PRAL), as having relatively high acid loads, meats, sugar, hard cheese and fish; neutral acid loads, cereals, grain products, rice and milk; and a negative acid load, fruits and vegetables. It has been proved that proteins increase endogenous production of acids, and, vice versa, plant-based diet contains potassium salts with anions of organic acids (metabolizing after intake into bicarbonate and thus alkalizing internal environment). Increased endogenous production of acids (excessive consumption of meat and proteins) then results in chronic low-grade metabolic acidosis. Buffering of this acidic pH by the alkaline calcium salts in the skeleton leads to bone loss. As a result, long-term diet high in proteins gradually decalcifies bones by the above-mentioned mechanism. For this reason it is recommended to limit reasonably proteins in diet in favour of vegetables.

Lack of proteins results in malnutrition and has an impact on both the peak bone mass and maintenance of bone quality in adulthood. In our population, such deficiency relates only to severe conditions [2, 3].

25.4 Fats

Currently, attention is focused on omega-3 and omega-6 fatty acids. A positive influence has been proved of omega-3 fatty acids on bone for their anti-inflammatory effect, on reduction of bone resorption, improvement of intestinal calcium absorption, increased rate of Ca deposition in bone and increase in bone collagen. Omega-3 fatty acids are found primarily in fish fat and certain plant oils (olive, rapeseed, linseed, etc.).

25.5 Fruits and Vegetables

The alkalizing effect of fruit and vegetables on homeostasis of internal environment in the organism has been known for a long time. Plant-based diet contains potassium salts with anions of organic acids, metabolizing after intake into bicarbonates

and thus alkalizing internal environment. For thousands of years, people had been eating food lower in Na and higher in potassium salts; while at present, our food is rich in acidifying sodium chloride, with potassium salts almost absent in animal products and cereals. In addition, fruits and vegetables contain a wide range of vitamins and minerals, antioxidants and many other bioactive substances having a positive effect on bone [2, 3].

25.6 Vitamins and Trace Elements

In terms of bone metabolism, one of the most important is vitamin K and certain other elements. Vitamin K1 positively influences osteocalcin production; it is involved in osteoblast induction, inhibition of osteoclast production. Its deficit results in decreased bone mass density (BMD) and increased risk of fractures. Vitamin K1 (phylloquinone) is contained primarily in green, leafy vegetables, olive oil, cheese, the liver, soya beans, cereal sprouts, broccoli, cauliflower, green tea, etc.

The newly discovered vitamin K2 (menaquinone MK4, MK7), which is contained in soya beans fermented by bacillus subtilis natto, is used as a traditional supplement of the Japanese food. It activates osteocalcin, Gla protein; it reduces Ca excretion, bone resorption, and has a positive effect on BMD.

In addition, certain positive effect has been proved of vitamin B6, vitamin B12, vitamin A, magnesium, trace elements of zinc and selenium, copper, manganese and boron. Recent investigations have focused on another trace element, strontium, and its osteoblastic and antiresorptive effect. Strontium can be found in water and soil (0.01–0.45 mmol/l) and certain foodstuffs (0.023–0.046 mmol/l). It has a complex effect on bone apatite crystals and has affinity for dental tissue. In general, strontium is contained in spices, seafood, whole grain bread, root and green, leafy vegetables and legumes [2, 3].

25.7 Balanced Diet

Based on the above given facts, the following basic principles of balanced diet have been recommended by WHO (Fig. 25.1). This diet should comprise about 15 % of proteins with prevalence of fish and white meat. The ratio of fat should be 30–40 %, with preference given to unsaturated fatty acids. They include plant oils, such as olive, rapeseed, linseed oil and nuts. Of animal fats, fatty fish is recommended for a high content of omega-3 fatty acids. Carbohydrates should prevail in a balanced diet, up to 45–55 %, mainly in the form of vegetables, fruits, legumes and fibre-rich foods with low glycemic index (rice, whole grain pasta, potatoes) [4, 5].

General and nutrition factors preventing development of osteoporosis, including major risk factors:

- *Age* is a major risk factor – osteoporosis is common in advanced age when the supply of all nutrients often becomes limited and one-sided – insufficiently varied diet.
- *Underweight in youth* (BMI 18.5) – mental anorexia and long-term psychiatric disorders.
- *Alcohol* – excessive consumption has a negative impact on bone.
- *Weight reduction diets* causing underweight, primarily in young individuals, have a negative impact on BMD (bone mass). Strict diets result in imbalanced and one-sided supply of nutrients. Low body weight may result in inadequate loading of bone, which is the main stimulus for its regeneration.
- *Acidifying effect* on internal environment is associated, for instance, with consumption of sugar-sweetened soft drinks (coca-cola, etc.), excessive intake of proteins, salt and caffeine – more than five cups of coffee daily (with excessive amount of sugar).

In terms of nutrition and its effect on bone, it is important to know that:

- A lifelong balanced diet is a prerequisite for healthy bones, similarly as a healthy lifestyle with a focus on factors improving bone quality (mainly physical activity) and elimination of risk factors.
- An organism needs sufficient supply of vitamin D: optimal annual level should be

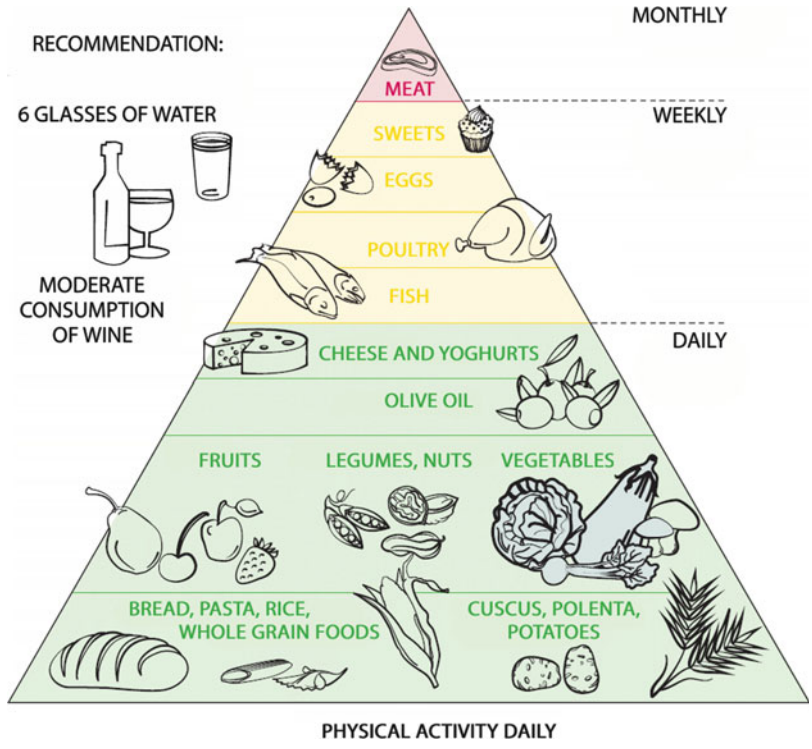

Fig. 25.1 Composition of a balanced diet (According to WHO)

achieved through sun exposure, food fortification and regular consumption of fatty fishes or supplements.

- Introduction of vitamin K2 in the treatment of osteoporosis in future, a balanced sodium-potassium ratio in the diet and adequate supply of trace elements, such as magnesium, zinc, selenium, copper, boron, and strontium, in a varied diet is a way to prevent osteoporosis.

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Neck and Shoulder Pain

26

Marie Sedláčková

26.1 Incidence

Shoulder pain is a highly frequent regional syndrome, the frequency of which significantly increases with increasing age. Smith and Campbell reported in 1987 that shoulder discomfort is the third most common reason for visits to primary care physicians in ambulatory practice. This report raised immediate response of a number of authors presenting other data, overview and prospective studies with quite different figures [1–3]. According to a high-quality prospective study published by Dutch authors [1], 11 general practitioners studied the incidence of painful shoulder. They registered 35,150 patients and found the incidence of 11.2/1000 patients/year. Bamji et al. set annual prevalence of painful shoulder at 2.36 % and incidence at 1.47 % on the basis of examination of 9215 cases of 658,469 registered patients. Similar statistic data is reported also by other authors [4]. We support the latter statistics.

What is the cause of this difference and what is the actual frequency of this painful condition?

26.2 Definition

The main pitfall both in terms of statistics and practice is the way of defining a "painful shoulder".

Shoulder pain may be caused by local structures within or around the joint or may be referred from other sources. Intra-articular disorders include acute or chronic inflammation or another lesion of the joint, tendons of surrounding ligaments or periarticular structures, as well as post-injury changes – i.e. the actual "painful shoulder", which accounts for a smaller number of painful conditions located in this region. External factors are more numerous. In addition to vertebrogenic pain, the frequency of which significantly grows with increasing age due to progressive degenerative changes of the spine and other paravertebral tissues, including nerves, pain may be caused also by functional changes affecting the joint mechanics (e.g. hemiplegic shoulder, spine and rib blocade, pathological position of the scapula and spasms of scapular muscles, etc.), and pain may radiate into the shoulder in case of pulmonary, subphrenic or abdominal pathology. Trauma and posttraumatic conditions are a separate chapter under the responsibility of orthopaedists and surgeons.

How to distinguish the actual "painful shoulder" from other disorders? The clue is so-called articular (= capsular) pattern of restriction of the shoulder range of motion. According to this pattern, any internal disorder of the joint is compensated by such a position of the joint that

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minimises the intra-articular pressure in the joint capsule. In order to achieve this goal, the organism reflexively activates or inhibits periarticular muscles.

In the shoulder, this pattern is characterised primarily by restriction of external rotation and abduction and gradually also of flexion.

26.2.1 Diagnosis of the Origin of Pain

A disorder causing pain in the cervicobrachial region is often hard to detect and the source of pain is difficult to define. A major contribution to the method of detection of the source of pain was made by experiments of Cloward, Feinstein, Dwyer and Dreyfus [5, 6], who by irritation of various structures of the cervical spine in healthy volunteers (intervertebral discs, short musculoligamentous structures and intervertebral joints) obtained data about cutaneous radiation of pain from strictly defined structures (Fig. 26.1).

As shown by figures, certain sites of cutaneous radiation of pain during irritation overlap. In addition, long-term irritation results in the activation of spinal neurons and diffusion of signal at the spinal cord level, which complicates detection of the exact source of pain based on this single indicator. The given findings can, however, help determine at least approximately the level of involvement, on which clinical examination, imaging methods and ultimately the therapeutic efforts should be focused, without wasting efforts at nonspecific attempts to treat a "painful shoulder".

26.2.2 Acute and Chronic Pain

A painful condition is regularly associated with a significant limitation of mobility of the affected region, impairment of the quality of life and restriction of self-care activities, which often turn into chronic condition. For clinicians, the concept of chronic pain is rather associated with its duration (pain persisting for more than 4–6 weeks), while physiologists and algesiologists perceive it as a manifestation of inability to control sufficiently and efficiently the respective disorder or pain caused by it, i.e. as a manifestation of central fixation of pain pattern, with unfavourable prognosis.

The opinion supported by algesiologists that chronic pain is a separate entity has not been generally accepted. It is a symptom of a condition which has a certain cause and develops in a certain way. In the authors' view, it is important to find out the share of the initial, underlying process in long-term pain, as it is closely related to the essential issue, how long it is reasonable to attempt at (using, where appropriate, also non-pharmacological treatment) controlling the underlying process and when and how to combine these procedures with purely analgesic therapy, in order to manage adequately the respective disorder.

Due to close relationship between the neck and shoulder, which is given primarily by common innervation (joint capsule, skin, subcutis and muscles of the shoulder are innervated mainly from C5, C6, and C7 nerve roots – see Fig. 26.2) as well as by muscles connecting the cervical spine and the shoulder girdle, this region is called cervicobrachial, and the pain affecting this region is referred to as cervicobrachial regional syndrome.

26.2.3 Defined Entities

Of this "mixed category", certain well-, or at least better, defined entities may be separated, such as:

- *Cervical radiculopathy* (irritation). It is characterised by radicular radiation of pain, neurological finding of iritation or failure of the given nerve root, with pain culminating at night. Pain caused by damage of C5–C8 radiates into the neck, shoulder and arm (Fig. 26.2).
- *Lesion or disease of the brachial plexus or spinal cord*: requires a detailed neurological assessment, including electrophysiological examination and other supportive methods. Care of this and the previous conditions is the responsibility of neurologists and physiotherapists.
- *Painful shoulder syndromes "Milwaukee shoulder" and "frozen shoulder"* are diagnosed,

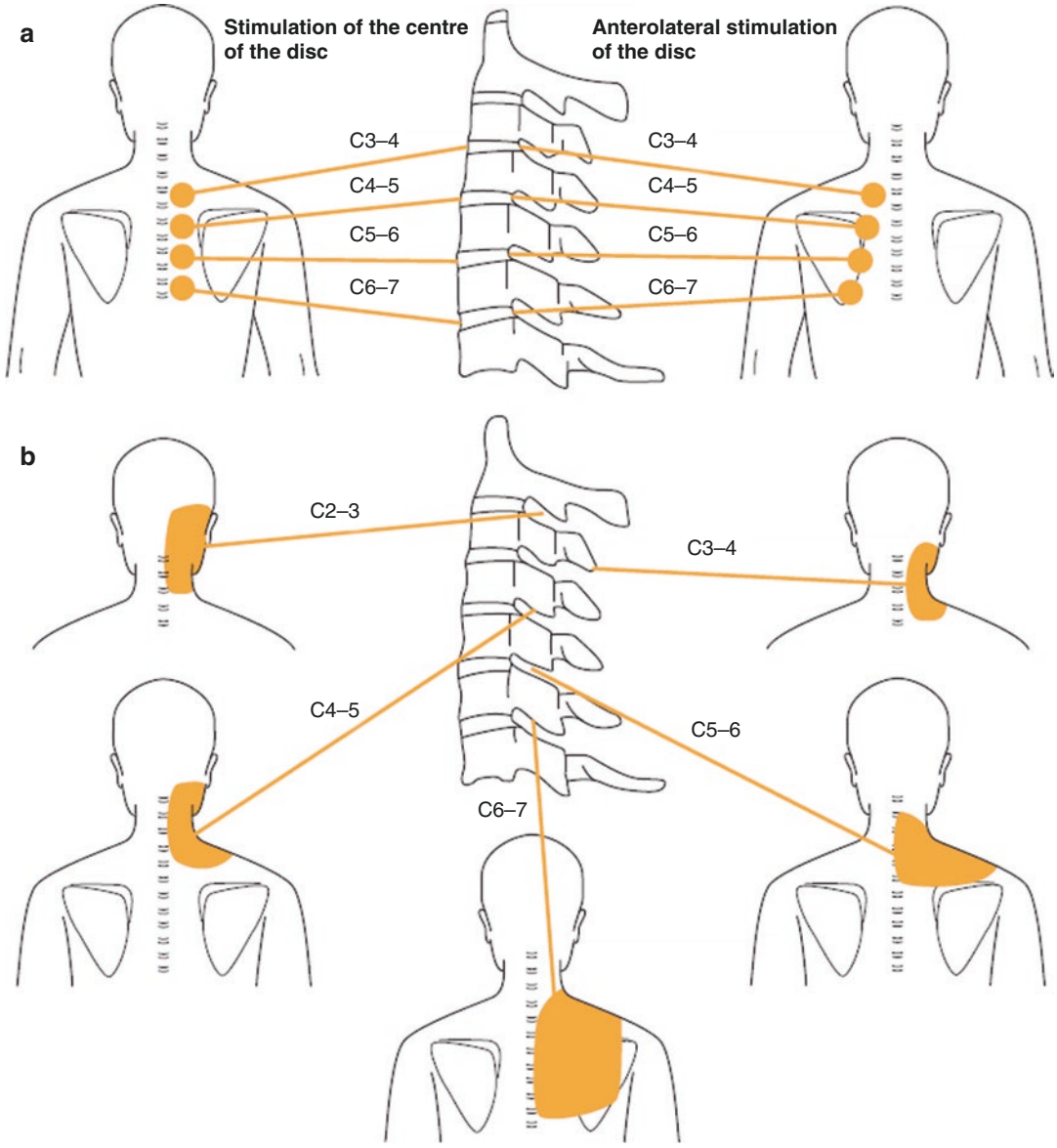

Fig. 26.1 Cutaneous radiation of pain during irritation of individual structures. (**a**) Radiation of pain during irritation of intervertebral discs (Modified after Cloward); (**b**) radiation of pain during irritation of deep musculoligamentous structures in interspinous space (Modified after Feinstein) [6]

specified and treated by rheumatologists, orthopaedic surgeons or physiotherapists.

- *"Milwaukee shoulder"* is an entity found almost exclusively in the elderly population. Clinical features include the presence of massive, often hemorrhagic effusions in one or both shoulders which, however, are not inflammatory (confirmed by cytologic examination of joint effusion) and almost do not respond to local application of steroids. Effusion contains hydroxyapatite microcrystals, moving freely in the joint space and tendons (McCarty) (Fig. 26.3), as well as a big amount of enzymes, collagenases and neutral proteases which destruct periarticular soft tissues and often result in tear of the

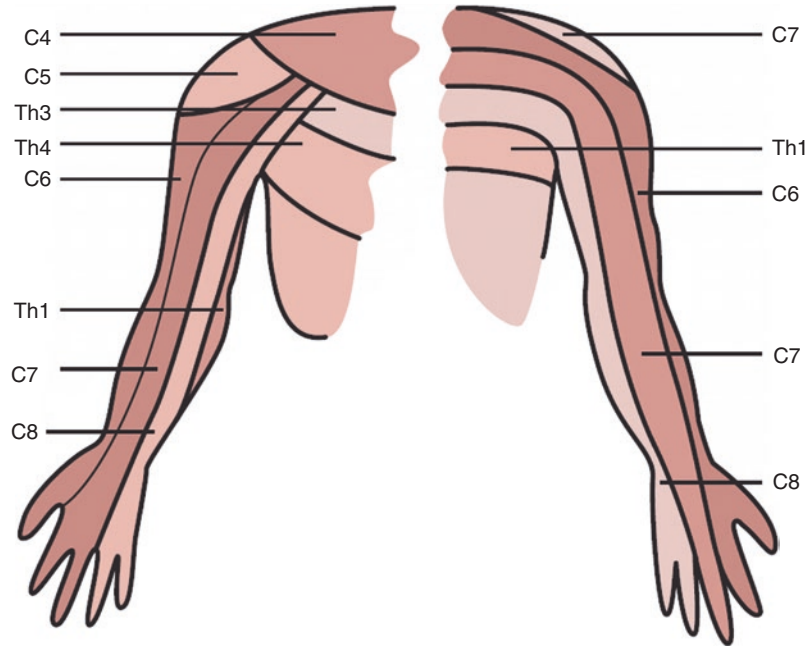

Fig. 26.2 Map of radicular innervation of the neck and arm. (Left front view, right rear view)

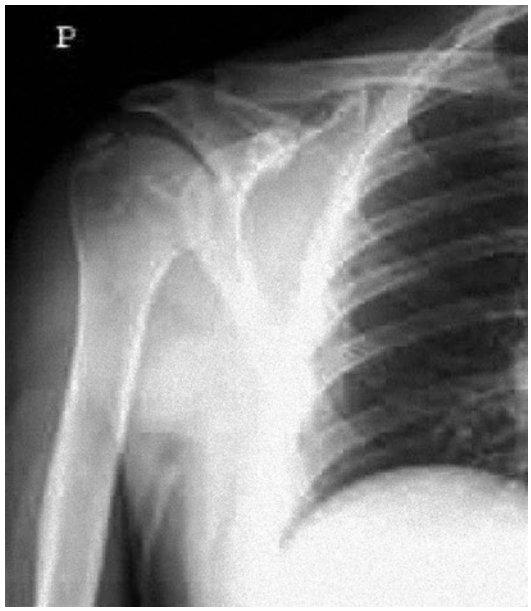

Fig. 26.3 Radiograph of calcification of the supraspinatus tendon

rotator cuff and subchondral osteolysis of the humeral head. The process is relatively painless, and thus the patients seek medical care only in the late stages of the disease when the joint is already severely damaged.

In terms of therapy, this condition is hard to control. We have achieved good results with application of radioisotope (yttrium, rhenium) in the affected joint. The cause of this disorder is unknown.

- *"Frozen shoulder"* is a manifestation of chronic unspecified capsulitis of shoulder, affecting predominantly diabetic patients and patients with disorders of the thyroid gland function. This type of inflammation is initially highly painful and later results in joint capsule fibrosis and more or less limited range of motion.

The disease often heals with a functional handicap [7].

- *Shoulder arthritis.* It is also manifested also by so-called capsular pattern of restriction of movement. It should be examined by rheumatologist for potential borrelia infection developing systemic disease and crystal arthritis and for exclusion of arthritis bacterial in ori-

gin. Bacterial infection is usually accompanied by fever and high general inflammation parameters (ESR, CRP) and should be treated by orthopaedic surgeons.

Elderly patients often experience degeneration and *spontaneous ruptures of muscles*, tendons and bursae in the region of the shoulder (Fig. 26.4). The most frequent is rupture of the long head of the biceps tendon in its intra-articular course (in the bicipital groove on the anterior aspect of the humeral head) or of its part and rupture of the subdeltoid or subacromial bursa. A simple clinical sign of rupture of the biceps tendon is pain on the anterior shoulder and a newly identifiable elastic resistance within the muscle belly. In case of complete rupture, patients are not able to perform arm flexion with hand in supine position. Muscle ruptures are diagnosed by sonography and in case of doubts, MRI is indicated. Elderly patients with this condition are treated predominantly non-operatively; they mostly develop alternative mobility stereotypes.

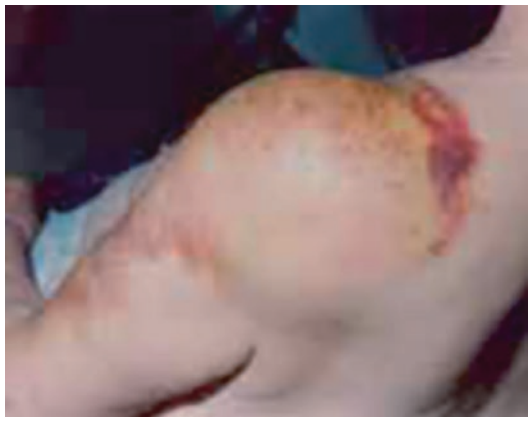

Fig. 26.4 An 82-year-old woman after spontaneous rupture of the subacromial bursa and rotator cuff

Rupture of the rotator muscles (partial or complete) is quite common in this age group, mostly after a longer period of exacerbating pain of the impingement syndrome nature primarily painful and limited abduction and flexion of the arm with hand in supine position, which signals marked degenerative changes in rotators and failing function of the rotator cuff. Failure of the cuff as a dynamic stabiliser of the humeral head position (Fig. 26.5) is accompanied by cranial subluxation of the humeral head with compression in the subacromial space (impingement syndrome). Long-term

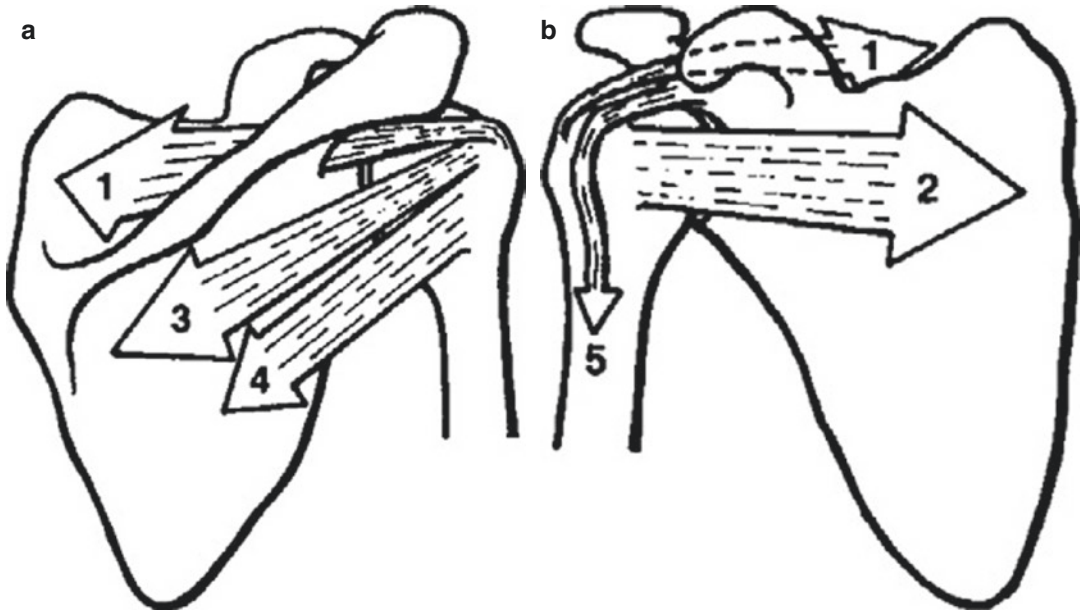

Fig. 26.5 Rotator cuff muscles stabilising the humeral head position. *1* Supraspinatus, *2* subscapularis, *3* infraspinatus, *4* teres minor, *5* the long head of the biceps tendon. (**a**) Rear view; (**b**) Front view

impingement causes severe degenerative changes in the glenohumeral and acromioclavicular joints – rotator cuff arthropathy.

- *Reflex sympathetic dystrophy*. Initially it affects the shoulder and later the whole arm. Its onset is influenced by still unexplained reflex mechanisms. It is believed to be associated with dysfunction of the central or peripheral nervous system. It usually follows a trauma, less often it results from an emotional stress situation. Clinical features are well known and include burning pain accompanied by increased temperature of the whole oedematous limb. Joints are swollen and their motion is painful (Phase I). Gradually there develop trophic skin changes, speckled osteoporosis, nail atrophy, localised hair loss, limitation of joint mobility and muscle weakness which are aggravating (Phase II). Phase III is characterised by irreversible changes on the skin and joints. The best results are ensured by early combined pharmacological treatment (analgesics, calcium, vasoactive medications) and suitable rehabilitation care (jacuzzi, soft techniques, exercises).
- *Rheumatic polymyalgia* has been dealt with in a separate chapter.
- *Thoracic outlet syndrome*. Diagnosis of compression of neurovascular bundle (Fig. 26.6) should be confirmed by a vascular specialist or a physician specialised in manoeuvres managing compressions (Adson's test, hyperabduction test, costoclavicular test, scalene test and Kelly's test).

The treatment is initially conservative; operative treatment is considered only in severe conditions and confirmed compression of the bundle by a defined structure – e.g. resection of the cervical rib.

- *Bone lesion – compression of the cervical vertebra, spondylodiscitis* (extremely rare in the cervical spine*), humeral head necrosis, neoplasms* and rarer *diseases of bone or nerve structures*. Suspicion or diagnosis is based on radiographic finding of unusual clinical features and usually requires additional imaging (CT, MR) and examination. Neoplasms may be associated with peripheral neuropathy, hypercalcaemia, other paraneoplastic manifestations (vasculitis, arthritis, neurological signs, etc.) or symptoms of a metastatic disease anywhere in the body.
- *Pain radiating from internal organs* (oesophagus, pharynx, trachea, lymph nodes, thyroid gland, aorta, heart, pericardium, lungs, diaphragm, mediastinum, duodenum) *or jaws*. Diagnosis is based on the patient's medical history, nature of pain, exacerbating or relieving factors and primarily on unlimited and pain-free mobility of the neck and shoulder.
- *Inflammatory muscle disease – polymyositis*. It is manifested mainly by muscle weakness of the girdle muscles; pain is not a dominant sign of the disorder. It is usually accompanied by elevated serum levels of muscle enzymes (CK, myoglobin) and myopathic EMG finding.
- *Other defined causes*, e.g. pain caused by *herpes zoster* may appear up to 1 week before the eruption of typical blisters. Fibromyalgia is characterised by multiple tender points and affects predominantly middle-aged and elderly

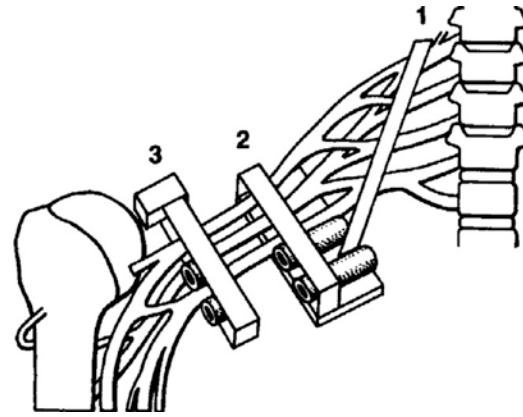

Fig. 26.6 Causes of compression of neurovascular bundle in the upper thoracic aperture. *1* Compression between scalene muscles, *2* compression in the costoclavicular space, *3* compression of neurovascular bundle passing beneath the pectoralis minor tendon [10]

women and is associated with other symptoms, such as insomnia and emotional instability.

26.2.4 Nonspecific Cervicobrachial Syndrome

A large part of patients, however, does not fit in the clinical presentation of these defined entities which may be called a *nonspecific cervicobrachial syndrome (NCBS)*. Several population studies were conducted in the north European countries. For instance, the Finnish authors [1] report lifelong prevalence of chronic cervicobrachial pain at 71 %, of which 41 % of patients complained of pain episodes in the last several months. Point prevalence is reported in 13.5 % of women and 9.5 % of men. Statistics of acute pain is not available due to difficult data collection.

Association was also investigated, of the frequency of cervicobrachial syndrome with other factors. A markedly positive association was proved in case of hard physical work; in persons with low education level (probably also manual workers) [2]; in conditions after neck injuries, primarily after whiplash syndrome (flexion-extension trauma of the neck); and in elderly persons suffering from depressions.

Surprisingly, positive association was proved in persons with defective posture (the reason may be also a rather vague definition of "defective posture").

However, it has been confirmed that long-term and repetitive flexed neck posture triggers pain in this region, most probably by stretching of intervertebral joint capsules [8].

NCBS is characterised by pain in the posterior neck, referring typically to one or both shoulders, arm, interscapular region or thoracic wall. Infrequently it radiates into the head and almost never exceeds the anterior border of the sternocleidomastoid muscles. Headache is most often present in pathology of the cervical spine extending from C3 proximally. Pain which is either radiating or resembles electrical impulses may indicate lesion of nervous structures.

The most severe complaints are caused by the presence of neurological symptoms, such as weakness and paresthesia or vision or hearing disorders reported by patients. In this respect, it depends whether these symptoms are associated with other defined neurological symptoms based on which the respective patient could be classified in one of the above-mentioned categories.

26.3 NCBS Treatment

There are not many relevant clinical trials that would allow objective assessment of effects of different therapeutic procedures. It seems [5] that manual techniques are slightly more effective than physical therapy or pharmacotherapy in NCBS treatment. A meta-analysis of these manual techniques showed that in acute disorders, mobilisation was more successful, while in chronic pain manipulation was more beneficial than mobilisation or other methods [5]. Based on practical experience, the most effective seems to be combination of these methods. In acute pain of the neck, it is recommended to introduce pharmacotherapy, relieve the acute condition by a cervical collar applied for a few days and then commence physical and/or manual therapy. The condition should be carefully checked after the commencement of the treatment for any pain exacerbation following physical and manual therapy. Beneficial measures include also choice of a correct pillow, adjustment of workstation and elimination of extended periods of extreme flexion.

26.3.1 Recommended Treatment of the Elderly

Due to specific conditions typical of advanced age, the American Geriatric Society published in 1998 comprehensive guidelines for management of chronic noninflammatory pain in older persons [9]. Selected general guidelines for chronic pain are listed below (Table 26.1). For the full text of the guideline, see the respective reference.

Table 26.1 Extract from the guidelines of the American Geriatric Society: additional recommendations for chronic pain management [9]

General principles of prescribing medications used to treat pain
Comprehensive pain assessment, including objective methods (questionnaires, VAS, etc.)
Scheduled administration of the drug is recommended. The as-needed approach should be reserved for episodic pain only
Use least invasive route of administration of the drug
"Start low and go slow" approach
Frequent patient's reassessment for dosage adjustment
Other medications used to manage pain
Creams and gels for local application or capsaicin as an adjuvant medication to treat mild and moderate pain
Local application of steroids
Tricyclic antidepressants (imipramine, nortriptyline, desipramine) and anticonvulsants (carbamazepine, gabapentin, valproic acid) may be useful in treatment of neuropathic pain
Non-pharmacological supportive treatment
Physical exercises and work therapy
Cutaneous mechanical stimulation (massage, worm or cold packs, pressure, vibrations)
Manipulative therapy, manual treatment and acupuncture
Psychological counselling
Psychotherapy
Meditation and relaxation techniques
Weight-loss programmes in obese patients

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Vertebrogenic Disorders

27

Ivan Buran

Elderly patients with back pain are often assessed merely in terms of the presence of arthritic changes, and they quite often hear that at their age, they have to get used to some sort of pain. The problems, however, arise from a complex etiopathogenesis and age-related factors. Vertebrogenic pain syndromes in the elderly are often associated with a number of factors, such as osteoporosis, atrophy of the gastrointestinal tract mucosa (and the resulting disorders of drug absorption and more frequent adverse effects of NSAIDs), blood count disorders, circulatory disorders, endocrinopathy, increased incidence of diabetes, vascular changes, bowel movement disorders, depression syndrome and arthritis. All these aspects should be taken into account in both the differential diagnosis and treatment of the vertebrogenic pain syndrome in the elderly.

27.1 Aetiopathogenetic Factors

27.1.1 Intervertebral Disc Disorders

These disorders may be of different degrees and types, reflected in clinical symptomatology.

