Rheumatic Disease in Geriatrics

Diagnosis and Management

Gleb Slobodin
Yehuda Shoenfeld
Editors

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Editors
Gleb Slobodin
Rheumatology Unit
Bnai Zion Medical Center
Haifa
Israel

Yehuda Shoenfeld
Zabludowicz Center for
Autoimmune Diseases
Sheba Medical Center
Tel-Hashomer
Israel

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Preface

Imaginary longevity with the global life expectancy over 80 years, a consequence of the fascinating progress in science, technology, and medicine, is becoming a phenomenon of real life. Alongside this, it has opened new horizons of medical research and practice to allow older people to stay active. Musculoskeletal complaints are among the most frequent in the elderly, and rheumatic diseases are countable for many of those. Rheumatology of the elderly is a medical science, which is based on the still-developing understanding of age-related modifications in the body systems and functioning, as well as on the knowledge of clinical presentations, diagnostic abilities, and available management tools for specific rheumatic disorders. Accordingly, this book *Rheumatic Disease in Geriatrics: Diagnosis and Management* provides insights into the broad spectrum of related terrains, from epigenetics of aging to the rehabilitation of older people with rheumatic diseases. Particular emphasis in this book has been given to practical approaches to elderly individuals with distinct age-related rheumatic conditions and disease presentations. While the availability of timely rheumatology service is far from being perfect over the world, this book is primarily intended for primary care physicians and geriatricians, who have to take care of elderly patients presenting with rheumatic complaints. Nonetheless, the comprehensive and updated contents of this book are aimed at rheumatologists as well.

We cordially thank our colleagues, researchers, and physicians, who responded to the invitation and contributed wonderful chapters to *Rheumatic Disease in Geriatrics: Diagnosis and Management.* We aspire to see this book useful for the medical community and, consequently, to older patients suffering from rheumatic diseases.

Haifa, Israel — Gleb Slobodin
Tel-Hashomer, Israel — Yehuda Shoenfeld

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Chapter 1
Prevalence of Rheumatic Disorders in Geriatric Population

Julianna Hirsch

People are living longer than ever before. By 2050, the world's population above age 60 is projected to reach 2 billion, up from 900 million in 2015 [1]. As the average age of the population rises, the incidence and prevalence of rheumatologic conditions climb as well, with some of the disease states primarily affecting the geriatric population or affecting them in a way unique as compared to their younger counterparts. Many of the rheumatic diseases may cause a great deal of hardship to the patient, resulting in chronic pain and handicap which can make navigating through daily life challenging. Rheumatic diseases have a high economic burden, which has increased since the advent of biologic medications and the enthusiastic utilization and success of these therapies. In 2013 medical expenses attributable to arthritis totaled $139.8 billion, with the highest expenditure being for ambulatory care [2]. Between 2013–2015, nearly 50% of people aged 65 or older reported arthritis diagnosed by a physician [3]. Now more than ever, General Practitioners are caring for a wider spectrum of diseases as a result of the aging of their patient population. Symptoms of rheumatic conditions fall high on the list of concerns patients present with and it is becoming the responsibility of the primary provider to recognize the symptoms, initiate treatment and refer to a rheumatologist when necessary. Health care providers may supplement their exam and laboratory values with sophisticated imaging techniques for diagnosis and management. Musculoskeletal ultrasound has proven itself to be a useful and reliable tool in the hands of a trained operator, which can be used as an adjunct to the clinical examination [4]. Rheumatic conditions within the geriatric population impose a heavy personal and economic load, warranting continued investigation and research to further characterize the common diseases and those that present with features unique to the geriatric population. The most common rheumatic conditions affecting the elderly include osteoarthritis (OA), rheumatoid arthritis (RA), gout and pseudogout, polymyalgia rheumatica (PMR), giant cell arteritis (GCA), and fibromyalgia (Table 1.1).

J. Hirsch (✉)
Department of Medicine, Mount Sinai St. Luke's-West, New York, NY, USA

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Table 1.1 Estimated prevalence of rheumatic conditions in the elderly population

Rheumatic condition	Prevalence (%)
Osteoarthritis	19.7–42.3
Pseudogout	7.8–18.5
Gout	9.3–12.5
Fibromyalgia	2.8–5.5
Rheumatoid arthritis	0.5–4.5
Polymyalgia rheumatica	1–4
Giant cell arteritis	0.15–1.15
SLE	0.05–0.3
Idiopathic inflammatory myopathies	0.025–0.065

1.1 Osteoarthritis

Worldwide, OA affects 50% of the population above the age of 65 and it has significant life altering effects, limiting activities of daily living in 25% of people with symptomatic OA and limiting motion in 80% of that population. The prevalence of OA differs depending on the author's definition of OA (namely whether the diagnosis of OA was given based on radiographical, pathological or clinical grounds) and the anatomical location it affects. In a study looking at people above age 65 in Germany, Italy, Sweden, the Netherlands, Spain and the United Kingdom, the prevalence of clinical OA in any joint ranges from 19.7% to 42.3% with an average of 30.4%. Hip OA has the lowest overall prevalence (5.9%) and knee OA has the highest overall prevalence (19%) across the six countries [5]. The prevalence of symptomatic knee OA in people above age 65 in the United States is between 13% and 20%, depending on gender and race [6]. OA has adverse effects on a large portion of the population and considerably limits function and enjoyment of life. Research in the field and advancements in therapy are lacking and require attention as the geriatric population continues to grow rapidly.

1.2 Rheumatoid Arthritis

RA has a high social and economic burden and is known to increase with age, affecting up to 2% of the geriatric population. The prevalence has increased from 0.5% to 0.75% in males and 0.95% to 1.45% in women above the age of 65 between 2004 and 2014 and has presumably continued in this direction [7, 8]. In addition, the disease affects the elderly differently than it does the younger age group due to differences in the physiology and immunology of the geriatric population when compared to young onset rheumatoid arthritis:

- More equal gender distribution (twice as many women as men versus four times as many women as men in the non-geriatric population)
- More frequent involvement of large joints

- Acute onset of disease with constitutional symptoms
- Lower or equal frequency of serology positivity
- Higher frequency of elevated inflammatory markers
- Spontaneous remission

The diagnosis of elderly onset RA requires prudent evaluation and should not be missed as highly efficacious biological therapies are available for this disorder [9].

1.3 Crystal-Related Arthropathies

Gout is the most common cause of inflammatory arthritis in the developed world and the prevalence also increases with age. There are multiple risk factors including damaged joints, side effects of other prescribed medications and comorbidities such as renal impairment and hypertension, that make the elderly more likely to develop gout. Although it commonly affects young and middle-aged men more than their female counterparts, this gender discrepancy dissolves with age due in part to the decrease in circulating estrogen, and with it, it's uricosuric effects in postmenopausal women [10]. The prevalence of gout worldwide varies widely. Gout has an atypical presentation in the elderly with features that can be challenging to recognize. In a study conducted in the United States (US), the prevalence of hyperuricemia (serum urate >7 mg/dL) in individuals above the age of 65 is 31.4%, corresponding to an estimated 10.7 million adults. The prevalence of clinical gout in people age 70–79 is 9.3% and in those above age 80 is 12.6%. The overall prevalence of gout within the total US adult population is 3.9% [11]. Studies performed outside of the United States arrive at similar results; there has been a steady increase in the frequency of gout over the years and a clear predilection for the geriatric population. Although chondrocalcinosis (or pseudogout) has a high prevalence in the geriatric population, there is a paucity of epidemiological data available with ranges reported between 7.8–18.5% [12–14].

1.4 Polymyalgia Rheumatica

Polymyalgia Rheumatica (PMR) is an inflammatory disorder that causes muscle pain and stiffness and occurs primarily in people above age 50. Women have a higher lifetime risk (2.4%) of developing PMR than men (1.7%). It is estimated that greater than 700,000 Americans have PMR. The overall prevalence of PMR in various countries ranges from 0.02% in Turkey to 1.5% in the United Kingdom (UK). The prevalence of PMR increases with age; in the US, 1% of a 70-year-old cohort and 4% of a 90-year-old cohort had PMR [15]. PMR carries with it an excellent prognosis but is a challenge to treat in the geriatric population due to polypharmacy and comorbid conditions.

1.5 Giant Cell Arteritis

PMR is closely linked to giant cell arteritis (GCA) with up to 21% of people with PMR having GCA as well. In the US, it is estimated that more than 200,000 people have GCA. The lifetime risk for GCA is 1% in women and 0.5% in men. The overall prevalence of GCA ranges from 0.0015% in Japan to 0.25% in the UK. Just as PMR, the prevalence of GCA increases with age; in the US, 0.15% of a 70-year-old cohort and 1.15% of a 90-year-old cohort have GCA [15]. The incidences of PMR and GCA are relatively low but the low mortality rates ensure a higher prevalence of PMR and GCA in the geriatric population making recognition of these disease states of particularly high importance.

Aside from GCA, the other vasculitides do not uniquely affect the elderly or they do not have as high of a prevalence as GCA [16].

1.6 Fibromyalgia

Fibromyalgia has been branded as a disease which most commonly affects younger women making its prevalence within the geriatric population worth mentioning. A meta-analysis estimated the pooled prevalence of fibromyalgia within different populations worldwide. The pooled prevalence of fibromyalgia within the Eastern Mediterranean population is 4.43%, within the European population is 2.64%, within the American population is 2.41% and within the Western Pacific population is 1.62%. The total prevalence of fibromyalgia in the general population is estimated to be 1.78% and can range from 0.01% to 15.2% depending on the population subset being examined [17]. The estimated prevalence of fibromyalgia within the geriatric population ranges from 2.8–5.5% in studies performed in Brazil, France, Sweden and the United States [18]. Fibromyalgia is associated with a great deal of pain, psychological stress, comorbid conditions, work disability and medical costs and can be markedly under-diagnosed [19]; it is therefore important to recognize the extent to which it affects the geriatric population in order to diminish the havoc it wreaks.

1.7 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) typically presents in younger females, but is sometimes diagnosed in older adults, and the late-onset version of the disease may differ clinically and serologically from that in the younger population. The elderly more often exhibit constitutional type symptoms as well as neuropsychiatric complications, serositis and Raynaud's while cutaneous lupus, glomerulonephritis, anti-double-stranded DNA and low complement levels more often affect younger lupus

patients [20]. However, the available studies on elderly-onset SLE are based on a small number of subjects, limited available data and variable follow-up times. Therefore, making conclusions from this data can be problematic. The prevalence of lupus in the UK in the 70–79 age range peaks at 0.05–0.3% depending on gender and decreases rapidly along with incidence in advanced age groups [21]. As the prevalence of lupus in the geriatric population is relatively low and the presenting symptoms and serology are different than the younger cohort, they often have a delayed diagnosis therefore making recognition of the disease crucial.

1.8 Idiopathic Inflammatory Myopathies

Idiopathic inflammatory myopathies (IIM) is a general term which includes dermatomyositis, polymyositis and inclusion body myositis amongst others which are less common. IIM affects the US population above age 65 with an overall prevalence of 0.035% in males and 0.05% in females and in the population greater than age 75 is 0.045% in males and 0.065% in females [22]. In an Australian study over a 30 year span, the overall incidence rate of IIM was highest in the 71–80 age group at 1000 per million person years, likely due to a high incidence rate of inclusion body myositis in this age group [23]. A Swedish study reports an overall incidence and prevalence in the general population of 11 per million/person years and 0.014%. The incidence rate and prevalence in the 70–79 age group were 35 per million person years and 0.042% [24]. Although there is a range of prevalence depending on the study and country, each study reports the geriatric population as having the highest prevalence of IIM and the estimated average age of onset is 66.9. People age 60–70 have the highest incidence of IIM comprising 42% of all IIM diagnoses [25]. In an Australian group, the prevalence of IIM in the general population was 0.0015% which increased to 0.0051% when the estimation was restricted to those above age 50 [26].

Rheumatologic diseases within the geriatric population often have unique presentations and disease courses. Both primary care providers and rheumatologists have the challenging task to tailor their practice to recognize and properly treat these diseases as the world population survives to increased ages.

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Chapter 2
Aging of the Musculoskeletal System

Michal Sagiv

Aging is a complex process based on sequential physiological changes over the extended period. One of the hallmarks of aging is the accumulation of alterations and damages at both macroscopic and microscopic levels that affects tissues, organs, cells, and subcellular organelles. The emerging focus in the biology of aging includes epigenetic and genetic changes, inflammatory response, oxidative stress, metabolic and endocrine regulation, decline in cell renewal by stem cells, and accumulated cell damage. These mechanisms representing the current knowledge of aging, are not specific and play a role in a variety of medical disorders, affecting elderly population. The main challenge associated with advancing adult age is the relationship between progressive alterations in physiologic functions, the gradual decline in functional capacity of an individual, the associated morbidity, and, finally, the loss of independence [1]. Virtually all components of the musculoskeletal system, which shapes the body, enables movement, protects internal organs, and provide a reserve for organic and inorganic molecules vital to the homeostasis, are being gradually affected during aging. Besides, cooperation of the various tissues of the musculoskeletal system in the molecular signaling networks and mechanisms is being impaired with aging as well [2]. For example, aging of muscle tissue leads to gradual decline in skeletal muscle mass and strength, alterations in muscle contraction, impaired motor performance, decrease in flexibility and loss of the muscle capacity to sustain and recover from injury. These changes can be accelerated in the presence of inherited or environmental factors, such as smoking, unhealthy eating, overweight, or inactivity [3]. Moreover, muscle loss can manifest as age-associated, termed sarcopenia, or aggressive, rapid muscle loss in association with illness, such as malignancy, organ failure, or massive trauma [4]. Muscles, bones, fibrous tissues of tendons and ligaments, joint capsules, articular cartilage and intervertebral discs are progressively affected during aging, resulting in accumulating age-related morbidity.

M. Sagiv (✉)
Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

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2.1 Bone

The tendency to depletion of bone mass is remarkable with aging. Bone remodeling cycle takes longer to complete, rate of mineralization decelerates, and bones become less stiff and strong and more fragile. Bone remodeling is a lifelong process that maintains bone in order to support bone marrow, shape the body, protect vital organs, and provide a source of minerals. During the process of remodeling, older and frailer bone is replaced with newer, more resilient one in an organized manner, which is balanced by the activity of the bone-resorbing osteoclasts and bone-forming osteoblasts. As a function of time, continuous mechanical stress leads to the accumulation of microcracks and microfractures. Normally, the presence of microcracks leads to activation of bone remodeling, in which osteoclasts remove the damaged bone area and then recruit and activate osteoblasts to build a new bone. With aging and menopausal transition, the once coordinated mechanism of bone remodeling is impaired, leading to gradual bone loss and increased fragility and osteoporotic fractures. Notably, men experience bone loss at later ages and slower rates than women [5]. At the cellular level, the process of bone loss manifests by decline in the proliferation of aged osteoblast precursors, shortened osteoblast and osteocyte life span, and increased adipogenesis [6]. Related hormonal changes include decreased levels and activity of gonadal steroid hormones and vitamin D, and increased levels and activity of the parathyroid hormone.