The most frequent disorder is lumbar disc herniation of varying intensity. A relatively specific condition encountered in elderly patients is detachment of the fibrous ring from vertebral endplates, the so-called hard disc [1, 2].

One of the factors contributing to damage of the intervertebral disc is hypomobility (typical of older population) leading to disturbance of the "pump" responsible for optimal nutrition. By pressuring and releasing soft tissues, physical activity pumps the extracellular and extravascular fluid in and out of the disc. The affected tissue should be mobilized as soon as possible before active or passive movements induce pain.

Experimental findings have proved that the disc has a chemical potential for generation of pain and inflammatory response [3]. It has been found out that the pH of the nucleus of a painful disc shows acidity while pH of a degenerated but painless disc slight alkalinity [4].

This finding only highlights the fact that a diagnosis of these disorders cannot be established only on the basis of radiography.

27.1.2 Intervertebral Articulation

In young individuals, intervertebral articulation is recognized as a primary source of pain in about 15 % of cases; the frequency of its involvement grows with increasing age [5]. Due to the disorder of the disc and reduction of its height, articular surfaces get into contact and damage mechanically each other; the joint capsules and ligamentous structures become lax. The resulting

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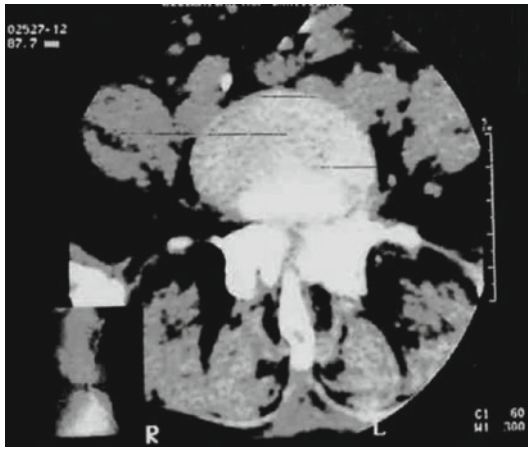

Fig. 27.1 Degenerative spinal canal stenosis

instability of the motion segment may cause displacement of the vertebrae in the sagittal and transverse planes. Attachments of paravertebral, primary autochthonous, muscles get closer, and as a result, they have a non-physiological length. The sclerotic adjacent parts of the joint are responsible for narrowing of the intervertebral foramen and the spinal canal (Fig. 27.1).

Arthritic changes often result in a different movement pattern than other spinal disorders. Movement is limited primarily in back and side bending, when articular facets get closer to each other. There may also occur claudication similar as in congenital spinal canal stenosis. Combination with vascular processes should be distinguished [6–8]. It is believed that degenerative changes sometimes lead to development of synovial cysts that may compress nerve roots [9].

27.1.3 Sacroiliac Joint

Disorders of this joint cause low back pain and occur often in association with lesions in other parts of the spine. Pain radiates to the S1 segment and to the groins (Fig. 27.2). The most common disorder is "mobility blocking" that does not always correlate with a radiographic finding and is detected by special tests. In men, it can be associated with the prostate disease [10, 11].

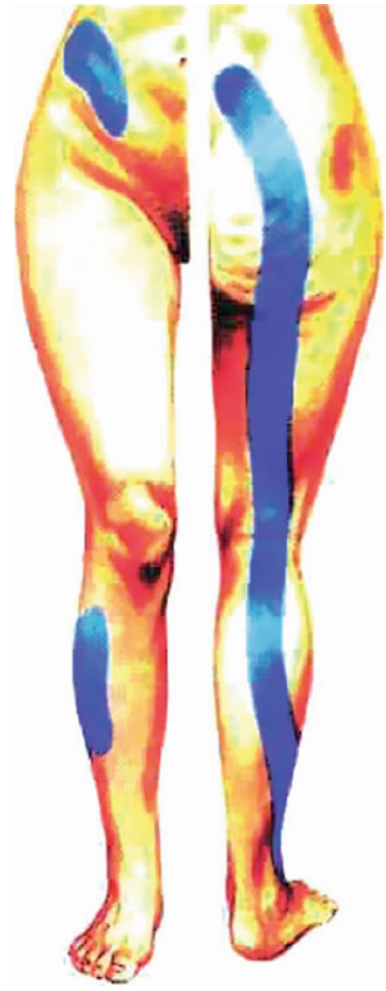

Fig. 27.2 Pain radiation in S1 lesion

27.1.4 Stabilization System of the Spine

Ligaments Ligaments alone cannot ensure the stabilization function in individual segments. Their attachments are a source of pain caused particularly by chronic overloading. The condition develops or exacerbates mainly as a result of the loss of muscle support. Discomfort increases in the evening or when the patient is tired; at rest the symptoms usually improve [12, 13].

Muscles Progressive age-related changes often combined with hypomobility and overweight

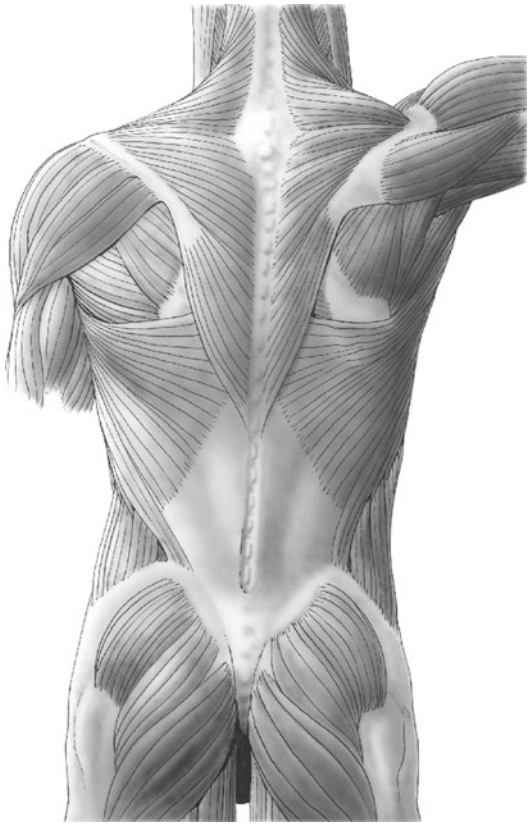

Fig. 27.3 Trunk muscles – dorsal muscles. *1* Trapezius, *2* deltoid, *3* infraspinatus, *4* latissimus dorsi, *5* aponeurosis lumbodorsal, *6* obliquus externus abdominis, *7* trigonum lumbale, *8* gluteus maximus, *9* teres major, *10* teres minor, *11* speculum rhomboideum, *12* sternocleidomastoideus (Courtesy of Grim et al. [32])

result in dysfunction of the muscular system and impairment of stabilization function of autochthonous muscles of the back and the diaphragm, pelvic floor and abdominal muscles.

Pain syndrome is as a rule associated with hypertonia of certain muscle groups and hypotonia in others. Hyperactive muscles are the source of pain which may generate painful irritation in the musculoskeletal system. There are two types of muscle activity during spinal movements.

Long superficial muscles of the back serve to move individual parts of the spine, but they do not ensure stabilization of two neighbouring vertebrae (Figs. 27.3, 27.4 and 27.5) [14, 15]. The deep stabilizing system is exposed to atrophy from inactivity, and in advanced age, this is accentuated by involutional changes. The stabilization system of the spine includes also the diaphragm and pelvic floor muscles, as well as lateral abdominal muscles that function as antagonists and synergists of the posterior muscles of the back [16–18].

Hypoventilation Pain syndrome is characterized by non-physiological breathing and decreased tone of abdominal and pelvic floor muscles (often associated with obesity), especially in the elderly. Activity in the area of axial organs as well as movements of the limbs require fixation of spinal segments. A significant role in spinal stabilization is played by the diaphragm.

Electromyographic studies have proved that regardless of the breathing phase, contraction of the diaphragm precedes limb muscle activity [19, 20].

Muscle dysfunction is treated by targeted rehabilitation, an integral part of which is training of proper breathing.

Lower Limb Joints Monitoring of the muscle activity in the standing position has revealed that the most marked activity takes place in the region of muscles controlling the sole and toes (Fig. 27.6) [21, 22]. Mobilization of lower limb joints should be an integral part of a comprehensive treatment of both chronic and acute complaints, especially in advanced age. Lower limb joints get blocked due to hypomobility as well as due to weight-bearing stereotypes, such as walking on the same type of ground (asphalt, pavement). Removal of the block restores function also in more remote regions.

Fascia By its elasticity, fascia controls reasonable activity of muscles; its stiffening limits muscular activity (similarly as tight-fitting clothes does not allow maximum range of motion). Age-related alterations are observed not only in the fibrous structures of the disc but also in ligaments and fascia; their biochemical structure changes, and they get stiff. The fascial layers that are supposed to glide over the underlying structures start to stick and drag. Therapy consists exclusively in rehabilitation.

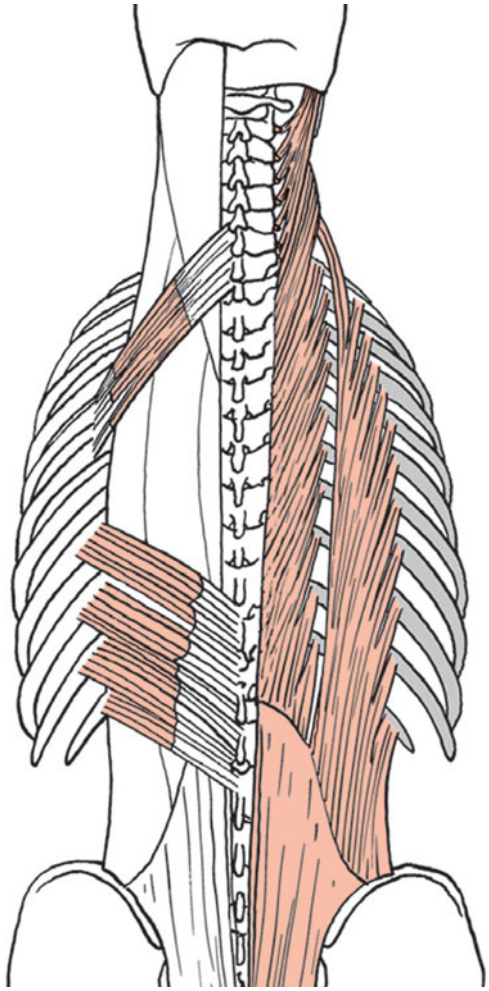

Fig. 27.4 Dorsal muscles (*left*) and sacrospinous (*right*) systems. *1* Serratus posterior superior, *2* m. serratus posterior inferior, *3* iliocostalis, *4* longissimus thoracis, *5* longissimus cervicis, *6* longissimus capitis (Courtesy of Grim et al. [32])

27.1.5 Psychic Factors

Spinal pain is a complex of perceptual phenomena including sensory stimulation and psychosocial factors. Acute pain usually does not induce psychogenic response, while chronic irritation results in hypersensitization of impulses; the afferent impulse has a tendency to propagate to the related regions, not affected before [23, 24].

Chronic pain causes neurotic restlessness, anxiety, frustration and insomnia. Depression syndrome develops within 6 months of pain duration. Chronic vertebrogenic pain syndrome may be a manifestation of hidden depression [26].

27.1.6 Vascular Processes

A pseudoradicular syndrome, often in association with vascular changes – varicosity – is characterized by the Hunter's canal entrapment syndrome.

The point tender to palpation is about four fingers above the medial condyle of the knee. It is often an accompanying syndrome of vertebrogenic disorders [26]. Back pain in the elderly must be differentiated from potential abdominal aortic aneurysm which is usually asymptomatic for a long time. It may be associated with lower limb claudication, syncopic conditions and dizziness. Auscultation and palpation findings are positive in about 50 % of cases. Diagnosis should be confirmed by CT or MRI [27]. Reports are available of familial occurrence of abdominal aortic aneurysm and genetic linkage to chromosome 19q13 [28].

27.1.7 Osteoporosis

Abrupt onset of thoracic or lumbar pain is often the first manifestation of decompensated osteoporosis. Osteoporosis associated with fractures that lead to reduction of height of individual segments of the spine (Fig. 27.7) is responsible for bringing the lower chest margin close to the iliac wings and for problems caused by direct contact of the lower ribs with the superior margin of the iliac crest or soft tissues between the chest and the pelvis [29].

Kyphotic thoracic deformity contributes to breathing disorders and dysfunction of stabilization function of the diaphragm.

27.1.8 Endocrinopathy

Long-term weakness and enthesopathic pain with numerous triggering points should raise suspicion of hypothyreosis or masked depression [12].

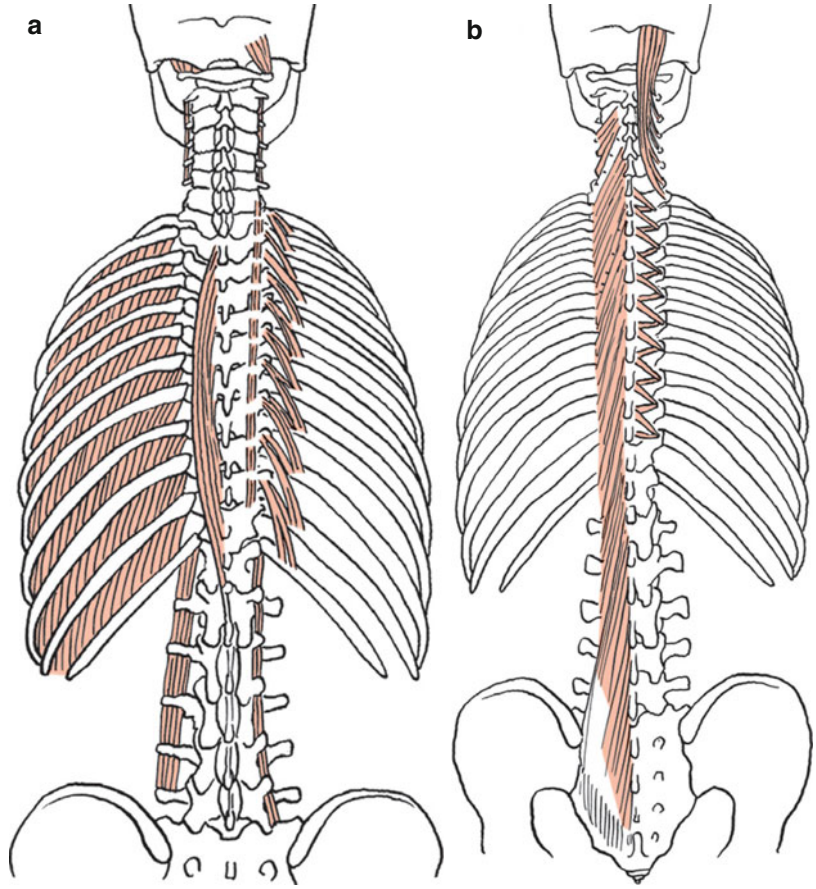

Fig. 27.5 (**a**) Dorsal muscles, spinospinal system and deep short muscles. *1* Rectus capitis lateralis muscle, *2* cervical intertransversarii muscles, *3* external intercostal muscles, *4* spinalis muscle, *5* lateral lumbar intertransversarii muscles, *6* medial lumbar intertransversarii muscles, *7* levatores costarum muscles, *8* thoracic intertransversarii muscles, and *9* obliquus capitis superior muscle (Courtesy of Grim et al. [32]). (**b**) Dorsal muscles and transversospinal system. *1* Multifidi muscles, *2* rotator muscles, *3* semispinalis capitis muscle (Courtesy of Grim et al. [32])

27.1.9 Gastrointestinal Disorders

They include predominantly defecation problems which improve after resolution of the condition. Trophic mucosal changes must be taken into account in the choice of NSAIDs; usually medications with short half-lives or COX selective inhibitors are indicated.

27.1.10 Visceral Pain

Disorders of visceral organs, such as endometriosis, nephrocalcinosis, prostatitis, pancreatitis, peptic ulcer, and intestinal cancer, stimulate sensory nerves, and their impulses lead to central structures through the same pathways as a somatic sensory input. As a result pain may be perceived in the region of somatic location, although the cause of the pain is visceral.

27.1.11 Malignancies

Malignity is suspected mainly in case of neuropathic pain accentuated at night, with low response to analgesics, the loss of body weight and subfebrile temperature.

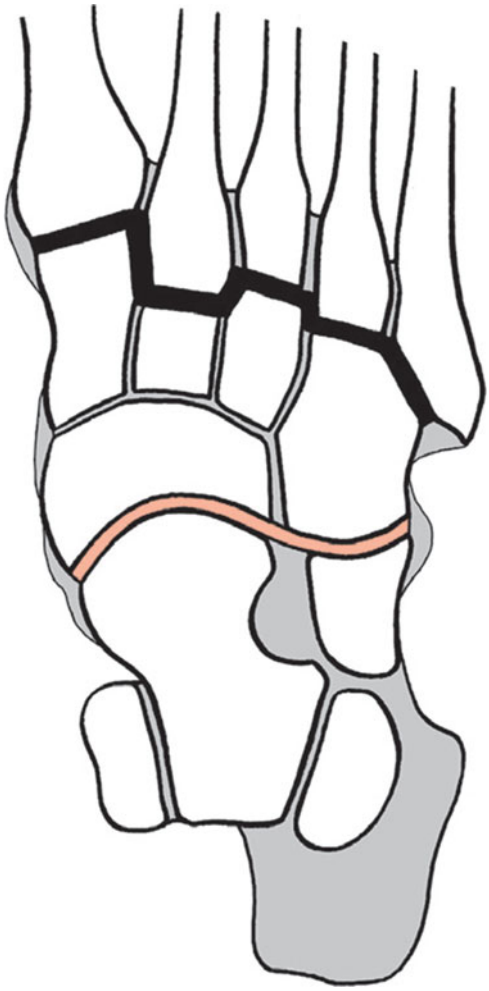

Fig. 27.6 Joints of the foot. Right foot transverse section. *1* Tarsometatarsal joint line (Lisfranc joint) – *black*, *2* cuneiform bones, *3* navicular, *4* joint line of the Chopart joint (talonavicular and calcaneocuboid joints) – *red*, *5* caput tali, *6* medial malleolus, *7* lateral malleolus, *8* calcaneus, *9* sinus tarsi, *10* cuboid (Courtesy of Grim et al. [32])

27.2 Paraclinical Examinations

Standard procedures include blood count, ESR, ECG and radiographic examinations of the affected regions. However, the condition should be assessed in view of the momentary clinical presentation, because morphological changes often manifest themselves as late as after the functional impairment. CT and MRI examinations of the spine are useful mainly in claudication vertebrogenic disorders. A gold standard of treatment of all vertebrogenic pain syndromes is a careful clinical examination, taking into account age-related specific features.

27.3 Treatment

Treatment consists primarily in administration of medications and is generally focused on pain relief and suppression of inflammatory processes. In elderly patients short-acting NSAIDs or COX-2 selective inhibitors are preferred. Higher than recommended doses used to treat vertebrogenic pain syndromes cause a ceiling effect, with increase only in adverse effects.

The method of choice to control chronic intensive pain is opioid patches [30]. Muscle relaxants should be used only in case of increased tension in the acute phase or in acute exacerbation of symptoms. In chronic pain, they decrease the general muscle tone, but muscle imbalance persists [31]. Neuropathic pain with accentuation at night can be successfully relieved by gabapentin and pregabalin.

The main efforts in solution of chronic vertebrogenic pain disorders should include physical activity and patient education focused on rehabilitation procedures to improve the functional capacity of the deep stabilizing system of the spine (autochthonous muscles, diaphragm, pelvic floor muscles and lateral abdominal muscles), including restoration of the function of lower limb joints [17, 18].

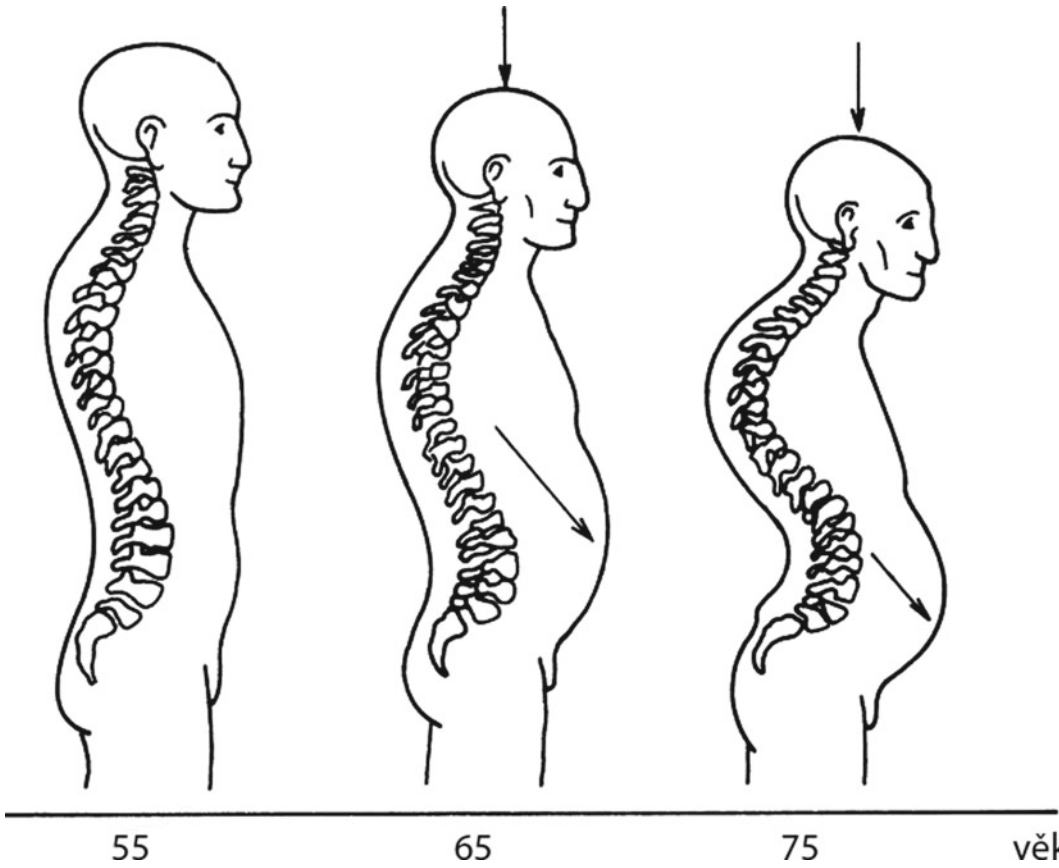

Fig. 27.7 Changes in osteoporosis. Ages 55, 65 and 75 (Courtesy of Blahoš [33])

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Pain

28

Ľubomír Lisý

Pain is a common complaint of the elderly. The number of individuals older than 65 years continues to rise. Pain management in older adults will be primarily a challenge for general practitioners. In advanced age, various conditions are associated with pain, joint disorders and malignancy in particular (Table 28.1). The prevalence of chronic pain in the elderly ranges between 25 and 50 %.

Geriatric nursing home residents have an even higher prevalence of pain, estimated to be between 45 and 80 %. These patients are often untreated or undertreated for pain which has a negative impact on the general health of the elderly and their quality of life. The consequences include depression, anxiety, social isolation, cognitive impairment, immobility and sleep disorders [1–3]. The cause of inadequate pain management may be lack of skills, inappropriate pain assessment and reluctance to prescribe more effective drugs.

Similarly as in other age groups, the elderly patients may have nociceptive, neuropathic or mixed pain (Fig. 28.1) [4, 5]. Nociceptive pain may be visceral or somatic in origin. Nociceptors are stimulated by inflammation or ischemic disorders. Patients with nociceptive pain are treated with both opioid and non-opioid preparations [6, 7], as well as by non-pharmacological interventions. Neuropathic pain is the result of a direct injury of the peripheral or central nervous system; in the elderly this type of pain is associated most frequently with post-herpetic neuralgia and diabetic neuropathy. Neuropathic pain usually does not respond to therapy used in nociceptive pain.

This type of pain can be controlled by medications from the group of anticonvulsants and antidepressants. The mixed category pain can be treated by medications used in both groups [8–10].

As pain in the elderly has often atypical manifestations, it is believed that its perception differs in older individuals (Tables 28.2 and 28.3). Although pain sensitivity and tolerance vary in individual persons and age groups, it is generally accepted that this variability has no substantial clinical impact. Similarly as other medications used in elderly patients, the administration of analgesics may be associated with a higher incidence of adverse effects. This propensity is due to changes in pharmacokinetics resulting from impaired renal and hepatic function as well as to changes in pharmacodynamics caused by increased sensitivity to analgesics, opiates in particular.

In addition, polypharmacy in the elderly contributes also to increased incidence of adverse drug reactions. Effective pain management consists in the identification of the nature of pain, choice of the proper analgesics, interdisciplinary approach to care and the use of non-pharmacological methods, where appropriate.

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Identification and assessment of pain in the elderly are demanding mainly in individuals with cognitive disorders. Pain may have atypical manifestations in these cases. Elderly patients do not always complain of pain, they may consider it to be a natural part of their age, or they may want to avoid unpleasant repeated diagnostic procedures and adverse effects of certain drugs. The presence of pain, especially in persons with dementia, may be signalled also by such signs as increased agitation, altered gait and social isolation (Table 28.4).

A comprehensive assessment should include examination of the medical history, physical examination and evaluation of laboratory findings. Pain intensity may be specified with the use of simplified visual scale.

Interdisciplinary assessment is recommended mainly in cases, where it is impossible to identify the primary source of pain.

Table 28.1 The most common causes of pain in the elderly

Degenerative joint diseases
Cancer-related pain
Osteoporosis-related pain
Herpes zoster
Arterial obliteration
Temporal arteritis
Rheumatic pain
Polyneuropathy
Trigeminal nerve neuralgia
Fracture-related pain

28.1 Pharmacological Pain Management in Elderly Patients

With age-related changes in pharmacokinetics and pharmacodynamics, a higher incidence of adverse effects of pharmacological pain management may be expected in the elderly patients. In addition, these patients are often polymorbid and receive more drugs, which increases the risk of drug interactions. Efforts at the management of pain are often associated with trials of various medications and their careful titration. Drug titration should be slower in the elderly than in young individuals. Particularly in case of mild pain, therapy should start with non-opioid analgesics followed, if necessary, by opioids to treat moderate to severe pain. The choice of analgesic medication should be based on identification of pathophysiology. Pain induced by inflammation, primarily due to irritation of nociceptors, should be treated with anti-inflammatory analgesics, while in neuropathic

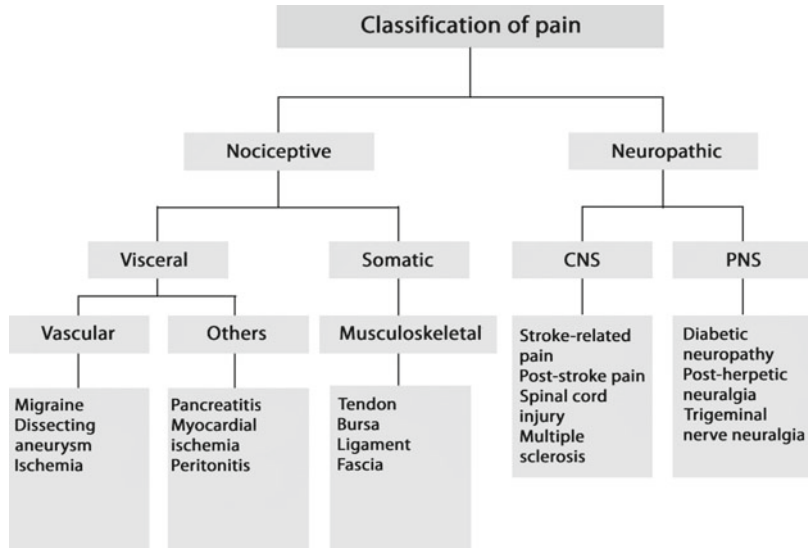

Fig. 28.1 Various pain types and their causes

Table 28.2 Categories of chronic non-malignant pain

Neuropathic pain	Inflammatory pain	Generalized pain
Nerve injury	Osteoarthritis	Fibromyalgia
Post-herpetic neuralgia	Rheumatoid arthritis	Musculoskeletal pain
Trigeminal nerve neuralgia	Tendonitis	Tension headache
Amputation	Myositis	Irritable bowel syndrome
Brachial plexus avulsion	Colitis	Whiplash injury
Peripheral neuropathy	Postoperative pain	Lumbago
Postoperative pain	Complex regional pain syndrome	
Syringomyelia	Cystitis	
Spinal cord injury		
Multiple sclerosis		
Stroke		

Table 28.3 Characteristic features of neuropathic and inflammatory pain

		Pain	
	Neuropathic	Inflammatory	Generalized
Positive signs and symptoms			
Spontaneous pain at the lesion site	Yes	Yes	Yes
Heat hyperalgesia	Rare	Often	Variable
Cold allodynia	Often	Rare	Rare
Hyperpathia	Often	No	No
Subsequent sensations	Often	Rare	Often
Specific symptoms	Paroxysmal and burning	Throbbing	No
Pain outside the lesion site	No	No	Yes
Negative signs and symptoms			
Loss of sensation in the innervation area	Yes	No	Yes
Motor innervation failure	Often	No	No

Table 28.4 Pain-related changes in behaviour in people with dementia

Somatic pain manifestations	Inability of verbal reporting of pain Reluctance to move Guarding the painful parts of the body Facial grimacing Increased sleep
Psychomotor pain manifestations	Inability to perform activities of daily living Decreased mobility
Psychosocial impact of pain	Inadequate communication, verbal and non-verbal Lack of interest in social activities Behavioural disorders

pain caused by injury to peripheral nerves of the central nervous system, anticonvulsants and antidepressants should be preferred. It is recommended to use always medications with the lowest incidence of side effects that must be carefully monitored.

28.2 Non-opioid Analgesics

Mild to moderate pain is most often of musculoskeletal origin and usually responses well to regular administration of acetaminophen. It is well tolerated by older patients provided their renal and hepatic functions are not impaired. Daily dosage of acetaminophen should not exceed 2 g. Long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of gastrointestinal bleeding, disorder of renal functions and cardiovascular complications. In order to reduce the risk of bleeding, NSAIDs may be combined with misoprostol or a proton pump inhibitor. However,

misoprostol is usually not well tolerated by elderly patients and therefore proton pump inhibitor should be preferred. Although the administration of selective cyclooxygenase 2 (COX-2) inhibitors is associated with a low risk of gastrointestinal bleeding, their use was reduced due to an increased risk of cardiovascular events.

28.3 Opioid Analgesics

Currently, opioid analgesics have been accepted for treatment of older patients to control chronic non-cancer moderate to severe pain. Addiction to these drugs is not known in the elderly and should not be used as a reason for undertreatment of pain. Morphine sulphate and oxycodone hydrochloride are available in a short-acting or extended-release form. Short-acting opioids may be used in treatment of intermittent pain, while extended-release opioids are administered for control continuous pain. The dosage of extended-release opioids can be titrated based on the frequency of use of the short-acting preparation. Opioids are supplied also in parenteral, sublingual, suppository (oxymorphone hydrochloride) and transdermal (fentanyl patch) forms. Physicians should know how to manage side effects of this treatment. Constipation should be prevented through the use of stool softeners and other prophylactic procedures mainly in the elderly. At the beginning of the therapy, sedation and delirium may occur until tolerance develops. Respiratory depression is not so frequent. Tolerance develops quite rapidly. Respiratory depression and sedation can be treated with naloxone hydrochloride. Patients should take a maintenance dose for several days, in order to prevent rapid return of the side effects of opioids. Antiemetics such as prochlorperazine or metoclopramide may be required at the beginning of the therapy. Falls, dizziness and gait disturbances are not uncommon; therefore, preventive precautions (assistive devices) are recommended. Tolerance develops to most side effects, such as respiratory depression, sedation, nausea and vomiting, but not to gastric hypomotility. Chewing or crushing opioid tablets must be avoided to prevent rapid absorption of the entire dose resulting in overdosing.

Certain opioids are not suitable for use in elderly persons. Propoxyphene is not more effective than acetaminophen and aspirin and is associated with ataxia, dizziness and neuroexcitatory effects due to its accumulation in the organism. Meperidine hydrochloride should not be used because of the accumulation of a nephrotoxic metabolite. Methadone hydrochloride has a long and variable half-life, which makes titration difficult. Its analgesic action is shorter than that of respiratory depression. Transdermal form of fentanyl is contraindicated in older patients not treated with opioids before. It has a variable absorption rate in older adults and a long residual effect even after removal of the patch. Tramadol hydrochloride having certain opioid properties is used to control mild to moderate pain. In older individuals it may be used only with caution as it provokes dizziness and also reduces the epileptic seizure threshold.

28.4 Adjuvant Therapy

Adjuvant therapy is quite commonly used in the elderly, mainly to treat chronic pain. Its use is based on a comprehensive assessment of the nature of pain, reflecting etiopathogenesis of pain.

Anticonvulsants, steroids, local anaesthetics and antidepressants may be used alone or in combination with non-opioid or opioid analgesics. Adjuvant medications are especially useful in the treatment of neuropathic pain [11]. Tricyclic antidepressants, such as amitriptyline hydrochloride and nortriptyline hydrochloride, are the most effective medications from the group of antidepressants. In older persons they are, however, associated with a higher risk of heart arrhythmia due to their anticholinergic effect. Gabapentin and pregabalin are the least risky drugs of the group of anticonvulsants when used in older polymorbid patients, as these drugs do not bind to protein in plasma and do not undergo hepatic metabolism. Only rarely pregabalin poses a risk

when used in combination with statins, as it may have a potentiating effect in terms of induction of rhabdomyolysis.

Selective serotonin-reuptake inhibitors are usually well tolerated and effective in patients with depression. Serotonin norepinephrine reuptake inhibitor in duloxetine is effective in the treatment of neuropathic pain and is relatively well tolerated.

28.5 Non-pharmacological Pain Management in the Elderly

Although – efficacy of non-pharmacological treatment to manage pain, non-pharmacological approaches may have an added benefit and should not be neglected. Their use may help reduce the amount of the medications used and protect patients against their adverse effects. Although efficacy of non-pharmacological management has not been adequately proved by evidence-based methods, practical experience clearly supports opinions on their favourable effect in pain management.

An important role in controlling pain in elderly patients is played also by psychotherapy as well as caregiver education.

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Pharmacological Treatment of Rheumatic Diseases

29

Marta Olejárová

Older patients (over the age of 65) and geriatric patients (over the age of 75) represent a majority of patients attending the rheumatology outpatient department. With the increasing age, both the prevalence and incidence of degenerative joint diseases grow, similarly as the frequency of crystal arthropathy (gouty arthritis, pyrophosphate arthropathy). Advanced stages of chronic inflammatory rheumatoid disease with the onset in younger and middle-aged groups of population can be observed as well. In view of aging of population in the advanced countries, the number of these patients will continue to rise.

Paradoxically, there is a lack of experience in pharmacological treatment of elderly patients, as new drugs or therapies are usually tested in middle-aged individuals without associated severe diseases; older patients are often excluded from clinical trials due to concerns about inadequate cooperation, a higher risk of adverse effects, risk of drug interactions in polypragmasia, etc. Pharmacokinetics and pharmacodynamics of a number of drugs, however, differ in elderly patients, and these differences may require substantial changes in dosage or drug dosage regimen.

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29.1 General Aspects of Pharmacological Therapy in the Elderly

Physiological changes of aging alter drug efficacy (pharmacodynamics), but mainly drug pharmacokinetics, which may have a direct impact on the incidence of adverse effects. The pharmacokinetics process consists in four basic phases, namely, absorption, distribution, metabolism, and elimination. Except for absorption, all the remaining phases are altered in the elderly patients. Distribution of water and fat soluble drugs is affected by a decrease in total body water and a higher percentage of fat to lean body mass. In addition, malnutrition and hypoproteinemia, more common in older patients, may reduce the bound fraction of the drug and increase the share of its free active fraction. Drug metabolism may be influenced by a decrease in liver blood flow and liver enzyme activity, e.g., activity of cytochrome P450 isoenzymes, but conjugation mechanisms are relatively well preserved also in older patients. Drug elimination is restricted due to decreased renal function which is by about one half lower than in young adults and is thus the most serious and the most frequent clinical change of pharmacokinetics [1].

Although there is still a lack of evidence regarding pharmacodynamic changes in elderly patients, the clinical practice shows that older patients demonstrate an exaggerated response to certain drugs, e.g., CNS depressants, including opioids [2].

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A major problem in older individuals is polymorbidity. In addition to the abovementioned renal insufficiency, complications may include hypertension, ischemic heart disease, ulcer diseases, and others. Treatment of these associated chronic conditions may cause drug interactions. Drugs to treat chronic diseases in the elderly are often not fully targeted, pharmacotherapy is inadequately determined, and its actual efficacy is not assessed, particularly in long-term treatment [2].

In addition, noncompliance with pharmacotherapy in elderly patients may lead to irregular drug administration resulting in under- or overdosing.

29.1.1 Analgesics Antipyretics

Paracetamol is a highly suitable analgesic for older patients. It is not addictive, it does not cause drowsiness, it is not associated with serious adverse effects observed in NSAIDs (gastrotoxicity, nephrotoxicity, etc.), and if administered at therapeutic doses, it is safe also in older patients [3]. Due to its short biological elimination half-time the risk of accumulation is low. To relieve pain, paracetamol must be administered at analgesic doses (a single dose of 650–1000 mg given three times a day maximum). The only risk is toxicity in overdosing that may occur accidentally rather in noncompliant patients. Therapeutic range of paracetamol is relatively narrow, with toxic effects occurring already with a daily dosage of 5 g (10 tablets per 500 mg).

Paracetamol may be combined with NSAIDs and opioids, although caution is required in case of hepatopathy. In the most common joint disease – osteoarthritis –paracetamol is recommended by all current international guidelines as the first choice for pain management. Meta-analyses have shown that its analgesic efficacy in osteoarthritis is comparable or only slightly lower than the effect of NSAIDs. NSAIDs are probably more effective in OA of the hip, but in the most common knee osteoarthritis, the effect is very similar [4].

29.1.2 Opioids

Opioid analgesics used to treat musculoskeletal pain in the older population include usually weak or moderate opioids (tramadol, codeine, oxycodone, etc.) and are prescribed in case of inadequate efficacy or contraindication paracetamol or NSAIDs, e.g., in advanced osteoarthritis contraindicated for operative treatment. Opioid analgesics may be also combined with NSAIDs or paracetamol. However, adverse effects are more common in the elderly, affecting primarily CNS (somnolence, confusion, delirium), often including also constipation. It is recommended to use lower starting doses at longer intervals with slow titration of the final dose. Renal function must be carefully monitored; sometimes laxative is temporarily used to relieve constipation [5].

29.1.3 Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used in elderly patients with caution, and where possible their administration should be avoided or minimized in terms of dosage and length of therapy. Each indication must be carefully considered. Older patients primarily have an altered pharmacokinetics, while the pharmacodynamic effect is probably the same as in younger population.

Drug absorption does not change in the elderly, while their distribution alters in view of the above described involutional tissue changes. NSAIDs have a high degree of plasma protein binding, resulting in an increased free drug fraction in hypoproteinemia with potential toxic effects. NSAID elimination is decreased in the elderly and the dosage should be adjusted accordingly. In NSAIDs with short- to medium-term elimination, half-time of renal elimination does not significantly change, but caution is necessary in NSAIDs with long biological half-time as it may get further extended and result in drug accumulation (piroxicam, phenylbutazone, and others) [6].

NSAIDs toxicity grows with increasing age; therefore, it has been generally accepted that NSAIDs should be avoided in elderly patients or at least their dosage minimized and used for the shortest possible time [7]. In addition to common GIT disturbances, older patients suffer more frequently from renal adverse effects (salt and water retention, renal insufficiency), adverse effects affecting CNS (confusion, impairment of cognitive functions and memory), as well as hepatotoxicity [8]. Advanced age has been established as a risk factor of NSAID gastropathy, including severe complications during long-term treatment with nonselective NSAIDs. The risk of gastropathy and their severe complications is lower with the use of COX-2 selective inhibitors (coxibs). Renal adverse effects are also more common in older population. Their risk with the use of coxibs and nonselective NSAIDs is comparable [6].

Another issue in long-term NSAID therapy may be their impact on blood pressure, i.e., hypertension decompensation. Also this risk is higher in the elderly, particularly those with a previous history of hypertonia. The risk of hypertension decompensation has to be taken into account primarily in coxibs.

Certain nonselective NSAIDs have also antiaggregation effect; therefore, bleeding complications may be encountered during the therapy. Coxibs do not have the antiaggregation effect and in addition they inhibit prostacyclin synthesis. Bleeding complications do not occur with this type of therapy; however, in case of long-term treatment, coxibs are associated with a higher risk of cardiovascular disease [9].

Therefore, in older patients, NSAIDs are second-line analgesics; less toxic preparations with short or medium biological half-time are preferable; long-term administration of nonselective NSAIDs and their use in patients with increased gastrointestinal risk requires gastroprotective prophylaxis (proton pump inhibitors, misoprostol).

Older patients should be informed in detail about potential adverse effects of the therapy (gastrointestinal disturbances, vomiting, abdominal pain, melena, swellings, increased blood pressure, etc.) and actively checked for them during follow-ups.

In older patients with polypragmasia, drug interactions should be considered. Since most NSAIDs are extensively bound to plasma proteins, they may displace other drugs from binding sites and thus increase their activity (e.g., oral antidiabetics, oral anticoagulants, sulfonamides). Hypoglycemizing effect was observed mainly in older NSAIDs, while in the newly developed (nimesulide, meloxicam), it has not been reported, yet. NSAIDs may reduce the efficacy of certain antihypertensive drugs (diuretics, beta-blockers, and ACE inhibitors).

The increased risk of adverse effects should be pointed out also in case of combination of NSAIDs; patients often receive various NSAIDs from various physicians, and older patients may also be more likely to self-medicate, buy OTC or "over the counter" NSAIDs, and use them with other NSAIDs.

As compared to the systemic treatment, topical NSAID therapy (gels, creams, sprays) is very suitable for the elderly. Systemic adverse effects, except for allergy reactions, have not been observed with local NSAIDs application which is adequately effective and at the same time a safe alternative for pain management in the elderly. The use of topical NSAIDs has been increasingly used in the clinical practice [10].

29.1.4 Glucocorticoids

Administration of low-dose oral glucocorticoids is the method of choice in mild inflammatory rheumatic diseases in the elderly. Particularly in elderly-onset rheumatoid arthritis, this therapy (where necessary in combination with NSAIDs) is often sufficient. Glucocorticoids are also the medication of choice to treat typical geriatric rheumatic diseases (polymyalgia rheumatica, giant cell arteritis).

In older patients a higher incidence of certain adverse effects has to be taken into account (hyperglycemia and decompensation of diabetes, glucocorticoid-induced osteoporosis, glucocorticoid-induced cataract, acceleration

of atherosclerosis, glaucoma, glucocorticoid-induced myopathy).

It is therefore recommended to use in older patients the lowest possible doses (preferably up to 7.5 mg/daily) and to combine glucocorticoids with calcium and vitamin D. NSAIDs with a higher risk of NSAID-induced gastropathy should be avoided [11].

Intra-articular and soft tissue glucocorticoid injections are beneficial in older patients, although contraindications of this therapy must be carefully considered. The highest risk associated with intra-articular therapy is development of septic arthritis. Intra-articular glucocorticoid application causes decrease of local immunity in the joint, and infection may result from hematogenous spread from a relatively remote site (oropharynx). The risk of infectious arthritis is generally higher in older patients, particularly in immunocompromised individuals (diabetes mellitus, immunosuppressive treatment, chemotherapy, etc.). Intra-articular glucocorticoid injections are followed in the first few hours after application by a significant systemic effect, including hyperglycemia and decompensation of diabetes.

Application of intra-articular glucocorticoid injections should be therefore indicated in elderly patients after careful consideration, followed by a short-time bed rest (3 days) under the control of the physician [12]. With respecting contraindications and adhering to these recommendations, intra-articular and soft tissue glucocorticoid injections are an effective, safe, and inexpensive pain management alternative in older patients [10].

29.1.5 Colchicine, Allopurinol, and Febuxostat

Therapy of acute gout in elderly patients is similar. The use of colchicine may be, however, limited by a higher incidence of severe hepatic or renal function impairment; it is less tolerated by older individuals and often associated with gastrointestinal disturbances. Glucocorticoids seem to be more beneficial in treatment of acute gout (particularly intra-articular injections) as they are in view of short-term therapy in this indication safer than, for instance, NSAIDs [13]. Nonsteroidal anti-inflammatory drugs should be avoided, or their dosage should be at least minimized also in long-term treatment of chronic gouty arthritis. Colchicine at low doses may be administered in this indication also to older patients; however, regular monitoring of renal functions is required [14].

Hypouricemic medications (allopurinol, febuxostat) are well tolerated by older patients; it is recommended to reduce allopurinol doses in patients with renal insufficiency, which may have a negative impact on the resulting treatment outcome (lower doses are not always enough to achieve the therapeutic goal – uricemia values <360 μmol/l). Febuxostat dosage does not have to be adjusted in case of mild to moderate renal insufficiency; therefore, its use in elderly patients could be more beneficial [13], although data from clinical trials of elderly patients is still missing. Another issue is cardiovascular safety of febuxostat.

In older, polymorbid patients, uricemia values may be increased by a number of medications commonly used at their age, primarily diuretics (thiazide diuretics, furosemide).

29.1.6 Synthetic Disease-Modifying Antirheumatic Drugs in Treatment of Rheumatoid Arthritis

Similarly as young patients, older patients with active rheumatoid arthritis are indicated for treatment with disease-modifying drugs mainly depending on the activity of the disease at the respective moment. Contraindications or complicated drug interactions are more frequent in older patients. The pros and cons of the therapy must be assessed on a case-by-case basis, and compliance of patients or their families with proper drug dosing should be ensured together with regular safety checks. Prior to introduction of administration of any drug of this group, patients' renal function must be checked, and in case of decreased glomerular filtration rate, the dose should be reduced. Generally it is recommended to start with lower doses and increase them as

required and in view of the patient's tolerance, under careful monitoring of the treatment safety.

Clinical trials and observational studies have shown that efficacy and safety of methotrexate (MTX) is in older individuals with normal renal function comparable with younger population [7].

MTX toxicity is obviously not increased by advanced age itself but by impaired renal functions associated with aging, as MTX is primarily cleared by renal excretion, with biliary excretion amounting to 10 % or less. Biological half-time of MTX elimination is 3–10 h with normal renal function, which would be beneficial in case of overdosing that may happen in elderly patients. Older patients may in addition to common adverse effects (hematotoxicity, gastrointestinal disturbances) develop also neurotoxic symptoms, such as mood changes, memory disorders, unpleasant feeling in the head, etc. [1]. In older patients, it is recommended to use a lower starting dose (2.5 mg weekly) and slowly increase it after 2 weeks by 2.5 mg up to 7.5 mg weekly, under systematic monitoring of blood count, liver enzymes, and renal functions. Folic acid supplementation is required, at the dose of 1 mg daily (or 10 mg once a week). The 7.5 mg MTX dose once a week should be maintained for several weeks to months in order to assess its efficacy and tolerability, before decision is made to increase the dose [11].

Sulfasalazine is equally effective in both elderly and younger patients. The complex pharmacokinetics of sulfasalazine does not substantially change with increasing age. Sulfasalazine is poorly absorbed; the absorbed part enters the enterohepatic circulation and is returned to the gastrointestinal tract via the biliary route. In the colon, sulfasalazine is metabolized by coliform bacteria to yield the two major metabolites, sulfapyridine and 5-amino-salicylic acid (5-ASA).

Sulfapyridine is absorbed in the colon and metabolized together with unchanged sulfasalazine in the liver and subsequently excreted through the kidneys. The 5-ASA molecule is not absorbed and is completely excreted from the body through feces. Patients' age affects pharmacokinetics only minimally; the doses should be reduced in case of impairment of renal functions. The incidence of adverse effects is comparable in older and younger patients; the elderly patients may more often exhibit hematological abnormalities caused also by folate deficiency common in older people. The recommended starting dose is 500 mg, with a slow increase up to the effective dose, depending on the patient's tolerance. Safety of treatment is in the elderly monitored in a standard way; no special measures are necessary [1].

The existing experience in the use of leflunomide does not show any significantly different toxicity in older individuals, although some authors report a higher risk of pancytopenia and hypertension (newly developed or exacerbated of the existing condition); no targeted studies, however, have been performed in the elderly. Leflunomide is very well absorbed and rapidly metabolized into an active metabolite, which undergoes intensive enterohepatic circulation, with a high degree of plasma protein binding. Leflunomide is metabolized through the liver, excreted primarily in the bile and less through kidneys. Biological elimination half-time is about 14 days; nevertheless due to intensive enterohepatic circulation, the active metabolite excreted in the bile is reabsorbed and may be therefore detected in the body for up to 2 years. In case of a toxic reaction, a washout procedure is undertaken with cholestyramine. Indications, contraindications, and safety monitoring are similar as in younger population [1].

Chloroquine and hydroxychloroquine are well tolerated also by older patients. Antimalarial drugs are well absorbed and have a high volume of distribution with a predilection for pigmented tissues (skin, retina). They are partially metabolized in the liver and excreted primarily through the kidneys. Biological elimination half-time is relatively long (1–2 months). Almost the only severe adverse effect is a relatively rare ocular toxicity. The risk of its development is increased by the patient's age and other risk factors, including a history of keratopathy and age-related macular degeneration, hepatic and renal disorders, and high fat level, treatment of more than 5 years. All these factors can be seen regularly in the elderly patients, and therefore they must receive hydroxychloroquine at a maximum dose

of 6.5 mg/kg/day and chloroquine 3 mg/kg/day [1] and undergo more frequent ophthalmic controls (one to two times a year) [1, 11].

Gold salts are currently second-line synthetic disease-modifying antirheumatic drugs in the treatment of rheumatoid arthritis. Despite their high efficacy, they are characterized also by severe adverse effects that although they are rare, they may result in severe organ damage (e.g., kidneys, hematopoietic system) with a fatal course. Nitritoid reactions accompanied by sweating, nausea, vomiting, and hypotension, including syncope, occur more frequently in older patients. The risk of adverse effect of gold is probably increased by ACE inhibitors.

Gold salts are applied in the elderly at a low starting dose (intramuscular application of 1–10 mg weekly) which is gradually increased to 25–50 mg weekly. Safety of treatment is in the elderly monitored in a standard way [1].

Azathioprine has not been tested specifically in older patients and therefore it must be administered to them cautiously. It may cause multiple drug interactions and increase efficacy and toxicity of allopurinol used by patients with gout and hyperuricemia, common in the elderly [1].

Pharmacokinetics of cyclosporine A does not change with increasing age, but it is considerably affected by multiple drug interactions of the drug and renal functions, which both are specific for older patients. A frequent adverse effect of cyclosporine A is also hypertension and nephrotoxicity. Therefore, they should receive small doses (25 mg twice a day) that may be combined with methotrexate. With this dosage, there is no need to monitor serum levels of cyclosporine; safety of treatment in the elderly is monitored in a standard way [1].

Penicillamine is not currently recommended for rheumatoid arthritis treatment due to lack of evidence regarding its efficacy and frequent and severe adverse effects. In older patients with lack of vitamin supply, penicillamine therapy may also lead to pyridoxine deficiency, and it is recommended to combine the therapy with supplementation of this vitamin. Penicillamine therapy starts at the dose of 125 mg daily, which is increased maximum by 125 mg a week [1].

29.1.7 Biological Disease-Modifying Antirheumatic Drugs in Treatment of Rheumatoid Arthritis

Based on the existing experience, biological therapy may be applied also in older patients. The age alone is not decisive for the efficacy and safety of the treatment, but the important factors are associated comorbidities that are common in older patients and may be a contraindication (congestive heart failure, malignancy, severe and chronic infections, chronic pulmonary disease, etc.). The risk of infection is generally higher in biological therapy, and older patients who suffer more frequently from infections should be vaccinated prior to commencement of the treatment against the most common pathogens causing severe infections in advanced age (against influenza, pneumococci, and hepatitis B) [1].

The group of TNF-alpha inhibitors includes the fused receptor for TNF-alpha etanercept and anti-TNF-alpha monoclonal antibodies (infliximab, adalimumab, and newly also golimumab and certolizumab). All of them are registered for treatment of RA as well as spondyloarthritis (ankylosing spondylitis, psoriatic arthritis). Efficacy and safety of treatment in the elderly was specifically studied only in etanercept. A meta-analysis of four clinical trials focused on the use of etanercept in rheumatoid arthritis has shown that efficacy of etanercept in the subpopulation of patients older than 65 years was comparable to that in younger age groups.

The incidence of adverse effects is also comparable or even lower in certain cases; infections, for instance, occurred in older patients less often than expected [15]. In other preparations, the details about efficacy and safety in the elderly from clinical trials are missing; however, the data from regi-stries of biological therapy suggest a good clinical efficacy and comparable safety of TNF-alpha inhibitors also in older patients with rheumatoid arthritis. A higher risk of infection in older patients was observed only in some registries [7].

Effects of rituximab have not been studied in elderly patients with RA either; nevertheless

broad experience in application of rituximab in older patients with B-cell lymphoma has proved its safety comparable with that in younger population. Prior to administration of rituximab, older patients should be vaccinated against the most common pathogens causing severe infections in advanced age (against influenza, pneumococci, and hepatitis B) [1].

The latest preparations of biological therapy for RA are abatacept, inhibitor of costimulation, and tocilizumab (interleukin 6 inhibitor), but data on their efficacy, pharmacokinetics, and safety in older patients is not available, yet. Abatacept may be used in case of inadequately effective TNF-alpha inhibitor therapy; however, they must not be applied in combination as it would significantly increase the risk of severe infections [1]. Tocilizumab is indicated to treat RA as a first- and second-line biological medication in case of failure of TNF-alpha inhibitor therapy. In addition to a higher risk of infections, cases of GIT perforation were reported in association with tocilizumab. Therefore, it should not be administered to patients with chronic intestinal diseases, including diverticulitis.

29.1.8 Symptomatic Slow Acting Drugs for Osteoarthritis

Oral symptomatic medications with long-term effect (glucosamine sulfate, chondroitin sulfate, diacerein, extracts of avocado and soybean) are a safe alternative treatment of osteoarthritis also in elderly patients. Their tolerability is very good, without severe adverse effects. Of great benefit for the elderly is the absence of drug interactions. Clinical trials with glucosamine sulfate and chondroitin sulfate used in patients with the mean age of patients around 60 years have shown the incidence of adverse effects comparable with placebo. Diacerein may cause mild to moderate diarrhea which usually subsides within the first 2 weeks and rarely requires discontinuation of the treatment.

Viscosupplementation with hyaluronic acid or hylan is also safe in older cooperating patients. General adverse reactions almost never occur; local adverse effects (in about 10 %) are usually mild and temporary. The therapy is associated only with general risks of intra-articular application which, if the technique is performed properly, are minimal. This type of therapy is recommended by a number of authors also in older patients [16].

29.1.9 General Recommendations for Treatment of Elderly Patients with Rheumatic Diseases

- Prior to commencement of a new therapy in older patients with rheumatoid diseased, it is necessary to check in detail comorbidities and concomitant pharmacotherapy.
- In addition to indications and contraindications, the choice of pharmacotherapy must take into account also potential drug interactions and reduce the number of concomitant drugs to minimum.
- Each prescription in older patients must be targeted, i.e., the goal of pharmacotherapy is set at the beginning of the therapy and has to be continuously monitored and evaluated. Inadequate therapy should be adjusted or discontinued and replaced.
- In general, it is recommended in older patients to start with lower doses and slowly increase them based on the patient's tolerance until achievement of therapeutic response. If there is no therapeutic response after common dosage, plasma drug concentration may be checked in certain cases (immunosuppressants).
- In older patients it is also advisable to simplify as much as possible the dosage regimen and provide the patient with a written overview of the therapy and dosage of drugs.
- Patients must be informed in detail about all potential adverse effects which should be assessed together with any drug interaction during each follow-up.

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Drug-Induced Rheumatic Syndromes

30

Jozef Holjenčík Jr., Jozef Rovenský, and Milan Kriška

More than 15 % of patients seek medical care for musculoskeletal complaints. Prevalence of musculoskeletal disorders grows with the increasing age. The most common of them are osteoarthritis, gout, rheumatoid arthritis, polymyalgia rheumatica and infectious arthritis. The initial diagnosis of a disease as systemic lupus erythematosus (SLE), idiopathic inflammatory myositis or dermatosclerosis is not common in older individuals and should be subject to additional diagnosis, taking into account mainly in older patients also drug-induced conditions.

Although iatrogenic death is rare, adverse effects of medications used daily are frequent, particularly in the elderly. Combination of ageing, comorbidities and polypharmacy makes the population of older persons vulnerable to adverse effects of drugs. In the ageing population, iatrogenic diseases are often masked by rheumatic diseases. On the other hand, rheumatic diseases may be associated with drug toxicity. Osteoporosis induced by long-term corticosteroid treatment or gastrotoxic effect of NSAIDs is well known, but drugs that may induce gout, SLE, arthralgia or myopathy are often neglected [10]. The overview below presents certain unusual rheumatic symptoms that may be caused by pharmacotherapy in elderly patients.

30.1 Drug-Induced Lupus Erythematosus

Systemic lupus erythematosus is a rare disease affecting predominantly young women. In 11–18 % of cases, the symptoms appear later, between 50th and 65th year of life [11]. Even more exceptional is the incidence of symptoms similar to SLE that are the result of action of certain groups of drugs. This form of SLE is called drug-induced lupus erythematosus (DILE). It is generally equally common in older males and females, probably because of their multiple drug exposure. Typical manifestations of drug-induced SLE are milder than in the idiopathic form. DILE is defined by development of symptoms similar to SLE, finding of positive antinuclear antibodies; it usually resolves on cessation of the offending drug.

DILE differs from SLE by a different antibody profile and a more favourable prognosis, with a lower variety of antibodies and predominance of

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the anti-histone ones [1]. Certain antibodies typically associated with the idiopathic SLE were occasionally identified also in drug-induced lupus (e.g. Coombs antibody, lupus anticoagulant, antiphospholipid antibodies).

In the past DILE was best described in patients using hydralazine, procainamide, methyldopa and chlorpromazine. Although the use of these drugs has a decreasing tendency, the incidence of drug-induced SLE remains the same, mainly due to new drugs with a potential to induce this syndrome, such as quinidine, minocycline, carbamazepine, ticlopidine and tumour necrosis factor inhibitors, e.g. infliximab, etanercept and adalimumab. DILE has been reported as an adverse effect after administration of more than 40 drugs and their number is continuously growing [12]. Drug-induced lupus is generally a rare condition, with an estimated incidence in the USA of about 30,000 cases per year, but the number of medications that may induce it is growing [10].

Clinical symptoms of DILE are similar to those in the idiopathic form. Diagnosis of drug-induced lupus is confirmed based on lupus-specific findings, such as 11 diagnostic criteria for lupus. However, in most patients, less than four of these criteria required for the SLE diagnosis are found. These criteria must be met during the use of the drugs known to cause DILE. It should be noted that a positive antinuclear antibody (ANA) is not enough to establish the DILE diagnosis. For instance, up to 50% of patients using higher doses of hydralazine will have a positive ANA finding, but only 10% of them develop drug-induced lupus. The time between drug exposures to onset of symptoms varies from months to years after initiation of the drug treatment, and the symptoms resolve after cessation of the offending drug [9]. Joints are affected in more than 80% of patients, with myalgia and arthralgia prevailing over arthritis. Common symptoms include unrest, subfebrile temperature and weight loss. Serositis and pneumonitis are typical of DILE caused by procainamide. Skin involvement, renal impairment and neurological disorders are rare in the classical DILE form [3].

DILE diagnosis is usually based on a high ANA titre (>1:1280); these ANA antibodies are directed against deoxyriboproteins, most often against histones. Antibodies against double-stranded DNA are rarely detectable and serum complement levels are usually within the normal range. DILE may be associated with findings, such as leukopenia, lymphopenia and hemolytic anaemia, quite often also lupus anticoagulant and antiphospholipid antibodies. Thrombosis and antiphospholipid syndrome are rare. Anti-histone antibodies are common both in DILE and SLE and cannot be therefore used to distinguish these two conditions.

DILE is generally considered to be a limited disorder the symptoms of which typically disappear several weeks after discontinued use of the offending medication, although positive ANA antibodies and other serological abnormalities persist much longer and completely disappear by up to 12 months. In addition to discontinued use of the respective medication, DILE treatment is mainly symptomatic and consists in the use of NSAIDs and sometimes also corticosteroids, mainly in case of severe cytopenia or pleural and pulmonary symptoms. Only rarely symptoms persist for more than a few months. Some patients respond favourably to treatment with antimalarial drugs; however, in such case it may be an initial manifestation of idiopathic SLE rather than DILE [9].

30.2 Statin-Associated Myopathy

Statins reduce cholesterol production through HMG-CoA reductase inhibition. The primary indication of these drugs is elevated levels of LDL cholesterol. Recently their use has significantly increased as a result of proved decrease of cardiovascular events in patients with advanced ischaemic disease with mild to moderate elevation of LDL cholesterol [7].

It has been demonstrated that statin treatment is generally safe and well tolerated. Currently, statins are used to treat millions of patients worldwide. Although the risk-benefit ratio is favourable in most of them, potential adverse effects should be considered in this context, including also statin-associated myopathy. Four myopathic syndromes associated with statins have been defined, namely, statin myopathy,

myalgia, myositis and rhabdomyolysis [10]. The incidence of proved statin myopathy seems to be relatively low (incidence 0.1 %). Clinical trials report the prevalence of statin-associated myopathy or weakness at less than 1 %. Myopathy includes myalgia, weakness and severe rhabdomyolysis [6]. Clinically apparent myopathy and rhabdomyolysis are rare, with rhabdomyolysis mortality rate estimated at 0.15 cases per 1 million prescriptions. Fatal rhabdomyolysis is rare and often accentuated and can be avoided. Cerivastatin was voluntarily withdrawn from the market worldwide in 2001, due to a higher incidence of fatal rhabdomyolysis at the highest recommended dose, as compared to other statins. For instance, its combination with fibrate gemfibrozil increases plasma concentration of statins and, consequently, the risk of rhabdomyolysis. Similarly, plasma concentration of statins is increased by concomitant use of drugs inhibiting cytochrome P450 (macrolides, cyclosporine) with statins [13].

Fluvastatin, atorvastatin and pravastatin are hydrophilic, while cerivastatin, lovastatin and simvastatin are lipophilic. Lipophilic drugs seem to be more myotoxic.

In general, the incidence of adverse effects has been documented in less than 0.5 % and myotoxicity in less than 0.1 %. All statins are associated with development of myopathy, and this risk may be further increased by certain comorbidities and drugs. Patients with a history of hypothyreosis, renal insufficiency, biliary obstruction, diabetes, recent trauma, surgery or elderly patients are exposed to a higher risk. The risk of myopathy is also increased by concomitant use of certain drugs, such as cyclosporine, fibrates and antimycotics of macrolide antibiotics inhibiting the specific cytochrome P450, the enzyme involved in statin metabolism, and thus contributing to drug interactions [4]. With the common dosage, the risk of myopathy is low. A number of studies and also meta-analysis of clinical trials have shown that the total incidence of myopathy is 11 cases per 100,000 patients treated with statins. In case of rhabdomyolysis, the number is even lower and ranges between 3 and 4 cases per 100,000 patients [7]. Drug interactions that are more common in the elderly due to polypragmasia lead to a higher frequency of adverse effects in concomitant use of statins with other drugs, particularly those that influence activity of cytochrome P450.

Most statins are highly bound to plasma proteins and the free fraction of the active drug is low. A majority of statins is metabolized by cytochrome P450, with the exception of pravastatin. Most drug interactions result from inhibition or induction in the cytochrome enzymatic system. However, pathogenesis of statin-associated myopathy is not quite clear. The suggested mechanisms include depletion of secondary messengers, induction of apoptosis, alterations of chloride-channel conductance within the myocytes and decreased cholesterol content of myocyte membranes, resulting in membrane instability [13].

The best way to avoid statin-associated myopathy is prevention. General recommendations include the use of the lowest therapeutically efficient dose and identification of drug interactions that increase the risk of myopathy. Patients should be instructed to stop taking statins and report to their doctor any symptoms of muscle pain, weakness or discoloration of urine. Physicians should not ignore these symptoms even if creatinine kinase is not elevated. In addition, asymptomatic elevation of creatinine kinase is not enough to establish the diagnosis of statin myopathy.

Patients with symptomatic myalgia should be examined, but they may continue to take statins if the symptoms are mild and tolerable, or reduction of drug dosage can be considered. Improvement of symptoms was reported after replacing the medication by a lipid-lowering drug. In case of severe symptoms, the treatment should be discontinued, and another lipid-lowering drug class should be considered, such as niacin, bile acid sequestrants or ezetimibe. There are no absolute contraindications to a combined treatment using statins and drugs with a proved higher risk of development of myopathy, because under certain circumstances, the benefit of such treatment may outweigh its risks [14].

In case of rhabdomyolysis, statin treatment should be discontinued, and the therapy then consists in aggressive hydration, induction of diuresis by mannitol and alkalinisation of urine to prevent renal damage [14].

30.3 Gout

Incidence of gout increases with increasing age and elevated serum uric acid levels. In the USA, the gout prevalence in total population is estimated at 0.84 %; in the age group over 65 years, this value increases to 2.19 %. Primary gout prevails in men. The most significant risk factor for gout is hyperuricemia developed by a majority of patients as a result of insufficient excretion rather than excessive production of uric acid. Hyperuricemia may be primary and secondary and, consequently, gout is primary and secondary. Primary gout is often associated with various diseases, such as obesity, hyperlipidemia, diabetes mellitus, hypertension or atherosclerosis, i.e. conditions typically occurring in elderly patients. Secondary gout may be induced by alcoholism, myeloproliferative and lymphoproliferative disorders, hypertension, medications or renal transplantation [8].

The onset or relapse of secondary gout may be caused by drugs that either elevate the general urate level in the body, such as cytotoxic drugs or drugs preventing renal urate excretion, e.g. diuretics, ethanol and acetylsalicylic acid at low doses. For this reason, drugs used by patients diagnosed with gout should be checked in terms of their potential contribution to development of hyperuricemia, gout or nephrolithiasis [10].

Problems may be posed by drugs used to treat gout. Allopurinol is rarely responsible for the development of vasculitis with erythematous rash, fever, eosinophilia or even toxic epidermal necrolysis, hepatitis and interstitial nephritis. Toxicity of both colchicine and allopurinol is significantly increased in case of renal insufficiency, and in this way these relatively harmless drugs may lead to life-threatening complications, if taken inappropriately or in combination with renal insufficiency [2]. According to some experts, intravenous colchicine preparations should be totally avoided. Fatal cases were reported with the use of as low a dose as 1 mg of colchicine administered intravenously. Severe colchicine toxicity may cause aplastic anaemia, shock, disseminated intravascular coagulation, renal failure, myopathy and rhabdomyolysis [8]. The risk group includes mainly elderly patients, with renal failure, patients taking both oral and intravenous colchicine and at the same time using statins, cyclosporine and grapefruit juice. It is also important to drink enough liquids.