2.2 Muscles

The metabolism of muscle tissue is a complex system, tightly regulated by nervous and endocrine systems [7]. One of the most crucial determinants of muscle dysfunction in the elderly is muscle atrophy. Sarcopenia is referred to the age-related loss in skeletal muscle mass and strength [8]. Muscle weakness in elderly is sometimes crippling and can result in frailty. Besides, decline in muscle mass and performance contribute to higher morbidity and mortality as muscles serve as well as a metabolic source of proteins [9]. Adults tend to lose muscle mass at a rate of 1–2% per year after the age of 50 years. With aging, the muscle loss becomes more significant and reaches 3–4% per year [10]. Histologically, older adults have shorter fascicle lengths resulting in a loss in sarcomeres. As a result, muscle density declines, the component of the intermuscular fat increases and the muscle produces less force. The biological and physiological mechanisms underlying these changes are multifactorial and poorly understood. Of interest, some evidence demonstrates that adults who exercise regularly and have a higher level of fitness in early life, will experience a faster rate of decline in elderly [11].

The alterations of the neural system are believed to have a substantial role in the age-related muscular dysfunction. As such, changes in the motor and premotor cortex with atrophy in areas surrounding the primary motor cortex, age-related changes

in white matter mass and length of myelinated nerve fibers have been implicated in the pathogenesis of the muscle disease in older persons [12]. Besides, decreased motor unit number and insufficient compensatory expansion in the number of fibers innervating every motor unit can be seen in the advancing age. These changes correlate with the remodeling of motor units, including modified fiber-type distribution with predominance of slow muscle fiber phenotype as a result of denervation of fast muscle fibers. Altered neuromuscular junctions result in the elevated presynaptic nerve terminal branching and modified postsynaptic distribution of receptor sites for neurotransmitters [13]. Deconditioned in elderly neurotransmission, including serotonergic, cholinergic, adrenergic, dopaminergic, GABAergic, and glutamatergic systems, can lead further to a reduction in muscle performance [14].

Humoral involvement plays an essential role in muscle atrophy and includes increased production of pro-inflammatory cytokines such as tumor necrosis factor alpha, as well as altered production of hormones [15]. The main hormones whose dysregulation significantly influences the age-related muscle loss include insulin like growth factor, growth hormone and sex hormones [16].

Modifications in sarcoplasmic reticulum Ca^{2+} release are believed to be a major cause of the contractile force impairment in the aging skeletal muscle. This effect of the advancing age on the excitation-contraction coupling, unrelated to muscle atrophy, is not entirely understood, and it is currently a major area of research. Besides, changes in cell death signaling, including activation of apoptosis, altered mitochondria-mediated pathways, impaired protein synthesis and turnover have been implicated in the aging process as well [17].

Finally, the numbers of satellite cells, which are muscle cell precursors and play a crucial role in the regeneration of muscle tissue are reduced in elderly. The cause of this decrement is not well understood and is thought to be related to the replicative senescence, the limited number of times that a cell can replicate and divide [18].

2.3 Tendons and Ligaments

Tendons and ligaments are composed of dense connective tissue abundant with fibrillar collagen to provide tensile strength. Tendons link muscles with bones and transmit and dissipate the muscle contraction forces over the bone tissue, while ligaments attach bone to bone and serve to stabilize the joints. The integrity of these attachments is essential for the normal functioning of the musculoskeletal system. With aging, the strength of tendons, ligaments, and entheses reduces, and a decline in joint range of motion occurs, generally in the range of 20–25%. Moreover, aging-related changes in tendons and ligaments make these structures more vulnerable to the injuries including tears and ruptures. Even though these injuries frequently occur at a younger age, the intensity of trauma required to cause damage can be minimal in the elderly. The age-related changes in tendons and ligaments include reduced synthesis and concentration of collagen and proteoglycans, which serve as

lubricants on the surface of the ligament and between the collagen fiber bundles, in parallel with diminished mucopolysaccharide and water content. Besides, reduction in tendon cell density, decreased blood flow, high rates of apoptosis, decreased numbers of progenitor stem cells, and low levels of cell proliferation contribute to the prevalent in the elderly tendinopathies and enthesopathies [19].

2.4 Articular Cartilage

Aging is associated with both higher prevalence of chondrocytes that have lost their ability to divide, and disruption of cartilage homeostasis secondary to cellular senescence [18]. The loss of chondrocytes may be worsened by trauma and excessive mechanical loading and mediated by the increased oxidative stress. Besides, older chondrocytes have a reduced ability to synthesize collagen and other components of the extracellular matrix. Stiffness of the collagen network in tissues, including articular cartilage, increases with age because of an increase in cross-links by advanced glycation end products (AGEs) [20]. AGEs can as well be linked to increased production of inflammatory cytokines, prostaglandin E2, and nitric oxide within the cartilage. Dehydration of the cartilage is likely related to decrease in proteoglycan contents. Both increased stiffness and dehydration make the cartilage more prone to fatigue failure. The functional consequence of these changes is a reduced plasticity and increased risk of injury. It is notable that lack of mechanical stimulation, or immobilization results in thinner and softer articular cartilage, while exercise has the opposite effect. Calcification of the cartilage is another significant age-associated phenomenon, related to the development of crystal-mediated arthritis and osteoarthritis [19]. Finally, decline in response to growth factors contributes to the decreased mitogenic and synthetic responses of the cartilage in elderly [19].

2.5 Intervertebral Discs

Age-related degenerative changes of the intervertebral discs do not always correlate with symptoms of back pain, and the significance of these clinically silent findings is unclear. The intervertebral disks are composed of an outer fibrous ring of connective tissue called the annulus fibrosus and an inner gel-like material called the nucleus pulposus. Endplates, located superiorly and inferiorly to the discs, consist of a thin layer of cortical bone covered by hyaline cartilage and connected to the vertebral bodies. Age-related changes occur within all these regions but predominantly in the nucleus pulposus, which becomes dehydrated and fibrotic. Notably, formation of fissures, cracks, and tears leads usually to disk herniation at the middle age. In elderly, as the nucleus pulposus becomes dehydrated, it is less likely to herniate. The dehydration is a consequence of the decrease in proteoglycans in the

nucleus pulposus and the increase in collagen cross-linking caused by the accumulation of AGEs products. Another age-related phenomenon contributing to these changes is the decline of the vascularization that can be intensified by the concomitant atherosclerotic vascular disease and diabetes [21]. Besides, an increase of apoptotic activity has been shown in the nucleus pulposus and the endplates.

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Chapter 3
Epigenetics of the Aging Musculoskeletal System

Boris Slobodin

3.1 What Is Epigenetics?

Supported by the Darwinian theory of evolution, the ability to inherit traits through generations was long considered to depend almost absolutely on genes. In the middle of the twentieth century, it became increasingly clear that DNA is the genetic material being passed through generations, and that genes consist of long sequences of DNA nucleotides. However, the information concealed in genes is static and has to be further expressed by cells to yield gene products necessary for life. While according to the Darwinian theory, spontaneous and random mutations in the DNA sequence combined with the selective pressure of the environment are the primary drivers of evolution, these events solely are insufficient to explain the ability of the living organisms to quickly respond to numerous changing environmental conditions and pass this information on to the next generations. For example, the impact of the paternal diet on the metabolism of their offspring [1] is one example of such non-genetic inheritance.

Another non-genetically inherited feature, the crossveinless trait of Drosophila fruit fly, was studied in the middle of the twentieth century by Conrad Hal Waddington, an English embryologist, and theoretical biologist. Waddington found that heat-treated flies exhibited a stronger tendency to develop the crossveinless phenotype compared to the flies grown in ambient conditions. Surprisingly, this phenotype also recurred in the offspring of the treated flies, which have never experienced heat conditions [2]. Trying to explain this phenomenon, Waddington developed an idea of "genetic assimilation" and further introduced the theory of "epigenetic landscape," underlying the ability of multiple stochastic factors to impact cell fate. Modern biology and medicine are well aware of the significant role

B. Slobodin (✉)
Department of Biomolecular Sciences, The Weizmann Institute of Science, Rehovot, Israel
e-mail: boris.slobodin@weizmann.ac.il

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the environmental conditions exert on living cells and organisms. As this awareness increases, the term "epigenetics" is being re-considered to provide common ground to the multiple molecular pathways of this molecular regulation.

In 2009, Berger and colleagues defined epigenetic trait as "… stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" [3]. The authors have defined three elements that should accompany a truly epigenetic trait. These are the "epigenator" signal that triggers a molecular "initiator", which establishes the trait. The molecular events comprising the trait are then sustained and propagated by the "maintainer," typically a non-specific effector of a broad range. Led by this definition, the authors defined several molecular pathways that fulfill these criteria, such as DNA methylation, certain types of post-translational modification of histones, and the non-coding Xist RNA, which contributes to the silencing of the mammalian X chromosome [3]. A more broad definition was used by the NIH Roadmap Epigenomics Project, that defined epigenetics as "… the regulation of gene activity and expression that are not dependent on gene sequence" [4]. Notably, while the first definition focused on the ability of epigenetic event to physically change the chromosomal architecture, the second definition focused on its ability to regulate gene expression. Perhaps the "…reversible heritable mechanisms capable of impacting gene expression without any alteration in the DNA sequence" [5] is currently the more widely accepted definition of epigenetics. According to this definition, regulation of gene expression by certain chemical RNA modifications can be considered as epigenetic [6]. In this section, will briefly describe three examples of epigenetic molecular events exerted on three chemically and biologically distinct molecules: DNA, proteins, and RNA. In all three cases, will focus on the methyl group, CH_3, being dynamically deposited on the mentioned molecules, and describe the regulatory effects of this process on gene expression. Readers interested in expanding their knowledge in epigenetic regulation, are encouraged to refer to the dedicated review papers, e.g. [7].

3.1.1 Methylation of DNA—CpG Islands

CpG islands are DNA regions (typically, >200 base pairs long) enriched by the consecutive 5′-CG-3′ dinucleotides. The cytosine within this dinucleotide can be methylated to form 5-methylcytosine. The precise number of CpG islands varies between species, and a majority of the mammalian CpG islands are methylated. The gene-related location of a CpG island is important: in the vicinity of promoters, methylated CpG islands exert negative effect on the gene expression, presumably due to restricted interactions between chromatin and transcription factors and recruitment of the specific methyl-interacting proteins. In the human genome, 72% of the promoters, including ubiquitously expressed house-keeping genes, have high CpG content [8]. In agreement with this finding, CpG islands are potential sites of transcription initiation due to the induction of the transcriptionally permissive

chromatin state [9]. Therefore, methylation of CpG islands serves as a means of turning off these otherwise transcriptionally active genomic regions. In addition to the crucial roles in mammalian development [10], altered patterns of DNA methylation were reported in multiple pathologies, such as cancer [11], hypertension [12], neurological disorders, immunodeficiency, and malignancies [10, 13], and others.

Since the CG dinucleotide appears symmetrically on both DNA strands (5′-CG-3′/3′-GC-5′), both neighboring cytosines are equally modified. Upon DNA replication, cytosines residing on the newly synthesized strand are *de-novo* modified by the dedicated DNMT1 methyltransferase according to the parental methylated strand. This strategy allows propagating site-specific methylation through multiple rounds of DNA replication.

3.1.2 Methylation of Histones—H3K9me3

Histones are small alkaline proteins present in the nuclei of eukaryotic cells. There are four core histones—H2A, H2B, H3, and H4, and a typical histone octamer consists of two copies of each of the histones and can bind 146 base pairs of DNA. The structure of the DNA wrapped around the histone octamer is termed nucleosome, and it contributes to the tight packaging of the cellular DNA. Linker histone H1 can bridge neighboring nucleosomes, facilitating further DNA compaction. Histones H3 and H4 possess relatively unstructured N-terminal tails, which protrude from the nucleosome structure and are subject to various post-translational modifications. There are at least nine types of histone modifications that can be deposited at multiple locations and form very complex modes of combinatorial regulation. Histone modifications modulate the strength of local interactions between the chromatin and histone octamer, thus contributing to the potential activity and accessibility of the chromatin. This combinatorial regulatory function of histones was named "the histone code" [14]. The tight association between histones and chromatin restricts the accessibility of the latter to the cellular transcription machinery and may lead to the transcriptional silencing, while "loose" states promote transcriptional activation.

One of the most studied histone modifications is termed H3K9me3, symbolizing three methyl groups deposited on the ninth lysine residue of histone 3. This modification is associated with heterochromatin, a structured chromatin state with restricted accessibility. The transcriptional repression of heterochromatin is mediated by heterochromatin protein 1 that binds H3K9me3 residues. Upon binding, it recruits methyltransferases to maintain and expand the epigenetic signal [15], facilitating the DNA compactness and, therefore, contributing to the transcriptional silencing of the chromatin. H3K9me3 is propagated continuously and produce repressed domains of up to 10Kbp, which can be maintained through multiple cell generations [16]. These domains silence the encoded genetic elements such as protein-coding genes and retroviral elements and significantly impact numerous

processes, such as cell fate [17], cellular reprogramming during development [18], response to extracellular stimuli [19], acute myeloid leukemia [20], and others.

3.1.3 Methylation of mRNA—m⁶A

Chemical modification of RNA—or epitranscriptome—is a rapidly developing field of research. More than 150 known chemical modifications can potentially decorate RNA molecules, and their impact on gene expression, although still poorly understood, promises to be enormously broad. Some modifications regulate the expression of multiple genes independently of the RNA sequences of their transcripts, are reversible [21], and heritable [22, 23]. Here, will focus on the RNA methylation termed N6-methyladenosine or, more commonly, m^6A.

m^6A is the most ubiquitous RNA modification known to the moment, as it decorates thousands of RNAs in multiple organisms. It is deposited co-transcriptionally [24] and is known to impact various levels of gene expression, such as mRNA stability [25], translation [26], and nuclear export [27]. The precise impact of m^6A modification may vary depending on its location within the given mRNA. For example, m^6A located in the untranslated regions (either 5′ or 3′) of an mRNA tend to stimulate translation of this particular mRNA into protein. In contrast, location of the same modification within the coding region is likely to exert an opposite effect. Inefficient transcription typically results in mRNAs with higher level of m^6A [24], which likely impacts multiple levels of their expression. m^6A was shown to play profound roles in multiple pathogenies, such in cancer, viral infections and metabolic diseases [28, 29].

3.2 Aging-Associated Epigenetic Changes

Aging is a universal biological process of a gradual decline in physiological capabilities, potentially affecting all tissues of an adult organism. As such, stochastic mutations accumulated in the DNA sequence over time, are unlikely to explain the gradual and inevitable process of aging [30]. Indeed, global impairment of gene regulation mechanisms was suggested long ago to be intimately involved in aging [31]. As such, aging may not directly depend on the specific genotype of an organism. In support of this idea, multiple organisms with identical genotypes were reported to age differently. For example, human monozygotic twins exhibit differential susceptibility to age-related diseases [32]. Another example comes from social insects, honeybees, which are divided into genetically identical queens and workers. This division dramatically impacts not only their life but also longevity: while the typical lifespan of a worker is only a few months, a queen can live for years [33]. These and other examples support the idea that regulation of gene expression and age-dependent deterioration of multiple physiological

functions are tightly interconnected [34]. If so, what are the epigenetic changes taking place and, possibly, playing a role in the process of aging?

Substantial epigenetic changes associated with aging lead to a sporadic and gradual loss of heterochromatin and transcriptional deregulation [5]. These effects may be partially explained by the progressive loss of histones that leads to a significant (up to 50%) reduction in nucleosomes and, therefore, reduced DNA compaction [35]. Lowered number of histones were observed in multiple eukaryotes, such as yeast, worms, and humans. In aging yeast for example, loss of nucleosomes leads to non-specific transcriptional induction of all genes and genomic destabilization [36]. Artificial increase of histones expression allows extending their lifespan, supporting the conclusion that reduced expression of histones is intimately involved in aging. Reduced DNA compaction is likely to significantly limit the regulation possibilities. In aging mice for example, immunological stimulation failed to result in synchronized transcriptional activation of $CD4^+$ T cells, leading instead to increased transcriptional heterogeneity [37].

Moreover, deregulation of multiple post-translational modifications of histones is tightly associated with aging. Particularly, the acetylation and de-acetylation patterns of histones are impaired in aging cells. Acetylated histones are less positively charged and therefore interact weaker with the negatively charged DNA. Thus, histone acetylation leads to reduced DNA compactness and promotes transcription-compatible chromatin states. Histone deacetylases (HDACs) remove the acetyl group from histones, contributing to the overall negative regulation of transcription. Expression of these enzymes changes with age and may impact longevity [38]. However, the aging-related changes in the chromatin structure are rather complex. In parallel to the overall reduction of the condensed chromatin, local senescence-associated heterochromatic foci (SAHF) appear, typically at new genetic loci [39]. Therefore, senescent cells experience global changes in the chromatin architecture. Histone methylation also contributes to this process, exhibiting a general increase in the activating modifications combined with the decrease in the repression-associated modifications [5]. In this sense, loss-of-function mutations in the H3K36 histone methyltransferase NSD1 accelerate human epigenetic aging, stressing the role of histone modifications in this process [40].

Progressive changes in DNA methylation is another process that accompanies aging contributing to the aging-associated transcriptional deregulation. DNA of aging mammalian cells is globally hypomethylated and locally hypermethylated, resembling the epigenetic background of cancer cells [41]. Aging-related hypomethylation of CpG islands contributes to chromatin decondensation and activation of previously silent genes and retrotransposons, which are mobile genetic elements typically residing within repressed repetitive genomic segments. Together with local *de-novo* hypermethylation of promoters of previously actively expressed genes, sometimes tumor suppressors, these events significantly contribute to the transcriptional deregulation in aging cells, as reviewed in [5]. Changes in the DNA methylation are progressive, correlate with the aging rates, and presumably affect all tissues of the aging organism [5, 42]. So-called methylation aging clocks employ these alternative methylation patterns to calculate the rate of molecular "epigenetic

aging" [43]. Interestingly, certain environmental and behavioral aspects also affect epigenetic aging. For example, a study testing individuals suffering from alcohol use disorder found that their epigenetic aging in terms of DNA methylation is significantly accelerated [44].

The effect of aging on m^6A RNA methylation currently remains mainly obscure due to the lack of sufficient research addressing this important question. The patterns of m^6A decoration of mRNAs in aging cells may be substantially altered due to profound changes in the transcription regulation. Since transcription rates negatively regulate m^6A [24], aging-associated pervasive transcription [36] should theoretically reduce the overall methylation levels. Indeed, a recent study performed in human peripheral blood mononuclear cells identified globally reduced level of m^6A in aging individuals [45]. Further research in this field is necessary to better understand age-related changes in m^6A in the different tissues as well as the effect of these alterations on the biology of aging cells and their possible involvement in age-related pathologies.

3.3 Epigenetic Regulation in Muscle

Muscle is a tissue that produces physical strength and is responsible for the body's posture and its motility. As such, muscles adapt to the current requirements of the individual, possessing a dynamic ability to hypertrophy when subjected to the increased effort and wane during periods of immobility or illness. Due to these dynamic processes, exercise-induced muscular hypertrophy necessitates enhanced gene expression. To support exercise-associated enhanced transcription, permissive histone modification, such as H3K36ac, are increased, and histone deacetylases are depleted from the nucleus [46]. Genome-wide analysis of methylated CpG sites in humans found that muscular hypertrophy leads to increased frequency of hypomethylation, which positively correlates with increased gene expression and muscle mass [47]. In rats, muscular atrophy is associated with dynamic changes in DNA methylation, which are reversible upon recurrent exercise [48]. Dynamic epigenetic changes in muscles are presumably the molecular basis of the impressive ability of this tissue to respond to various stimuli, and, therefore, a rapidly expanding field of research. Interested readers can refer to several recent publications, for example [49–51], that cover this topic in depth.

A single cell study found that the overall DNA methylation levels in mouse muscle stem cells slightly increase with age [52]. Importantly, while the CpG islands, promoters, and enhancers are hypomethylated in aging cells, bodies of active genes could be heavily methylated. CpG islands displayed most of the heterogeneity in their methylation patterns. Cumulatively, the alternative patterns of DNA methylation substantially impact the overall transcriptional output, as discussed above. Age-associated hypermethylation of gene bodies was confirmed in another study [53] and found to correlate negatively with gene expression. The authors identified 500 differentially methylated CpG sites in the muscle cells of old and young individuals.

In another study, enhanced histone acetylation (H3K27ac) in aged muscle cells resulted in activation of enhancers, increased expression of extracellular matrix-related genes and decreased myogenic potential [54]. Overall, muscle aging and sarcopenia are intimately associated with impaired epigenetic regulation and reduced cellular ability to precisely exert complex transcriptional activities. For the readers interested in a deeper coverage of the related topics, we recommend several recently published works, such as [55, 56].

3.4 Epigenetic Regulation in Bones

Bones are tissues of continuous remodeling, being constantly produced by osteoblast and osteocyte cells and resorbed by osteoclasts. Interactions between these cell types impact the equilibrium between the two opposite processes and, to a large extent, predetermines the long-term physiological output [57]. Naturally, epigenetic regulation of gene expression plays a central role in the physiological bone processes. For instance, transcription of *SOST* gene, encoding for sclerostin inhibitor of bone formation, is regulated via methylation of the CpG-rich region in its' promoter vicinity [58]. Upon osteoblast-osteocyte transition, osteocytes significantly reduce methylation of this region, leading to increased expression of sclerostin and reduced bone formation. Histone modifications also play an essential role in the bone homeostasis, as reviewed in [59]. Particularly, hyperacetylation allows for transcriptional upregulation accompanying osteogenesis [60], and artificial inhibition of HDAC activity further facilitates this process. Expression of RUNX2 master transcription factor regulating osteoblast differentiation and bone development also depends upon dynamic and differentiation-dependent histone modifications [61]. A recently published study found that regulation of m^6A deposition on mRNAs is critical for intact osteogenesis [62]. Loss of expression of FTO enzyme removing m^6A modifications (so-called "eraser") led to increased vulnerability of osteoblasts to genotoxic stress. The authors found that loss of FTO activity reduces the expression of mRNAs encoding proteins such as Hspa1a and Ube2v, which are associated with DNA repair and therefore help to protect osteoblasts from genotoxic damage. These findings emphasize the role of RNA modifications in regulation of stress responses. Overall, adequate epigenetic regulation underlies the dynamic transcriptional networking taking place during bone homeostasis, stress response, and remodeling. Readers interested in further information regarding epigenetic regulation in bones are encouraged to refer to the dedicated reviews, for example [63, 64].

Aging profoundly affects bone tissue, leading to age-related pathologies, such as osteoporosis (OP) and osteoarthritis (OA). Genome-wide analysis comparing DNA methylation patterns in trabecular bones of either OP or OA patients identified marked hypomethylation of 217 genes in OP patients [65]. As many of these genes encode transcription factors, these findings suggest substantially altered transcriptional networks in these patients. Another study found that cartilages but not

bones of osteoporosis patients exhibit accelerated aging in terms of DNA methylation [66]. This observation suggests that different tissues may experience variable rates of aging, which could potentially become a risk factor for age-related pathologies. Another study tested the expression of multiple genes encoding histone- and DNA methylation-modifying enzymes in conditions reducing bone formation, such as estrogen deficiency, hypoxia, and oxidative stress [67]. The authors identified diminished expression of multiple enzymes in osteoblast cell culture and in trabecular bone tissue of postmenopausal osteoporosis patients. Besides, they showed a positive correlation between the expression of these enzymes and the quantity and quality of bone tissue, emphasizing the importance of intact epigenetic regulation for adequate bone formation. Several studies demonstrated the importance of RNA modifications in osteogenesis. For instance, conditional deletion of METTL3 enzymatic "writer" of m^6A modification in mice bone marrow mesenchymal stem cells reduces osteogenic potential and resembles pathological phenotypes of osteoporosis [68], while overexpression of this enzyme prevents estrogen deficiency-induced osteoporosis. While reduced m^6A deposition is likely to impact numerous mRNAs, the authors found that it particularly affects the production of parathyroid hormone receptor-1 (Pth1r) protein, reducing the parathyroid hormone signaling axis and disrupting the related osteogenic processes. These findings were confirmed in a more recent study that found reduced expression of METTL3 in osteoporosis in both humans and mice, and partially restored bone mass formation upon over-expression of METTL3 in mice [69]. The authors attributed this effect of m^6A on osteogenic potential of bone marrow stem cells by the m^6A-regulated balanced expression of both RUNX2 transcription regulator and several micro-RNAs, such as pre-miR-320. Overall, multiple studies have connected impaired epigenetic regulation to age-related bone pathologies and readers interested in further reading are encouraged to refer to several recently published review papers, such as [70–72].

3.5 Summary

Epigenetic regulation is a growing field of biomedical research with a significant impact on the molecular understanding of numerous cellular processes. Epigenetic pathways uncovered in the last decades are intimately connected to various physiological conditions, such as differentiation, stress response, aging, and age-related diseases. A growing body of evidence indicates that in some cases, altered epigenetic regulation could be the molecular basis underlying pathologies. Future research shall further scrutinize the complex interactions between inadequate gene regulation and age-related diseases in order to consolidate our understanding of their molecular triggers and pave the way towards novel epigenetic-centered therapeutic approaches.

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Chapter 4
Immune Responses in the Elderly

Zahava Vadasz and Elias Toubi

4.1 Immune Senescence and Aging

Aging is mostly associated with immune changes showing a decline and/or enhancement of many parameters when compared to young, healthy individuals, defined as immune senescence. Immune dysfunction in the elderly is characterized by increased susceptibility to infections and the decline in immune responses to vaccines [1, 2]. These changes occur mainly due to the failure of aged T cells to translate recognition of non-self-antigens (bacteria and viruses) with HLA and to induce T cell activation, clonal expansion, and differentiation into effector cells. In parallel with this scenario, aging is associated with increased subclinical pro-inflammatory responses, and inflame-aging suggested to play a role in many diseases in the elderly such as cancer and autoimmune diseases [3]. Many gerontologists view immune senescence as an adaptive response needed for survival and longevity rather than leading to various diseases. In addition to increased infections, age-related decline in immune functions is associated with an increased incidence of autoimmunity due to its impact on immune regulatory and tolerogenic mechanisms of the immune system [4, 5]. In this chapter, we will cover some of the main aspects of these seemingly paradox issues of immune senescence.

Z. Vadasz (✉) · E. Toubi
The Proteomic and Flow Cytometry Unit, Division of Allergy & Clinical Immunology, Bnai-Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel
e-mail: zahava.vadas@b-zion.org.il

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4.2 Innate Immune System and Aging

Aging affects innate immune responses by a wide diversity of changes, mostly affecting macrophage functions, including toll-like receptor signaling, phagocytosis, natural killer (NK) cell functions, and others.

4.2.1 Macrophages and Aging

Macrophages play a leading role in the battle against pathogenic microorganisms via phagocytosis and the production of reactive oxygen species. Besides, macrophages release a vast range of mediators such as pro-inflammatory cytokines and chemokines that are crucial to the adaptive immune responses, antigen presentation, and activation of both B and T cells. In tissues, macrophages express a range of germline-encoded pathogen recognition receptors (PRRs), the binding of which enable macrophages to recognize conserved microbial products defined as pathogen-associated molecular patterns (PAMPs). These include toll-like receptors (TLRs), Nod-Like receptors (NLRs), and RIG-1 like receptors (RLRs) [6, 7]. The activation of TLRs in macrophages induces the production of inflammatory cytokines such as TNF-α, IL-6, and IL-1. It has been shown that many aspects of macrophage functions are down-regulated in the process of aging. In many studies, macrophages from old mice secreted lower amounts of TNF-α and IL-6 compared to macrophages from young mice in response to LPS or other TLR ligands. On the other hand, macrophages from old mice secreted increased amounts of IL-10 and prostaglandin E2 following their stimulation with LPS. Of the possible mechanisms explaining the above dis-regulations is their impaired intracellular signaling, namely the reduction of LPS induced phosphorylation of p38 and JNK mitogen-activated protein [8]. In another study, the finding of decreased TLR4 expression was suggested to be responsible, in part, for the observed alteration in TLR signaling in macrophages of older mice. Age-related reduction in IL-6 and TNF-α by human monocytes following TLR1/2 ligands was also reported. In addition to this finding, decreased surface expression of TLR1,4 on aged human monocytes has been shown as well. Macrophages from old mice expressed lower MHC class II molecules on cell surface compared to macrophages from younger mice when stimulated with IFN-γ, thus contributing to their impaired antigen presentation. Reduced STAT-1 phosphorylation in macrophages from old mice in response to IFN-γ suggests that aging is associated with defects in intracellular signaling in macrophages. Finally, aged macrophages failed to maintain sufficient clearance of pathogenic microorganisms when compared to young mice. Impaired phosphorylation by CD14+ monocytes was also reported in older human individuals [9].

4.2.2 NK Cells and Aging

Natural killer (NK) cells are essential effector cells of the innate immune system in the defense line against viruses. In older individuals, increased incidence of viral infections was found to be associated with defects in NK cell activity, cytotoxicity, and their ability to secrete immune-regulatory cytokines and chemokines. Immune senescence of NK cells is different between the various subsets [10]. CD56 (bright) cells are decreased in elderly individuals, whereas CD56 (dim) cells and CD57+ (highly differentiated NK cells) are increased. This NK redistribution in the elderly explains their altered proliferation and the failure to maintain CD16-dependent cytotoxicity. Functionally, CD56 (negative) NK cells are of reduced cytotoxic capacity and IFN-γ production and are characterized by a low KIR expression. They were found to be in association with the accumulation of end-stage-differentiated T cells and reduced CD4/CD8 ratio [11, 12]. In respect to this, CD56 (negative) NK cells are expanded in individuals >60 years of age and CMV+EBV+ elderly individuals, suggesting that they may play a role in the susceptibility of older people to these infections [13].

4.2.3 Innate Lymphoid Cells—Group 2 (ILC2) and Aging

Groups 2 innate lymphoid cells (ILC2) are essential members of the innate immune system, playing a role in tissue repair during many infections, mainly respiratory ones. They are the dominant lymphoid population in the lung, being front protective responders by producing type 2 cytokines [14]. Interleukin-33 (IL-33) was shown to mediate the activation of both ILC2 and T regulatory cells during parasite infections, promoting metabolic resources necessary to protect the host. During aging and with high-fat diet-induced obesity, ILC2 induced protective responses are diminished, and their role in pulmonary infections is compromised [15]. The effect of aging on ILC2 development and function was the subject of recent studies. One of these reported that aging induces compartmentalized changes in ILC2 development. Aging enhances bone marrow early ILC2 development through Notch signaling, but the newly generated circulating ILC2 were unable to settle in the lungs and to replace the declining mature lung ILC2 compartment in aged mice. Aged lung ILC2 are functionally compromised and fail to produce protective cytokines during influenza infection. Transfer of lung ILC2 from young mice increased resistance to influenza infection in old mice. In another recent study, group 2 innate lymphoid cells were shown to be implicated in defense responses, tissue repair, and immunopathology of several diseases of the human respiratory system [16, 17]. The exact role played by ILCs in human health and disease, namely, in young versus aged people, remains poorly understood.