30.4 Drug-Induced Arthralgia

Many drugs have been found to contribute to arthralgia, including primarily chinolons, acyclovir, interferons, interleukins (IL-2, IL-6), tacrolimus, vaccines against tuberculosis, statins, fibrates, beta-blockers, raloxifene and tamoxifen. Tendinopathy and synovitis were seen less frequently. Similar cases cannot be associated with DILE due to the absence of SLE-specific symptoms. These events may be common, e.g. in case of interferons, or rare, e.g. in beta-blockers. In any case, unexplained articular or periarticular pain which coincides with the administration of these drugs is a sufficient reason for discontinuing their use. Although the time to resolution of symptoms depends on pharmacokinetic properties of the drug, most patients must be followed up for several days or weeks to check whether the symptoms improved after cessation of the therapy [10].

30.5 Vasculitis and Scleroderma

Incidence of certain forms of vasculitis, angioedema, scleroderma or myositis is so improbable in elderly patients that it should be considered by the physician in terms of a secondary disease induced by infection, tumour (i.e. paraneoplastic syndrome) or drugs. Although the last option is relatively rare, a growing number of case reports show that polypharmacy may cause these unusual autoimmune diseases. Drugs that may induce these conditions include, for instance, allopurinol, hydrochlorothiazide, penicillamine, carbidopa, bleomycin and others [5]. These drug-induced disorders are usually less severe than idiopathic diseases and are limited as concerns the extent of tissue involvement. Aetiology of most of these events is unclear. Discontinuation of the use of the respective drug is as a rule sufficient to resolve the symptoms.

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Rehabilitation in Rheumatic Diseases

31

Helena Tauchmannová and Zuzana Popracová

Rheumatic diseases are a prototype of diseases affecting the elderly population.

In clinical and physiological terms, aging means gradual depletion of reserves of individual organs as well as decrease of control over biological homeostasis. It is an irreversible process which over the years reduces the function of cells, tissues, organs and the whole organism.

It is generally assumed that part of the process of aging is also decline of intelligence. In fact it is necessary to distinguish between fluid and crystallised intelligence. Fluid intelligence (Gf), e.g. the capacity to think logically, associative memory and abstract reasoning, is declining, while crystallised intelligence (Gc) measured by test of verbal ability in terms of both vocabulary and general knowledge is maintained, similarly as the ability to learn, although the process of learning is slower [2].

It has become also generally accepted that old people are ill and dependent on other persons or on the society. In reality only a minority of old people become disabled and dependent. Surveys show that only 40 % of 85-year-old persons need assistance in their routine daily and self-care activities. Biological age does not always correlate with chronological age. Certain individuals exhibit progressive age-related changes as early as at the age of sixty, while only a slight decline of physiological reserves can be seen in many 80-year-olds.

Elderly patients should undergo global medical, functional and psychosocial assessment, including assessment of their intellectual abilities and the environment in which they live [6]. Age-related changes that must be taken into account include impairment of vision, hearing, memory impairment, reduced function of the musculoskeletal system (loss of muscle mass, tension and performance) and lack of movement coordination.

Overall reduction of activity in older patients impairs the functions of cardiovascular, respiratory, musculoskeletal, renal and central nervous system.

Inactivity affects primarily one of the most fundamental qualities of human life – mobility. Muscle atrophy, contractures, muscle imbalance and joint axial malalignment all impair function of the joint, and its restricted mobility, particularly in case of large lower limb joints, affects the patient's general mobility.

Inactivity may be caused by multiple factors. One of them are rheumatic diseases.

31.1 Osteoarthritis

Osteoarthritis (OA) is a heterogeneous joint disease that may have a different aetiology but a similar clinical, biological, pathological and

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radiographic progress. The disease is characterised by degenerative process which primarily involves articular cartilage and is associated with secondary reparative changes. Unlike age-related symptoms, OA triggers degradation processes in the cartilage, leading to its destruction.

OA is a model disease, the incidence of which grows with physiological aging. After the age of 80 years, it occurs almost in all individuals. Recovery or improvement of physical activity of patients with OA is an important part of the therapy not only to maintain physical fitness but also mental abilities, mainly in older patients.

Patients should be treated in a comprehensive way and informed about the nature of the disease, including the fact that it is not an inflammatory condition that would require a continuous pharmacotherapy. Patients should know that of primary importance in OA management are the factors of healthy lifestyle, such as reduction of extra body weight, well-balanced diet and regular physical activity. Pharmacological therapy should be used only in the phase of joint decompensation, with continuous pain, including pain at rest, on motion and at night, and sudden, marked restriction of the function. The basis of non-pharmacological OA treatment is physical therapy and the use of various means of physical medicine.

Physical therapy helps maintain the function, improves coordination, contributes to general fitness of patients and serves as a prevention of falls and various injuries, commonly sustained by the elderly. It helps them compensate the common stress and other pitfalls of everyday life.

The elderly should follow the principle "use it or lose it" [4], reminding them that inactivity leads to restriction or loss of mobility.

31.2 Osteoarthritis of Small Joints of the Hand

A typical finding are hard or bony swellings of distal and proximal interphalangeal joints, Heberden's and Bouchard's nodes and in the advanced stage also axial malalignment.

They are accompanied by frequent episodes of inflammatory exacerbation and gradual development of deformity which, however, rarely impair the hand function. Prognosis of OA of small joints is good, and after subsidence of the acute phase, DIP and PIP joints are usually asymptomatic. Women are often affected by this condition as early as during menopause. OA of small joints of the hand (DIP and PIP) is highly associated with arthritis of the knee joints. The most severe and painful is rhizarthrosis – arthritis of the thumb carpometacarpal (CMC) joint, which is in addition to joint symptoms characterised by hypotrophy of the short muscles of the thenar and restricts the basic function of the thumb, the grip or grasp. Rhizarthrosis is often hereditary and is common in women at the age around 50 years.

Rehabilitation Procedures In the phase of irritation, the joint of the hand must be immobilised by a brace, particularly in case of involvement of the thumb CMC joint which is typically swollen, very painful during motion and sensitive to pressure. After resolution of acute conditions, it is necessary to restore the ability of the thumb to move across the palm and oppose the other finger tips, train pincer and other types of grip. All exercises should be performed against resistance, and patients are trained to perform them by themselves. Except for cosmetic effect, Heberden's and Bouchard's nodosity do not cause any difficulties; pain may be relieved by two-chamber hydro-galvanic bath. In younger persons nodes may be removed surgically.

31.3 Osteoarthritis of the Hip

Osteoarthritis of the hip often results from congenital defects, injuries and heavy physical activity or secondary to other systemic diseases (endocrine, metabolic), or it may occur without evident cause.

OA of the hip usually develops insidiously, sometimes over decades, without marked symptoms. Only in a minority of patients it proceeds more rapidly, with episodes of sudden exacerbation, intensive pain and restriction of mobility. Pain may radiate into the groins, the greater trochanter and into the medial knee, which sometimes leads

to diagnostic errors. The initial episodic pain is gradually accompanied by pain after heavier physical activity and in the acute phase also by pain at night. Muscle attachments around the hip are usually tender to pressure; occasionally there occurs a small joint effusion. Muscle imbalance associated with OA of the hip results in shortening, later in contractures of extrarotators, flexors and adductors. Due to shortening of flexors and weakening of hip muscles, anteversion of the pelvis increases and results in deepening of the lumbar lordosis and increased tension of paravertebral muscles. The limb seems to get shorter, the affected joint does not adequately tolerate weight bearing and the patient walks with a noticeable limp.

OA of the hip affects both males and females; in younger age groups, it is more common in men; later in life the incidence is the same in both sexes. It may occur also as an isolated disorder without involvement of other joints.

Rehabilitation Procedures The essential part of therapeutic procedures to treat arthritis of weight-bearing joints are healthy lifestyle factors, i.e. well-balanced diet, reduction of overweight and in older age categories also control of energy output.

In the acute phase, it is most important for the patient to follow bed rest regimen for 2–3 days which, in addition to pharmacotherapy, helps relieve symptoms of pain and inflammation. During the bed rest, it is necessary to position the limb in such a way to avoid its excessive rotation and to prevent flexion contracture by lying prone several times a day. The tone of abdominal, femoral and hip muscles should be maintained by isometric contractions, preventing atrophy due to inactivity. Isometric exercises against resistance (absolutely resisted exercises) help restore muscle strength. Stretching of shortened muscles gradually releases painful contractions. Ideally, exercises in OA of the hip should be performed with the suspended limb or in water which increases the therapeutic effect by a combination of the lifting force and hydraulic pressure and warm bath. Aquatic exercises are performed in all directions within the pain-free range. The speed of the motion is regulated by intensity of the resistance provided by water. Exercise intensity and water temperature are adjusted to the patient's age and general health. After subsidence of acute symptoms, patients may start walking with crutches without weight bearing of the limb. Full weight bearing of the limb must be gradual, cautious and within the pain-free range. Older patients should always use a walking stick. Active exercises are commenced in the phase of compensated arthritis, but their duration and frequency must be carefully regulated, as active movements alone already put relatively high demands on the affected joint. Muscle strength is increased by common techniques (isometric and resistance exercises), where appropriate, an adjustable-load pulley may be used. The principle of rehabilitation of the joint is to load but not overload the joint, which applies to all activities of patients with osteoarthritis.

Restoration or improvement of muscle strength and balance prior to hip surgery is of essential importance, similarly as training of walking with crutches or walking stick.

Proper conservative treatment of the hip osteoarthritis should focus on restoring muscle balance in the spine-pelvis-hip region, local and general thermotherapy and targeted physical therapy, including custom-made shoes and the use of orthopaedic devices.

31.4 Osteoarthritis of the Knee

Knee joint is a hinge-type weight-bearing joint with a complex arrangement of articulating bones which makes the knee highly vulnerable. It is reinforced by a robust tendon system, strong intra-articular ligaments and multiple bursae.

The intra-articular cavity consists of three compartments. Involvement of the tibiofemoral compartment results in varus deformity, involvement of the fibulofemoral compartment results in valgus deformity and involvement of the patellofemoral compartment restricts the range of motion in the knee. There are large bursae around the knee joint – the popliteal bursa at the posterior aspect of the knee and the suprapatellar bursa

extending superior to the patella. In younger age groups, OA of the knee is more common in men, while later in life its incidence is higher in women, especially the overweight ones. It affects predominantly the medial and patellofemoral compartments. OA of the knee in women is commonly associated also with OA of other joints. The involvement is usually bilateral. Secondary osteoarthritis develops most often due to a knee joint trauma (injury to menisci, medial collateral ligament or post-operative injury) as a result of hypermobility and other severe systemic (metabolic, endocrine and hematologic) diseases.

Typical of the acute phase of osteoarthritis is pain in the knee, function limitation, swelling and effusion which may fill also the neighbouring bursae. Effusion prevents free quadriceps contraction and contributes to its atrophy, particularly of the vastus medialis. Quadriceps inactivation for 24 h reduces its strength by 25 %. Long-term effusion results in the joint capsule and tendon laxity, which leads to joint instability.

Moreover, pain and effusion are often compensated by antalgic posture of the knee joint in mild semiflexion which has to be gradually removed by positioning in order to avoid flexion contracture. Effusion evacuation is a precondition of initiation of effective physical therapy.

In the active stage, the strength of quadriceps must be maintained by isometric activation for 4–6 s several times a day. If the joint is warmer, cryopads may be applied locally. During subsidence of OA manifestations, it is necessary to restore muscle balance primarily by relaxing the robust ischiocrural muscles which tend to keep the knee joint in flexion. The most important for function of the knee joint is maintenance of full extension to allow adequate distribution of the body weight on joint structures. Even a slight flexion posture in the knee disturbs the general static balance and results in development of an incorrect gait pattern. An important role for joint mobility is played by the patella. Limitation of its motion always affects the range of motion of the knee. Mobilisation of patella in craniocaudal and lateral direction improves conditions for a successful physical therapy. Shifting and taping the patella medially considerably relieves pain in the affected knee joint. To achieve extension, it is desirable to use limb suspension, a positioning plate or a pad placed under the heel in bedridden patients.

After subsidence of acute symptoms, isometric exercises for the quadriceps are combined with its exercising against resistance, with the knee at different angles.

The same attention should be paid to the gluteal muscles that together with weak knee extensors complicate walking up and down stairs and standing up from a chair. Patients should start to walk with a support as soon as possible and limit weight bearing of the affected lower limb, such as sophisticated knee braces that fix the joint and at the same time allow its motion. In case of a permanent varus deformity of the knee, their continuous use is inevitable. Valgus deformity exceeding 25° requires surgical correction. In both cases it is important to use orthotic insoles, with elevated medial part to correct valgus deformity and elevated lateral part to correct varus deformity. The optimal way to maintain the general fitness during the phase of limited physical inactivity is walking at a suitable pace as aerobic exercise.

31.5 Osteoarthritis of the Ankle and Joints of the Foot

OA of the ankle and joints of the foot is quite infrequent and develops usually within a general, long-term OA or as a result of a joint abnormality and after trauma. It affects predominantly the subtalar joint and restricts pronation (eversion and abduction) and supination (inversion and adduction).

Hallux valgus, bunion, is caused by arthritis of the first metatarsophalangeal joint, which is usually enlarged and tender to pressure and often with a deviation or even dislocation. Valgus deformity of the great toe may be prevented by inserting a small plate between the great and second toes. Physical therapy consists in a simple set of exercises for the ankle and the foot, accentuating flexion and extension in TMT, MTP and DIP joints and stretching of the plantar fascia. Patients should permanently wear orthotic insoles or custom-made stable shoes.

31.6 Omarthritis of the Shoulder

Omarthritis is a rare condition, occurring usually secondary to the rotator cuff lesion or rupture. The shoulder is generally painful with a gradual limitation of active range of motion in terms of external rotation, with audible crepitus. In elderly patients, predominantly women, so-called Milwaukee shoulder can occasionally be seen, which is characterised by destructive OA, bleeding into the joint cavity and pain in the joint radiating to the anterior chest. In the acute phase, pharmacological and intra-articular treatment of the shoulder should be combined with immobilisation of the joint, in older patients in abduction (30°), partial intrarotation and pronation of the forearm. After subsidence of pain, exercises to relax the shoulder girdle should be initiated by the patient lying initially prone with the limb hanging over the edge of the bed so that the limb weight stretches the joint capsule.

Later the same exercises should be repeated in the standing forward bend, with gradual weight lifting (using, e.g. iron) and with relaxed circular motion (Codman's exercises). Exercises should be performed in all three planes until the joint capsule is relaxed. Although the elderly are mostly unable to achieve full function, it is important for them to achieve such a function allowing them to manage activities of daily life and self-care activities.

31.7 Osteoarthritis of the Elbow

Osteoarthritis of the elbow is a rare condition, occurring as a rule within general OA or following a trauma and overloading of the joint. The function is impaired by limited extension and partially also pronation, sometimes associated with compression of the ulnar nerve, resulting in paresthesia of 4th and 5th fingers. Further limitation of extension should be prevented by a hinged brace. It is important to maintain the function of the elbow allowing patients to manage eating and other self-care activities. Physical therapy is focused on relaxation of shortened elbow flexors, with a slightly forced extension.

31.8 Osteoarthritis of the Spine

Involvement of apophyseal joints of the spine is known as *spondyloarthritis*, which is similar to arthritis of peripheral joints. Involvement of intervertebral discs – *spondylosis* – may develop simultaneously and is associated with formation of osteophytes along anterior and posterior edges of vertebrae. OA of the spine is highly frequent in the cervical and lumbar segments. Degenerative process proceeds gradually, changing the posture and increasing the cervical and lumbar lordosis. Similarly as spondyloarthritis, spondylosis may go unnoticed from the clinical viewpoint for a long period or may have only mild manifestations such as low back pain experienced now and then by almost all people in the civilised world. These disorders of the spine are termed as vertebrogenic pain syndromes, which except for the location of the disorder say nothing about their causes. They may manifest themselves by sudden sharp pain restricting the patient's mobility. The source of pain may, however, be also structures other than intervertebral discs or apophyseal joints. Disorders may be caused by impairment of the function of muscles, ligaments, fascia, subcutaneous tissue and skin. Frequent painful conditions require neurological follow-up and pharmacological treatment.

Muscle imbalance as the cause of pain is characterised by shortening of the pectoral and weakening of scapular muscles in the upper part of the trunk and shortening of the lumbar and weakening of the abdominal muscles in its lower part.

The aim of physical therapy is to correct the posture, uneven height of shoulders, abnormalities of scapula position, limb length and the pelvic tilt and mainly to restore the muscle balance.

First, shortened muscles are stretched, and the motion in individual spinal segments restored. This is followed by strengthening weakened muscles. Only after correction of muscle imbalance it is possible to restore the muscle coordination and proper muscle stereotypes.

Pharmacological treatment used in the painful episodes is combined with orthotic devices, such as cervical collars, flexible or rigid lumbar corsets.

Part of the solution of painful conditions is their prevention, including information provided particularly to geriatric patients, about the importance of healthy lifestyle, targeted and positioning exercises and avoidance of certain activities to protect the spine.

31.9 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory condition of unknown aetiology with a variety of clinical features and characteristic findings of antibodies against intracellular antigens. It affects predominantly younger individuals, women nine times more often than men. It may develop at any age. The most common clinical features include nausea, fever, fatigue, weight loss, arthralgia or arthritis, vasculitis and Raynaud's phenomenon and only later symptoms of organ involvement (skin, kidneys, lungs, cardiovascular and central nervous system). Although rehabilitation has a secondary role in SLE treatment, it is important even if patients do not experience any disorders of the musculoskeletal system. More than 90 % of patients complain of fatigue which is attributed to decreased aerobic capacity and lower aerobic threshold [9]. Certain authors have documented that fatigue is caused by impaired diffusion of oxygen in the peripheral muscles affected by inflammation in the active SLE form. A low aerobic threshold may partially explain why patients with SLE get quickly tired. Fatigue may be addressed by aerobic fitness exercises [3]. Physical therapy is also used to control depression which considerably conduces to increased fatigue of the patient [5]. Aerobic fitness workout should include exercises on treadmills with adjustable slope and speed and exercises on bicycle ergometer. Depending on the patient's clinical condition, aquatic exercise may be incorporated. Intensity of physical therapy should be gradually increased (three to five times weekly 15–30 min). Many patients exhibit muscle disorders leading to muscle imbalance, development of compensation mechanisms and ultimately wrong stereotypes. These patterns should be eliminated by targeted physical therapy and other means of physical medicine [8].

In up to 90 % of patients with SLE, there may occur arthritis, which slowly disappears and, unlike other systemic rheumatic diseases, it does not contribute to joint destruction. Only in about 5 % it causes fixed deformities [7].

It is most common in small joints of the hand (PIPs, MCPs and wrist joints), taking a toll on fine motor skills, but may affect also small joints of the foot and considerably complicate gait. Deformities of hands may include swan-neck deformity, MTP subluxation, finger ulnar deviation, Z-shaped deformity of the thumb and wrist subluxation [1].

The most severe SLE complication is involvement of the central nervous system, often ending in stroke. The underlying organic disease is most commonly vasculitis which causes minor heart attacks, hemorrhagic foci and perivascular gliosis. Rehabilitation is based on time-tested facilitation techniques according to Kaiser-Kabat or Bobath.

In pulmonary involvement manifested as atelectatic pneumonia or pleuritis, the methods of respiratory re-education are used, including bronchial hygiene, relaxation, breathing gymnastics and motor skill retraining.

Myositis in the acute phase requires bed rest. Subsequently, patients restore their muscle strength by isometric exercises with submaximal and maximal muscle contractions.

Necrosis of large joints may be very painful, or it may be asymptomatic and then limits the possibility of an early therapeutic intervention. Loading of the affected joint is not permitted; the limbs are suspended in a sling and placed in a pain-free position. Electroanalgesia is used to relieve pain. Anti-gravity exercises should be avoided at the beginning of physical treatment. In case of a more marked muscle weakness, isometric contractions with submaximal intensity are used. Necrosis occurs in younger patients treated with glucocorticoids. It affects predominantly the hip and shoulder joints and the wrist. Despite application of all options of the conservative treatment, it is not always possible to prevent destruction of the affected joint. Even in such

case, it is important to postpone as much as possible joint replacement as an unsuitable intervention in young individuals.

31.10 Rheumatoid Arthritis

Rheumatoid arthritis is an inflammatory condition involving joints where inflammation is triggered and maintained by autoimmune mechanisms. It occurs in all synovial joints, but most often it affects small joints of limbs, including periarticular structures, bursae, tendons and ligaments. The disease may develop at any age, but most frequently it occurs between the 20th and 55th year of life. EORA (elderly-onset RA) develops after the age of 60 years and has its specific features. The incidence in men and women is almost the same. The onset of the disease is often abrupt. Unlike in younger patients, this form affects more often large joints (e.g. shoulders) and may be oligoarticular.

It impairs joint function and, as a result, considerably decreases the patients' quality of life. Systemic manifestations include mainly high values of erythrocyte sedimentation rate and seronegativity (absence of RF). The course of the disease is quite malignant and is associated with severe functional impairment and destructive changes. Both the treatment and rehabilitation are complicated due to potential polymorbidity and the related polypharmacy.

Rehabilitation of patients with EORA is focused on prevention of flexion contractures, maintenance of the existing range of motion and muscle strength and the use of walking and other orthotic devices (wrist brace, knee brace, orthotic shoes). Due to longer intervals of morning stiffness, the patients should perform exercises early in the afternoon. One of the priorities is maintenance of muscle strength of lower limbs by simple isometric stretching of quadriceps. Another priority is maintenance of the range of motion in shoulders by raising arms overhead in a lying and sitting position and by circular motion. Rehabilitation is also focused on improvement of the patient's mobility and general fitness. Patients should use assistive devices facilitating activities of daily living. In general, patients' compliance with therapeutic and rehabilitation programmes is decreasing with age. Exercise capacity…

Any age has its specific features; the elderly patients require a specific approach to therapeutic rehabilitation focused on maintenance of their self-care abilities and the quality of life.

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Surgical Treatment of Sequelae of Rheumatic Diseases

32

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32.1 Introduction

Operative treatment of the sequelae of rheumatic diseases is an integral part of care of patients with this type of disease. Surgical interventions in patients with rheumatic diseases older than 60 years are specific not only due to specific course of the underlying disease but also due to increased incidence of comorbidities that have a considerable impact on the patients' ability to undergo surgery and on the possibilities of the subsequent convalescence. The patients' willingness to undergo surgery and their ability to cooperate within postoperative rehabilitation are influenced also by their physical condition and mental changes.

32.2 General Aspects

The mainstay of indication of elderly patients for operative treatment is a proper assessment of the patients' general health status and their capacity to withstand surgery. This phase is quite difficult and requires ample experience on the part of the physicians responsible for indication and assessment.

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The capacity to withstand a surgery is highly individual in the elderly patients. A higher calendar age has merely an indicative value. It generally urges the need for a meticulous preoperative examination but says nothing about the patient's biological capacity. The whole decision-making process is complex and should be for practical reasons divided into several phases.

32.3 Preliminary Indication

Indication of a patient with rheumatoid disease for surgery is based on a preliminary decision whether any of the options of operative treatment can be used in the given case.

Preliminary indication must be considered by the attending rheumatologist in cooperation with the orthopaedic surgeon. In this phase elderly patients with rheumatoid disease and other diagnosed comorbidities must be assessed in terms of appropriateness of operative treatment, including risk-benefit analysis.

In general, the burden put by the surgery on the patient decreases from the centre to the periphery, with the most demanding operations being those of the spine and large joints, the hip in particular. Upper limb surgery is as a rule less demanding than lower limb operations. Operative treatment of the hand and foot is usually well tolerated and may be performed under local anaesthesia.

Patients with rheumatic diseases most often have a concomitant cardiac and renal involvement.

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Their most severe forms are in combination with advanced age which is an absolute contraindication for surgery, and therefore, surgical option is not offered to these patients.

Other absolute contraindications include progressive atherosclerosis, various forms of senile dementia, progressive Alzheimer's disease and mental disorders not allowing adequate cooperation during postoperative rehabilitation.

Relative contraindications include Parkinson disease limiting the possibilities of rehabilitation and various forms of vascular diseases increasing the risk of embolism (varices) or local healing disorders (vasculitis). Caution has to be taken mainly in case of trophic changes in the limbs that are not only a warning signal of inadequate blood supply but also a source of potential infection. It is absolutely inevitable to treat and heal these defects prior to surgery.

Attention should be paid also to diabetes, the milder forms of which are not contraindicated for surgery. Surgery is feasible also in more severe forms of the disease provided that medication has been appropriately adjusted. Nevertheless, increased risk of healing disorders and infectious complications must be always taken into account, particularly in surgical interventions in the periphery.

In elderly patients, mainly in those with a longer history of rheumatoid inflammatory processes, it may be expected that they have undergone one of the forms of corticoid treatment and will probably show a decreased adrenaline response to the burden put by surgery. This situation alone is not a contraindication, but the corticoid dosage during operation and in the immediate postoperative period must be adequately increased. The surgeon should be ready to face potential problems caused by severe manifestations of osteoporosis and cutaneous atrophy.

Combinations of milder forms of the mentioned diseases in connection with a rheumatic diseases and advanced age should be also treated with caution, as their risks are not summed, but multiplied. If a conclusion is made on the basis of preliminary assessment of all factors that the operation will be beneficial and is probably feasible, such conclusion is communicated to the patient.

32.4 Patient Education

Informing patients about the possibility of operative treatment and obtaining their standpoint is of essential importance. Patients must be informed about the type of surgery, its course and subsequent rehabilitation, the expected outcome and potential risks. Elderly patients often reject the proposed intervention due to their age and prefer to cope with certain difficulties or functional limitations. Except for the risk of spinal cord compression due to shifts of the cervical vertebrae, all other indications in patients with rheumatic diseases are relative, and complaints are perceived differently by patients. Therefore, we respect the patients' negative attitude and do not urge the need for surgery. Only a positively motivated patient can provide a guarantee for the necessary cooperation in the postoperative period.

32.5 Preoperative Examination and Preparation

Patients consenting to surgery undergo a detailed preoperative examination focused on evaluation of the known and common potential risks. As it is sometimes a relatively complicated process in terms of time and cost, which has to be often adjusted to the latest findings, it is preferable to admit the patient to the hospital. Ideally, examination is performed by a physician or facility having the necessary experience with the impact of individual orthopaedic operative interventions on the patient's general health status in the postoperative period and ability to assess the risks and propose preventive measures. It is also important to perform the surgery as soon as possible, after completion of internal assessment.

After transfer to the orthopaedic department, the patient undergoes preoperative anaesthesiological assessment, and, where appropriate, additional steps in the preoperative preparation are suggested. Special attention in this phase should be paid to patients with symptoms of atlantoaxial instability or to those who already underwent cervical spine stabilization before. Control radiography, CT scanning and neurological examination

are performed to obtain the latest findings and choose the proper form of anaesthesia in order to avoid neurological complications [1]. Similar attention must be paid to patients with the cervical spine involvement in ankylosing spondylitis.

Surgery follows without undue delay. Emphasis in preoperative preparation is put on the patient's adequate hydration and balance of minerals, potassium and sodium in particular.

Chronic medication is limited to the necessary minimum. Patients receiving methotrexate are advised to discontinue medication approximately 2 weeks prior to surgery. In patients with biological therapy, the operation is preferably scheduled in the middle of the time interval between individual applications. Corticoid-dependent patients, including those with a past history of receiving higher doses of corticoids, are converted from oral application to intraoperative intravenous substitution. The dosage ranges from tens to hundreds mg daily based on the complexity of the operation and the degree of corticoid dependence. All patients with some form of diabetes are converted immediately before the surgery to intravenous application of insulin. Emphasis is put on antithrombotic prevention by heparin derivatives and short-term intraoperative prevention by intravenous antibiotics.

32.5.1 Compensation of Blood Loss

Blood loss is compensated immediately intraoperatively and, if necessary, in the following postoperative days to prevent the risk of ischemic myocardial, renal and CNS changes. Blood and erythrocyte mass from donors are preferred. Autotransfusion is not suitable in elderly patients, mainly in those with rheumatoid disease, as the baseline blood count values are often decreased and after blood collection they would get back to normal only slowly. Blood substitute solutions are used only minimally as they put an extra burden on the organism and modify blood sedimentation rate, and during degradation, they may cause undesirable sudden drops in blood pressure, i.e. they induce situations that are difficult to cope with by the risky elderly patients.

32.5.2 Rehabilitation and Follow-Up Care

Rehabilitation and follow-up care provided to older patients are highly demanding in professional, time and economic terms. The convalescence phase is usually longer and requires highly specialized care. It puts great demands mainly on the nursing and rehabilitation staff. Rehabilitation must be timely and intensive, with adjustments to the patients' specific needs and their immediate and general health status. Daily operation of the orthopaedic department usually does not allow providing patients with sufficiently intensive care, and therefore it is suitable to refer them after management of the acute surgical phase to a specialized rehabilitation facility for a longer-term individualized rehabilitation. Another reason is that many seniors do not have adequate home background to continue convalescence and rehabilitation in the outpatient mode.

32.5.3 Types of Surgery Performed in Patients with Rheumatic Diseases

Surgical interventions in older patients with rheumatic diseases may also be divided into preventive and reconstructive procedures [2]. Preventive interventions include synovectomy and tenosynovectomy. Reconstructive interventions include osteotomy, arthrodesis and arthroplasty, subdivided into resection and total replacement procedures. Their use differs in individual joints or joints in the linkage system.

Elderly patients often have a long history of rheumatoid disease which in case of severe forms results in progressive destructive changes in large joints of lower limbs as well as small joints of the wrist, subtalar region, hand and forefoot. A high risk is associated with cervical spine instability accompanied by displacement of vertebrae that may cause spinal cord compression. Destructive nature of all mentioned changes, combined in older patients with alterations of their general health status, requires a single-step and simple solution. Therefore joint reconstructions, primarily arthrodesis and arthroplasty, are preferred.

32.6 Large Limb Joints Surgery

This category includes hip, knee, shoulder and elbow surgery. These surgeries are more common in weight bearing joints of lower limbs. In the past, hip surgeries were predominating, while currently the number of hip and knee surgeries is more or less equal. The frequency of shoulder operations is continuously growing, and more extensive surgeries of the elbow in patients over the age of 70 are not infrequent, either.

Synovectomy Due to structural changes of articular surfaces in elderly patients, the preventive role of synovectomy is minimal. Therefore, it is performed rarely, as a palliative intervention in case of uncontrollable recurrent effusion in large joints, occurring mostly in the knee, less often in shoulder and elbow. Preference is given to open synovectomy over the otherwise commonly used arthroscopic technique [3]. The reason is a more radical approach in open synovectomy which allows also to remove the affected fibrous joint capsule and to treat the adjacent bursae. The effect is, however, only temporary. Another disadvantage is a relatively demanding several-week rehabilitation which, if not managed or neglected, leads to joint rigidity or instability.

Corrective Osteotomy This procedure is being in general abandoned, especially in the elderly. The reason is its rather short-term effect, difficult technique and complicated fixation of the osteoporotic bone. Modern total arthroplasty and the related operative techniques can manage malalignments and destruction of large joints with better and more long-term functional outcomes and a shorter period required for convalescence.

Arthrodesis This method is most commonly used in the knee joint. Indication includes cases that cannot be treated by joint replacement (e.g. recurring infections, bone loss defects) or where arthroplasty repeatedly failed (Fig. 32.1).

In the long run, it eliminates pain and improves weight bearing capacity and stability at the expense of certain limitation of function, e.g. when walking up and down stairs, driving a car or sitting in a restricted space. Arthrodesis of the knee is not recommended in patients with limited mobility, who spend most of the day sitting, and the limb fixed in extension is uncomfortable.

Arthrodesis in flexion can be used to stabilize a "floating" severely damaged elbow. However it is technically highly difficult, and therefore preference is given in older patients to custom-made braces.

Priority in the hip and shoulder is given to mobility rather than stability. Arthrodesis of these

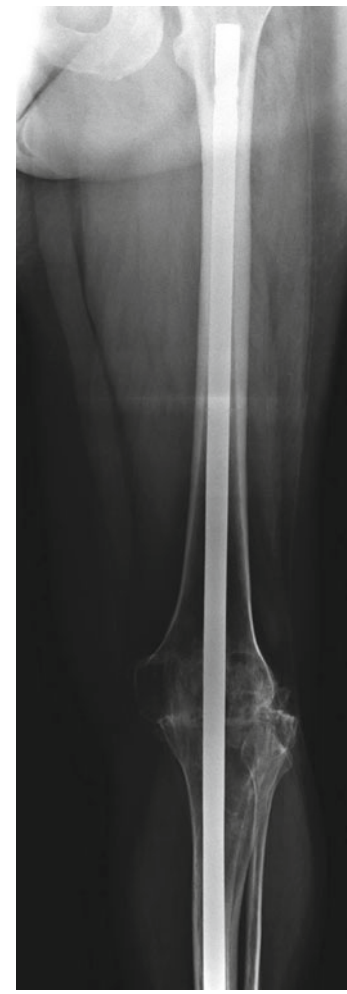

Fig. 32.1 Arthrodesis of the knee joint with a nail

joints is almost never performed in older patients. Preference is given to arthroplasty and, in extreme cases, mainly in the hip joint, to resection arthroplasty (Fig. 32.2). The same applies to the conditions after removal of the hip joint replacement, where the patient's local or general condition does not allow reimplantation. After several weeks, there occurs robust scarring in the region of the joint. Rigid fibrous scar tissue then allows walking over short distance and preserves the joint motion necessary for comfortable sitting. The toll is the decreased weight bearing capacity and limb shortening of varying extent, requiring the use of axillary crutches and orthotic shoes.