4.3 Adaptive Immune Responses and Aging

4.3.1 T Cells and Aging

T cells are the leading players on the ground of adaptive immune responses, responsible for the recognition and response of both self and non-self-antigens. Chronic immune-mediated inflammation is mediated by different phenotypes of effector T-helper (Th) cells. On the other hand, the maintenance of self-tolerance and suppression of autoimmune disorders is achieved when T regulatory cells are numerally and functionally available [18]. The proper definition and understanding of all subtypes of effector T cells are crucial for the classification and diagnosis of all rheumatic diseases. This will enable clinicians to target these cells better and inhibit their enhanced pro-inflammatory function. Not less important is the ability to improve the function of T regulatory cells by targeting their relevant molecules. CD4+ T cell compartment shrinks with aging while the T cell receptor diversity is well maintained until the eighth decade of life, but then it collapses. It is also well shown that the reactivation of the thymus and the repopulation of the peripheral T cell compartment do not take place in most individuals older than 50 years. Stimulation of the TCR initiates a cascade of tyrosine phosphorylation signals regulated by a network of tyrosine kinases and phosphatases of both activating and inhibiting functions. The mutation or deletion of some of these phosphatases was shown to induce autoimmunity. In bone marrow transplant studies, reactivation of the thymus and repopulation of the peripheral T cell compartment was no longer achievable in individuals older than 50 years. Aged individuals fail to develop a compensatory increase in peripheral T cell turnover, consistent with thymic production being irrelevant at this stage [18]. Besides, age-associated repertoire skewing is accelerated by increased T cell loss due to defective DNA repair mechanisms and compensatory increased peripheral replication leading to telomere shortening and TCR repertoire contraction. Telomeres are essential in maintaining chromosome integrity and in controlling cellular replication. Telomerase activity decline with age in activated T-cells attributed in part, to the change in physiological conditions such as increased blood glucose, and pro-inflammatory cytokines such as interleukin-6 [19]. Compared to younger adults, CD4 memory T cells from healthy older individuals exhibit a higher up-regulation of oxidative phosphorylation with increased production of reactive oxygen species and intra-cellular secreted ATP and increased catabolic state in lipid metabolism [20]. The so-called dangerous γδT cells are of limited clonal diversity and found to be strongly expanded in lymph nodes of aging mice. They are characterized by the swift production of IL-17 upon ex-vivo stimulation and of impaired anti-tumor responses in old mice, proposing a link between γδT cells and increased risk of cancer development in aged mice [21]. In a recent study, IL-17-producing auto-reactive CD4-intermediate T cells were increasingly observed in aged mice. However, they were found to be different from typical Th17 cells by expressing higher levels of immune-suppressive receptor PD-1 [22].

4.3.2 T Regulatory Cells and Aging

The aging process is characterized by the imbalance between pro- and anti-inflammatory mechanisms leading to the loss of compensatory reserve and accumulation of unrepaired damage. The finding of a chronic low-grade inflammatory state which exists in many older individuals, even when they are apparently healthy, was reported to be associated with T regulatory cell and NF-kB dysregulation [23]. Single-cell RNA sequencing and multi-dimensional protein analyzes were assessed in thousands of CD4+ T cells obtained from young and old mice, aiming to define these dysregulated functions. Cytotoxic and activated regulatory T cells were found to be rare in young mice but gradually accumulate with age, providing some explanation for the existing chronic inflammation and immunity decline in aged mice [24]. Conventional T cells, mainly T regulatory, are elevated in adipose tissues during aging and have been implicated in the pathogenesis of metabolic diseases. These changes contribute to the associated metabolic dysfunctions, including insulin resistance and inflammation in adipose tissue, namely the so-called "inflamm-aging" [25]. Aging is associated with an increased incidence of cancer being the result of decreased anti-tumor immune responses. This was shown to be in part due to changes in T-cell function in the elderly. In lymph nodes of aged mice, T regulatory cells are characterized by increased expression of many regulatory markers such as CTLA-4, PD-1, ICOS, LAG-3, and IL-10, compared to T regulatory cells from young mice. In respect to these findings, elderly tumor-bearing mice demonstrated decreased IFN-γ by CD8+ and CD4+ T cells within tumors, compared to young mice [26]. The relation between aging and induced T regulatory cells (iTreg) was assessed in a mouse model of hepatic ischemia-reperfusion injury (IRI). In this model, aged mice suffered more serious injury than young mice, with higher serum levels of liver enzymes and higher histological scores from liver biopsies. Induced Treg cells from young mice demonstrated stronger immune-suppressive ability in vitro. Adoptive transfer of iTregs ameliorated liver IRI and was followed by liver recovery in association with decreased levels of IFN-γ, and IL-17. This suggests that liver injury in aged-mice is a result of decreased iTreg function [27]. In a very recent study, an increased number of circulating T follicular regulatory cells (Tfr) defined to be FoxP3+ was found to correlate significantly with aging in healthy volunteers. The suppressive effect of Tfr cells on B cell function in elderly subjects was diminished when compared to that in younger individuals. This was attributed to their failure to produce the regulatory cytokine IL-10 [28].

4.4 B Cells and Aging

Immunosenescence is characterized by a decrease in total B cells (CD19+), contributing to the insufficient ability of the elderly to control infectious diseases and to their inadequate response to new antigens and vaccination. CD19+ B cell

populations include several subsets, i.e., naïve B cells (CD27−IgD+), IgM memory (CD27+IgD+), switched memory (CD27+IgD−) and late memory double-blind (CD27−IgD−) cells [29]. Aiming to characterize B cell immunosenescence better the number of CD19+CD27+ memory cells, as well as serum levels of IgD, were analyzed in both young and older people. The percentage of memory CD19+CD27+ B cells was significantly increased in old individuals, whereas serum levels of IgD were decreased in comparison with young subjects [30]. Looking at naïve B cells (IgD+CD27−) in the elderly, they were found to be significantly diminished, whereas double negative (DN) IgD−CD27−B cells are found to be increased, explaining why IgM levels are higher in young people. These changes in B cell repertoire are suggested to be a hallmark of B cell immunosenescence [31, 32]. Increased IgD−CD27− (DN, memory B cells) in the elderly were shown to be IgG+ but of low CD80 and DR expression, indicating that they cannot serve as antigen-presenting cells. These are late memory and exhausted cells lacking the ability to interact with T cells [33]. In respect to the above, it was found that in older individuals, serum levels of B-cell activating factor (BAFF) and the proliferation-inducing ligand (APRIL), both pivotal survival factors for B cells, are decreased and in correlation with poor B cell survival [34]. The replenishment and diversity of B cell repertoire, as well as their ability to recognize and respond to new antigens, is significantly reduced in the elderly. In addition to decreased naïve B cell population in the elderly, the deterioration in B cell diversity was shown to be a consequence of reduced germinal center activity and to the progressive increase in the number of peripheral memory class-switched B cells (e.g., $IgD^{-}CD19^{+}CD27^{+}$). The above B cell aberrations lead to a selective shift toward the production of IgG/IgA, resulting in an overall contraction of the B cell repertoire, limiting the number of potential new clones available to respond to new antigens. In old individuals, activated memory B cells exhibit deterioration in their capacity to differentiate into mature plasma cells, followed by a decline in the production of specific antibodies. Increased late memory B cells ($IgD^{-}CD95^{hi}CD27^{-}$) in aged people were reported to spontaneously secrete TNF-α contributing to the well-known increased inflammatory state commonly described in elderly dysregulation of immune homeostasis and decreased B cell function [35–38]. Efficient humoral immune responses are dependent on several maturation steps, such as the generation of isotype-switched and high-affinity maturation of antibodies within germinal centers. These maturation processes are dependent in part on the activation of cytidine deaminase (AID). The stability and the production of AID are significantly reduced in aged B cells from both humans and mice. This reduction is caused in part by the reduced mRNA stability strictly related to "inflamm-ageing." In respect to this, the expression of the two pro-inflammatory micro-RNAs (miRNAs) miR-155 and miR-16, that respectively, bind the 3′-untranslated region (UTR) of AID mRNA, inducing its degradation, were found to be increased in the elderly. MiR-155 has been shown to be involved in the initiation and development of B cell malignancies, typically frequent in the elderly. It has been recently demonstrated that miR-155 is up-regulated in diffuse large B cell lymphoma and chronic lymphocytic leukemia. Moreover, it was shown that its over-expression is associated with poor prognosis in these malignancies, postulating miR-155 as a possible diagnostic and prognostic biomarker in B

cell malignancies. In addition, it was found that both miR-155 and miR-16 were demonstrated to be over-expressed in rheumatoid arthritis, demonstrating the potential pro-inflammatory role of these two miR's [39–41].

4.4.1 Reduced Ability of Older People to Respond to Newly Encountered Antigens and Vaccinations Reflects the Age-Related Impairment of Humoral Immune Response

In adults, influenza vaccine elicits both memory adaptive immune responses to epitopes that are shared with previously encountered viruses and primary (new) responses to new antigenic epitopes in the vaccine. Thus, it was speculated that memory adaptive immune responses will be predominant in the elderly due to their several previous exposures to influenza viruses or vaccines; however, it was found that there is an age-related decrease of the influenza vaccine-specific antibody response. In order to try to find the reasons for this phenomenon, several studies have been conducted. In one publication, it was reported that B cells from elderly people had a significant reduction in the expression of the co-inhibitor B and T lymphocyte attenuator (BTLA) before vaccination compared to young volunteers. It was also demonstrated that BTLA expression on mature B cells is associated with the increase in the level of influenza-specific IgG antibody titers. Moreover, it was also found that the BTLA expression is involved in the isotype switching from IgM to IgG. Thus, the decline of BTLA expression on B cells might be related to a decrease in specific antibody production in the elderly [42, 43].

4.5 Summary

Immunosenescence is responsible for the decreased ability of older people to fight infections, namely to develop a sufficient response to new antigens and vaccination. The decline in effective immunity is due to changes in T, B, and NK cell subpopulations, both in their numbers and functions. Altered immunity in the elderly is associated with increased levels of pro-inflammatory molecules and the persistence of chronic low-grade inflammation. Specific therapeutic strategies are required in order to maintain balanced and efficient immune responses, mainly by effector T and B cells.

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Chapter 5
Pharmacokinetics of Anti-Rheumatic Drugs in a Geriatric Patient

Lee Hilary Goldstein

5.1 Introduction

Medical treatment for the elderly can be challenging from a few aspects. The diagnosis might be challenging as symptoms and the course of the disease may differ, and as such decisions or choice of the treatment may differ. The medication chosen might have unexpected effects on the elderly patient, in terms of efficacy and safety, as the elderly are seldom included in clinical trials, and as result, there is often sparse evidence on the right dose, safety etc.

A few points should be considered when deciding on drug therapy in the elderly in general, and specifically when choosing drug therapy in elderly patients with arthritis and possibly chronic pain.

First, as in patients of all ages, the choice of drug must take into account the patients prior medical history and other diseases. The drug may influence other diseases. For example, non-steroidal anti-inflammatory drugs (NSAIDS) may worsen hypertension, or peptic disease. Stable diseases may worsen due to new medications. As the elderly are frailer, with less reserves, this type of influence on other diseases may be more prominent.

Second, differences in drug pharmacokinetics in the elderly should be considered. Elderly patients ability to metabolize and excrete medications, declines and changes with age. Renal function declines gradually with age, and glomerular filtration rate (GFR) declines on average 7.5-10 ml/min/per decade [1, 2]. The age related loss of muscle mass makes the serum creatinine concentration less reliable as a marker of GFR. Drugs such as methotrexate can accumulate in renal failure and increase the risk of toxicity. Renal function should be estimated in every patient,

L. H. Goldstein (✉)
HaEmek Medical Center, Afula, Israel

Bruce Rappaport School of Medicine, Technion, Haifa, Israel
e-mail: goldstein_le@clalit.org.il

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especially in the elderly. Formulas for estimating renal function, such as MDRD [3], CKD-EPI [4] and Cockroft-Gault [5] should be used or creatinine clearance should be formally measured. Some drug metabolism changes with age, although, for most drugs, metabolism is not age dependent [6, 7]. Generally speaking, the elderly accumulate drugs, with less ability to excrete them, and have higher levels of drugs, leading to more adverse reactions and safety issues. Dose should often be adjusted appropriately.

Third, differences in pharmacodynamics should be anticipated in the elderly. Often, end organs are more sensitive to drug effects, with may affect efficacy and drug safety. For example the risk of NSAID induced hypertension is higher in the elderly [8].

Forth, drug-drug and drug-herbal interactions must be taken into account, as for patients of all ages. As the elderly are often treated with many drugs due to other medical history the chance of a significant drug-drug interaction, is substantial.

In this chapter we will focus on some of the more common drugs used for rheumatic diseases in the elderly, and focus on these previous four points: possible influence on other diseases, dose adjustments, drug safety and drug-drug interactions with some common medications.

5.2 Methotrexate (MTX)

Methotrexate is an antimetabolite that interferes with DNA synthesis, repair, and cellular replication by inhibiting dihydrofolate reductase and is used in low doses for the treatment of rheumatoid arthritis, and psoriasis. Methotrexate has potential for serious toxicity, causing bone marrow failure, severe gastrointestinal mucositis and liver enzyme abnormalities [9].

Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently than younger subjects. In a subanalysis of pooled clinical trials that assessed age on the responsiveness of rheumatoid arthritis disease activity found that the decrease of disease activity, radiographic abnormalities and improvement of disability was comparable over all ages, and discontinuation rates did not differ either, although they had no further safety analysis [10].

Dose adjustments: In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population [9]. Since serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (i.e., creatine clearance) should be considered. Serum methotrexate levels may also be helpful.

Safety: Renal is the primary route of excretion and occurs by glomerular filtration and active tubular secretion and toxicity of low dose methotrexate treatment is often caused by impaired renal excretion or folate deficiency. Post-marketing

experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age [9], although in multiple clinical trials, age itself did not affect the safety nor efficacy of methotrexate [11–14]. However, impaired renal function, often associated with old age, was associated with a fourfold risk for severe toxicity [13]. Low dose methotrexate is relatively complicated to comply with, probably more so, for the elderly, due to the fact that methotrexate is taken once weekly, and also due to the fact that folic acid is also not administered daily. Complicated instructions like these can be a source of medication errors leading to toxicity or lack of efficacy if not taken appropriately. In addition, the elderly, especially the bedridden, who are at risk of dehydration, or who have borderline renal and bone marrow function, may be at greater risk for side effects.

Drug-drug interactions: Interactions that impair the renal excretion of methotrexate, such as salicylates, NSAIDs, and sulfamethoxazole are possibly more dangerous in the elderly due to age associated renal failure and caution should be used with such combinations [9].

5.3 Non-Steroidal Anti Inflammatory Drugs (NSAIDS)

NSAIDs are frequently used due to treat arthralgia and arthritis due to their good analgesic and anti-inflammatory properties. The important safety issues with NSAIDS are gastrointestinal bleeding, NSAIDs prothrombotic effect, and influence on blood pressure and renal function. These issues are relevant at all ages although are more pronounced in the elderly. A recent evaluation of adverse events as a cause of hospitalization in patients 65 or older implicated NSAIDs in 23.5% of cases [15].