Joint Replacement This is the most commonly used reconstructive surgery in the elderly. Technically it is applicable for all large joints of limbs. An appropriately indicated and implanted joint replacement eliminates pain and preserves the function of the joint or even restores it, if already lost. Currently, there is no age limit for it. Its main contraindication is any infection in the organism leading to loosening or failure of the implant, neurological or muscles disorder affecting the postoperative function of the total replacement and severe internal conditions limiting the possibilities of anaesthesia.

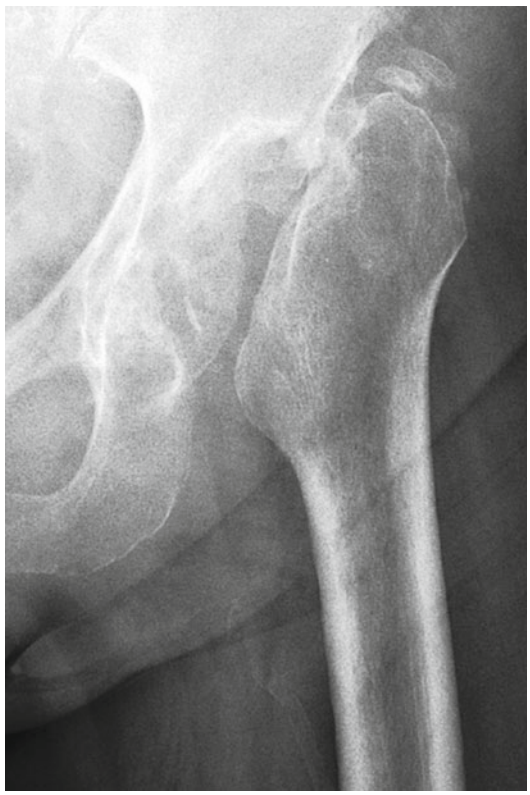

Fig. 32.2 Girdlestone resection arthroplasty of the hip joint

The hip joint is still the most common of the joints indicated for total arthroplasty as the damage to the joint by inflammation is often combined in this region with secondary osteoarthritic changes progressing even at sites where inflammation resolved a long time ago.

Hip disorders include a combination of rheumatic destruction with proximal femur fractures, less frequently a combination of rheumatic destruction with developmental dysplasia of the hip, and aseptic necrosis of the femoral head resulting from a long-term corticotherapy. All the above-mentioned pathological conditions of the hip are further complicated, mainly in women, by severe osteoporosis caused by several factors (menopause, corticotherapy, inactivity, damage to connective tissue).

These complicated conditions of the hip are most commonly treated by total joint replacements (including both the acetabular and femoral components) fixed by bone cement. There are several reasons for their use.

First, osteoporotic bone is difficult to prepare, and only under favourable circumstances a precise and stable bed can be created for primary fixation of cementless implant components. Secondly, blood loss is lower with the use of cemented implants, as the bone cement closes the exposed cancellous bone of the pelvis and femoral canal. Thirdly and most importantly, cemented joint replacements allow full weight bearing from the first postoperative days. This considerably facilitates and accelerates the necessary early mobilization of the patients also in case of movement coordination disorders or a frequent polyarticular involvement.

Sometimes highly painful and dysfunctional hip must be treated in patients with a poor general health status. This happens mainly in situations

when the joint damaged by rheumatism was further affected by a femoral neck fracture or when the underlying disease was followed by rapidly progressing necrosis of the femoral head associated with its resorption. These patients suffer from intensive pain, are almost immobilized and are difficult to treat even in bed. These cases are often a vital indication for surgery.

The patient is usually operated on under spinal anaesthesia, and the operative time should be reduced to minimum. For this purpose, hemiarthroplasty is used, i.e. cemented implants consisting of the femoral component only. A range of available sizes of the implant allow choosing a component that fits the patient's native acetabulum which remains in place. This solution considerably reduces the operative time and the burden put on the patient, eliminating the most demanding part of the operation on the pelvis. The disadvantage is a shorter life expectancy of these implants, and therefore the procedure should be reserved as an emergency solution for biologically old patients with limited mobility.

Knee Joint Knee total arthroplasty is the second most common joint replacement. Its indication is not limited by age. Life expectancy of an appropriately indicated and properly implanted knee joint replacement may exceed twenty years [4]. Indication for knee replacement is rather relative. Perception of problems is highly subjective. Isolated knee joint replacement in the presence of untreated involvement of the neighbouring joints will only minimally improve the patient's mobility, treatability and self-care capacity.

Indication for the operation requires a careful assessment of the patient's general ability to cooperate in the postoperative period as the knee joint is considerably more demanding in terms of intensity and duration of active postoperative rehabilitation than the hip joint. For the above given reasons, it is necessary to respect in older patients more than ever their attitude to potential operation and not to press them. An exception is the presence of a severe valgus deformity with a simultaneous good function of the adjacent joints. This type of deformity tends to accelerating progression depending on the degree of deformity and may cause full loss of walking ability in a relatively short time. In addition, late correction of severe valgus deformities is associated with a number of technical and surgical compromises often leading to a reduced life expectancy of the implant.

Implants are cemented. The burden put on the patient is lower than in hip surgery. Blood loss is markedly lower thanks to the use of pneumatic tourniquet. Due to superficial placement of the implant, any disorder of surgical wound healing is burdened with a higher risk of development of implant infection. Knee replacements may be seriously endangered also by small contaminated skin defects, e.g. trophic ulcers, or in patients with rheumatoid disease, by relatively often infected plantar pressure sores. A very serious and underestimated risk is posed by untreated interdigital mycoses, quite frequently seen in older patients, that are an entry point for highly dangerous streptococcal infections. Erysipelas on the limb with implanted endoprosthesis leads almost in 100 % of cases to its failure, and also its reimplantation is burdened by a high rate of failures. Successful treatment and healing of all the mentioned foci are basic prerequisites for indication for knee replacement [5].

Shoulder Joint The number of implanted shoulder replacements is currently rapidly growing, although they still lag far behind the number of joint replacements implanted in lower limbs. As shoulder is not a weight bearing joint, even relatively progressive destructions may be associated with only insignificant subjective complaints. The range of motion gets insidiously limited, and mainly older patients relatively well adapt to this limitation. Therefore in purely rheumatology indications, shoulder replacement is performed mainly in younger patients with the aim to manage pain but mainly to maintain maximum mobility in the joint and self-care capacity and ideally also capability for work. A fully functional shoulder replacement requires early indication and a highly demanding and relatively intensive long-term rehabilitation. The situation is different in older patients. The shoulder disorder as a rule develops over a long time, and they get used to it.

As they usually have a number of other more serious health problems, they usually reject the operation. They may change their attitude at the moment when this condition is further complicated by a concomitant trauma, commonly by a proximal humerus fracture after a fall or necrosis of humeral head and its resorption. These conditions are associated with a severe functional limitation and significant pain.

Endoprosthesis of a suitable type is then indicated also in cases when the type of damage and the patient's health do not provide a guarantee of full recovery of the range of motion in the joint. Indication for operation in this context aims at elimination of pain and long-term maintenance of the best possible functional outcome. Shoulder replacements of all types are not associated with a high surgical burden, and blood loss is minimal. The surgical burden can be further minimized by the use of cemented proximal humerus hemiarthroplasty where the artificial joint articulates with the original glenoid (Fig. 32.3). The extent of recovery of the range of motion is usually limited by the patient's ability to rehabilitate and mainly by the condition of the rotator cuff, which is largely responsible for the functional outcome and is difficult to reconstruct if damaged. In patients with a good general health status and sufficient prerequisites for the following rehabilitation, the functional outcome may be further improved by a reverse shoulder endoprosthesis (Fig. 32.4), compensating the rotator cuff defect [6]. Its implantation, however, requires adequate bone quality in the region of the glenoid and scapular neck allowing a stable fixation of the respective component. Unfortunately, these prerequisites are only exceptionally met in older patients. Contraindications of shoulder replacement are similar to those in other joint replacements. A special contraindication for all types of shoulder replacements, including the reverse ones, is axillary nerve palsy, because without its function it is impossible to achieve the required stability of the implanted endoprosthesis. Rheumatologists should be aware of the fact that a healed shoulder replacement of any type is not a contraindication for axillary crutches.

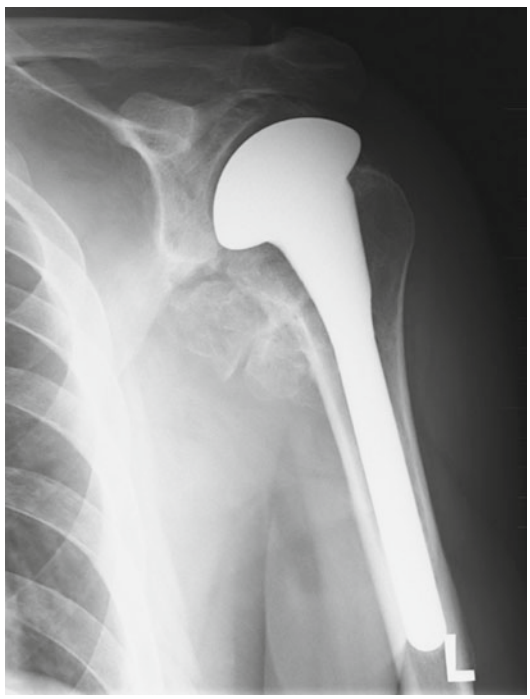

Fig. 32.3 Proximal humerus hemiarthroplasty

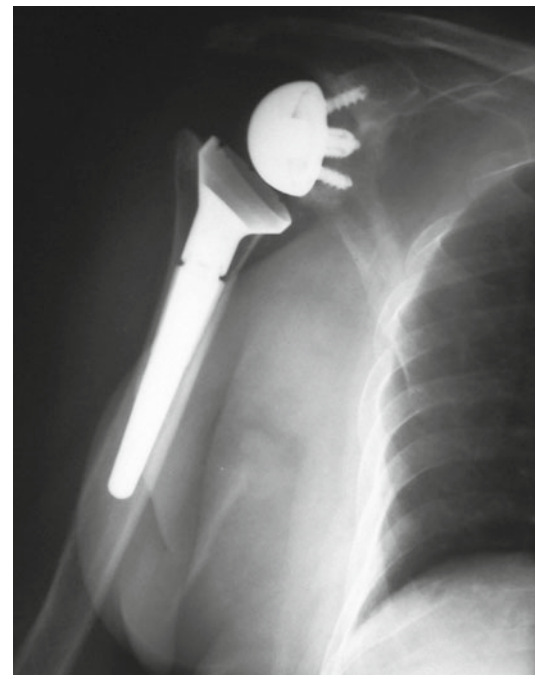

Fig. 32.4 Reverse shoulder replacement

Elbow Joint Elbow endoprostheses are still indicated relatively rarely (Fig. 32.5a, b). They are quite vulnerable, demanding in terms of rehabilitation and still burdened with quite a high rate of complications [7]. In patients with rheumatic diseases, they are used infrequently, only in cases when bilateral ankylosis of the elbow in incorrect position negatively affects the patient's basic self-care capacity.

The burden put on the patient by the surgery is minimal. A drawback of these endoprostheses is the need for an intensive long-term consistent rehabilitation, the risk of rapid wear and tear with the use of crutches and a danger of periprosthetic fractures by fall on the limb which are fatal for the endoprosthesis.

32.6.1 Wrist and Hand Surgery

In addition to preventive synovectomy and tenosynovectomy, the procedures include a wide range of reconstructive interventions [8]. The burden of these interventions is minimal, and a number of them may be performed in local or field block anaesthesia. Blood substitutes are not required. Indication for these procedures may be beneficial to the patient at any age. Older patients, however, often get well adapted even to severe deformities and often reject operation.

Synovectomy and Tenosynovectomy They are useful in this location regardless of age. A timely indication, mainly in extensors in the carpal region and flexor tendons of fingers, may prevent their rupture and the resultant severe functional impairment of the hand in terms of grip or grasp.

Tendon Reconstructive Surgery Untreated synovialitis and deformities in the carpal region may lead to spontaneous ruptures of tendons of extensors, less frequently of flexors, that considerably affect the ability to grasp. Ruptured extensors of individual fingers are reinserted to the tendons of other fingers, with the following synkinesis. Sometimes the extensor indicis proprius can be used to replace the tendon. In the elderly, the success rate of flexor reconstruction is minimal.

A frequent problem in older patients are so-called "trigger" fingers, unable of active extension after normal flexion. Passive manipulation of the finger into full extension is accompanied by pain-

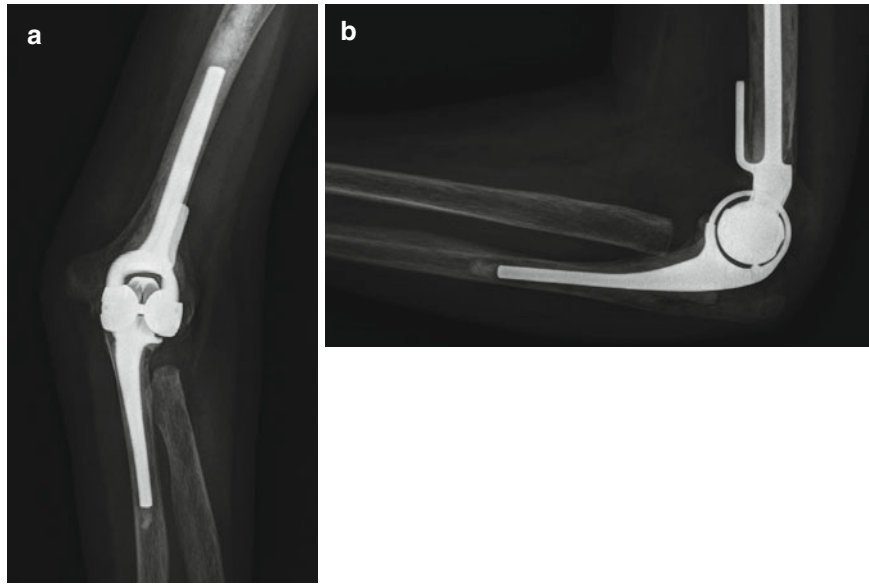

Fig. 32.5 Elbow joint replacement. (**a**) AP projection; (**b**) lateral projection

ful popping or snapping in the palm. The onset of the disorder is sudden and gets worse over time. It is not extremely painful, but it may be annoying as it occurs several times a day. It results from thickening of the flexor tendon within the distal aspect of the palm. This thickening causes abnormal gliding and locking of the tendon within the tendon sheath. Specifically, the affected tendon is caught at the edge of the first annular (A1) pulley. Inflammation can be treated by careful local application of a small amount of corticoid in the area of tendon sheath. Corticoid must not be applied directly to the tendon as there is a risk of its rupture. Where conservative treatment fails or the condition recurs, surgery is indicated, consisting in cutting through the tendon sheath to open it from a minimal incision under local anaesthesia.

Arthrodesis This procedure is highly beneficial at any age. It may have a noticeable cosmetic and functional effect, and at the same time, it prevents tendon ruptures, mainly in the region of the displaced carpus. The burden put by surgery on the patient is minimal. Arthrodesis of the carpus (Fig. 32.6a, b), regardless of the technique used, facilitates the use of crutches, as the wrist is then capable of full weight bearing and provides a reliable pain-free support. The second most beneficial procedure in terms of functional effect is fusion of usurated, subluxated or even dislocated metacarpophalangeal joint of the thumb. The affected thumb cannot adequately oppose the other digits, resulting in dropping of heavier objects, for instance, of a cup of water. Arthrodesis performed in correct position restores adequate thumb opposition.

Arthrodesis is also a rewarding and relatively simple procedure at the level of the damaged carpometacarpal joint of the 1st ray of the hand (Fig. 32.7a, b) and in severely affected

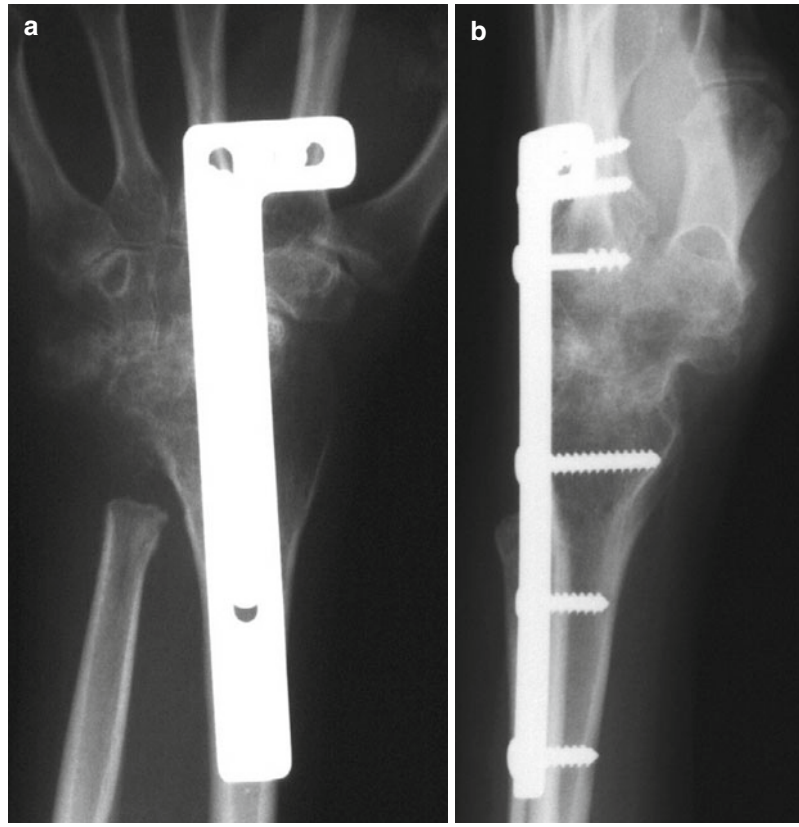

Fig. 32.6 Carpal arthrodesis by plate. (**a**) AP projection; (**b**) lateral projection

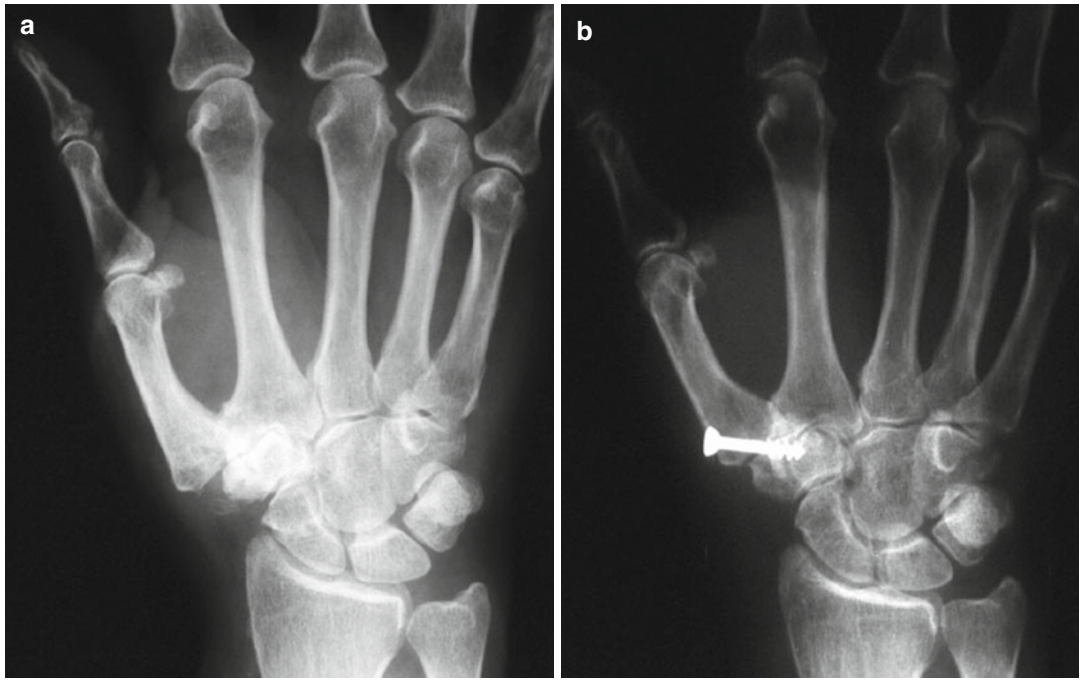

Fig. 32.7 Arthrodesis of the carpometacarpal joint of the 1st ray of the hand. (**a**) Pre-op; (**b**) post-op

interphalangeal joints of fingers. This procedure is particularly effective in bizarre deformities encountered in psoriatic arthritis.

Resection and Osteotomy These procedures are exceptional in hand and wrist surgery in patients with rheumatic diseases and are almost never performed in the elderly.

Arthroplasty These interventions can be performed to treat the carpometacarpal joint of the thumb, metacarpophalangeal and interphalangeal joints of the hand as well as in the wrist, although they are rarely used in older patients.

32.6.2 Ankle and Foot Surgery

These interventions are one of the most common procedures in patients with rheumatic diseases and are indicated also in older patients. The reason is a high rate of quite severe lesions and deformities in this region resulting from the rheumatoid disease and its combination with natural wear and tear of this statically extremely loaded part of the human body [9]. In addition to chronic pain, they can make it very difficult to wear normal shoes and thus significantly limit the patients' activities of daily living. They also may cause chronic pressure sores of the loaded parts of the foot that are painful and may be the entry point of dangerous infections. In terms of general surgical burden, blood loss or rehabilitation, these procedures are not very demanding. The only limitation is that they require quite a long period of non-weight bearing of the lower limb which may be a serious complication in older patients with a typical polyarticular involvement. Therefore, one-step complex solutions are preferred in older patients, with the shortest possible time necessary for convalescence even at the expense of the function or cosmetic effect. Prior to decision about surgery, it is always necessary to consider whether the condition cannot be resolved by orthotic devices, such as modified and custom-made footwear or different types of orthotic insoles and correctors.

Synovectomy and Tenosynovectomy They are not frequently used in older patients. Where necessary, they are performed arthroscopically in synovialitis of the talocrural joint, unresponsive to common conservative therapy. It is necessary to distinguish between arthritis of the joint and tenosynovialitis in the region of the tendon sheaths of peroneal muscles passing behind the lateral malleolus, extensors in the region of retinacula on the anterior aspect of the ankle and flexors passing behind the medial malleolus. These disorders are treated by tenosynovectomy from individual incisions in the respective region in order to prevent spontaneous tendon ruptures. In other tarsal and forefoot joints, synovectomy is usually part of the reconstructive procedures.

Arthrodesis This procedure is used to treat severe destructions in the region of the talocrural joint and mainly subtalar joints, the deformity of which is during clinical examination often confused with ankle involvement. A proper diagnosis requires radiographs of the ankle and foot in two projections. In case of suspected osteonecrosis of the talus, that might protract or prevent healing of the planned arthrodesis, it is suitable to use also NMRI. Surgery usually includes fusion of several neighbouring joints forming one functional unit to avoid repeating the surgery of another joint in the short run. A typical example is a triple arthrodesis in the region of the Chopart joint, consisting in fusion of the talocalcaneal, talonavicular and calcaneocuboid joints. It is combined with wedge osteotomies to restore orthograde position of the foot in all three planes. Progressive multi-level deformities require pantalar arthrodesis, combining the triple subtalar arthrodesis with ankle fusion (Fig. 32.8a, b). These interventions are supplemented by internal fixation in order to avoid fixation of the limb by the plaster of Paris and reduce the time to heal to minimum. In spite of this, it is necessary to limit weight bearing of the limb always for several weeks. External fixators are not suitable for use in elderly patients, as they have problems to cope with them psychically and are often unable to take care properly of the limb fixed in this way. In the region of the forefoot, preference is given in older patients to resection procedures that are less demanding in terms of the method of fixation and the period of the necessary postoperative non-weight bearing.

Osteotomy This procedure is currently very popular in the treatment of forefoot deformities, particularly of sequelae of the acquired flatfoot, including hallux valgus [10]. However, it is not very suitable for use in older patients due to technical difficulties associated with osteoporotic bone and the related impossibility of adequate fixation. It also requires a relatively long period of non-weight bearing for the sake of proper healing.

Resection Arthroplasty It is traditionally the most common reconstructive procedure on the forefoot in older patients with osteoporosis. The space of the resected joint heals with a rigid fibrous scar tissue which is pain-free, keeps the respective segments in correct position and provides sufficient range of motion.

The cosmetic effect of the procedure and the achieved function are less optimal than in corrective osteotomies, but they allow a much sooner weight bearing. Its disadvantage as compared to arthrodesis is a certain risk of deformity recurrence. Appropriately performed resection arthroplasty, however, provides older patients with a considerable subjective relief; putting on shoes is easier; the procedure reduces the risk of plantar pressure sores and improves functional capability in patients with lower activity demands. The advantage is a shorter period of convalescence not so demanding in terms of nursing care. The most common intervention is resection of the proximal end of the proximal phalanx of the great toe (Keller resection arthroplasty) for hallux valgus, resection of plantar prominence of metatarsal heads in the acquired flatfoot (Hoffmann operation) (Fig. 32.9a, b) or resection of proximal phalanx head to correct hammertoes (post-operation) and their combination.

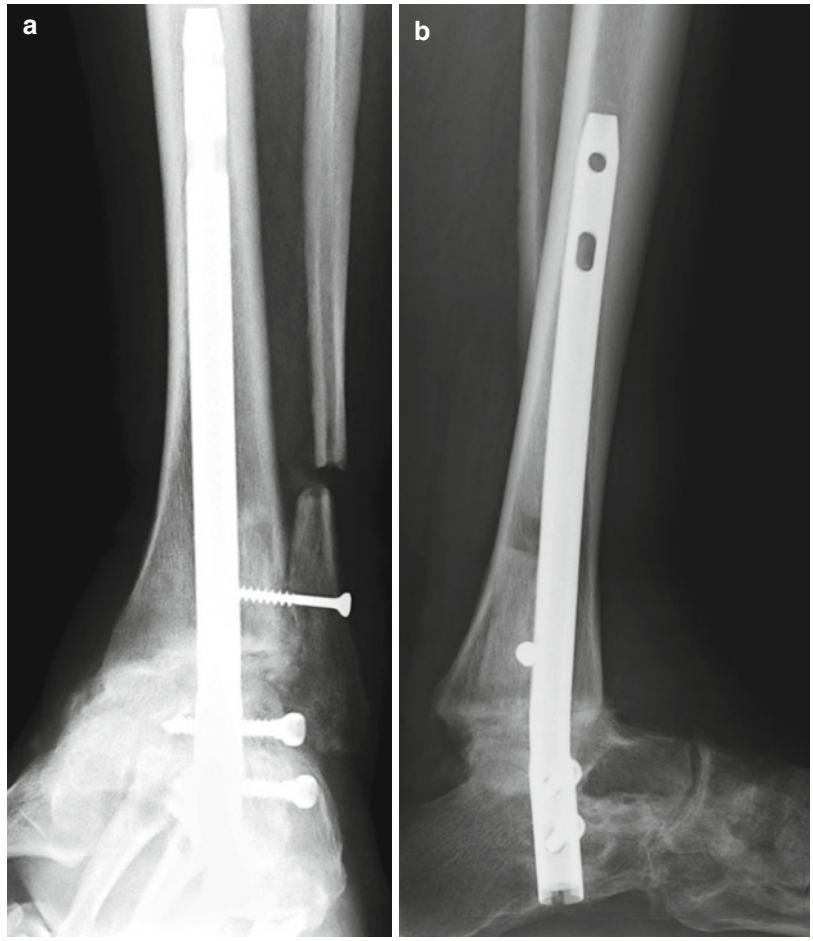

Fig. 32.8 Combination of ankle and talocalcaneal arthrodesis with intramedullary nail. (**a**) AP projection; (**b**) lateral projection

Arthroplasty Replacements of ankle and the metatarsophalangeal joint of the thumb are commonly available today. However, they are not quite suitable for use in older patients as they require high-quality bone necessary to fix the implant and are followed by a demanding postoperative phase.

32.6.3 Spine Surgery

These interventions put a high general burden on the organism and convalescence. Therefore, they are as a rule not performed in older patients. The most frequent problems of the elderly, compression fractures and deformities of osteoporotic vertebral bodies, mostly in the lumbar spine, are treated by braces, adequate medication and physical therapy.

The only condition indicated for spinal surgery in older patients is atlantoaxial subluxation caused by inflammatory destruction of ligaments of the atlantoaxial articulation followed by atypical movement and a shift of C1 in relation to C2 vertebra. One of the consequences is narrowing of the spinal canal with an insidious development of cervical myelopathy. They occur commonly in severe cases of rheumatoid arthritis, although they have been reported also in psoriatic arthritis.

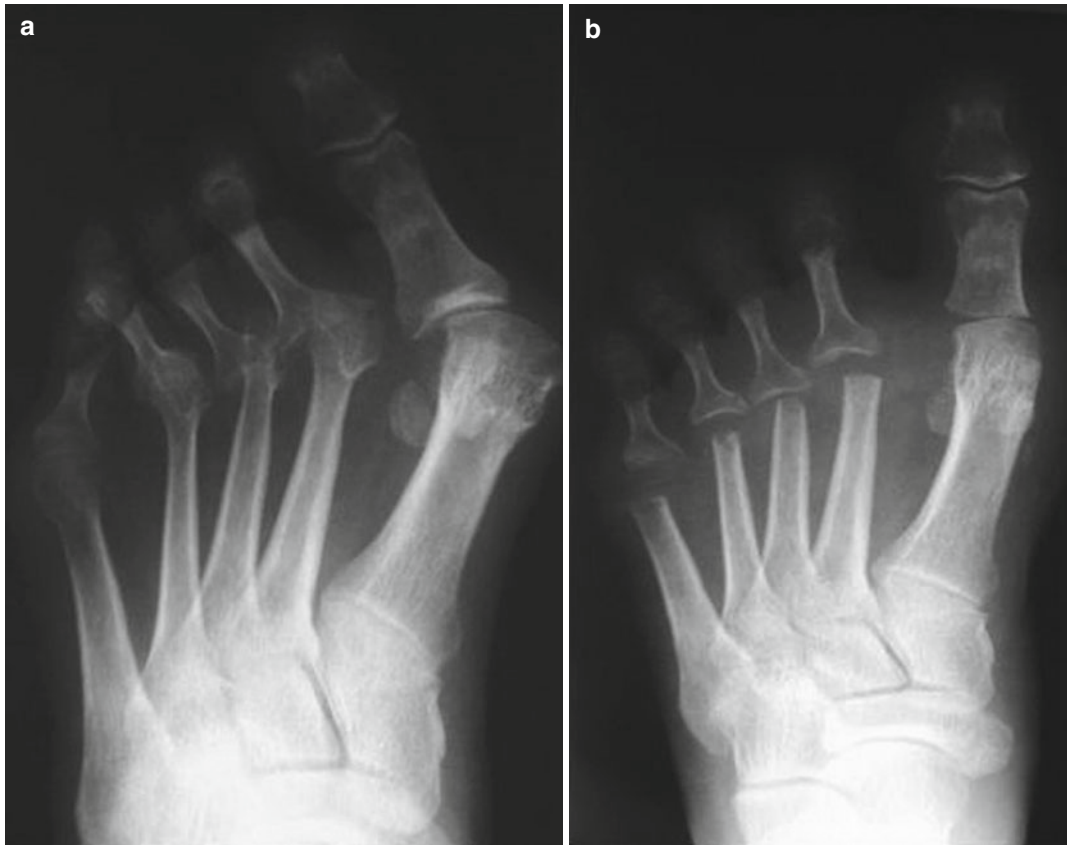

Fig. 32.9 Resection arthroplasty of the proximal end of the proximal phalanx of the great toe for hallux valgus and of plantar prominence of metatarsal heads II–V. (**a**) Rheumatic deformity prior to operation; (**b**) postoperative radiograph

In ankylosing spondylitis, a similar condition may be induced by disruption of the integrity of the osteoporotic dens axis. The course of the disorder may be asymptomatic or associated with various neurological symptoms. In addition to spinal cord involvement, there may occur also compression of vertebral arteries. Clinical manifestations may include paraesthesia and palsy of upper extremities, balance disorders, tinnitus, vertigo, headache, swallowing disorders and symptoms of transient ischemic attack. The most severe forms may lead to sudden death. The basic diagnostic examination is a plain AP and lateral radiograph and transoral projection on the dens. It is important to assess the retrodental interval that should be at least 14 mm. A pathological finding should be supplemented by neurological examination, NMRI, CT examination and electrophysiological tests. Dynamic radiographs are used for functional assessment of stability of the proximal C1/2 spine. Milder forms may be fixed by a brace. Patients are always registered and followed up regularly. In younger patients, a relative indication for spinal surgery is pain in the craniocervical junction unresponsive to conservative treatment and a progressive radiographic finding. An absolute indication, regardless of age, are symptoms of neurological deficit and its progression. The aim of the surgery is to achieve fusion of unstable segments of the cervical spine using internal fixation [11]. The operative technique depends on the type and extent of the damage. Based on the type of

procedure, postoperative care consists in fixation by brace of various duration, long-term rehabilitation adjusted to the patient's needs and consulted with the surgeon and follow-up care provided by neurologist and spinal surgeon.

Conclusion

Surgical procedures may be a useful part of the comprehensive care of elderly patients with rheumatoid disease. However, their indication requires prudence and comprehensive assessment of the patient's condition by a rheumatologist, internal medicine specialist, anaesthesiologist and surgeon. Rather than age, the global decisive criterion should be the actual biological potential of the particular individual. An indispensable part of success is also the patient's ability and willingness to cooperate during long-term rehabilitation in the postoperative period.

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Paget's Disease of Bone

33

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Paget's disease is a chronic disorder characterised by increased resorption and deposition of bone mass, causing various skeletal deformities. It is the second most common bone disorder, following osteoporosis. It is manifested by excessive resorption of bone by osteoclasts and subsequent secondary increase of osteoblast activity. As a result the normal bone tissue is gradually replaced by vascular connective tissue, resulting in a thickened, disorganised trabecular pattern of bone which is of lower quality and has decreased mechanical resistance. The disease, also known as osteitis deformans, was first described by the English pathologist Sir James Paget, at the end of the nineteenth century [1].

The form of the disease occurring in adults has a strong genetic component, with focal increases in bone remodelling. It may involve one or more bones of the skeleton simultaneously. It affects predominantly the pelvis, skull, vertebrae and long bones. Paget's disease complications can be found in one bone (monostotic form) or more bones (polyostotic form) and cause deformities, fractures, neoplastic degenerations, lesions of the joints, the central nervous system and blood vessels.

33.1 Epidemiology

Prevalence of this disease is difficult to determine as it often develops without symptoms and is diagnosed by radiography, indicated for some other reason. The probability of development of the disease increases with increasing age and is most common in the fifth- and sixth-age decade. Some studies report its worldwide incidence of

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about 1/100,000. Its prevalence is strongly linked to European ancestry [1]. In Great Britain the prevalence in older population is almost 10 %. Its incidence is higher in Great Britain, North America, Australia, New Zealand, France and Germany, while in Switzerland, Scandinavia, Ireland and southeast Europe, it is quite rare.

33.2 Aetiology

There are several theories describing etiopathogenesis of Paget's disease, but its cause remains unclear. The disease has a strong genetic predisposition. Many families have been identified, where it affects two or more generations in a way consistent with an autosomal dominant mode of inheritance. A positive family history is reported in about 15 % of cases. First-degree relatives of patients with this disease have about a sevenfold greater risk for its development. The disease may be associated with more loci such as SQSTM1 [1] (which encodes sequestosome-1, known as ubiquitin-binding protein p62) on chromosome 5q35 and TNFRSF11A (RANK) on chromosome 18q21–22 [2].

Other theories suggest potential environmental factors contributing to the development of the disease, namely, through measles or paramyxovirus infection [1, 3]. Electron microscopic studies revealed intranuclear inclusions in osteoclasts of patients with Paget's disease. Studies utilising indirect immunoflorescence techniques have demonstrated that these inclusions are similar to measles virus nucleocapsids (morbilli). Other studies revealed inclusions consisting of respiratory syncytial (RS) virus nucleocapsids. These findings suggest that various viruses may play an important role in the onset and further progress of Paget's disease.

33.3 Pathophysiology

Initial changes developing with progress of the disease consists in increased bone resorption at sites of excessive remodelling. This results in alteration of bone architecture and disorganisation of collagen lamellae, increase in number of osteoblasts and osteoclasts and production of low-quality bone matrix. Increased production and hyperactivity of osteoclasts are considered to be major abnormalities. They are probably caused by disorder of RANK-NF-kB signalling. Osteoclasts are increased in size and contain pleomorphic nuclei. As a response to increased resorption, osteoblasts increase in activity to make new bone material and produce osteoid. Disorganised deposits reduce resistance of bone, which is susceptible to bowing or fracture [4].

In the initial phases of the disease, bone turnover may be highly increased, sometimes as much as 20 times higher than the standard. This turnover is related to elevated serum bone alkaline phosphatase levels. Bone resorption stimulates release of calcium and phosphate ions from the bone, although serum levels of these electrolytes are within the reference range in patients with Paget's disease. It is explained by increased deposition of minerals in the newly formed bone, and the feedback effect on secretion of parathyroid hormone.

33.4 Clinical Features [5–8]

Most patients have no complaints, and the disease is revealed usually by radiographic examination of the pelvis or spine, requested for some other reason, or by elevated serum alkaline phosphatase levels. Sometimes patients may notice a swelling or deformity of long bones or walking disorder caused by unequal limb length. Enlarged skull goes often unnoticed by the patient. Some patients may initially complain of pain in the face or headache; lower back and lower limb pain are quite frequent.

Paget's disease is later manifested by bone deformities, such as skull hypertrophy and bowing of affected bones. It affects predominantly the pelvis and the sacrum (60 %), followed by the spine (50 %), skull and femur (40 %), tibia, humerus and clavicle (20 %), while it is infrequent in the hands, feet and facial bones. Pathological fractures may occur mainly in

weight-bearing joints. Fractures are of different patterns, including complete (transverse) or incomplete, with predominance on the convex aspect of bones.

The affected bone shows increased vascularity of bone marrow leading to skin vasodilation and its reddening. If disseminated, the disease may lead to heart failure due to an increased cardiac output, caused by high blood flow. Patients do not exhibit increased calcium excretion, although it may be higher in phases of higher bone resorption, incresing the incidence of urolithiasis. Hyperuricaemia and gout are common in men and may be associated with calcific periarthritis.

Hearing loss is usually caused by a direct damage to the middle ear ossicles, cochlear bone involvement or damage to the eighth cranial nerve. Severe neurological complications arise from excessive bone growth at the base of the skull and from brainstem compression. Spinal cord compression may cause paraplegia; pathological fractures of vertebrae are not infrequent.

The most feared complication is sarcoma, with an incidence of less than 1 %. Tumours commonly occur in the femur, humerus, skull, facial bones, pelvis and rarely in vertebrae. Prognosis is not good in sarcoma cases, and ablative surgery is rarely successful.

33.5 Diagnosis [9, 10]

In general, patients are asymptomatic at the onset of disease. In the progressive stage, physical examination helps identify deformities of extremities and the skull (Fig. 33.1a).

Diagnostic suspicion arises if laboratory and imaging methods reveal elevated serum alkaline phosphatase levels and bone changes. However, in about 10 % of patients, concentration of alkaline phosphatase may be within the reference range. In such case certain markers of bone resorption may be helpful, such as hydroxyproline, pyridinolines, N- or C-telopeptides, P1NP and bone alkaline phosphatase. There is good correlation of bone markers with disease activity, as seen by bone scintigraphy. Calcium and phosphorus levels are commonly within reference ranges, but 20 % of patients may have elevated parathyroid hormone levels, and sometimes elevated uric acid levels.

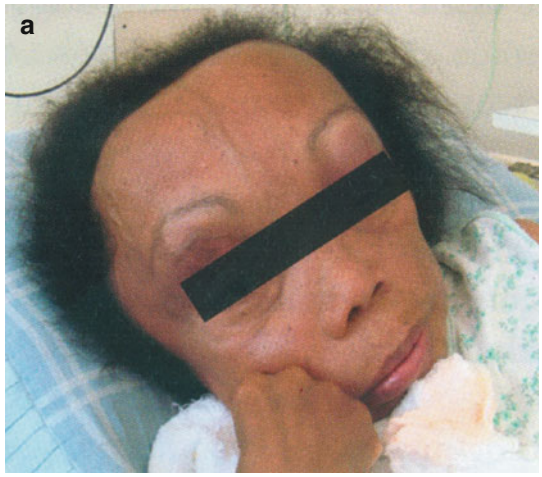
Due to their typical nature, changes are readily identifiable by imaging techniques. Paget's disease has several typical features, such as cotton-wool appearance of skull bone, due to enlarged osteolytic region and bone hypertrophy (Fig. 33.1b). Computed tomography and nuclear magnetic resonance imaging are used to assess nerve compression and ill-defined stress fractures and to examine tumour transformation (Fig. 33.1c). Bone scintigraphy is helpful in detecting the scope of the disease (Fig. 33.2). In some patients, scintigraphic changes may appear prior to radiological changes.

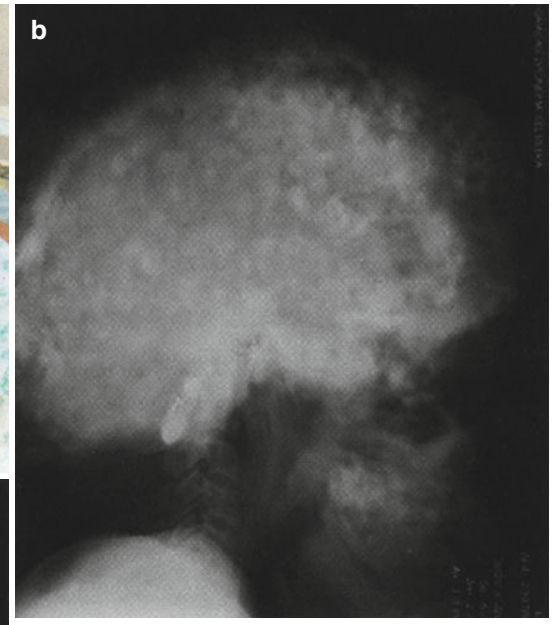
33.6 Treatment

Major therapy targets are to eliminate pain and restore normal bone metabolism. Treatment of bone remodelling should return lamellar bone formation back to normal and decrease bone vascularity and serum alkaline phosphatase levels. Goals are to slow down the progression of the disease and prevent development of deformities, fractures and osteoarthritis (Table 33.1).

Specific treatment of Paget's disease is indicated in patients with symptoms, in asymptomatic patients with elevated serum alkaline phosphatase levels, preoperatively to reduce bleeding and infrequently in hypercalcaemia, due to the patient's immobilisation in the polyostotic form of the disease.

Patients with Paget's disease, with typical bone pain, are treated by specific therapy in combination with analgesics and non-steroidal anti-inflammatory drugs. Laboratory tests of serum alkaline phosphatase level help distinguish active disease, if its level is twice to four times higher than the reference range. Some authors propose to initiate specific treatment only in case of involvement of the regions susceptible to development of severe complications (skull, spine and weight-bearing joints).





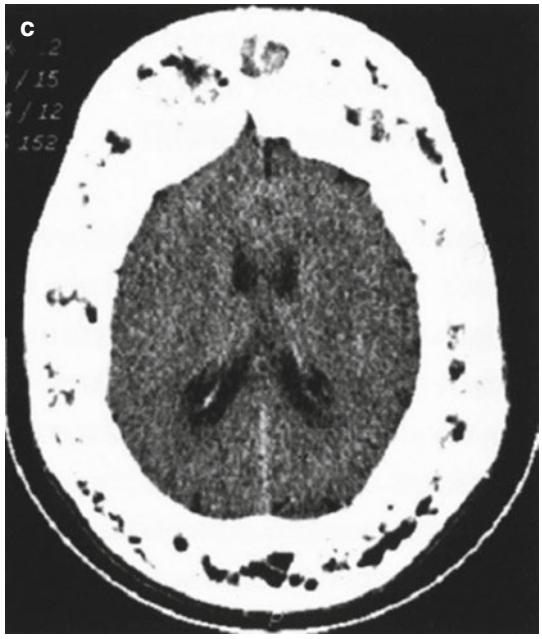


Fig. 33.1 Clinical symptoms of Paget's disease shown by imaging methods. (**a**) Female patient with more than 20-year history of untreated disease. Significant skull bone changes and complete loss of hearing. (**b**) Radiography of the patient's skull with cotton-wool appearance of bone due to lytic lesions. (**c**) CT scan of the patient's head with marked thickening of the calvaria

33.6.1 Specific Pharmacological Treatment

Drugs suppressing the progress of Paget's disease include bisphosphonates and calcitonin, osteoclast activity inhibitors [11, 12]. Drugs with higher toxicity, such as mithramycin or gallium nitrate, used to treat severe hypercalcaemia, are not recommended in Paget's disease. Calcitonin of salmon origin or synthetic calcitonin suppresses resorption of bone and may be administered through the subcutaneous or intranasal route. It is less effective than bisphosphonates. Calcitonin is usually used as a second-line drug in case a patient cannot receive bisphosphonates, or as a support therapy in pain management. The initial dose ranges from 50 to 100 units; it is used daily or every 2–3 days. The most com-

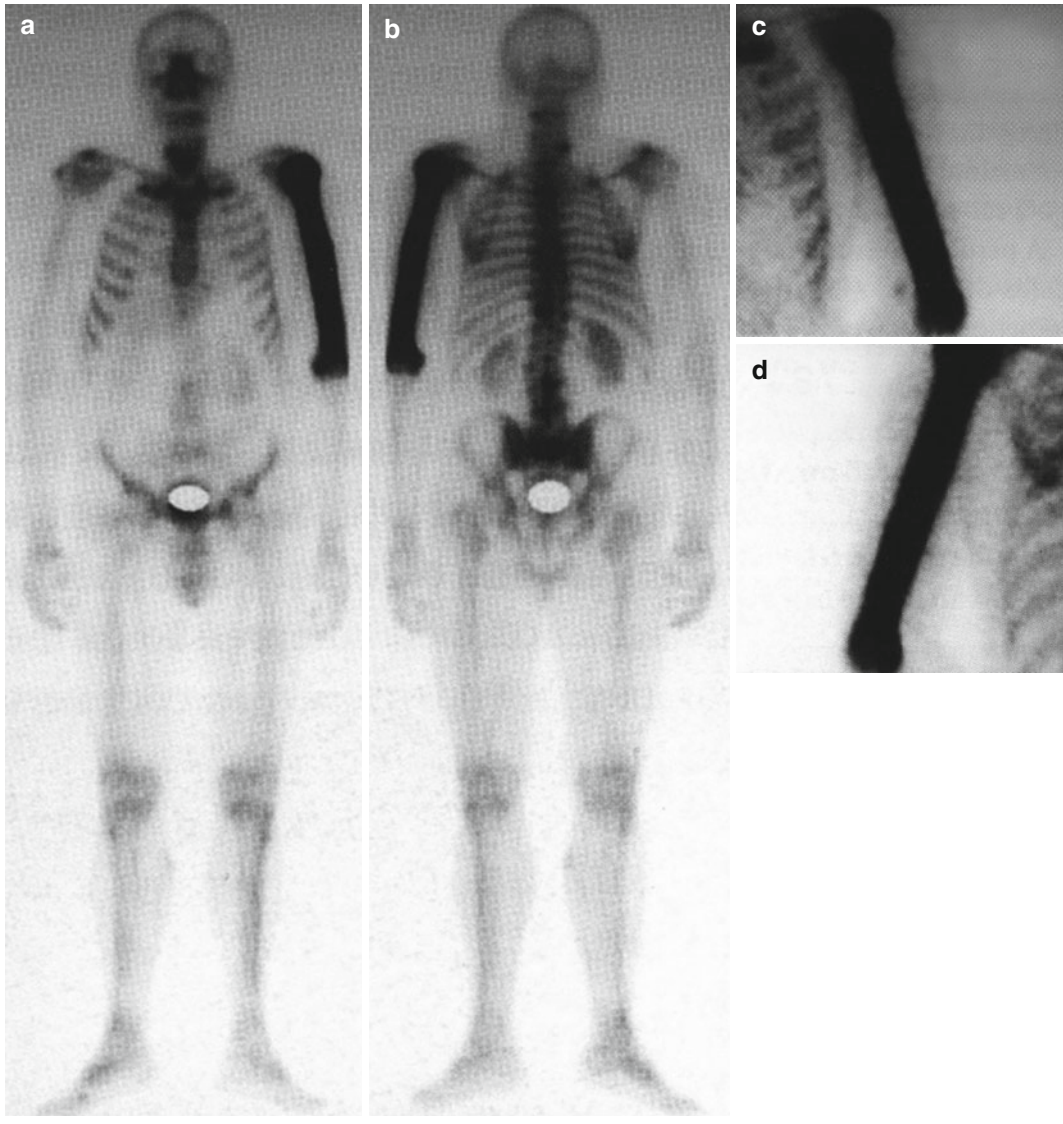


Fig. 33.2 A 56-year-old patient, whole-body bone scintigraphy shows diffusely increased uptake in the left humerus (monostotic form). (**a**, **c**) Front view, (**b**, **d**) rear view

mon adverse effects include nausea, vomiting and flushing. Efficacy of the drug may gradually decrease due to development of antibodies against fish protein.

Bisphosphonates play a dominant role in the treatment of Paget's disease, particularly the most recent ones, such as alendronate, risedronate, ibandronate, pamidronate and zoledronic acid. All of them act through decrease of bone turnover, with mineralisation maintained within the reference range.

Alendronate and risedronate are administered orally, pamidronate and zoledronic acid intravenously and ibandronate both orally and intravenously. All of them are effective and their use is relatively safe. The most common adverse effects associated with bisphosphonate treatment include flu-like symptoms lasting for several days and then resolving spontaneously, musculoskeletal pain, osteonecrosis of mandible after dental intervention, gastrointestinal symptoms and

Table 33.1 Main clinical symptoms of the Paget's disease and their treatment

Clinical presentation	Symptoms	Treatment
Musculoskeletal	Pain and local increase of temperature Bone deformities[a] Osteoarthritis[a] Pathological fractures[a] Acetabular protrusion[a] Vertebral canal stenosis Surgical bleeding	Analgesics Antiphlogistic drugs Bisphosphonates Calcitonin Operative treatment, rehabilitation Psychological support
Endocrine	Elevated alkaline phosphatase Normal or hypercalcaemia Hyperuricaemia Nephrolithiasis	Bisphosphonates Vitamin D Allopurinol
Neurological	Hearing loss and tinnitus[a] Dizziness Damage to cranial nerves Basilar artery compression Cranial hypertension	Hearing aids Bisphosphonates Calcitonin
Cardiovascular	Retrosternal pain High-output cardiac failure Aortic stenosis[a] Atherosclerosis[a]	
Neoplastic	Sarcoma Giant cell tumour	Surgical resection

[a]Conditions not indicated for suppressive treatment of Paget´s disease due to its ineffectiveness

hypocalcaemia. Their use is not recommended in case of impaired renal function.

In younger patients with a local form of the disease, oral bisphosphonates are used successfully. Alendronate may be used at the daily dose of 40 mg, once a day for the period of 6 months. Risedronate is given once a day at the dose of 30 mg over 2 months. All oral bisphosphonates are poorly absorbed and must therefore be taken in the morning on an empty stomach, only with a glass or two of plain tap water. It is important to instruct the patient not to lie down after taking bisphosphonate, to avoid gastrooesophageal reflux and oesophageal irritation. The most severe complication is oesophageal perforation with the subsequent fatal mediastinitis. This fact has to be taken into account in prescribing bisphosphonate to elderly patients, who have problems with mobility or are bedridden, or in the presence of hiatal hernia and chronic oesophagitis.

Pamidronate is administered intravenously at the dose of 30 mg in 500 ml of infusion solution during three consecutive days. It is well tolerated but patients may develop resistance. Zoledronic acid is the strongest bisphosphonate for treatment of Paget's disease. It is administered intravenously at the dose of 5 mg in 100 ml of physiological solution or 5 % glucose via a 15-min infusion. It is usually well tolerated and maintains a long-term biochemical remission of the disease in the majority of patients, over the period of 1–2 years. The disadvantage is a higher price of the medication and the need of administration via infusion.

Patients requiring surgical intervention, mainly at the site of local activity of Paget's disease, should use bisphosphonates 3 months prior to surgery in order to decrease hypervascularity and postoperative blood loss [13].

Tests of serum alkaline phosphatase levels are used to monitor therapy efficacy, namely, every 3–6 months, until normalisation of serum levels, and then once to twice a year. In patients with a normal level of alkaline phosphatase, it is useful to perform whole-body bone scintigraphy 6–12 months after treatment completion. Vitamin D and calcium supplements may be recommended in some patients.

Indication of bisphosphonates and calcitonin to treat Paget's disease must respect the valid indications specified in the summary of product characteristics (SPC) in each given country.

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34 Involutional Osteoporosis: Sarcopenia, Frailty Syndrome and Falls

Jiří Jenšovský

It is necessary to treat the patient, not the disease.
Sir William Osler

Our society is doomed to struggle against pandemic of civilization diseases. One of the most common of them is osteoporosis. There are several reasons for it, one of the most significant of which is lengthening of human lifespan. In eighteenth century, life expectancy in Europe was 39 years, while two centuries later, it was already 80 years. In 1900, the age median in the USA was 23 years, and a century later, it was already 36 years. Civilization diseases in fact reflect maladaptation to this phenomenon. In connection with the longer life expectancy, the lifestyle of population in advanced countries has dramatically changed – starting from unhealthy dietary habits over to the development of technologies allowing substantial reduction of physical activity in most human activities. Pandemic incidence of involutional osteoporosis and its implications have therefore become in recent decades one of the main healthcare priorities. Although a number of diagnostic (DXA, FRAX) and therapeutic procedures have been developed, we are increasingly aware of the need for a comprehensive approach to what we call "osteoporosis" and its incorporation into the context of the current geriatric medicine [2, 5, 35].

For some time now, a gold standard of the osteology has been examination by dual-energy X-ray absorptiometry (DXA). WHO definition based on negative standard deviations of measured parameters compared to the reference population has significantly contributed to diagnosis and development of therapy of this condition. On the other hand, it has led to a simplified perception of this disease. Perceiving osteoporosis as a summary of bone properties – density, alterations in architecture and geometry, etc. – is reduced to the risk of fractures. There are two types of fractures prevailing in the elderly population, namely, osteoporotic fractures associated with a significant decrease in bone density and changes of microarchitecture and fractures resulting at this age from the increasing frequency of falls [1, 4].

It is, namely, the latter type of fractures that leads to a significant disability and accumulation of handicaps in geriatric patients. It has been generally accepted that age-related fractures occur in persons with bone mineral density (BMD) values *outside* the reference range for osteoporosis specified by WHO (Fig. 34.1). It is also known that application of classic densitometric parameters to persons in higher age decades is quite impossible. This fact has been so far underestimated and has not been incorporated in most of the studies investigating the effects and efficacy of antiosteoporotic drugs. The reasons range from difficulty of classification of fall risks up to methodological

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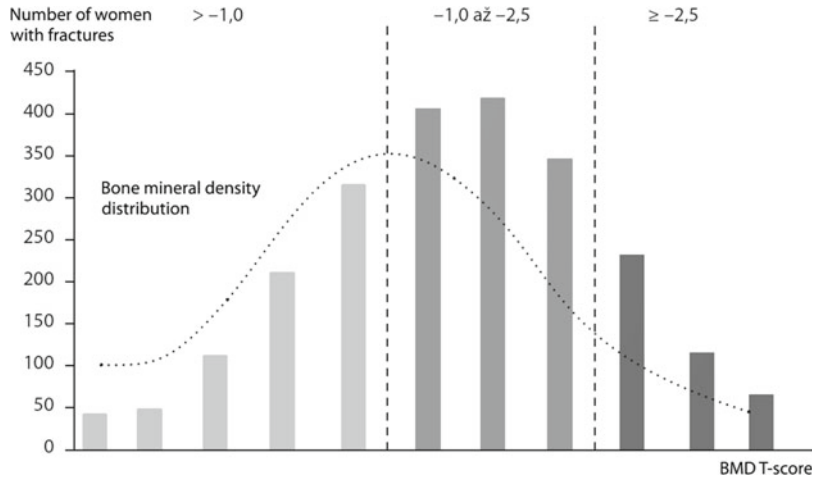

Fig. 34.1 Based on bone mineral density (*BMD*), a majority of women with fractures do not have osteoporosis (WHO) (Adjusted after: Siris et al. [34])

problems. However, even this field has currently experienced a significant progress. The inability to identify persons at risk of age-related fractures results in underestimation of the social impact of this pandemic and logically also to undertreatment of these individuals.

The ageing process is associated with irreversible decrease of function and anatomical involution of the *neuro-musculo-skeletal system* as a whole [14, 25]. Therefore our efforts should not be focused only on increase in bone density or changes in its architecture, and a more comprehensive approach is required, perceiving a geriatric patient as a whole. Thus, the aim should not be a mere reinforcement of the bone stock but primarily *reduction of the risk of falls* ("no fall, no fracture" concept). A recent Canadian study shows that although prescription of antiosteoporotic drugs differs across provinces up to four times, the global incidence of femoral neck fractures is the same [7].

34.1 Sarcopenia

In 1989, Irwin Rosenberg proposed the term "sarcopenia" to describe age-related decrease of muscle mass. At the same time, the processes of decrease of bone and muscle mass are closely interconnected at several levels, including primarily the functional and mechanical interaction, systemic agents – hormones, cytokines, etc., co-participating in both processes and common genetic factors. Orwoll calls it a "crosstalk" between muscle and bone. These two processes have a common underlying basis, namely, *imbalance*. In osteoporosis it is imbalance between resorption (RANK-RANKL system) and formation (Wnt signalling pathway), while in sarcopenia it is imbalance between synthesis (phosphatidylinositol-3 system) and muscle degradation (myostatin, sexagens, decreased activity of the growth hormone axis, etc.).

As people age, they lose 20–30 % of muscle mass; at the age over 90, it is up to 50 %. Women lose on average 1 kg and men 2 kg of muscle mass per age decade. Incidence of sarcopenia is reported in about 5–13 % of persons between 60–70 years of age and in about 10–50 % of individuals older than 80 years. Similarly as osteoporosis and its consequences, also sarcopenia and its consequences have a significant impact on the health status of geriatric patients, representing a huge economic burden. For example, in the USA, the annual cost of consequences of osteoporotic fractures was calculated at 16.3 billion USD while that of sarcopenia at as much as 18.5 billion USD (Fig. 34.2). *Sarcopenia increases twice the risk of falls and three times the risk of limitation of self-care capacity of patients* [8, 11]. Analyses of groups of geriatric patients have shown that an absolute majority of them suffer both from sarcopenia and osteoporosis. Therefore this condition is sometimes called "sarcoporosis". One of the

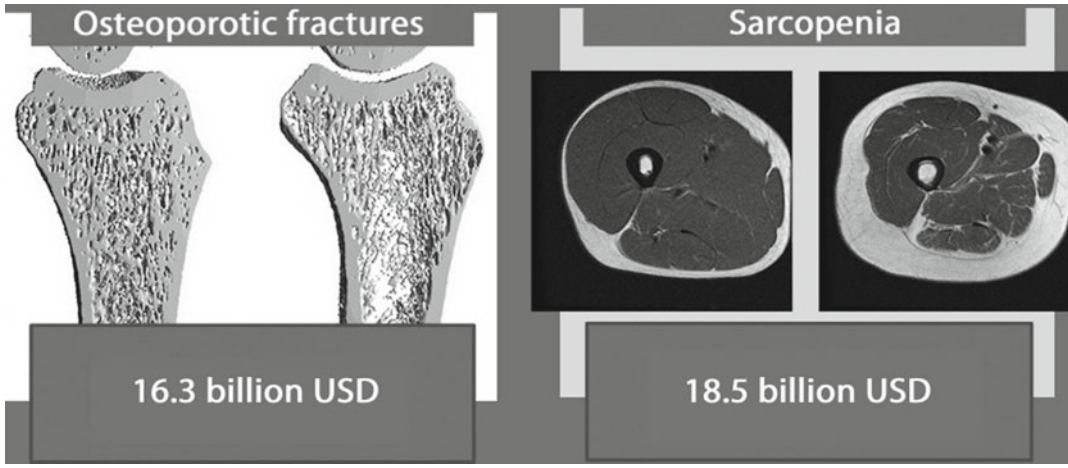

Fig. 34.2 Sarcopenia – consequences (cost in USD) (Modified after: Janssen et al. [18])

Table 34.1 Evaluation of muscle mass, strength and performance

Variable	Experimental examinations	Clinical examinations
Muscle mass	Computer tomography (CT)	BIA
	Magnetic resonance imaging	DXA
	Dual energy X-ray absorptiometry (DXA)	Anthropometry
	Bioimpedance analysis (BIA)	
	Total or partial body potassium per fat-free soft tissue	
	Anthropometry	
Muscle strength	Handgrip strength measurement by dynamometer	Handgrip strength measurement by dynamometer
	Knee flexion/extension	
	Peak expiratory flow	
Physical performance	Short physical performance battery, SPPB	SPPB
	Usual gait speed	Usual gait speed
	Timed get-up-and-go test	Get-up-and-go test
	Stair climb power test	

Modified after Gojda [16]

priorities in the near future, which is currently intensively addressed, will be adoption of definition of sarcopenia, similarly as in osteoporosis.

Sarcopenia is certainly not a mere synonym for decrease of muscle mass. Its other symptoms include also functional disorders – decrease of muscle strength and of physical performance.

Muscle mass decrease seems to be responsible for up to 60 % of decrease of physical performance and impaired ability of patients with sarcopenia to perform activities of daily living, the rest being the question of muscle strength and quality. There are a number of methods for measuring muscle mass, strength and performance that are used primarily experimentally, although several procedures are routinely used in the clinical practice (Table 34.1). The simplest and best available combination of methods is measuring muscle mass by DXA, muscle strength by handgrip and physical performance by the test of the usual gait speed. Similarly as osteoporosis categorized into mild, more severe osteopenia and osteoporosis, sarcopenia may be divided into similar stages (Table 34.2).

Sarcopenia has also very similar etiopathogenetic causes as osteoporosis. It may be primary,

age related, secondary, associated with limited mobility due to physical inactivity, or associated diseases or malnutrition.

Sarcopenia is clinically well identifiable and may be suspected in persons with asthenic habitus. A separate group, which poses a clinical problem, are obese individuals who also suffer from decrease of muscle mass for some reason, but in them this problem is often considered much later (*sarcopenic obesity*).

34.2 Sarcopenia: Causes

(a) Primary – age related
(b) Secondary

- Activity related – bed rest, sedentary lifestyle, deconditioning or zero-gravity conditions
- Disease associated – advanced organ failure, inflammatory disease, malignancy or endocrine disease
- Nutrition associated – malabsorption, gastrointestinal disorders or use of medications that cause anorexia

Table 34.2 EWGSOP conceptual stages of sarcopenia

Stage	Muscle mass	Muscle strength	Physical performance
Pre-sarcopenia	↓		
Sarcopenia	↓	↓ or ↓	
Severe sarcopenia	↓	↓	↓

Modified after Cruz-Jentoft et al. [8]

In terms of interaction of sarcopenia and osteoporosis, the most alarming clinical situation occurs in patients with femoral neck fracture. It has been demonstrated that a *ten-day bed rest in these patients may lead to a loss of up to 1.5 kg of* lean body mass (LBM) *which from the functional viewpoint equals a 15% loss of muscle strength of lower extremities*. No surprise, these patients have a poor prognosis unless they are promptly operated on, mobilized and supplied with adequate amounts of substrates for protein synthesis.

The effect of pharmacological treatment on sarcopenia remains questionable. The candidate medications are included in Table 34.3: however, practical use and available evidence-based data currently relate only to vitamin D and alfacalcidol [9, 10, 27, 29, 32, 33]. An essential therapeutic and preventive measure is regular physical activity. As mentioned above, limited mobility or immobility leads quite rapidly to significant progression of sarcopenia and subsequently, in the

Table 34.3 Pharmacological treatment of sarcopenia

Drugs	Observational studies	RCT	Safety/tolerability	Availability	Indication for sarcopenia
Testosterone	Yes	Yes	Prostate cancer, erythrocytosis, hyperviscosity, sleep apnoea, CV events	Yes	Men with androgen deficit and low testosterone level
SARM	No	Yes	Elevated ALT/AST, haematocrit, lipid profile	No	No
GH	Yes	Yes	Arthralgia, gynecomastia, soft tissue oedema, DM	Yes	No
Ghrelin	Yes	Yes	Swelling, myalgia, increased appetite	No	No
GH secretagogue	No	Yes	Fatigue, insulin resistance, insomnia, elevated ALT/AST	No	No
Oestrogens	Yes	Yes	VTE, CV disease, stroke, breast cancer	Yes	No
Leptin	Yes	No	?	No	No
Vitamin D	Yes	Yes	Low toxicity	Yes	Possible

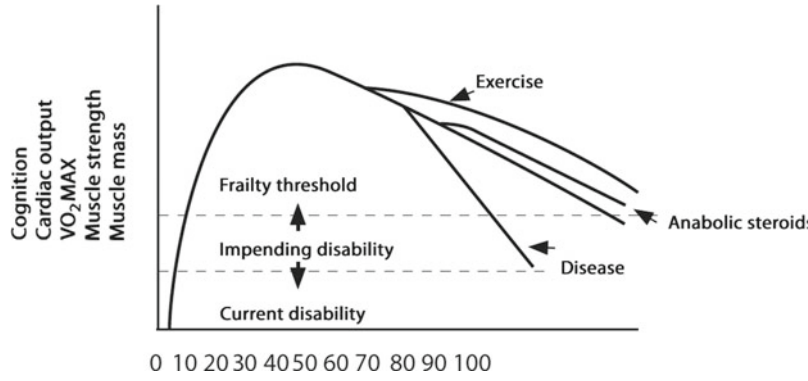

Fig. 34.3 Frailty development (Modified after: Morley [26])

longer run, also to decrease in BMD (*osteopenia follows sarcopenia*). In this context, the old adage holds true: *use it or lose it*.

Both sarcopenia and osteoporosis are age-related processes, resulting from decreased muscle mass and quality, with similar etiological moments and almost the same pathogenesis. They also have similar consequences for human health – increased risk of falls and fractures. Sarcopenia is therefore currently intensively investigated by a whole number of research teams worldwide; in Europe it is primarily the European Working Group on Sarcopenia in Older People (EWGSOP).