NSAIDs can be COX2 selective, or non-selective, designating the cyclooxygenase inhibited. Both are anti-inflammatory and analgesic although the COX-2 selective NSAIDS were designed to have less gastrointestinal side effects. However, both types have safety issues, cardiovascular and gastrointestinal, as we will elaborate further down.

5.3.1 NSAIDs Safety Issues

Cardiovascular effect: NSAIDS are associated with an elevated cardiovascular risk, vascular death, coronary events and heart failure irrespective of age. Despite multiple trials that have directly and indirectly assessed and compared the cardiovascular safety, there is still uncertainty as to which of the many chemically distinct NSAIDs are the safest to use in patients with comorbidities such as heart disease or hypertension.

Both specific (COX-2) NSAIDS and non-specific (COX-1 + COX-2) NSAIDS have pro-thrombotic properties due to COX-2 inhibition and decreased prostacyclin

(PGI_2) formation. PGI_2 interacts with multiple components of the vascular system that terminate coagulation, and blocking its function causes a prothrombotic state. PGI_2 is the most potent endogenous platelet inhibitor, upregulates thrombomodulin and depresses tissue factor expression [16]. In addition to being prothrombotic, NSAIDS prevent the anti-platelet activity of aspirin by displacing the aspirin from the platelet COX-1, and by doing so reduce the anti-thrombotic effect of aspirin [17].

NSAIDS may worsen heart failure due to multiple effects. First, the prothrombotic effect may worsen cardiac ischemia and thus worsen systolic and diastolic dysfunction, and heart failure. In addition NSAIDS reduce sodium excretion by 50–70% [18], causing sodium and water retention, and resultant edema and exacerbation of symptomatic heart failure.

Current guidelines recommend assessing cardiovascular risk before prescribing NSAIDS for all patients, regardless of age. The FDA latest warning on NSAIDS issued in 2015 stated that all NSAIDS, selective or not, confer an elevated cardiovascular risk, and that the current evidence does not point to any specific NSAID as being better or worse in this respect [19]. However, there is no consensus on this issue, as the Pan-American League of Associations for Rheumatology (PANLAR) guidelines, published in 2016 suggest that for patients with high cardiovascular risk, naproxen is preferable based on a systematic review of population based studies [20].

Hypertension: Prostaglandins (PGs) play a key role in renal hemodynamics, in ion transport and hormone synthesis. They maintain the balance between hypertensive and antihypertensive mechanisms in the organism. Thromboxane A_2 and prostaglandin H_2 have vasoconstrictive effects and decrease kidney blood flow, whereas prostacyclin and prostaglandin E_2 counteract these effects, primarily due to their vasodilating effect, causing an increase in renal blood flow and sodium and water excretion. By preventing formation of prostaglandins, NSAIDs (selective or not) may increase blood pressure particularly for hypertensive patients, often cancelling the effect of their blood pressure lowering therapy. Anti-hypertensives such as beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and diuretics effect may be cancelled by NSAIDS, however, calcium channel blockers antihypertensive response is relatively preserved [21]. The blood pressure increase is more pronounced in the elderly [22], causing systolic blood pressure to rise by approximately 5–6 mmHg [21]. In hypertensive patients, even a small decrease in the diastolic blood pressure by 5–6 mm Hg due to effective therapy can lead to a 67% decrease in the risk of cerebral stroke and a 15% decrease in the risk of ischemic heart disease [21]. NSAIDS seemingly mild effect on hypertension may, in fact have a major impact on cardiovascular morbidity.

Renal function: Renal function in the elderly is often reduced due to age related factors and other common elderly comorbidities such as hypertension, diabetes and atherosclerosis. NSAIDS, particularly high dose, may further worsen renal function due to the vasoconstrictive effect of COX-2 inhibition of the afferent renal artery [23, 24], particularly when co-administered with other medications such as angiotensin enzyme/receptor inhibitors or with other conditions such as dehydration or hypotension [25]. In a nested case-control study using patients aged 65 and over,

hospitalized with acute renal failure, use of NSAIDs increased the risk of acute renal failure by 58% [26]. The deterioration of renal function is often reversible, but less so for the elderly, as evident in a Danish registry study, where 36% of elderly patients with end-stage renal failure requiring renal replacement therapy were on NSAIDs during the preceding 3 years, which might infer that the outcome could have partially be caused by NSAIDs [27].

Beers criteria suggest avoiding NSAIDS in the elderly, particularly in the elderly with creatinine clearance less than 30 ml/min [28].

Gastrointestinal: Non-COX-selective NSAIDs, are associated with an increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those >75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in ~1% of patients treated for 3–6 months and in ~2–4% of patients treated for 1 year; these trends continue with longer duration of use and in patients with additional risk factors such as peptic disease, concomitant aspirin, high dose NSAIDS and old age. Patients over the age of 65–70 have a two- to five-fold higher risk for gastrointestinal bleeding [29].

In general NSAIDS should be used at all ages at the lowest effective dose for a shorter period of time. If prescribed as an analgesic, NSAID treatment should be terminated after 7 days if no benefit is reported. If prescribed as an anti-inflammatory drug, it should be terminated after 3 weeks if no benefit is reported. If it is possible concomitant therapy with corticosteroids, anticoagulants, low-dose aspirin or antiplatelet agents should be avoided [19].

In the elderly, chronic use of non-selective NSAIDs should be if avoided, if possible, according to the 2019 Beers criteria, and if necessary should be used with gastro protective proton pump inhibitors or misoprostol. All NSAIDs, selective or not should be avoided in the elderly with impaired renal function [28]. The latest guidelines published by the American College of Rheumatology (ACR) [12], and by PANLAR suggest avoiding NSAIDS if possible, using acetaminophen and other analgesics, or local NSAIDS, if possible.

5.4 Colchicine

Colchicine, is an anti-inflammatory agent indicated for gout flares and Familial Mediterranean Fever (FMF) [30, 31] of all ages, although clinical studies with colchicine did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Colchicine interrupts polymerization of beta-tubulin into microtubules, and consequently prevents the activation, degranulation, and migration of neutrophils to sites of inflammation. In addition colchicine interferes with the neutrophil intracellular inflammasome complex, which is responsible for activation of interleukin-1beta [32].

Colchicine is well absorbed with a bioavailability of 45%, and not affected by food. It is a substrate for P-glycoprotein, metabolized by cytochrome 3A4

(CYP3A4), and partially excreted unchanged in the urine (45–60%) and feces. As colchicine is metabolized by cytochrome 3A4 (CYP3A4), and is a substrate for P-glycoprotein (Pgp), concomitant moderate- to high-potency inhibitors of cytochrome P450 3A4 and Pgp-can result in potentially life-threatening toxicity. Medicines such as clarithromycin, erythromycin, cyclosporine, diltiazem, verapamil, ketoconazole, and fluconazole should not be co-prescribed with colchicine or the dose of colchicine should be reduced [32, 33]. Grapefruit juice, a moderate CYP3A4 inhibitor should also be avoided.

Safety: The common safety issues for colchicine are gastrointestinal such as diarrhea, nausea and vomiting**.** Serious adverse effects such as myelosuppression and rhabdomyolysis are associated with renal failure and drug-drug interactions.

As many elderly patients have renal failure, colchicine should be used with caution in this population and doses adjusted accordingly to renal function. For patients with mild (Clcr 50–80 ml/min) and moderate (Clcr 30–50 ml/min) renal impairment, no adjustment of doses is required but patients should be monitored for adverse events and toxicity. However, in patients with severe renal failure dose reduction should be considered with careful monitoring [32]. According to Beers Criteria, colchicine should be used with caution, with reduced dose in older adults with CrCl less than 30 ml/min due to increased risk of bone marrow toxicity, gastrointestinal and neuromuscular adverse events [28].

Dose adjustments in the elderly:

Gout: The ACR guidelines recommend a loading dose of colchicine 1.2 mg, followed by colchicine 0.6 mg within 1 h, and 0.6 mg at 12- and 24-h intervals as required until the gout flare fully resolves [31] The safety profile of this dosing regimen has not been examined in the elderly so the EULAR gout treatment guideline recommend to avoid the initial loading dose and prescribe colchicine 0.6 mg twice a day for the duration of the gout flare, with suitable dose reduction for comorbidities and drug interactions [30].

Patients treated with strong CYP3A4 inhibitors (such as most anti-retrovirals, clarithromycin, itraconazole, ketoconazole and telithromycin) should be treated by a loading dose of colchicine of 0.6 mg followed by 0.3 mg 1 h later, and refrain from repeat dosing for 3 days. Patients treated with moderate CYP3A4 inhibitors such as aprepitant, diltiazem, verapamil, erythromycin, fluconazole and grapefruit juice should be treated by a single loading dose of 1.2 mg, and no further dosing for at least 3 days. Patients treated with strong Pgp inhibitors (such as cyclosporine) should be treated with a loading dose of 0.6 mg only and again not repeated again for the next 3 days [32]. No specific recommendations for drug adjustments due to drug interactions exist for the elderly.

FMF: The recommended dosage of colchicine in adults is 1–1.8 mg daily [34]. No specific recommendations exist for the elderly, so dose should be adjusted according to renal function and concomitant medications. For patients treated with strong CYP3A4 or Pgp inhibitors such as most anti-retrovirals, clarithromycin, itraconazole, ketoconazole cyclosporine and telithromycin 0.6 mg daily, and for patients treated with moderate CYP3A4 inhibitors the dose is 1.2 mg daily [32].

5.5 Leflunomide

Leflunomide, a pyrimidine synthesis inhibitor with anti-inflammatory activity is indicated in adults for the treatment of active rheumatoid or psoriatic arthritis.

Following oral administration, leflunomide is metabolized by CYP 1A2, 2C19, and 3A4 to teriflumide, an active metabolite, which is responsible for essentially all of its activity in vivo. Teriflumide has a very long half-life (2 weeks) and is eliminated via the feces and the kidneys. Leflunomide is a usefull DMARD for treating patients with rheumatic arthritis however 20–40% of patients cease treatment due to toxicity. Genetic polymorphism in *CYP1A2* and *CYP2C19* may be linked to increased toxicity [35, 36].

Of the total number of subjects in controlled clinical (Phase III) studies of leflunomide, 234 subjects were 65 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other postmarketing studies have reported that the safety profile of, and adherence to leflunomide is not different in older patients with chronic inflammatory joint diseases such as rheumatic or psoriatic arthritis to that observed in younger patients [37]. No dosage adjustment is needed in patients over 65 [38].

Safety: Leflunomide treated patients are more prone to unintentional weight loss, in comparison to other DMARDS. In a meta-analysis of all phase II and III studies, during the first 6 months in patients receiving leflunomide, 10% lost 5–8.5 kg and 2% lost at least 9 kg, and 4% lost 10% of their baseline weight [38]. In a large database study comparing the BMI of over 32,000 rheumatoid arthritis patients, leflunomide-treated patients demonstrated weight loss in comparison to other DMARDS. It was associated with an increased risk of weight loss after adjustment for multiple potential confounders (OR 1.73, 95% CI 1.55, 1.79; $P < 0.001$) [39]. The underlying reasons for weight loss among leflunomide-treated patients are unclear although predictors of weight loss, such as age, were similar to those in the overall population. Speculations are that gastrointestinal side effects and decreased appetite as a result of treatment with leflunomide may contribute to weight loss however, genetic polymorphisms of CYP2C9 and CYP1A2 may too be predictive of therapy cessation due to side effects, including weight loss [35, 40].

Weight loss can be of concern in older frail patients, so despite the fact that no specific dose adjustments are required with leflunomide in the elderly, weight should be followed.

5.6 Allopurinol

Allopurinol is a xanthine oxidase (XO) inhibitor which is administered orally. It reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation and is indicated for management of patients with primary or secondary gout, for patients receiving chemotherapy which is expected to

cause elevations of serum and urinary uric acid, due to tumor lysis and for the management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients.

Allopurinol is well absorbed from the gastrointestinal tract, and rapidly oxidated to oxipurinol which has a longer plasma half-life (approximately 15 h). Approximately 20% of the ingested allopurinol is excreted in the feces and 80% is eliminated by the kidneys therefore, changes in renal function have a profound effect on dosage [41].

There are no specific dosage recommendations for the elderly treated with allopurinol. As in all patients, dose in the elderly should be corrected for renal function, often decreased in this population. Lower doses should be used to initiate therapy in any patients with decreased renal function and they should be observed closely during the early stages of administration of allopurinol. In patients with severely impaired renal function, the half-life of oxipurinol in the plasma is significantly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels [41].

When treating the elderly it is worth noting that intercurrent diseases often cause worsening of renal function, and dose of allopurinol should be adjusted appropriately.

5.6.1 Safety

The important safety issues of allopurinol for patients of all ages are worsening kidney function, temporary worsening of gout, and hypersensitivity reactions. There are no specific safety issues for the elderly as is evident from a sub-analysis of data from the CONFIRMS study, a phase 3, double-blind, randomized, controlled trial examining the efficacy and safety of febuxostat and allopurinol. This sub analysis indicated that allopurinol is equally safe and effective in those aged >65 years compared with a younger population [42].

The most dangerous safety issues with allopurinol, at all ages are hypersensitivity reactions that can be life threatening. Allopurinol should be discontinued at the first appearance of a skin rash, or any other signs of an allergic reaction. Fatal, severe hypersensitivity reactions, such as DRESS (drug reaction with eosinophilia and systemic symptoms), Steven-Johnson syndrome, vasculitis, irreversible hepatotoxicity have been reported [41]. These hypersensitivity reactions are more common in patients with renal failure, patients on concomitant therapy with amoxicillin and in patients of Thai or Han Chinese descent due to common polymorphism of HLA-B. Current guidelines recommend that prior to initiation of allopurinol, rapid polymerase chain reaction–based HLA–B∗5801 screening be considered in subpopulations where both the HLA–B∗5801 allele frequency is elevated and the HLA–B∗5801–positive subjects have a high risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse chronic kidney disease and all those of Han Chinese and Thai descent) [43].

An increase in acute attacks of gout has been reported during the early stages of administration of allopurinol, possibly due to mobilization of urates from tissue deposits which cause fluctuations in the serum uric acid levels. Accordingly, maintenance doses of colchicine generally should be given prophylactically when allopurinol is begun in gout patients [30, 41, 43].

Patients with impaired renal function should be carefully observed during the early stages of administration of allopurinol due to the fact that some patients with pre-existing renal disease or poor urate clearance have shown a rise in BUN during initial administration of allopurinol. If increased abnormalities in renal function appear and persist the dosage should be decreased or the drug should be withdrawn.

5.6.2 Interactions

Drug drug interactions with allopurinol are not more common in the elderly and similar precautions that should be taken as for younger patients.

In patients receiving azathioprine or mercaptopurine, the concomitant administration of 300–600 mg of allopurinol per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of azathioprine or mercaptopurine. Allopurinol impairs conversion of both to their inactive metabolites by inhibiting xanthine oxidase, which may result in prolonged half-life and accumulation of azathioprime or mercaptopurine leading to increased toxic effects of both on bone marrow [41, 44]. This effect on mercaptopurine is only for oral administration as the interaction is a first pass interaction, irrelevant for intravenous mercaptopurine administration [45].

The occurrence of hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function receiving thiazides concurrently. For this reason, in this clinical setting, such combinations should be administered with caution and patients should be observed closely. Rare reports indicate that cyclosporine levels may be increased during concomitant treatment with allopurinol. Monitoring of cyclosporine levels and possible adjustment of cyclosporine dosage should be considered when these drugs are co-administered [41].

To conclude: Allopurinol's safety and efficacy in the elderly is comparable to the young, Dosing should start at the low dosing range considering renal function. Toxic effects and hypersensitivity reactions should be monitored.

5.7 Febuxostat

Febuxostat is a selective, novel, non-purine analog XO inhibitor for the treatment of chronic hyperuricemia in patients with gout. It is well absorbed (84% bioavailability) and has a mean terminal elimination half-life (t1/2) of approximately 5–8 h. Febuxostat is primarily metabolized in the liver by conjugation (UDPGT

enzyme system) and oxidation (cytochrome P450 (CYP) system). Approximately 50% is eliminated unchanged in the feces and 50% eliminated by the kidneys, although no adjustments of dose are necessary in patients with mild to moderate renal impairment. In patients with severe renal impairment dose reductions are recommended. No specific dose adjustment is necessary in the elderly, however renal function must be taken into account. For all ages the starting dose is 40 mg/day which is increased to 80 mg/day if uric acid is still high. In patients with creatinine clearance <30 ml/min the dose is limited to 40 mg/day [46].

The efficacy and safety of febuxostat in the elderly (over 65) is comparable to the young as was evident in the subanalysis of 374 elderly gout patients of the CONFIRM study. Feboxostat was well tolerated despite high rates of comorbidities an concomitant medications [42].

5.7.1 Drug Interactions

Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity. Where the combination with mercaptopurine/azathioprine cannot be avoided the concomitant administration of febuxostat will require a 20% reduction in dose of azathioprine or mercaptopurine [46].

5.7.2 Safety

The most commonly reported adverse reactions in clinical trials and post-marketing experience are gout flares, rashes, liver function abnormalities, diarrhea and nausea. Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis, anaphylactic reaction/shock, and DRESS have been reported post-marketing [46]. Although cutaneous reactions have been described with febuxostat, there is no cross reactivity with allopurinol. Therefore, a history of allergic reaction to allopurinol is not a contraindication to febuxostat, but these patients need to be carefully followed [30, 46].

Gout Flares: Febuxostat treatment should not be started until an acute attack of gout has completely subsided as gout flares may occur during initiation of treatment. Flare prophylaxis for at least 6 months with a NSAID or Colchicine is recommended [46].

Cardiovascular: Treatment with febuxostat in patients with ischemic heart disease or congestive heart failure is not recommended. Gout is associated with increased rates of cardiovascular disease [47], and the risk of cardiovascular mortality is higher in people with gout and coronary heart disease compared with those with coronary disease who do not have gout [48]. Phase III studies with febuxostat

suggested a possibly higher rate of cardiovascular events [49–51], so the FDA requested further study on the cardiovascular safety of febuxostat. The CARES study was a large, multicenter, double-blind, noninferiority randomized controlled trial designed to determine the comparative CV safety of febuxostat and allopurinol in patients with gout and CV disease. In total, 6190 patients (50% over 65 years of age) underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months. Febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events, however cardiovascular mortality was 34% higher (95% CI, 3–73%), and all-cause mortality was 22% higher (95% CI, 1–47%) for febuxostat in comparison to allopurinol. The high all-cause mortality was driven mainly by cardiovascular mortality [52]. Real world data on cardiovascular safety of febuxostat is constantly accumulating. A pharmacovigilance study using the US Food and Drug Administration (FDA) Adverse Event Reporting System database indicated potential signals of febuxostat-associated CV thromboembolic events [53]. In a real large world study on a the Taiwan National Health Insurance Research Database comparing 88,000 matched new users of febuxostat and allopurinol, febuxostat users had a 22% (95% CI, 13–33%) higher risk for heart failure hospitalization, a 19% (95% CI, 5–36%) higher risk for atrial fibrillation hospitalization, and a 19% (95% CI, 3–36%) higher risk for cardiovascular death. No difference was found for all-cause mortality. The cardiovascular effect was dose dependent and higher febuxostat doses had a greater impact [54]. In another population-based cohort study and meta-analysis from Taiwan, febuxostat did not show an increased risk of cardiovascular disease and related death [55].

As a result of these data a boxed warning was added to the prescribing information for febuxostat, and health care professionals are advised to reserve febuxostat for patients who have failed or do not tolerate allopurinol [56]. It is worth mentioning, that although the evidence is compelling, the cardiovascular safety studies compared febuxostat to allopurinol, and not to placebo, so it's impossible to say whether febuxostat is harmful, or that both allopurinol and febuxostat actually reduce cardiovascular events, with allopurinol better in this aspect from febuxostat. Further studies are required in this aspect.

In respect to the elderly more data is accumulating on the cardiovascular safety of febuxostat in this population, who often have comorbid diseases such as ischemic heart disease and heart failure. In an observational study on 255 heart failure outpatients on average 76–78 years of age followed for 5 years, the cumulative cardiovascular survival was significantly higher in patients treated with febuxostat in comparison with allopurinol treatment [57]. In a cohort of 99,744 Medicare patients with gout (median age 76), there was no difference in the risk of myocardial infarction, stroke, new-onset heart failure, coronary revascularization, or all-cause mortality between patients initiating febuxostat compared with allopurinol. The risk of heart failure exacerbation was slightly lower in febuxostat initiators [58].

To conclude: Febuxostat should be used for gout only if allopurinol treatment is inadequate or intolerable, due to the cardiovascular risk of febuxostat. No further specific recommendations exist for the elderly although several studies indicate that the cardiovascular risk in the elderly may differ from the young.

5.8 Opioids

Patients at all ages, afflicted with connective tissue diseases, arthritis and vasculitis occasionally suffer of chronic pain. Non opioid therapy is preferred for treatment of chronic non cancer pain as up to date there is no evidence supporting the long term benefit of opioids in pain and function. Most placebo-controlled randomized clinical trials were of no longer than 6 weeks duration and extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury). Acetaminophen remains first-line pharmacologic treatment for older adults with mild to moderate pain, and as NSAIDS are not preferable in many elderly patients, given their significant cardiovascular, gastrointestinal, and renal risks, a trial of opioid is appropriate for elderly patients not responsive to first-line therapies and who continue to experience significant functional impairment due to pain [59, 60].

The latest CDC guidelines published in 2016 states that opioids should not be considered first-line or routine therapy for chronic pain outside of active cancer, palliative, and end-of-life care, and should be used only when benefits for pain and function are expected to outweigh risks and be used at lowest effective dose, irrelevant of the patient's age. The benefits and harms of continued opioid therapy should be reassessed every 3 months or more frequently especially in the elderly [61].

Apart from multiple side effects such as constipation, nausea, confusion and somnolence, opioids may cause opioid physical dependence (adaptation to a drug that produces symptoms of withdrawal when the drug is stopped), tolerance (diminished response to a drug with repeated use) and worse, may cause opioid use disorder, comprising of unsuccessful efforts to control use, resulting in social problems and a failure to fulfill major role obligations at work, school, or home. Opioid therapy prescribed for acute pain is associated with greater likelihood of long-term use. The higher the dose used for acute pain, the higher the likelihood of long term use [62].

The elderly pose a special risk for opioid use for a number of reasons. First, the elderly often have some degree of renal dysfunction, and opioids in the elderly are associated with a high risk of falling, fall-related injuries, hospitalization, and all-cause mortality [63–65]. The lowest effective dose should be prescribed, often lower than the recommended starting dose for adults. High doses are associated with higher risk for overdosing. Immediate and not extended release formulations should be preferred [28, 61]. In all patients and especially in the elderly, the physician must consider whether cognitive limitations might interfere with management of opioid therapy, and if so determine whether a caregiver can responsibly co-manage medication therapy [61]. Prior to prescribing opioid analgesics to older patients, physicians should be satisfied with arrangements for safe storage of the medication [59].

5.8.1 Dosing

The "start low and go slow" approach is essential when dosing opioids. Opioids should be started at 25–50% of the recommended dose for adults [66]. For example, a typical oral starting dose of morphine or oxycodone in a younger person is

5–10 mg, whereas 2.5–5 mg represents an appropriate dose for older persons. The time to maximal effect of opioids does not change with aging. The onset of action for oral preparations is approximately 30 min reaching peak plasma levels (peak effect) in approximately 1 h and lasting approximately 3–4 h. In older adults longer time interval (usually 6 h) between doses of short-acting preparations at the initiation of opioid therapy should be used [67]. When a dose increase is considered, it should not be escalated until a steady state has been reached (reached at around 4–5 half-lives of the drug).

5.8.2 Pharmacokinetics

Decrements in renal function decrease the excretion of codeine, morphine, hydromorphone, oxycodone and tramodol, and dose adjustments, even with low doses of these agents, should be made accordingly, along with close monitoring for toxicity [68]. The volume of distribution of fat-soluble opioids, such as fentanyl, may increase because of the increased fat-to-lean body mass ratio that accompanies aging, increasing the drug's effective half-life. The decreased volume of distribution that occurs owing to decreased total body water with aging may also result in increased plasma levels of more hydrophilic opioids (e.g., morphine) compared with levels observed in younger persons [69].

5.8.3 Safety

The important side effects of all opioids include constipation, nausea, vomiting, sedation, confusion, and respiratory depression. Tolerance develops to most of these side effects, with the exception of constipation. Opioids cause nausea which develops in about 30% of patients. If severe nausea occurs, low-dose haloperidol (0.5 mg) or ondansetron (4 mg) scheduled or "as needed" typically manage nausea until it resolves over the first week of therapy [67]. Constipation, a universal complaint in patients taking an opioid is caused by m-receptor binding in the gastrointestinal tract, resulting in slower transit time and increased water reabsorption. Prophylaxis with a bowel stimulant such as senna or bisacodyl should be scheduled daily together with opioid initiation. Osmotic agents, such as polyethylene glycol can be added to stimulant laxatives when needed. Bulk-forming agents such as psyllium are generally ineffective.

Opioid use in the elderly is associated with falls and confusion, particularly at the initiation of therapy [64], however, pain itself may also cause falls and confusion and interestingly, higher opioid doses have been associated with a lower delirium risk in a study of hospitalized hip fracture patients [70].

Respiratory depression is rare in opioid-naive patients whose treatment is initiated at low doses. The risk is higher for the elderly especially concurrently with CNS depressants such as benzodiazepines [67].

5.8.3.1 Tramadol

A weak mu-opioid agonist with additional serotonin and norepinephrine reuptake inhibition, has similar side effect profile as other opioids. In addition tramadol has an increased seizure risk and risk for serotonin syndrome, particularly with concomitant use of serotonergic drugs. The half-life can be prolonged by a factor of approximately 1.4 in patients over 75 years of age. Dose adjustment in elderly patients (up to 75 years of age) without clinically relevant hepatic or renal impairment is normally not necessary. In patients over 75 years, the elimination half-life of tramadol may be prolonged so immediate release formulations should be used [71]. Dosage should be adjusted to renal function.

Suggested dose for the elderly: Immediate release Tramadol should be initiated at 25 mg/day or twice daily and increased in 25-mg increments every 2–3 days to an initial goal of 100 mg/day [59]. Maximal daily dose is 300 mg for patients over the age of 75 [71].

5.8.3.2 Oxycodone

Oxycodone is a full opioid agonist similar to morphine in its action but has a relatively high bioavailability. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative, and safety issues are similar to other opioids. Oxycodone can be formulated as immediate release, slow release with or without naloxone, added to mitigate gastrointestinal effects such as constipation.

Oxycodone has a high oral bioavailability of 87%, it is metabolized in the liver and excreted in the urine. Plasma concentrations of both oxycodone and more so naloxone are elevated in patients with renal impairment; however, the clinical relevance of a high naloxone exposure in renal impaired patients is unknown. So caution and medical monitoring is particularly necessary for patients with severe renal impairment [72]. The elderly have slightly elevated concentrations of oxycodone and naloxone so generally speaking, dosing should be adjusted for renal function, although it is wise for the elderly to start at low doses, as for all opioids.

Interactions: Oxycodone can increase anticholinergic adverse effects of medications with anticholinergic activity such as tricyclic antidepressants, anti-histamines, antipsychotics, antiparkinsons etc. CYP3A4 inhibitors, such as macrolide antibiotics, azole-antifungal agents, protease inhibitors, cimetidine and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A reduction in the dose of oxycodone may be necessary. CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St. John's Wort, cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations [72].

Suggested starting dose for the elderly: Oxycodone: 2.5 mg every night, then 2.5–5.0 mg every 4–6 h [59].

5.8.3.3 Codeine

Codeine sulfate is an opioid agonist relatively selective for the mu-opioid receptor, but with a much weaker affinity than morphine. The analgesic properties of codeine come from its conversion to morphine, although the exact mechanism of analgesic action remains unknown. Elderly patients (aged 65 years or older) may have increased sensitivity to codeine. Codeine is metabolized by conjugation and N-demethylation to inactive metabolites and by CYP2D6 to morphine (5–10%). Patients who have ultrarapid metabolism via CYP 2D6 may develop high levels of morphine and should be dosed with lower doses codeine. Approximately 90% of the total dose of codeine is excreted through the kidneys, of which approximately 10% is unchanged codeine. Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Patients with renal dysfunction and elderly patients should be started with a lower than normal dosage of codeine and with longer dosing intervals. Dose should be titrated slowly while monitoring for signs of respiratory depression, sedation, and hypotension [73].

Suggested starting dose for the elderly: 10 mg every 6 h, as needed [59].

5.9 Corticosteroids

Corticosteroids are anti-inflammatory, immunosuppressive and anti-proliferative. The anti-inflammatory effect results from decreased formation, release and activity of mediators such as kinins, histamine, prostaglandins and leukotrienes. Also, corticosteroids decrease vessel permeability and inhibit cell margination and migration to the area of injury resulting in decreased access of cells to the site of injury.

Naturally occurring corticosteroids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, such as prednisone, methylprednisolone and prednisolone are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

5.9.1 Pharmacokinetics

Oral corticosteroids are well absorbed. All undergo metabolism in the liver with inactive metabolites excreted in the urine. Active prednisolone is partially excreted in the urine, so patients with kidney failure (and as such, the elderly) may need lower doses. As prednisone converts to prednisolone, it too may accumulate in renal failure, and lower dosing is also appropriate in the elderly [74–76].

Glucocorticoids undergo metabolism in the liver by cytochrome P450 3A4 (CYP 3A4) and other transformations and are substrates of P-glycoprotein membrane efflux transporters. Medications that strongly inhibit or induce CYP 3A4 and/or P-glycoprotein transporters may significantly alter the glucocorticoid serum concentration. Medications that increase the systemic glucocorticoid concentration include estrogen derivatives, such as oral contraceptives and strong inhibitors of CYP 3A4 including macrolide antibiotics such as clarithromycin, antiretrovirals such ritonavir and antifungals such as posaconazole and voriconazole. Strong inducers of CYP 3A4 such as carbamazepine, phenobarbital and rifampin may reduce glucocorticoid concentration [76].