34.3 Frailty Syndrome

Frailty syndrome (FS) is one of the core geriatric syndromes, which is considered a cornerstone (holy grail or raison d'etre) of the current geriatric medicine. Its principle is accumulation of age-related deficits compromising the ability to withstand stressors and to maintain immune system homeostasis. Physiological reserves are decreasing with the increasing risk of adverse consequences of ageing. To put it simply, it is a process of accelerated, *unsuccessful ageing* [12, 41]. Biological age is naturally influenced by a number of various deficits acquired by a particular person during the whole life and may largely vary between individuals. Accumulation of deficits and handicaps is growing exponentially at the end of life. FS is a vulnerable state of an individual associated with a high risk of an external trigger event provoking a cascade of consequences with adverse effects, complications (falls, injuries, recurrent infections, repeated hospital stay, worse convalescence, a higher risk of iatropathogenic factors), such as immobility, inability to perform activities of daily living or death in the worst case [21, 41, 42]. On the other hand, if properly detected, this state may be successfully treated and other problems may be effectively prevented. Thus, it is sort of "therapeutic window" in the ageing process associated with possible reversibility. Chronologically, it proceeds from the "frailty phenotype" through "prefrail" phase to the actual FS and its potential consequences (Fig. 34.3). The FS principle is based on the concept that human beings are not only a sum of individual parts and that it is necessary to evaluate comprehensively their state and risks. This phenomenon goes against the mainstream of the current atomized and overspecialized medicine, and as such it is not reflected in the current health insurance payment system.

In terms of diagnosis, there are on the one hand relatively complicated questionnaires evaluating a number of potential risks for an individual, with the resulting frailty index assessment (e.g. K. Rockwood's approach), and on the other hand, there exists a substantially more simple and in terms of clinical practice more practical assessment and classification of the frailty phenotype based on syndromology (L. Fried's approach – Fig. 34.4). Persons with a negative score are classified as "robust". The presence of two of the above-mentioned symptoms defines the "prefrail" state of the frailty process, and the presence of three symptoms corresponds to the

"frailty" state. FS prevalence in the population is estimated at 10–25 % in persons older than 65 years and at 30–45 % in those older than 85 years [26, 38, 39]. Adapted Fried's criteria have been adopted by the American Geriatrics Society and have been recently introduced also in osteology. Similarly as in sarcopenia (sarcopenic obesity), the frailty syndrome may also pose a diagnostic problem in individuals with overweight, who are affected by the syndrome form called "*fat-frail syndrome*". It is generally known that obese persons have usually better BMD values than asthenic individuals, but they are more susceptible to falls and, consequently, to fractures. The vicious "frailty cycle" starts by decreasing regular physical activity, contributing to additional physiological decrements in functional reserve capacity of multiple organ systems.

1. unintentional weight loss of 4–5kg in 1 year
2. self-reported exhaustion
3. weakness / grip strength
4. slow walking speed
5. low physical activity

***presence of 2 criteria = pre-frail state**
***presence of 3 criteria = frailty state**

Fig. 34.4 The Frailty Working Group of the American Geriatrics Society: adapted Fried's criteria (Adapted after Fried et al. [13])

Therefore the primary preventive and therapeutic approach must always be regular physical activity.

The only preparation that has been so far assessed in terms of the effect on reduction of fracture risk in various categories of patients with FS is *strontium ranelate* (Protelos). A group of 5082 persons has been analysed, of which 2346 were classified as robust, 2472 as intermediary and 264 as frail. It has been demonstrated that the effect of strontium ranelate on reduction of the risk of vertebral fractures is significant in all the groups and that it even grows with the increasing fracture risk (robust-prefrail-frail), with the decreasing number needed to treat (NNT) (Figs. 34.5 and 34.6).

34.4 Falls

As mentioned above, the primary aim of therapy of what we call osteoporosis cannot be a mere increase of mechanical bone resistance, but decrease of the risk of falls and thus also the fracture risk. Annually, a total of 28–35 % of persons older than 65 years and up to 42 % of individuals older than 70 years sustain a fall. About 50 % of falls lead to injuries, 10–15 % of falls result in severe injuries, and 1–2 % of falls result in femoral neck fracture. Fear of falling leads in 60 % of persons over the age of 65 to decrease in physical activity [3, 17, 22, 30, 40].

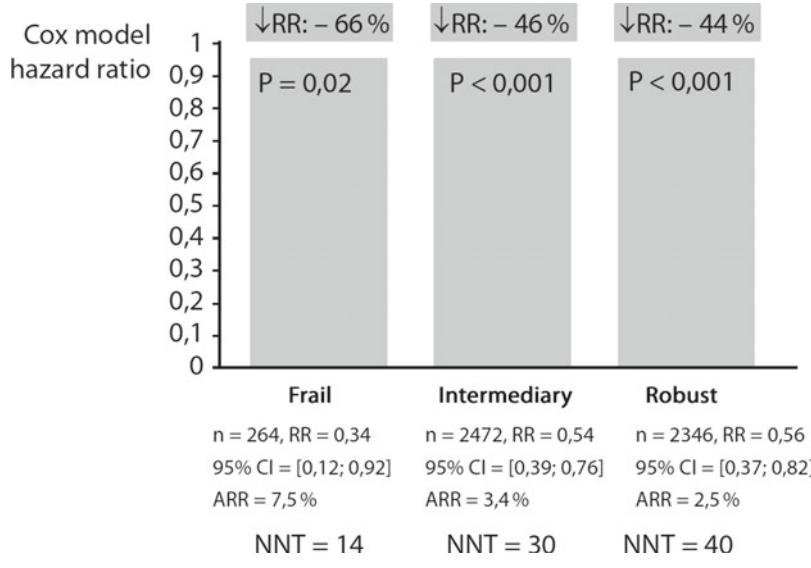

Fig. 34.5 The efficacy of strontium ranelate against vertebral fractures – first year (Modified after Rolland et al. [28])

All "osteoporotic" studies have a classical design – decline of BMD below −2.5 SD and division of patients between those with and without fracture. There exist only a few studies performed on a sample of persons with BMD values better than −2.5 SD. It is generally known that 50 % of femoral neck fractures are observed in persons outside the reference range for osteoporosis according to the WHO criteria for BMD.

In the OFELY study, a cohort of 672 women was followed up for the average period of 5.3 years. It has been demonstrated that falls are an independent predictor of osteoporosis-related fractures with OR 1.76 (CI 1.0–3.0) [36]. In 9516 women older than 65 years included in the SOF study, who were followed up on average for 4.1 years, a fall in the preceding year was predictive of the risk of femoral neck fracture with RR 1.6 (CI 1.2–2.1). The risk of femoral neck fracture was by 30 % higher in women with more frequent falls [6]. Similar outcomes were confirmed by a number of other studies (EPOS, SOMA, COSHIBA, etc.). The problem is that falls, their definition, frequency and risk assessment have not been so far included into classical studies evaluating the effect of individual preparations on reduction of fracture risk. Indoor and outdoor falls have naturally different characteristics, similarly as falls sustained by institutionalized older people and people living in their own homes. Falls have not been assessed in terms of risk classification according to frailty syndromology or extent of sarcopenia. A fundamental study summarizing these issues was published by Cooper under the title Frailty and sarcopenia, definitions and outcome parameters [5].

Frailty syndrome increases twice the risk of falls and three times the risk of hospitalization. In the Lang's study [21], FS was increasing during 9 years of follow-up the risk of fall by 40 %, the risk of femoral neck fracture by 40 %, the risk of non-vertebral fractures generally by 30 % and mortality by as many as 80 %. FS significantly reduces the interval until the next fall (HR 1.53, CI 1.07–2.18) and increases the risk of multiple falls (OR 1.74, CI 1.10–2.55) and the risk of multiple fractures (OR 3.67, CI 1.47–9.15).

Currently, the outcomes of the Global Longitudinal study of Osteoporosis in Women (GLOW*) cohort study are analysed and gradually published* [15, 40]. The study involved 723 physicians' practices from the EU countries, North America and Australia; a total of 60,393 postmenopausal women were followed up for three years, *BMD was not measured*, but the *risk of falls* was evaluated. In the studied group, 22 % of women were classified as frail and 31 % as prefrail. FS increased the fracture risk (OR 1.23, CI 1.07–1.42), the risk of disability

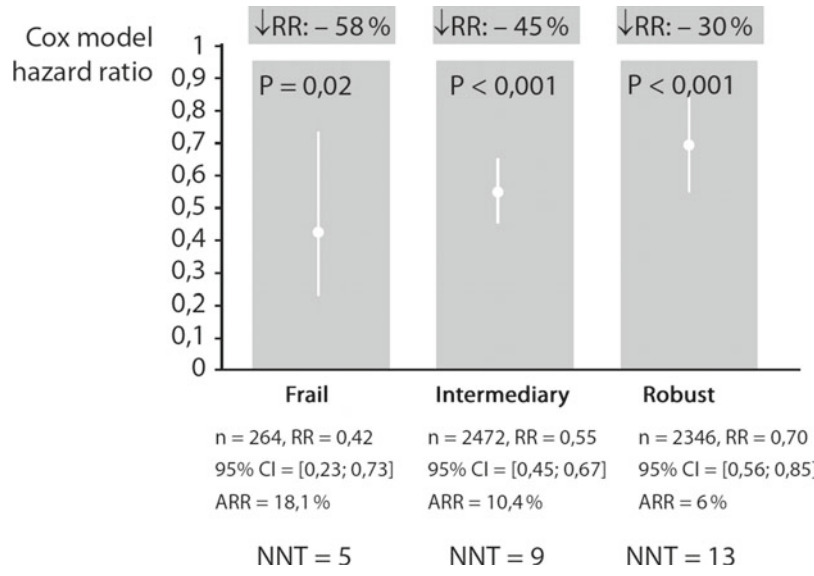

Fig. 34.6 The efficacy of strontium ranelate against vertebral fractures – third year (Modified after Rolland et al. [28])

(OR 2.29, CI 2, 09–2, 51) and the risk of recurrent falls (OR 1.68, CI 1.54–1.83). During the period under investigation, accidental fracture was sustained by 6.8 % of patients. The fracture risk was the highest in women with neurological comorbidities – Parkinson's disease (HR 3.89, 2.78–5.44), multiple sclerosis (HR 2.7, 1.9–3.8) and prior cerebrovascular events (HR 2.0, 1.67–2.46). Rheumatoid arthritis increased the fracture risk with HR 2.15 (1.53–3.0) (Fig. 34.7).

How is the information about falls obtained from the patients treated in the clinical practice? The scoring systems that are not so often used include the *Garvan fracture risk calculator* (www.garvan.org.au) and *the QFracture* (www.qfracture.org). The first of them registers and assesses the history of previous falls and fractures using the system of 0, 1, 2 and more than 2 events; the latter one is based only on a binary response (yes/no). *FRAX,* a fracture risk assessment system which is most frequently used in the clinical practice, does not assess risk of falls [23].

However, according to the standpoint of International Osteoporosis Foundation (IOF), "*It is recommended that FRAX users be made aware that non-consideration of falls (especially recurrent falls) is likely to underestimate 10 year fracture risk"*.

Therefore the expert group came up with the following text: "*Data from Study of Osteoporotic Fractures suggest that, in comparison to individuals without a fall in the previous year, a history of each fall (up to 5 falls or more) in the previous year increases the 10 year hip fracture risk by approximately 30 % in women."* [24]

Can falls be effectively prevented? The basic approach consists in improvement of physical fitness of persons at risk. Exercises include gait and balance training, muscle strengthening, endurance exercises, and exercises to improve flexibility and spatial orientation. This approach may reduce the risk of falls (RR 0.66, 0.77–0.63) as well as fractures (RR 0.36, 0.19–0.70). A highly effective preventive measure is modification of pharmacotherapy. It has been proved that elderly persons using more than three types of medications face a higher risk of fractures. Education programme – campaign for general practitioners – has significantly reduced the risk of falls (RR

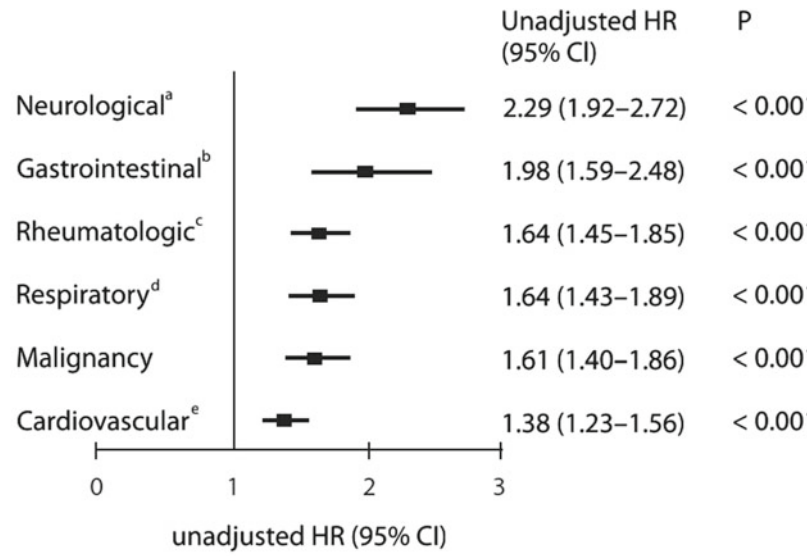

Fig. 34.7 Kaplan-Meier 3-year estimate of fracture incidence by disease groups (Modified after Gregson et al. [15])

[a]Parkinson disease, multiple sclerosis, cerebrovascular event
[b]bowel inflammatory disease, celiac disease
[c]osteoarthritis, rheumatoid arthritis
[d]chronic obstructive pulmonary disease, asthma
[e]type 1 diabetes mellitus, hypertension, hypercholesterolemia, ischemic heart disease

0.61, 0.41–0.91). The effect of reduction of psychotropic medications influencing vigilance is even more marked (RR 0.34, 0.16–0.73). A priority must always be maintaining the basic physical activity, i.e. *gait* [19, 20, 31].

This was best documented by the study "Gait Speed and Survival in Older Adults" [37] which analysed outcomes of nine studies, involving 35 485 persons with the mean age of 74 years and a total of 17 582 deaths. Gait speed was associated with survival in all studies (Fig. 34.8). The risk of death per 0.1 m/s higher gait speed was each year reduced by 12 % ($p = 0.001$). Based on the basic parameters of age, sex and gait speed, it is possible to express a highly valid prognosis as concerns survival of geriatric patients. First of all it is necessary to monitor changes in gait speed as its sudden slowing may be an unfavourable signal and a reason for consideration and recommendation of an intervention. Walking speed can be tested simply in the hospital corridor with stopwatch. "Healthy ageing" is associated with the gait speed of 0.8–1.0 m/s; gait speed faster than 1.2 m/s suggests better than average life expectancy.

34.5 Who in Fact Has Osteoporosis and What Is "Osteoporosis"?

The above-mentioned facts show that although typical patients are often osteoporotic according to DXA criteria of WHO, they often rather fall within the reference range of osteopenia and have a certain absolute fracture risk according to FRAX, mostly a certain degree of pre-sarcopenia, or even sarcopenia, and a certain degree of expressed frailty syndrome. They often have also osteoarthritis which probably shares many common features with osteoporosis. It has been found out that, for instance, strontium ranelate, used to treat osteoporosis, may positively influence also progression of osteoarthritis.

All these issues have been recently summarized by a study of an international expert group under the title: "What's in a name? What constitutes the clinical diagnosis of osteoporosis?" and subsequently by a study "What's in a name revisited: should osteoporosis and sarcopenia be considered components of dysmobility syndrome?' [2, 35].

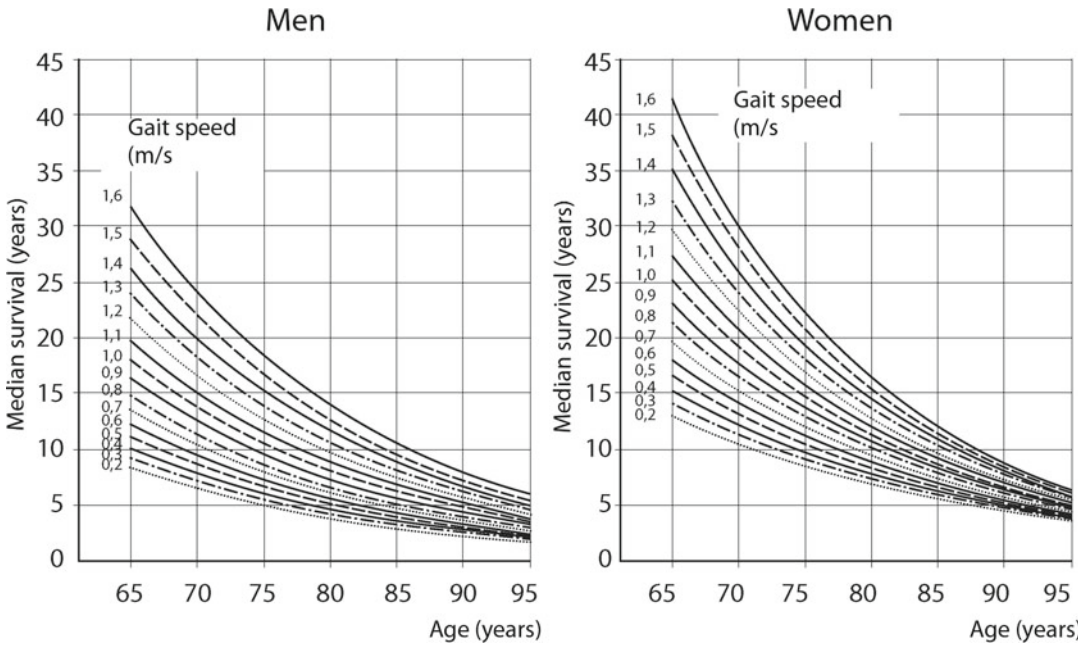

Fig. 34.8 Expected median survival depending on age and gait speed (Modified after Studenski et al. [37])

Osteoporosis seems to be a clinical, relatively quite broad syndrome rather than a nosological entity, and in view of incorporation of the terms of sarcopenia and frailty syndrome, some authors suggest to introduce an umbrella term "dysmobility syndrome". A fracture as a consequence of this condition should then be perceived as a *perignosis* rather than diagnosis, with clinical intervention similar to that we use in the metabolic syndrome risk. It is necessary to identify persons at risk of falls and fractures, assess their risk profile and tailor a comprehensive, customized treatment programme. The number of persons who do not have "osteoporosis" according to the valid definition, but fall and sustain fracture more frequently, is rapidly growing. Administration of calcium, vitamin D and antiosteoporotic drugs is in terms of prognosis of geriatric patients an inadequate approach which ignores assessment of the risk of falls.

In the next 50 years, the number of Europeans older than 55 years will double, with the highest increment in the category of persons older than 85 years. At the same time, the current healthcare systems are set up to treat "acute" conditions in younger age groups and are not prepared to face the needs of rapidly growing geriatric medicine. The European Union is aware of this fact, and therefore, its agency EMA came up in 2011 with the programme Geriatric Medicines Strategy: Innovative Therapeutic Interventions-Physical Frailty Sarcopenia, highlighting the need for:

- Development of an operational definition of at-risk subpopulations
- Qualification of biomarkers of muscle anabolism and catabolism and indicators of muscle function
- Development of advanced therapeutic approaches in preclinical settings
- Implementation of innovative clinical development methodologies for prevention of physical frailty-sarcopenia
- Scientific and regulatory consensus

Physicians in the clinical practice must abandon the established "osteocentric" approach to their geriatric patients and take into account that the aim is not to prevent fractures in fragile bones, but primarily to prevent falls and fractures in persons at risk [1]. Geriatric patients with deteriorating *neuro-musculo-skeletal system* require a comprehensive care. Patients cannot be divided into those with or without osteoporosis, but, for instance, into fit, independent or frail, as suggested by EMA. Currently a number of various pharmacological options of treatment of individual components of the frailty syndrome are intensively investigated. However, the basic principle must always be maintaining regular physical activities of the persons at risk. *We don't stop moving because we grow old; we grow old because we stop moving.*

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35 Systemic Enzyme Therapy in Comprehensive Treatment of Degenerative Rheumatic Diseases in the Elderly

Martin Wald and Jozef Rovenský

Drugs for systemic enzyme therapy (SET) provide one of the options of pharmacotherapy of osteoarthritis and other painful disorders of the musculoskeletal apparatus. These oral preparations containing proteolytic enzymes of plant and animal origin combine primarily anti-inflammatory, anti-oedematous and analgesic effects. Due to a good tolerability, they are a safe alternative for persons who for some reason cannot receive nonsteroidal anti-inflammatory drugs NSAIDs). Good tolerability and safety in a long-term treatment is beneficial mainly for older patients with NSAIDs contraindication due to age and potential comorbidities. Therapeutic polypragmasia, common in the elderly, is associated with risks of dangerous interactions if drugs are used concomitantly with NSAIDs [1].

The main active ingredients of SET drugs (Wobenzym® and Phlogenzym®) are proteolytic enzymes (trypsin, chymotrypsin, bromelain, papain), pancreatin (enzyme mix with proteolytic, lipolytic and amylolytic activity) and flavonoid rutin [2]. They are administered orally in the form of acid-resistant tablets. Enterosolvent coating protects enzymes against their damage in the acidic environment of the stomach. Absorption of enzymes which is a prerequisite for a systemic effect takes place in the upper part of the small intestine. Absorption of undamaged enzyme molecules with the preserved activity has been repeatedly proved both experimentally and clinically by means of selective immunoanalytical and enzymatic methods [3, 4].

The primary aim of conservative treatment of osteoarthritis is to manage pain and preserve an optimal function of the joint. SET drugs may be applied as an adjuvant therapy not only in acute inflammatory exacerbations and in chronic painful conditions within conservative treatment but also after surgical treatment of arthritis.

The advantage of these drugs consists in combination of anti-inflammatory (or better inflammation modulating) and anti-oedematous effects together with the ability to relieve pain, to improve antibiotic tissue penetration and to promote haematoma absorption [5].

Prolonged swelling with haematoma and impaired microcirculation and both venous and lymphatic drainage of tissues affected by inflammation or damaged by surgery or trauma may significantly hinder healing.

Reduction of swelling by SET preparations improves microcirculation, similarly as the positive influence on the rheological properties of blood, associated with the fibrinolytic and antiaggregation effect of proteolytic enzymes [6, 7]. Improved microcirculation promotes venous and lymphatic drainage. All this conduces to a better

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oxygen supply to tissues, supply of nutrients, removal of metabolic waste products and, consequently, healing. These effects contribute also to secondary analgesic effect of SET drugs. However, they obviously have also a primary analgesic effect, i.e. a direct influence on degradation of pain mediators and pain receptors. Accelerated absorption of haematoma is attributed to stimulation of the activity of phagocytic cells by proteolytic enzymes contained in these preparations [8]. If there develop infectious complications of healing (e.g. postoperatively), the vehicle effect of enzyme preparations promotes absorption and penetration of antibiotics to tissues, thus improving the therapeutic effect [9, 10].

In view of new findings about the role of free oxygen radicals in the pathogenesis of osteoarthritis, attention has focused on the SET antioxidative effect [11]. Additional explanations of the positive effect of SET in arthritis and other inflammatory disorders of the musculoskeletal apparatus are provided by studies dealing with the role of lymphatic blood vessels, lymphatic circulation and lymphatic swelling at different sites affected by inflammation [12–15], mainly because lymphatic swelling has been for a long time a generally accepted indication for SET, Wobenzym® (WE) in particular.

Safety and efficacy of SET medical preparations was proved by a number of randomised double blind trials controlled by placebo or active comparator as early as in the 1980s and 1990s of the last century.

Later the outcomes of minor clinical assessments were confirmed by two large multicentric retrolective cohort studies [16, 17]. Data obtained from these studies were processed by the method of epidemiological retrolective analysis. The first one compared the efficacy and safety of Wobenzym® (pancreatin, papain, bromelain, trypsin, chymotrypsin, amylase, lipase, rutin) or Wobenzym N (pancreatin, papain, bromelain, trypsin, chymotrypsin, rutin) (WE) and NSAIDs (most often diclofenac, ibuprofen or piroxicam). The study was conducted in 203 centres and included a total of 1426 patients (863 patients, WE, versus 563 patients, NSAIDs). Patients with rheumatic diseases (most often vertebrogenic syndrome, activated arthritis, soft tissue rheumatic syndromes, rheumatoid arthritis, Bechterev's disease or combination of these diagnoses) were treated in 1990–1997. The primary criterion of assessment of efficacy was a change in the intensity of symptoms at the end of the treatment. Evaluation with the use of several statistic methods revealed a significantly more successful treatment with WE as compared to NSAIDs ($p < 0.0001$) with a markedly lower incidence of adverse effects (WE 1.6 % of patients vs. NSAIDs 15.3 % of patients).

The other study compared efficacy and safety of Phlogenzym® (PHL – bromelain, trypsin, rutin) and NSAIDs in 3326 patients (70 % PHL vs. 30 % NSAIDs) with rheumatic diseases (involving limb and spinal joints, soft tissue rheumatic syndromes) treated in 1993–1995 by 380 general practitioners.

Success of the treatment was measured by the extent of resolution of rheumatic symptoms at the end of the therapy. Statistical analyses showed a very good efficacy of the enzyme preparation that was not worse than the effect of NSAIDs (non-inferiority test), with predominantly excellent or good tolerability and infinitely lower incidence of adverse effects as compared to NSAIDs. In addition, the study provided interesting information about "application patterns" in routine medical practice. PHL was more commonly prescribed to patients that were treated before by antirheumatic drugs and analgesics in which the previous therapy did not have a satisfactory effect. The limited use of adjuvant treatment with "pure" analgesics in combination with enzyme preparations indicates their good analgesic effect.

The following two prospective randomised, double-blind studies focused on the analgesic effect of a combined enzyme preparation PHL in arthritis of the knee [18] and hip [19] joints. Both studies used diclofenac (DC) as the active comparator.

A study focused on osteoarthritis of the knee joint included a total of 103 patients with a painful exacerbation of radiologically verified osteoarthritis. The treatment took 6 weeks, where 52 patients received PHL and 51 patients were in the diclofenac group. The patients were examined prior to commencement of medication and then

at 2, 4 and 6 weeks. Primary efficacy criteria were Lequesne's algofunctional index (LFI – scoring pain and restriction of the joint function) and a "complaint index", including pain at rest, pain on motion and restricted function. Considerable improvement could be seen in both groups of patients. Within the 6-week observation period, the mean value of the LFI decreased from 13.0 to 9.4 in the PHL group and from 12.5 to 9.4 in the diclofenac group. Statistical evaluation of primary criteria showed comparability of both preparations.

Almost identical outcomes were provided by a study of a similar design, focused on the PHL effect in patients with confirmed osteoarthritis of the hip. A total of 90 patients with acute painful exacerbation of osteoarthritis were treated for 6 weeks, where 45 patients received PHL and 45 patients were included in the diclofenac group. Primary efficacy criteria were LFI and WOMAC index (Western Ontario and McMaster Universities Osteoarthritis Index – scoring joint pain, stiffness and function).

Statistical analysis based on non-inferiority test again proved a comparable effect of PHL and diclofenac, with a very good tolerability of PHL.

The outcomes of the above-mentioned studies comply with the previously published data and have confirmed that both WE and PHL can be considered as an effective and safe alternative to diclofenac and other similar NSAIDs in painful inflammatory exacerbation of osteoarthritis and other rheumatic disorders of the musculoskeletal apparatus [20]. Such information is highly valuable mainly in the context of recent reports of cardiotoxicity of diclofenac comparable to rofecoxib [21].

Drugs for SET are also well applicable as a postoperative adjuvant therapy after surgical treatment of arthritis. Accelerated absorption of postoperative swellings and haematomas significantly contributes to healing and facilitates rehabilitation [22–25].

Recently, the debate has focused also on a potentially negative effect of nonselective NSAIDs and selective COX-2 inhibitors on bone healing after fractures or surgical interventions. A recommendation was issued by the 48th Annual Meeting of the Orthopaedic Research Society, Dallas, February 2002, stating that the patients that have received a dental implant or a joint replacement and used nonselective NSAIDs or coxibs to treat arthritis should at least temporarily discontinue the therapy during the period of bone healing [26].

A meta-analysis of 44 studies dealing with this issue has concluded that the short-term use of nonselective NSAIDs or selective COX-2 inhibitors at low doses in soft tissue injuries is not detrimental, but has an inhibitory effect on bone healing [27]. Patients after bone and joint injuries or surgery (including surgical treatment of arthritis) or after dental surgery could thus be another group benefiting from administration of SET drugs.

As a result, drugs for SET can be added to the range of preparations for pharmacotherapy of arthritis where a dominant role is still played by NSAIDs. Their use is, however, associated with a number of risks and contraindications primarily for the elderly patients. SET drugs thus may become, particularly in this group of patients, a safe part of comprehensive conservative procedures and be applied as adjuvant therapy also after surgical treatment of osteoarthritis.