5.9.2 Safety

The incidence of corticosteroid-induced side effects may be increased in elderly patients and are dose-related. Osteoporosis is the most frequently encountered complication, which occurs at a higher incidence rate in corticosteroid-treated geriatric patients as compared to the young [77]. Corticosteroids decrease bone formation and increase bone resorption by inhibiting osteoblast function and by decreasing absorption and increasing excretion of calcium. The risk for glucocorticoid induced osteoporotic fractures increases with age, dose and duration of glucocorticoid therapy [78]. Indirect glucocorticoid effects that also predispose patients to an increased risk of fracture include reduced muscle mass leading to an increased risk of falls, decreases in renal calcium resorption and levels of sex hormones, and alterations in parathyroid hormone pulsatility [79]. Screening for fracture risk should be performed soon after the initiation of glucocorticoid treatment by using bone mineral density testing and the fracture risk assessment tool (FRAX) [74]. Patients who receive glucocorticoids should be counseled about adequate dietary intake of calcium (1000 mg per day) and vitamin D (600–800 IU), weight-bearing exercise, and avoidance of smoking and excessive alcohol intake [78]. The 2017 guidelines of the American College of Rheumatology [80] recommend pharmacologic treatment to prevent additional fractures in any patient with a previous osteoporotic fracture who is receiving glucocorticoids and for patients who are at least 40 years of age if, according to the FRAX tool, the risk of major osteoporotic fracture is 20% or higher or the risk of hip fracture is at least 3%. Pharmacologic treatment is also recommended for men who are 50 years of age or older and for postmenopausal women. Oral bisphosphonates are recommended as first-line agents to prevent glucocorticoid-induced fractures unless there are contraindications or unacceptable side effects [78, 80].

Corticosteroids should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency, as they can cause elevation of blood pressure, salt, and water retention, and increased excretion of potassium and calcium. Dietary salt restriction and potassium supplementation may be necessary. Patients may experience elevated fasting and post prandial glucose levels and

worsening of diabetes control. New onset hyperglycemia is uncommon however risk increases with higher doses, increased age and other risk factors for diabetes such as family history, obesity and history of diabetes mellitus [81, 82].

Corticosteroids are associated with central nervous system effects ranging from euphoria, insomnia, mood swings, personality changes, severe depression to psychotic manifestations. The elderly are at higher risk for depression, mania, delirium, confusion, or disorientation [83]. Corticosteroids are listed as one of the medications that worsen delirium in the Beers Criteria list [28].

In summary, corticosteroids are potent anti-inflammatory drugs and should be used at the lowest possible dose and for the shortest possible duration due to safety issues that are more prominent in the elderly such as osteoporosis with elevated fracture risk, disorientation, delirium, diabetes and due to potential worsening of chronic conditions such as hypertension, diabetes and heart failure.

5.10 Sulfasalazine (SSZ)

SSZ is a well-established DMARD that is most commonly used as a second-line agent in rheumatoid arthritis combination therapy but is also indicated to treat other inflammatory arthritides and inflammatory bowel disease. SSZ is composed of 5-aminosalicylic acid and sulfapyridine which possesses the anti-arthritic effect. Sulfasalazine is metabolized by intestinal bacteria to sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is acetylated to form acetylsulfapyridine. Approximately 60% of the Caucasian population are slow acetylators and have a 40% longer half-life of sulfapyridine. Slow acetylators have higher risk for adverse effects such as agranulocytosis [84]. Elderly patients with rheumatoid arthritis showed a prolonged plasma half-life for sulfasalazine, sulfapyridine and their metabolites but the clinical impact of this is unknown [85]. Sulfapyridine and it's metabolites are primarily eliminated in the urine and the majority of 5-aminosalicylic acid stays within the colonic lumen and is excreted via the feces.

Genetic polymorphisms may play a role in the efficacy and toxicity of the drug. A prolonged half-life and accumulation of the sulfapyridine metabolite of SSZ with a subsequent increase in toxicity may be seen in slow acetylators and patients with glucose-6-phosphate dehydrogenase deficiency are at increased risk of hemolytic anemia after initiation [84–86]. Sulfasalazine is associated with gastrointestinal, central nervous system (headache, dizziness), cutaneous, and hematologic (agranulocytosis) adverse reactions. Severe hypersensitivity reactions, such as DRESS may occur and crystalluria with intratubular precipitation of salazopirine metabolites, with subsequent acute kidney injury may occur too.

Efficacy and toxicity in the elderly are comparable to the young [87] and no specific dose recommendations exist for the elderly [85, 86]. Maintaining adequate hydration and monitoring renal function is prudent in older individuals treated with SSZ due to crystalluria and kidney injury [40].

5.11 Summary

Many of the medications used for arthritis and other types of vasculitis have specific safety issues, relevant for the elderly. Drugs should be used appropriately in the elderly population, who are often frailer, have additional comorbidities and take additional medications which all can effect safety and efficacy.

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Chapter 6
Biologic Drugs and Small Molecules for an Elderly Patient with the Rheumatic Disease

Shira Ginsberg

Rheumatic disease of the elderly is becoming more common as the population age increases. While the same rheumatic disorders may present differently in older people, treatment goals must be similar to that in the younger population, namely, achieving remission or at least low disease activity as soon as possible, preventing pain and longer-term damage that can lead to loss of function and limitation in daily activities, improving quality of life and increasing life expectancy. However, many physicians are reluctant to provide modern highly efficacious treatments to the elderly population, even in cases of a severe and aggressive disease, because of fear of adverse effects, poorly understood drug-drug interactions or other causes.

Studies have demonstrated that synthetic disease-modifying anti-rheumatic drugs (sDMARDS) in older patients with rheumatic disease are administered less common or given at the reduced dose, sometimes compromising drug efficacy. Similarly, physicians are less likely to prescribe biologic therapies (biologic DMARDs, or bDMARDs) to elderly patients [1]. Consequently, comparing to their younger counterparts, the older persons can have their rheumatic disease more frequently undertreated, suffer from joint pain in a greater extent and have higher rates of disability [2, 3]. Being reluctant to utilization of biologics in the elderly, physicians do not have a choice but to administer glucocorticosteroids in higher doses and for prolonged periods of time, even if glucocorticosteroids have been repeatedly shown to have more adverse effects and serious adverse effects when compared to biologic therapies in patients with rheumatic disease [4–6].

Modern biological therapies have cardinally changed the prognosis and well-being of patients suffering from a variety of rheumatic conditions, allowing prevention of both disease-associated damage and related co-morbidities (Table 6.1). The goal of this chapter is to review the efficacy and, particularly, safety of currently available bDMARDs and small molecules for the treatment of rheumatic diseases in

S. Ginsberg (✉)
Internal Medicine, Bnai-Zion Medical Center, Haifa, Israel

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Table 6.1 bDMARDs and small molecules, approved for the treatment of rheumatic diseases (as for 2020)

TNF-α inhibitors	**IL-6 inhibitors**	**Co-stimulation inhibitors**	**Anti-B cell therapy**	**JAK inhibitors**	**IL-17 inhibitors**
Infliximab[1,2,3]	Tocilizumab[1,4]	Abatacept[1]	Rituximab[1,5,7]	Tofacitinib[1,3]	Secukinumab[2,3]
Etanercept[1,2,3]	Sarilumab[1]		Belimumab[5]	Baricitinib[1]	Ixekizumab[3]
Adalimumab[1,2,3]				Upadacitinib[1]	
Certolizumab[1,2,3]					
Golimumab[1,2,3]					
IL-12 / IL-23 inhibitors	**IL-1 inhibitors**	**Phosphodiesterase inhibitor**			
Ustekinumab[3]	Anakinra[1,6]	Apremilast[3,9]			
	Canakinumab[6,8]				

Approved for the treatment of:
[1]Rheumatoid arthritis, [2]Ankylosing Spondylitis, [3]Psoriatic arthritis, [4]Giant Cell Arthritis, [5]Systemic lupus erythematosus, [6]Autoinflammatory diseases, [7]ANCA-associated vasculitis, [8]Gouty arthritis, [9]Behçet's disease

elderly patients, with emphasis on risks and benefits of their use in this specific population, as compared to younger individuals.

Before starting the discussion on the features of different groups of biologic therapies, it is worth mentioning that all candidates for treatment with bDMARDs and small molecules should be screened for active or latent tuberculosis (TB) and hepatitis viruses. Besides, these patients should be vaccinated, preferably before starting bDMARDs and small molecules, as recommended by current immunization guidelines. Live vaccines should be avoided, if possible, after treatment with bDMARD and small molecules has been started [7, 8].

6.1 Tumor Necrosis Factor-Alpha (TNF-α) Inhibitors

TNF-α inhibitors have been formally approved for the treatment of rheumatoid arthritis (RA), psoriatic arthropathy (PsA), ankylosing spondylitis (AS), and as well have been reported efficacious in case studies of patients with many other systemic rheumatic diseases, including vasculitidies, some systemic autoimmune diseases, Behçet's disease and sarcoidosis [9–13].

Five currently available TNF-α inhibitors include

- *Infliximab*, which is a chimeric IgG1 monoclonal antibody, administered intravenously (IV) every 4–8 weeks;
- *Etanercept*, a genetically engineered protein that consist of two extracellular domains of TNF receptor linked to FC portion of IgG1, administered subcutaneously (SC) once or twice a week;
- *Adalimumab*, a fully human monoclonal antibody given by SC injection every other week;
- *Golilumab*, a transgenic human monoclonal antibody, injected SC once a month;
- *Certolizumab pegol*, a humanized antibody, administered SC every other week or on a monthly basis.

In general, TNF-α inhibitors may be used as monotherapy or in combination with methotrexate, with the combination treatment being repeatedly reported more efficacious, particularly in patients with RA [14]. Methotrexate should be administered along with infliximab in RA patients to decrease the production of the anti-infliximab antibodies and improve the efficacy and survival rate of the biologic.

Comparisons of efficacy and safety of TNF-α inhibitors in younger and older patients with rheumatic diseases have been reported and summarized by several investigators [3, 15–21]. The majority of studies concluded that the benefits of TNF-α inhibitors, including control of the disease activity, improvement in patient-reported outcomes, as well as drug retention rates were similar in all age groups. However, other studies reported decreased improvement in RA activity score, Health Assessment Questionnaire (HAQ) and short form health survey (SF-36) scores in elderly RA patients, treated with TNF-α inhibitors, comparing to younger individuals as well as higher rate of infections among elderly RA patients. On the

other hand, the reported finding that mean HAQ score improved less in the subgroup of patients older than 75 years, can just reflect longer disease duration and more aggressive disease in the older cohort in this particular study, meaning that biologic therapy should be administered without delay in elderly patients with active rheumatic disease resistant to standard treatment, also because of the age-related slower rates of rehabilitation [22, 23].

Safety of TNF-α inhibitors in the elderly patients with rheumatic diseases has been repeatedly reported comparable to that in younger individuals; however, some studies indicated higher rates of serious adverse events in older persons [17, 20, 21]. Thus, the knowledge of potential side effects, risks and contraindications related to treatment with bDMARDs is fundamental for the right choice of a therapeutic for a particular individual with his distinctive co-morbidities. In this regard, patients with clinically significant congestive heart failure, demyelinating disorders, chronic or frequent infections, or those with systemic lupus erythematosus or lupus-like disease, as well as patients with current or recent hematological or solid malignancy should usually avoid use of TNF-α inhibitors [24].

6.2 Anti-Interleukin (IL) 6 Medicines

Tocilizumab is a humanized monoclonal antibody against IL-6 receptor, prescribed as monotherapy or in combination with sDMARDS, which can be administered IV or SC. Tocilizumab has been approved for the treatment of RA and Giant Cell Arthritis (GCA) [25].

The efficacy of tocilizumab in elderly patients with RA was evaluated in several studies. In one of them, 203 patients with RA, aged 65 or more and treated with tocilizumab, demonstrated similar efficacy of the drug on the disease activity outcome measures as their younger counterparts [26]. Another study, analyzing the effects of tocilizumab in 61 elderly RA patients, found slightly diminished drug efficacy in this specific cohort [27]. In both studies, however, older patients had longer disease duration, higher inflammatory markers, higher comorbidities and higher disease activity at the baseline, as compared to younger individuals.

The GIACTA trial demonstrated overwhelming advantage of tocilizumab, added to glucocorticoids as compared to the glucocorticoid monotherapy in patients with GCA. Administered in SC injections, tocilizumab treatment resulted in sustained remission in the majority of GCA patients and dramatically decreased cumulative glucocorticoid dose. The rate of adverse effects and severe adverse effects was not increased in GCA patients, treated with tocilizumab [28].

As with majority of bDMARDs and small molecules, tocilizumab should be avoided in patients with active infections. Also, patients with diverticulitis have been reported to develop bowel perforation, while treated with tocilizumab [25]. Complete blood count and liver enzymes should be followed every 6–10 weeks in tocilizumab-treated patients.

Sarilumab is another human monoclonal IgG1 antibody that binds to IL-6 receptor and inhibits IL-6 activity. It is approved for RA treatment and administered as a subcutaneous injection every other week. In general, efficacy and safety of sarilumab is comparable to that of tocilizumab; however, in an exploratory analysis from the studies of sarilumab in RA patients, patients aged more than 65 had more severe adverse events [29, 30].

6.3 Rituximab

Rituximab is an anti-B cell therapy currently used for the treatment of rheumatic diseases. It is a chimeric mouse/human monoclonal antibody against CD20 molecule. The drug, engaging CD20, leads to the apoptosis and depletion of the peripheral blood B cells. The B cell recovery occur within a few months, and the drug can be re-administered after the period of 4 month or more. Rituximab is approved for the treatment of RA and ANCA-related vasculitidies and is frequently used off label for the treatment of patients with systemic lupus erythematosus, dermatomyositis and other autoimmune conditions [31].

Rituximab has been found to be efficacious in elderly people with RA, but studies have demonstrated both decreased improvement in disease parameters and significantly increased rate of severe infections in RA patients aged 75 or more [2, 31–33].

While being an appropriate treatment for the patients with concomitant CHF or malignancies, rituximab can cause secondary hypoglobulinemia, lasting for prolonged periods. Thus, alternative treatment should be chosen for elderly patients with chronic or frequently repeated infections. Intravenous immunoglobulin should be considered for patients who develop hypoglobulinemia and severe infection after rituximab treatment. Hepatitis B virus status should always be checked before starting rituximab treatment and specific prophylaxis started when necessary [34].

6.4 Belimumab

Belimumab is a human immunoglobulin monoclonal antibody that binds to the soluble B-cell survival factor (BLyS), which results in circulating B cells reduction.

The drug can be administered IV or SC and is approved for the treatment of patients with SLE.

The data on the efficacy and safety of belimumab regarding elderly patients is limited, as clinical studies did not include enough patients aged 65 or older. The current recommendations are to use belimumab with caution in the older people, while no dosage adjustment is required [35–37].

6.5 Abatacept

Abatacept is the only co-stimulation inhibitor, currently approved for the treatment of RA and PsA. It is a soluble human recombinant fusion protein, acting as a cytotoxic T-Lymphocyte associated antigen 4 (CTLA-4), which binds to the B7-1/B7-2 molecules on the surface of antigen presenting cell and prevents T-cell activation.

The drug is available as an IV monthly infusion or SC injection, administered weekly.

Two Japanese studies of 508 and 227 patients with RA, respectively, did not find difference in the efficacy of abatacept in persons older than 65-years old and younger individuals [38, 39], while another bigger analysis of data on 1017 patients, with 103 patients being at least of 75-year old, concluded that RA patients at age of 75 or older, treated with abatacept, have a significantly lower likelihood of achieving a good response after 6 months of treatment. It was demonstrated as well, that older patients treated with abatacept, showed an excessive incidence of severe infections, mainly bronchopulmonary, and more events of malignancies, although a lack of a control group prevented the authors from identifying excess risk except for the expected increase in malignancy rates in the elderly population [40].