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Index

A
Abatacept, 313
Adalimumab, 28, 30, 88
Adjuvant therapy, 304–305
Adson's test, 290
Algodystrophic syndrome, 100, 199
Alkaptonuria (AKU)
  aetiology and pathogenesis, 234
  ankylosing spondylitis, 239
  clinical features
    alkaptonuric ochronosis, 235, 236
    calcification, 237
    histiocytes, 238
    homogentisic acid, 235
    internal organs, 236
    ochronotic enthesopathy, 239
    ochronotic pigment, 235
    shoulder joints, radiographs of, 238
    spinous process, 237, 238
    urine, characteristic findings in, 236
    urolithiasis, 237
    vacuum phenomenon, 237
  clinical signs, 233
  diagnosis of, 240
  differential diagnosis, 240–241
  epidemiology and genetic aspects, 234–235
  historical background, 233–234
  osteoporosis, 239
  rheumatoid arthritis, 239
  therapy, 241–242
Allopurinol therapy, 220
Alzheimer's disease, 11, 12, 31, 330
American College of Rheumatology (ACR) classification
  giant cell arteritis, 67
  vasculitis, 49, 50
American Gastroenterological Association, 264
American Geriatric Society, 291, 292, 356
Amputation, 79, 160, 173, 182–184, 212
Amyloid arthropathy, 94–95
Anakinra, 28–29
ANAs. *See* Antinuclear antibodies (ANAs)
Aneurysm
  aortic aneurysm, GCA patients, 75–76
    abdominal aorta, 78
    diagnosis, 79–81
    granuloma, 78
    hypertension, treatment of, 81
    iliac arteries, 78
    inflammatory infiltrate, neoangiogenesis with, 80
    internal elastic membrane, 78
    multinucleated cells, 77–79
    myocardial infarction, 77–78
    symptoms, 79
  definition, 75
  dissecting aneurysm, 75–77
  etiology of, 75
  false aneurysm, 75
  true aneurysm, 75
Ankylosing spondylitis (AS)
  anti-cytokine therapy, 28–30
  DISH, 271
  osteoporotic dens axis, 341
  RS3PE syndrome, 93
  spondyloarthritis, 15
Antibodies against tissue transglutaminase (AtATG), 255
Anti-endothelial cell antibodies (AECA), 56
Antigliadin antibodies, 263, 264
Anti-gout therapy, 217
Antineutrophil cytoplasmic antibodies (ANCA), 56
Antinuclear antibodies (ANAs)
  deoxyriboproteins, 316
  DILE diagnosis, 316
  paraneoplastic syndromes, 105–108
Antiphospholipid syndrome (APS), 101
Aortitis, 64–65, 102
Aquatic exercises, 323
Arthralgia
  arthritis, 265
  drugs, 318
  granulomatosis with polyangiitis, 55
  Takayasu's arteritis, 50
Arthroscopic technique, 134, 332
Articular chondrocalcinosis, 94, 95
Atlantoaxial instability, 330
Auranofin, 20–21
Autoimmune hemolytic anemia (AIHA), 40
Azathioprine, 36, 53, 59, 88, 312

J. Rovenský (ed.), *Gerontorheumatology*, DOI 10.1007/978-3-319-31169-2

B
Baker cyst, 4
Balanced diet, 283–284
Barrett's esophagus, 46
Behçet's disease (BD)
  aetiology and pathogenesis, 57
  auxiliary examinations, 58
  clinical features, 57
  clinical manifestations, 58
  definition, 57
  diagnosis, 58
  differential diagnosis, 58–59
  disease prognosis, 59
  incidence, 57
  laboratory findings, 58
  therapy, 59
Belimumab, 37
Biological therapy
  ankylosing spondylitis, 28–30
  EORA, 28–31
  older patients, 312–313
  psoriatic arthritis, 28–30
  rheumatoid arthritis, 313
  SLE treatment, 37
  systemic scleroderma, 47
  YORA, 29
Biomin H, 278
Bisphosphonates
  antiresorptive preparations, 279
  calcitonin, 346
  gastrointestinal effects, 279
  osteoporosis treatment, 259
  Paget's disease, 347
BMD. *See* Bone mineral density (BMD)
Bobath technique, 326
Bone and joint involvement
  clinical manifestations, 262–263
  diagnosis, 261, 263–264
  enteropathic arthritis, 265
  etiopathogenesis of, 262
  gluten-free diet, 261
  HLA-B27-positive patients, 265
  metabolic osteopathy, 264–265
  polyarticular involvement, 265
  prevalence of, 261
  Sjögren's syndrome, 265
  small intestine mucosa, 261
Bone densitometry, 246–248, 251, 277
Bone mineral density (BMD), 258, 283, 351, 352, 357
Bone scintigraphy, 94, 161, 172, 345, 347, 348
Bouchard's node, 322
Bruns-Garland syndrome, 199
Butterfly exanthema, 34, 35
Buttonhole deformity, 3, 4

C
Calcitonin, 280, 346, 349
Calcium pyrophosphate arthropathy, 15
Carbohydrate mechanism disorders, 153
Carbolochronosis, 240
Carboxy-terminal propeptide of type 1 procollagen (P1CP), 161
Carboxy-terminal telopeptide of type 1 collagen (1CTP), 161
Carpal arthrodesis, 337
Carpal tunnel syndrome, 3–4, 211
Catastrophic antiphospholipid (CAPS), 101
Celiac sprue (CS)
  bone and joint involvement (*see* Bone and joint involvement)
  metabolic osteopathy (*see* Metabolic osteopathy)
Cervicobrachial syndrome, 286, 291
Charcot diabetic spondyloarthropathy (CHDS), 200
"Charcot knee," 225
Charcot osteoarthropathy (CHOA). *See* Diabetic charcot neuropathic osteoarthropathy
Charcot spondyloarthropathy, 197
Cheiroarthropathy, 194
Chloroquine, 311
Chondrocalcinosis
  ankles and feet, 226–227
  calcifications, 223
  classic skiagraphy, 223
  elbows joint, 227–228
  hyaline cartilage, 223
  knees, 224–225
  pelvis, 225–226
  shoulders joint, 227–228
  spine, 229–231
  sternoclavicular joint, 227–228
  ultrasonography, 231
  wrists and hands, 228–229
Chondroitin sulphate (CS), 130
Chondroprotective effect, 129, 132, 272
Coeliac disease
  classification, 257–258
  clinical features, 256
  clinical symptoms of, 257
  complications of, 258
  definition, 255
  epidemiology, 255–256
  osteoporosis, 255
  serological markers, 256–257
  small intestine mucosa, 257
  target groups, screening of, 259
  therapy and follow-up, 258–259
Consortium of Rheumatology Researchers of North America (CORONA), 29
Costoclavicular test, 290
"Coxa profunda," 226
Coxibs, 309
Crystallised intelligence, 321
C somatomedin, 156
Cyclic citrullinated peptides (CCP), 14
Cyclooxygenase 2 (COX-2), 128–129, 298, 304, 309, 365
Cyclosporine, 19–20, 312
Czech Gastroenterological Society, 264

D
Degenerative spinal canal stenosis, 294
Demyelinating disease, 28
Denosumab, 280
Densitometry, 251, 258, 264, 277, 278
Diabetes collagenase. *See* Cheiroarthropathy
Diabetes mellitus (DM), 151, 152, 160, 163, 185, 191, 193, 269, 270
Diabetic charcot neuropathic osteoarthropathy
  clinical features
    acute stage, 161–163
    chronic stage, 161–164
    "6 D" changes, 164
    polyneuropathy, 165
    subacute stage, 161
  continuous diabetologic and orthopaedic care, 186
  diabetic foot, 151
  diagnosis, 160–161
  differential diagnosis
    algorithm of, 174
    diabetic foot, 172
    hesitation and delayed well-targeted disease, 173
    infected and noninfected structures, 174
    infective inflammatory diseases, 175
    Morton´s syndrome, 175
    needle/open biopsy, 173
    neuropathies, 176
    OM diagnosis, 176
    osteomyelitis, 175
  epidemiology, 152–153
  etiopathogenesis
    angiopathy, 155
    autonomic neuropathy, 155
    cheiroarthropathy, 156
    diabetic foot syndrome, 153
    foot, diabetic lesions of, 153
    "The French theory," 154
    "The German theory," 154
    infection, 157
    inflammation, 156
    metabolic causes, 156
    motor peripheral neuropathy, 155
    neuropathic foot, 160
    non-enzymatic glycation, 153
    oxidative stress, 153
    peripheral somatic neuropathy, 155
    plantar pressures, 157, 159
    Schon's classification system, 157–158
    sorbitol pathway, 153
    trauma, 156–157
    valgus deformity, 158, 160
  historical background, 152
  imaging techniques, 168
    biochemical examination, 172
    computer tomography, 167, 169–171
    isotope examination, 170, 172
    MRI, 169–171
  interventional diagnosis, 172
  polyneuropathy, 152
  radiology
    abnormalities, 167
    atrophic and hypertrophic changes, 166
    complete destruction and disintegration, 166
    destructive form, 165
    Eichenholtz´s scheme, 166
    hyperostosis, 166
    mutilating form, 165
    osteolysis, 166
    osteopenia, 165–166
    Sanders and Frykberg classification, 167
    spontaneous subluxation and dislocation, 166
  therapy
    bisphosphonates, 178
    comprehensive rehabilitation treatment, 185–186
    conservative treatment, 177
    foot deformity, 178
    operative treatment, 178, 182–185
    scavenger system and nerve metabolism, 177
    tibia, immobilisation of, 178–181
  type 1 diabetes, 151
  type 2 diabetes, 151
Diabetic scleroderma, 211
Diacerein, 130–131
Diffuse idiopathic skeletal hyperostosis (DISH), 201–202
  aetiology and aetiopathogenesis, 269–270
  clinical manifestations, 270–271
  differential diagnosis, 271
  elderly patient, 271–273
  heterotopic bone tissue, 269
  ossifications, 269
  Resnick's criteria, 269
  therapy, 273–274
DILE. *See* Drug-induced lupus erythematosus (DILE)
Disease Activity Score (DAS), 29
Disease-modifying antirheumatic drugs (DMARDs)
  and biological therapy, 28–31
  cyclosporine, 19–20
  gold salts, 20–21
  hydroxychloroquine, 20
  leflunomide, 19
  methotrexate, 18–19
  sulfasalazine, 20
Disease-modifying OA drugs (DMOADs). *See* Symptomatic slow-acting drugs for OA (SYSADOA)
DISH. *See* Diffuse idiopathic skeletal hyperostosis (DISH)
Drug-induced lupus erythematosus (DILE), 315–316
Drug-induced rheumatic syndromes
  DILE, 315–316
  drug-induced arthralgia, 318
  drug toxicity, 315
  gout, 318
  iatrogenic diseases, 315
  scleroderma, 318
  statin-associated myopathy, 316–317
  vasculitis, 318
Dry eye syndrome, 8
6D syndrome, 200
Dual energy X-ray absorptiometry (DEXA), 246, 351
Dupuytren's contracture, 211, 212

E
Eichenholtz classification, 164–166
Elbow joint replacement, 336
Elderly-onset rheumatoid arthritis (EORA), 327
  age factor, 1, 27
  vs. classic rheumatoid arthritis, 6, 9
  clinical manifestations
    ankle joints, 4
    Baker cyst, 4
    buttonhole deformity, 3, 4
    carpal tunnel syndrome, 3–4
    DIP and PIP joints, stages I and II arthritis, 7, 9
    hallux valgus, 5, 8
    hammertoe deformity, 5
    hip joints, 4, 6
    knee joints, 4–6
    MCP joints, 9
    mild synovitis, 3
    morning stiffness, 3
    prodromal symptoms, 3
    rheumatoid coxitis, 4
    shoulder joint, involvement of, 4, 5, 8
    swan neck deformity, 3
    ulnar drift of hands, 3, 4
  crystal-induced arthritis, 15
  definition, 1
  differential diagnosis, 14
  erosive osteoarthritis, 15–16
  extra-articular symptoms, 3, 6, 8–9
  feature of, 1, 2
  female/male incidence ratio, 1, 2, 27
  hepatitis C virus infection, 16
  HLA-DR4, role of, 2
  immunodeficiency and chronic inflammation, 11–12
  immunological changes, 9–10
  immunopathological condition, 9–10
  laboratory examinations, 13–14
  occult malignancy, 16
  osteoporosis, 25–26
  pathogenesis, 1–2
  PMR and EORA/PMR patients, 13
  prevalence of, 2–3
  RS_3PE, 14–15
  and RS_3PE syndrome, 92–93
  spondyloarthritis, 15
  treatment, 1
    analgesics, 17
    DMARD treatment (*see* Disease-modifying antirheumatic drugs (DMARDs))
    glucocorticoid treatment, 18
    non-pharmacological treatment, 16
    NSAIDs, 17–18
    pharmacological treatment, 16–17
    therapeutic procedures, 16
Elderly-onset SLE (SLE-E)
  clinical manifestation of, 33–35
  diagnosis, 36
  incidence of, 33
  treatment, 36–37
Electroanalgesia, 326
ELISA method, 2, 14, 172, 249, 264
Endoprosthesis, 145, 334, 335
Enteropathic arthritis, 265
Enthesopathy, 210
EORA. *See* Elderly-onset rheumatoid arthritis (EORA)
Erosive osteoarthritis, 15–16, 115–116, 119
Erythrocyte sedimentation rate (ESR), 13
Etanercept, 28
European Working Group on Sarcopenia in Older People (EWGSOP), 355
Extensor tenosynovitis, 14

F
Falls, involutional osteoporosis, 356–359
"Fat-frail syndrome," 356
Fehling's solution, 240
Fibrocartilaginous disc (lamina interpubica), 225
Fibromyalgia, 290
Fibrous cartilage, 231
Floating hyperglycaemia, 152
Fluid intelligence, 321
Focal segmental necrotising glomerulonephritis, 57
Forestier's disease. *See* Diffuse idiopathic skeletal hyperostosis (DISH)
Forestier's hyperostotic spondylosis, 201
Fornasier's classification, 201
Fracture risk assessment system (FRAX), 358
Frailty syndrome, 355–356
"The French theory," 154
Frozen shoulder, 288

G
Gait speed, 359
Gammagraphy, 170
Garvan fracture risk calculator, 358
"The German theory," 154
Giant cell arteritis (GCA)
  aethiopatogenesis, 62
  aortic aneurysm (*see* Aneurysm)
  clinical manifestation
    cardiac involvement, 64–65
    headache, 62
    liver involvement, 65
    neurovascular manifestations, 63
    ocular manifestations, 63
    palpation tenderness, temporal area, 63
    pulmonary involvement, 65
    renal involvement, 65
  definition, 75
  diagnosis, 66–67
  differential diagnosis, 67
  extremities, involvement of, 63–64
  gangrene, 71
  giant cell, detail of, 71
  incidence, 61–62
  increased temperature gradient, 69
  ischaemic complications, 70
  laboratory findings, 65–66

mononuclear cell infiltration, 71
with oculomotor nerve palsy, 70
paraneoplastic syndrome, 102, 103
right lower leg, amputation of, 71
symptoms, 61, 62
treatment, 68–69
Girdlestone resection arthroplasty, 333
Global Longitudinal study of Osteoporosis in Women (GLOW), 357
Glomerulonephritis, 50
Glucocorticoids
EORA, 18
osteoarthritis, 129
osteoporosis, 24, 26
polymyalgia rheumatica, 67–69
SLE patients, 36, 37
Glucosamine sulphate (GS), 130
Gluten-sensitive enteropathy, 245
Gold salts, 20–21, 312
Goodpasture's syndrome, 55
Gouty arthritis
clinical symptoms of, 216
diuretic treatment, 217–219
early atypical tophaceous gout, 217
elderly patients
clinical signs in, 215
gout therapy, 220–221
polyarticular gout, 215–216
small joints involvement, clinical features, 216–217
Granulomatosis with polyangiitis (GPA)
aetiology and pathogenesis, 55
auxiliary examinations, 55
clinical manifestations, 55
definition, 54–55
diagnosis, 55
differential diagnosis, 55
disease prognosis, 56
laboratory findings, 55
therapy, 55

H
Haemochromatosis arthropathy. *See* Hereditary haemochromatosis
Hallux valgus, 5, 8
Hammertoe deformity, 5
Hansen malum perforans, 183, 184
Haversian system, 276
Health Assessment Questionnaire (HAQ) Disability Index, 29–31
Healthy ageing, 359
Heberden's nodes, 211, 322
Hepatitis C virus, 16
Hereditary haemochromatosis
arthropathy
clinical features, 142
diagnosis of, 145–146
epidemiology, 143
pathophysiology, 142–143
prognosis, 144–145
radiological changes, 143–144
treatment, 146–147
clinical features, 141
diagnosis of, 141
genetics of, 140–141
pathophysiology of, 139–140
screening, 146
vs. secondary haemochromatosis, 139
treatment and prognosis, 141–142
Herpes zoster, 290
"Hip strategy," 155
Hoffmann operation, 339
Homogentisate 1,2-dioxygenase (HGD), 233–235
Hormone therapy, 63, 279
Hunter's canal entrapment syndrome, 296
Hyaline cartilage, 231
Hyaluronic acid (HA), 131–132
Hydroxychloroquine, 20, 311
Hyperabduction test, 290
Hyperaemia, 161, 163, 170
Hyperuricemia, 87, 220, 269, 312, 318
Hypoglycemizing effect, 309
Hypomobility, 293, 295
Hypouricemic medications, 310

I
Impingement syndrome, 289
Infliximab, 30, 88, 312, 316
Institute of Rheumatology, 272
Insulin-dependent diabetes mellitus (IDDM), 210
Insulin-like growth factor 1 (IGF-1), 156, 256
International Osteoporosis Foundation (IOF), 358
Intra-articular disorders, 285
Intraepithelial lymphocytes, 258
Intramyocellular lipid (IMCL), 192, 193
Involutional osteoporosis. *See also* Senile osteoporosis
ageing process, 352
civilization diseases, 351
DXA, 351
falls, 356–359
frailty syndrome, 355–356
osteoporosis, 359–360
sarcopenia (*see* Sarcopenia)
WHO, 351
Isometric exercises, 323

K
Kaiser-Kabat technique, 326
Kawasaki syndrome (KS)
aetiology and pathogenesis, 53
auxiliary examinations, 54
clinical manifestations, 53
definition, 53
diagnosis, 54
differential diagnosis, 54
disease prognosis, 54
laboratory findings, 54
therapy, 54

Keller resection arthroplasty, 339
Kelly's test, 290
Keratoconjunctivitis sicca (KCS), 8, 9
Kerckring folds, 257
K. Rockwood's approach, 355
Kyphotic thoracic deformity, 296

L
Large limb joints surgery
  ankle and foot surgery
    arthrodesis, 339, 340
    arthroplasty, 340
    osteotomy, 339
    resection arthroplasty, 339
    synovectomy and tenosynovectomy, 339
  arthrodesis, 332–333
  corrective osteotomy, 332
  elbow joint, 336
  joint replacement, 333–334
  knee joint, 334
  shoulder joint, 334–335
  spine surgery, 340–342
  synovectomy, 332
  wrist and hand surgery
    arthrodesis, 337–338
    arthroplasty, 338
    resection and osteotomy, 338
    synovectomy and tenosynovectomy, 336
    tendon reconstructive surgery, 336–337
Late-onset peripheral spondyloarthropathy, 95
Leflunomide, 19, 311
Lequesne's algofunctional index (LFI), 364
L. Fried's approach, 355
Limited joint mobility (LJM) syndrome, 156, 194, 203, 210
Lipoprotein-associated phospholipase A2 (Lp-PLA2), 193

M
Magnetic resonance imaging (MRI), 169–170
Marsh classification, 257, 259, 263
Metabolic osteopathy
  antigliadin antibodies, 249
  bone biopsy, 253
  bone densitometry
    skeletal demineralization, L-spine BMD value, 247
    skeletal osteoporosis, L-spine BMD value, 251–252
  bone trabecula, 246, 248
  cancellous bone trabecula, 253
  celiac sprue, 245
  enterobiopsy, 249
  genetic predisposition, 249
  gluten-free diet, 250
  malabsorption symptoms, 249
  metastatic tumor disease, 246–248
  mucosal lesions, 245
  osteopenia, 245–246
  outcomes, 248
  patients laboratory and clinical findings, 250
  skeletal scintigraphy, 253
  small intestinal mucosa, 246, 249
  treatment, 248
  triggering mechanism, 249
Metabolic syndrome (MS). *See* Musculoskeletal system, metabolic syndrome
Methotrexate (MTX), 18–19, 28–31, 311
Methylsulfonylmethane (MSM), 134
Microscopic polyangiitis (MPA)
  aetiology and pathogenesis, 56
  auxiliary examinations, 57
  clinical manifestations, 56
  definition, 56
  diagnosis, 57
  differential diagnosis, 57
  disease prognosis, 57
  incidence, 56
  laboratory findings, 56–57
  therapy, 57
Milwaukee shoulder, 287–288, 325
Mixed connective tissue disease (MCTD), 40
Mixed paraneoplastic syndromes, 100
"Mobility blocking" disorder, 294
Modern total arthroplasty, 332
Mönckeberg's sclerosis, 155
Morton´s syndrome, 175
Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, 87
MPA. *See* Microscopic polyangiitis (MPA)
Multicentric reticulohistiocytosis (MR), 102–104
Muscle strength, 125, 276, 323, 326
Muscular paraneoplastic syndromes, 99
Musculoskeletal system, metabolic syndrome
  ankle and foot, structural changes, 203–205, 207
  Bruns-Garland syndrome, 199
  clinical manifestations, 199
  diabetic muscle infarction, 198–199
  dyslipoproteinaemia, 192
  elbow, structural changes, 210
  etiopathogenesis, 192
  hand, structural changes, 210–211
  knee joint, structural changes, 203
  ligamentous changes, 197
  lipid metabolism disorders, 192
  mesenchymal tissue damage, stimulation factors
    calcification, 194
    cheiroarthropathy, 194
    familial hypercholesterolaemia, 195
    fatty tissue disorders, 193
    hyperinsulinaemia, 193
    immunogenetic inflammatory disorders, 194
    LADA, 192
    LJM, 194
    Lp-PLA2, 193
    neuroangiopathy, 195
    neuropathy, 195
    triggering mechanism, 194
  metabolic flexibility, 191
  muscle changes, 197–198
  osteoarticular changes, 195–197
  pelvis and hip joints, structural changes, 203
  reflex sympathetic dystrophy syndrome, 199
  shoulder, structural changes, 207–210

spine
osteopenic structural changes, 200
osteoproductive structural changes, 201–202
treatment, 211–212
type 2 DM, 191
WHO, 191
Myalgia, 317
granulomatosis with polyangiitis, 55
polyarteritis nodosa, 52
Takayasu's arteritis, 50
Myelodysplastic syndrome (MDS), 102
Myositis, 317

N
Neck and shoulder pain
acute and chronic pain, 286
bone lesion, 290
brachial plexus/spinal cord, lesion of, 286
cervical radiculopathy, 286
definition, 285–286
diagnosis of, 286
fibromyalgia, 290
frozen shoulder, 288
herpes zoster, 290
incidence, 285
inflammatory muscle disease, 290
internal organs pain, 290
Milwaukee shoulder, 287–288
NCBS, 291–292
reflex sympathetic dystrophy, 290
rheumatic polymyalgia, 290
shoulder arthritis, 288–290
Needed to treat (NNT), 356
Neuro-musculo-skeletal system, 352, 360
Neuropathic pain, 128, 297, 298, 301, 303–305
Nociceptive pain, 129, 301
"No fall, no fracture" concept, 352
Non-insulin-dependent diabetes mellitus (NIDDM), 210
Nonspecific cervicobrachial syndrome (NCBS), 291–292
Non-steroidal anti-inflammatory drugs (NSAIDs), 17–18, 220, 273, 303, 308–310, 315, 316, 363
adverse effects of, 127–128
classification, 126–127
mechanism of action, 127
selective COX-2 inhibitors, 128–129
Nutrition
balanced diet, 283–284
calcium, 281–282
fats, 282
fruit and vegetables, 282–283
proteins, 282
vitamin D, 282
vitamins and trace elements, 283

O
Ochronosis. *See* Alkaptonuria (AKU)
Omarthritis, 325
Opioid analgesics, 304
Orthokine therapy, 132
Ossification of the posterior longitudinal ligament (OPLL), 270, 271
Osteoarthritis (OA)
AC joint, arthritis of, 122
clinical features, 114
definition, 111
diagnostic criteria, 123–124
DIP and PIP joints, arthritis of
degree II arthritis, 119
erosive osteoarthritis, 115–116, 119
gelatinous cysts, 115
joint space narrowing, 118
lateral subluxations and deviations, 115
marginal osteoproductive changes, 118
rhizarthrosis, 115, 118
epidemiology, 111–112
feet, 120
of hip, 114, 115
knee joints, 114–117
left elbow, 121
pain, causes of, 113
pathogenesis, 112–113
risk factors, 113–114
secondary OA, 122–123
shoulders, 121
socioeconomic impact, 112
spine, 122–124
symptoms, 114
treatment, 129–130
avocado/soya unsaponifiables, 131
chondroitin sulphate, 130
diacerein, 130–131
general measures, 125
glucocorticoids, intra-articular treatment, 129
glucosamine sulphate, 130
hyaluronic acid, 131–132
local transdermal treatment, 129
non-opioid analgesics, 126
NSAIDs, 126–129
opioid analgesics, 129
orthokine therapy, 132
orthopaedic (orthotic) devices, 125
patient education, 125
physical therapy, 125
rehabilitation therapy, 125
subchondral bone, 132–133
surgical interventions, 134
vitamins, minerals and nutritional supplements, 133–134
Osteocentric approach, 360
Osteoclast differentiation factor (ODF), 24
Osteogenic osteomalacia, 104
Osteomalacia, 265
Osteoporosis (OP)
aetiopathogenesis of, 275
bisphosphonates, 259
elderly population, 281
genetic predispositions, 281
nutrition
balanced diet, 283–284
calcium, 281–282

fats, 282
fruit and vegetables, 282–283
proteins, 282
vitamin D, 282
vitamins and trace elements, 283
physical activity, 281
in RA patients
antiresorptive treatment, 25, 26
bone density, reduction of, 24, 26
DMARD treatment, 24
glucocorticoid treatment, 24, 26
incidence of, 23, 26
inflammatory process, 23, 24, 26
osteoclasts, 23–24
risk factors, 23, 24
vertebral fractures, prevalence of, 24
YORA and EORA patients, 25–26
secondary osteoporosis, 281
Osteoprotegerin ligand (OPGL), 24

P
Paget's disease
aetiology, 344
bone disorder, 343
bone remodelling, 343
clinical features, 344–345
clinical symptoms of, 345, 346
diagnosis, 345
epidemiology, 343–344
osteitis deformans, 343
pathophysiology, 344
specific pharmacological treatment, 346–349
Pain
adjuvant therapy, 304–305
chronic non-malignant pain, 303
consequences, 301
dementia, 303
elderly patients
non-pharmacological pain management, 305
pharmacological pain management, 302–303
inflammatory pain, 303
interdisciplinary assessment, 302
neuropathic pain, 301, 303
nociceptors, 301
non-opioid analgesics, 303–304
opioid analgesics, 304
pharmacokinetics, 301
polypharmacy, 301
radiation, 294
types and causes of, 302
PAN. *See* Polyarteritis nodosa (PAN)
Paracetamol, 308
Paraneoplastic rheumatic syndromes
algodystrophic syndrome, 100
APS and CAPS, 101
cancer immunotherapy, arthropathy, 100
cause of, 99
criteria, 99
cutaneous, 99
giant cell arteritis, 102, 103
malignant diseases, ANAs in, 105–108
multicentric reticulohistiocytosis, 102–104
muscular, 99
osteogenic osteomalacia, 104
paraneoplastic arthropathy, 100
polymyalgia rheumatica, 102, 103
relapsing polychondritis, 101–102
RS_3PE syndrome, 104–105
SLE-like syndrome, 100–101
vascular, 100
Parkinson's disease, 330, 358
Pellegrini-Stieda syndrome, 203
Penicillamine therapy, 312
Peroxisome proliferator-activated receptors (PPARs), 198
Phalen's sign, 211
Phenylalanine, 234
Phenylketonuria, 234
PMR. *See* Polymyalgia rheumatica (PMR)
Podobaroscope, 159
Polyarteritis nodosa (PAN)
aetiology and pathogenesis, 52
auxiliary examinations, 52
clinical manifestations, 52
definition, 51–52
diagnosis, 52
differential diagnosis, 52–53
disease prognosis, 53
laboratory findings, 52
therapy, 53
Polyarticular tophaceous gout, 216
Polymerase chain reaction (PCR), 235
Polymyalgia rheumatica (PMR). *See also* Giant cell arteritis (GCA)
clinical features, 62
diagnosis, 66
and EORA/PMR patients, 13
incidence, 61
laboratory findings, 65–66
paraneoplastic syndrome, 102, 103
renal involvement, 65
and RS_3PE syndrome, 91–92
symptoms, 61, 62
treatment, 67–69
Polymyositis, 290
Positive Schirmer's test, 40
Potential renal acid loads (PRAL), 282
"Prayer sign," 211
Proximal humerus hemiarthroplasty, 335
Pseudoradicular syndrome, 296
Psoriatic arthritis (PsA), 15
anti-cytokine therapy, 28–30
bizarre deformities, 338
Pulmonary involvement, 45–46

R
Raloxifene, 279, 318
RANK. *See* Receptor activator of nuclear factor (RANK)
Raynaud's phenomenon, 45, 326

Reactive arthritis, 58
Reaven syndrome X, 191
Receptor activator of nuclear factor (RANK), 24, 156, 163, 275
Reflex sympathetic dystrophy syndrome, 94, 199
Reiter syndrome. *See* Reactive arthritis
Relapsing polychondritis (RP)
  arthropathy, 84
  association with other diseases, 86–87
  cardiac involvement, 85
  characteristics, 101
  diagnostic criteria, 87
  differential diagnosis, 87–88
  in elderly patient, 86
  epidemiology, 83
  etiology and pathogenesis, 83–84
  laboratory findings, 87
  mixed paraneoplastic syndrome, 101–102
  ocular manifestations, 86
  red and swollen auricles tender to palpation, 84
  renal involvement, 85–86
  respiratory system, involvement of, 85
  saddle-nose deformity, 84
  symptoms, 84, 101
  treatment and prognosis, 88–89
Remitting seronegative symmetrical synovitis with pitting oedema (RS_3PE) syndrome, 104–105
  amyloid arthropathy, 94–95
  articular chondrocalcinosis, 94, 95
  clinical features, 91
  differential diagnosis, 94
  EORA patients, 14–15, 92–93
  hand arthritis, 94
  inflammatory rheumatic diseases, 93
  late-onset spondyloarthropathy, 95
  mixed connective tissue disease, 94
  paraneoplastic syndrome, 96
  and polymyalgia rheumatica, 91–92
  psoriatic arthritis, 93
  reflex sympathetic dystrophy, 94
  sarcoidosis, 95–96
  Sharp's syndrome, 94
  and tumours, 93–94
  Whipple's disease, 96
Resection arthroplasty, 341
Resnick's DISH diagnosis criteria, 269, 270
Respiratory syncytial (RS) virus nucleocapsids, 344
Reverse shoulder replacement, 335
Rhabdomyolysis, 317
Rheumatic diseases
  crystallised intelligence, 321
  fluid intelligence, 321
  inactivity, 321
  osteoarthritis
    ankle and joints of the foot, 324
    degenerative process, 322
    elbow, 325
    hand, small joints of, 322
    hip, 322–323
    knee, 323–324
    omarthritis, 325
    pharmacological therapy, 322
    physical therapy, 322
    physiological aging, 322
    spine, 325–326
  pharmacological treatment, elderly patients
    allopurinol, 310
    analgesics antipyretics, 308
    biological disease-modifying antirheumatic drugs, 312–313
    colchicine, 310
    drug elimination, 307
    drug metabolism, 307
    febuxostat, 310
    general recommendations, 313
    glucocorticoids, 309–310
    malnutrition and hypoproteinemia, 307
    NSAIDs, 308–309
    opioids, 308
    polymorbidity, 308
    symptomatic medications, long-term effect, 313
    synthetic disease-modifying antirheumatic drugs, 310–312
  rheumatoid arthritis, 327
  sequelae of
    blood loss, 331
    general aspects, 329
    large limb joints surgery (*see* Large limb joints surgery)
    patient education, 330
    preliminary indication, 329–330
    preoperative examination and preparation, 330–331
    rehabilitation and follow-up care, 331
    surgery types, 331
  SLE, 326–327
Rheumatic polymyalgia, 290
Rheumatoid arthritis (RA)
  EORA (*see* Elderly-onset rheumatoid arthritis (EORA))
  incidence and prevalence of, 2–3
  osteoporosis (*see* Osteoporosis)
  rehabilitation, rheumatic diseases, 327
Rheumatoid coxitis, 3
Rheumatoid factor (RF), 2, 13–14
Rheumatoid nodulosis, 6
Rhizarthrosis, 115, 118
Rituximab, 312–313
Robust-prefrail-frail, 356
Rosenbloom's criteria, 210
Rotator cuff muscles, 289
RS_3PE syndrome. *See* Remitting seronegative symmetrical synovitis with pitting oedema (RS_3PE) syndrome

S

Sacroiliac synchondrosis, 226
Sanders–Frykberg anatomic classification, 159
Sarcoidosis, 95–96

Sarcopenia
asthenic habitus, 354
causes, 354–355
consequences, 353
etiopathogenetic causes, 353
muscle mass, strength and performance, 353
RANK-RANKL system, 352
"sarcoporosis," 352
Wnt signalling pathway, 352
Scalene test, 290
Scavenger mechanism disorder, 196
Secondary amyloidosis, 8
Senile osteoporosis
age-related factors, 276
antiresorptive protein, 275
bone resorption, 275
clinical features
examination, 277–278
osteoporosis, 277
treatment, 278–280
vertebral spinous process, 277
idiopathic and involutional osteoporosis, 276
immobilisation, 276
pathological intervention, 275
primary osteoporosis, 276
risk factors, 276
Sharp's syndrome, 94
Shoulder disorder, 334
Sicca syndrome, 43
Sjögren's syndrome, 8, 262, 265
clinical manifestations, 41
diagnostic criteria, 39–40
extraglandular manifestations, 39
incidence of, 39
laboratory findings in, 41
revised international classification criteria, 42
revised rules for classification of, 42
sicca syndrome, differential diagnosis of, 43
systemic connective tissue diseases, 40
Skeletal scintigraphy, 253
Skiagraphy, 223, 226, 229, 231
SLE. *See* Systemic lupus erythematosus (SLE)
Spine, vertebrogenic disorders
endocrinopathy, 296
fascia, 295
gastrointestinal disorders, 297
hypoventilation, 295
ligaments, 294
lower limb joints, 295, 298
malignancies, 297
muscles, 294–297
osteoporosis, 296, 299
psychic factors, 296
vascular processes, 296
visceral pain, 297
Spondyloarthritis, 15, 325
SSc. *See* Systemic scleroderma (SSc)
Statin myopathy, 316, 317
Stiff hand syndrome, 211
Strontium ranelate, 279, 356
St Vincent Declaration, 185
Sudeck's disease. *See* Reflex sympathetic dystrophy
Sulfapyridine, 311
Sulfasalazine, 20, 311
Summary of product characteristics (SPC), 349
Symptomatic slow-acting drugs for OA (SYSADOA), 129–130
avocado/soya unsaponifiables, 131
chondroitin sulphate, 130
diacerein, 130–131
glucosamine sulphate, 130
hyaluronic acid, 131–132
Synovial fluid, 231
Systemic enzyme therapy (SET)
"application patterns," 364
"complaint index," 365
conservative treatment, 363
diclofenac, 364
good tolerability and safety, 363
LFI, 364, 365
lymphatic swelling, 364
microcirculation, 363
NSAIDs, 363, 364
Phlogenzym, 364, 365
rheumatic diseases, 364
therapeutic polypragmasia, 363
Systemic lupus erythematosus (SLE), 315–316, 326–327
definition, 33
elderly-onset SLE
clinical manifestation of, 33–35
diagnosis, 36
incidence of, 33
treatment, 36–37
etiopathogenetic factors, 33
Systemic scleroderma (SSc)
cardiac involvement, 46
incidence of, 45
laboratory findings, 46
pulmonary involvement, 45–46
Raynaud's phenomenon, 45
renal manifestation, 46
symptoms, 45, 46
treatment, 46–47
visceral manifestations, 45

T

"Table desk sign," 211
Takayasu's arteritis (TA)
aetiology and pathogenesis, 49–50
auxiliary examinations, 50–51
clinical manifestations, 50
definition, 49
diagnosis, 51
differential diagnosis, 51
disease prognosis, 51
laboratory findings, 50
therapy, 51

Temporal arteritis (TA). *See* Giant cell arteritis (GCA)
Tenosynoviosclerosis, 203, 211
Tenosynovitis, 6
Teriparatide, 280
Thiazide diuretic therapy, 217
Thiberge–Weissenbach syndrome, 238
Time-tested facilitation techniques, 326
Tinel's sign, 211
Tocilizumab, 313
Tofacitinib, 31
Tramadol, 129
Transient ischaemic attacks (TIA), 63
Trigger fingers, 211, 336
Type 1 complex regional pain syndrome, 199

U
"Use it or lose it" principle, 322
Utsinger's classification, 201

V
Vasculitis
  Behçet's disease, 57–59
  classification of, 49, 50
  definition, 49
  granulomatosis with polyangiitis, 54–56
  Kawasaki syndrome, 53–54
  microscopic polyangiitis, 56–57
  polyarteritis nodosa, 51–53
  Takayasu's arteritis, 49–51
Vertebrogenic disorders
  aetiopathogenetic factors
    intervertebral articulation, 293–294
    intervertebral disc disorders, 293
    sacroiliac joint, 294
    spine, stabilization system of, 294–297
  paraclinical examinations, 298
  treatment, 298
Vertebrogenic pain syndromes, 325
Viscosupplementation, 313

W
Wegener's granulomatosis. *See* Granulomatosis with polyangiitis (GPA)
Weight reduction diets, 283
Whiplash syndrome, 291
Whipple's disease, 96
World Health Organization (WHO), 191, 283, 284, 351, 357, 359

Y
Younger-onset rheumatoid arthritis (YORA)
  vs. EORA, 1
  multiple DMARD treatment, use of, 29
  osteoporosis, 25–26