6.6 Janus Kinase (JAK) Inhibitors

Tofacitinib is an oral, partial and reversible, competitive Janus Kinase (JAK) inhibitor that is approved for the treatment of RA and PsA. It binds to the adenosine triphosphate binding site in the cleft of the kinase domain of JAK1 and JAK3 and blocks transmission of inflammatory signaling through these intracellular molecules, including IL-6 and interferon-mediated signaling [41].

Tofacitinib is administered orally and has a short half-life with a rapid absorption and elimination. It reaches the peak plasma concentration within 1 h and its half-life time is approximately 3 h.

A large meta-analysis, which included data on more than 600 RA patients aged 65 years or more treated with tofacitinib, showed no difference in general clinical response, as measured by American College of Rheumatology 20% response (ACR-20), ACR-50 and HAQ outcomes, between older and younger patients. However, stricter ACR-70 response was found lower in the elderly persons. In addition, higher rate of severe infections was observed in the older individuals, treated with tofacitinib [42].

In general, the frequency of herpes zoster infection, permitted by the inhibition of interferon signaling, can be twice as high in patients treated with tofacitinib, as compared to other groups of biological medicines [43, 44].

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2. *Upadacitinib* blocks JAK1 only. Both medicines have been approved for treatment of RA as a monotherapy or in combination with methotrexate. The dose of baricitinib should be reduced in patients older than 75 years or in patients with renal impairment. The experience with baricitinib and upadacitinib in elderly patients is still limited, but a post hoc analysis of two phase 3 studies, evaluating efficacy and safety of baricitinib in RA patients, reported similar efficacy but more frequent adverse effects, including serious infections, in elderly patients [45, 46].

6.7 Anti-IL 17 Medicines

Secukinumab is a human IgG1 monoclonal antibody that neutralizes the effects of IL-17A, is approved for the treatment of psoriatic arthritis and ankylosing spondylitis given as a SC injection [47]. *Ixekizumab* is a recombinant humanized IgG4 monoclonal antibody that also acts against IL-17A and is used today in rheumatology to treat psoriatic arthritis. It is given as a SC injection as well [48].

Both drugs have similar efficacy and safety in elderly and young patients with skin psoriasis; however, more data needs to be accumulated on their use in older patients with rheumatic disease [49–52].

6.8 Anti-IL 12/23 Medicines

Ustekinumab is a human IgG1 monoclonal antibody that blocks g140 particle, which is a part of both IL-12 and IL-23 receptors. It is approved for the treatment of psoriatic arthritis and administered in SC injections [53]. Similarly to IL-17 inhibitors, most data on the use of ustekinumab in elderly is based on clinical studies in patients with skin psoriasis, where both efficacy and safety of the drug did not differ between younger and older persons [52, 54, 55].

6.9 IL-1 Inhibitors

IL-1 is involved in the synthesis of the major inflammatory mediators and plays a dominant role in the innate immune response and inflammation [56].

Anakinra is a recombinant interleukin-1 receptor antagonist administered daily by subcutaneous injection and approved for the treatment of active rheumatoid arthritis and several autoinflammatory diseases.

Clinical trials with anakinra, which included over 750 patients aged 65 years or older, have demonstrated no differences in safety or efficacy of the drug as compared to the younger persons [57].

Canakinumab is an anti-IL-1beta monoclonal antibody that is indicated for the treatment of autoinflammatory diseases, systemic juvenile idiopathic arthritis, adult-onset Still's disease and gouty arthritis. It has a long half-life time and is administered SC every 4–8 weeks. Data on the efficacy and safety of canakinumab in elderly patients is lacking [58].

6.10 Apremilast

Apremilast is a small molecule, which inhibits phosphodiesterase 4, an intracellular enzyme, involved in the regulation of inflammatory mediators. The drug is taken orally twice a day and is indicated for the treatment of PsA and oral ulcers associated with Behçet's Disease [59, 60].

Over 140 PsA patients of 65 years and older were treated with apremilast in the clinical studies with the similar efficacy and safety profile as compared to the younger patients [61–64].

6.11 Summary

In the majority of studies, biological therapies and small molecules had similar efficacy and safety profile in the elderly patients with rheumatic disease as in younger persons. Thus, aiming at the same treatment goals of remission or low disease activity, damage prevention and improved well-being in all ages, we postulate that the biologics in the older patients with resistant rheumatic disease should be utilized in a similar manner as in their younger counterparts. It should be remembered, however, that the frequency of severe infections in older people, particularly in persons aged 75 years or more and treated with biological therapies or small molecules can be increased, probably because of the senescence of the immune system and accumulating comorbidities. Thus, preferential use of short-acting medicines and formulations, which can be annulated rapidly, can be preferred in this cohort. Choosing the right anti-rheumatic biologic treatment in an elderly individual, while multiple biologic medicines and small molecules of similar efficacy are available, is a challenging task and should also be based on a patient's background and comorbidities as well as on the known safety profile of a specific drug (Table 6.2).

Table 6.2 Prevalent comorbidities and the choice of bDMARDs and small molecules to avoid

Comorbidity	Medicine to avoid
Active tuberculosis or any other active viral or microbial infection	All bDMARDs and small molecules
Current malignancy	All bDMARDs and small molecules, excluding Rituximab
Heart failure, class III–IV	TNF-α inhibitors
Demyelinating disorder	TNF-α inhibitors, IL-6 inhibitors
Inflammatory bowel disease	Etanercept, IL-17 inhibitors
Uveitis	Etanercept
History of diverticulitis	IL-6 inhibitors, JAK inhibitors
Significant hyperlipidemia	IL-6 inhibitors, JAK inhibitors
COPD	Abatacept
Thrombotic disorders	Baricitinib
Significant renal failure	Baricitinib
Recurrent herpes zoster	JAK inhibitors

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Chapter 7
Ophthalmic Complications of the Rheumatic Diseases and Anti-Rheumatic Drugs (in Elderly)

Xia Ni Wu, Asaf Bar, Karin Hershcu, Lazha Sharief, and Oren Tomkins-Netzer

The eye is composed of many unique structures that together refract and transduce light for visual perception. Normal ocular function requires a specific and stable extracellular environment, which is maintained by functional blood-ocular barriers. These restrict the free passage of blood constituents and immune cells, and together with immunoregulatory systems mediated by regulatory T-lymphocytes, create an immune-privileged microenvironment. Conditions that result in alterations to the function of these systems can result in an increased likelihood of developing intraocular inflammation, termed uveitis. Many systemic diseases have ocular manifestations, including diabetes mellitus, arterial hypertension and numerous systemic autoimmune disorders. While ocular involvement may only be part of a systemic disease, we rely on visual function for daily activities and most ocular pathologies are symptomatic, so the eye may be the presenting organ. Patients with rheumatic diseases can develop ocular involvement and complications as part of their systemic

X. N. Wu
Moorfields Eye Hospital, London, UK

A. Bar
Ophthalmology Department, Wolfson Medical Center, Holon, Israel

K. Hershcu
Ophthalmology Department, Bnai Zion Medical Center, Institute of Technology, Technion, Haifa, Israel

L. Sharief
Moorfields Eye Hospital, London, UK

Ophthalmology Department, Kings College Hospital, London, UK

O. Tomkins-Netzer (✉)
Ophthalmology Department, Lady Davis Carmel Medical Center, Ruth and Bruch Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

Institute of Ophthalmology, University College London, London, UK
e-mail: orentn@clalit.org.il

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disease or as a consequence of treatment. In this chapter we describe common ocular conditions found in rheumatic patients, ocular manifestations of rheumatic diseases and ocular side effects of systemic immunosuppression.

7.1 Ophthalmic Complications of Rheumatic Diseases

7.1.1 Dry Eye (Keratoconjunctivitis Sicca)

Dry eye, also known as keratoconjunctivitis sicca or dysfunctional tear syndrome, is a very common disease that involves the tears and the ocular surface and is related to disturbances in the normal function of the lacrimal system [1]. There is an imbalance between tear production and evaporation, with instability of the tear film. Inflammation can precipitate or exacerbate the cycle due to the increased concentrations of pro-inflammatory mediators in the tears, ocular surface inflammation, and damage to the lacrimal secreting cells. Prevalence ranges from 20% to 44% in people over the age of 50 years [2, 3], depending on genetic and environmental factors, and is higher among patients suffering from rheumatic diseases [4]. Autoimmune disorders that are known to be related to dry eyes are primary Sjögren's syndrome, secondary Sjögren's syndrome that can be associated with rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, polymyositis and dermatomyositis, primary biliary cirrhosis and graft-vs-host disease. Certain medications can also result in dry eye disease, such as antihistamine and anticholinergic drugs.

Signs and symptoms of dry eyes may include a foreign body sensation, blurred vision, photosensitivity, increased ocular discharge, ocular discomfort and even severe pain. Symptoms typically worsen towards the end of the day or following visual tasks such as reading or working in front of a screen. These can be quite debilitating, and many patients describe them as having a significant impact on their quality of life. Findings on eye exam include tear dysfunction (reduced tear production and/or rapid tear evaporation) and alterations to the ocular surface (Fig. 7.1) [5]. Vision can also be affected as the dry ocular surface scatters light transmission resulting in a deterioration in visual quality. Severe dry eye can manifest as a filamentary keratitis and can cause severe discomfort. Furthermore, the damaged ocular surface predisposes to infectious keratitis which can lead to irreversible blindness.

Therapeutic interventions should be customized to the patient as the disease can be caused by multiple etiologies [5]. Table 7.1 lists practical therapeutic approaches as well as treatment options that typically require coordination with an ophthalmologist. Patients should be advised that dry eye is a chronic condition which requires continued treatment and may require a multi-pronged approach for symptom relief [6]. Non-pharmacological measures include minimizing environmental factors that reduce humidity (air conditioners, dry windy conditions), and limiting activities that require visual concentration as these result in less blinking. The most common

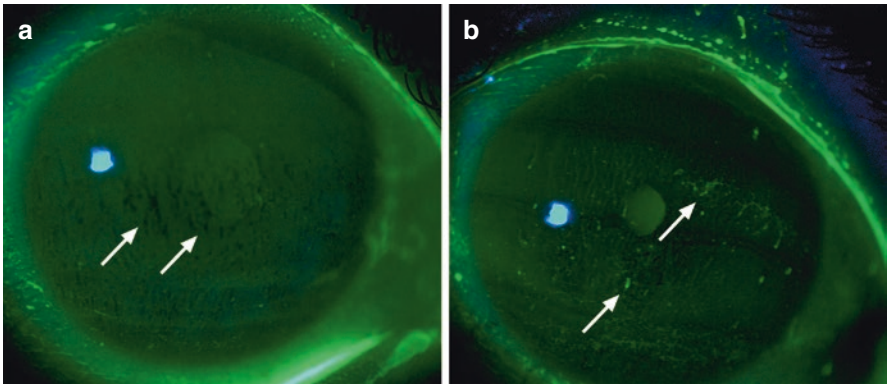

Fig. 7.1 Fluorescein corneal staining patterns in eyes with dry eye. (**a**) Breakup of the tear film appears dark areas on the corneal surface (arrows). Breaks in the tear film that appear within 10 s are considered pathologic. (**b**) Areas of fluorescein staining demonstrate damage to the epithelial layer that appear as superficial punctate keratitis (arrows)

Table 7.1 Treatment options and recommendations for dry eyes

Initiated by treating physician
Awareness of environmental factors or activities that promote symptoms
Increase humidity (e.g. humidifier in the room)
Use spectacles (avoid contact lenses)
Take breaks from close work
Avoid use of periocular makeup
Avoid corneal laser corrective surgery (e.g. LASIK)
Extensive, prolonged use of topical lubricating drops even when symptoms resolve
To be initiated together with an ophthalmologist
Use ocular ointments at night
Topical corticosteroids
Topical cyclosporine A 0.05%
Oral pilocarpine 5 mg, start at OD (up to 4–6×/day)
Doxycycline 50 mg BD for up to 6–12 weeks
Topical acetylcysteine 5–10% in cases of filamentary keratitis
Autologous serum drops
Therapeutic soft contact lenses
Placement of punctal plugs

treatment for dry eye is the use of topical ocular lubrication, administered several times a day. Preservative-free solutions are recommended for patients that require high frequency and long-term treatment to avoid toxicity to the cornea. Drops are suitable for daytime use, gel and ointments are suitable as bedtime treatment, but can be used during the day for patients that require more lubrication.

Topical cyclosporine A 0.05% twice daily addresses the local inflammatory aspect of the disease [7]. It is common to combine topical steroids when cyclosporine is initiated, to provide faster initiation of the anti-inflammatory effect. Patients should be informed that achieving the benefits of cyclosporine may take a few months of regular treatment. Autologous serum drops are made by drawing blood from the patient and can be helpful for severe dry eye with corneal damage. Dietary supplementation with omega-3 fatty acids has been recommended previously, however recent large studies have not demonstrated an effect [8]. Certain patients may require punctal occlusion or even surgical intervention. Treatment is typically lifelong and patients should be encouraged to continue treatment even when symptoms resolve.

7.1.2 Uveitis

Uveitis is defined as intraocular inflammation and can be an extra-articular manifestation of many forms of rheumatic disease. It may involve different parts of the eye and is categorized according to the primary site of inflammation: anterior, intermediate, posterior, or panuveitis when several sites are involved equally [9]. Patients may describe blurred vision, floaters, ocular pain or discomfort, redness, and photopsias. Etiologically the inflammation can result from either infectious or non-infectious causes, and while most cases remain undifferentiated [10], a thorough history, examination, and targeted investigations may identify the underlying systemic disease. A compatible disease may already be known, however it is worthwhile to remember Hickam's dictum particularly if the clinical features or course is atypical.

Approximately 50% of patients with uveitis have an associated systemic inflammatory disease [11]. The commonest non-infectious associations were HLA-B27-associated spondyloarthropathies in adults, and juvenile idiopathic arthritis (JIA) in children [12, 13]. About a third of ankylosing spondylitis patients will have sudden-onset alternating recurrent anterior uveitis [13]. Between 60% to 80% of Behçet's disease patients have ocular involvement, usually bilateral and chronic panuveitis with occlusive retinal phlebitis [14]. In 7% of psoriatic arthritis, Crohn's disease, and less commonly ulcerative colitis patients, uveitis and scleritis may be associated with skin and joint disease [15]. Relapses of uveitis do not always coincide with systemic disease and should be considered even when the extraocular disease appears to be controlled. Uveitis may also present as an adverse reaction to drugs like tumor necrosis factor α (TNFα) inhibitors, intravenous bisphosphonates, and checkpoint inhibitors [16].

The coexistence of uveitis and arthritis is not well understood. Both the eye and the joint share some biochemical similarities, such as the presence of hyaluronic acid, type II collagen, and aggrecan [17]. Genotyping of patients with

HLA–B27-associated uveitis shows that ankylosing spondylitis and acute anterior uveitis share HLA–B27 itself, the interleukin-23 receptor (IL-23R), and endoplasmic reticulum aminopeptidase 1 [18]. Conversely, there are identifiable genes such as IL-6R and IL-18R1 (and probably IL-10) that seem to influence only the susceptibility to acute anterior uveitis.

Uveitis can result in the development of ocular complications that can lead to irreversible vision loss [19]. In patients with JIA, regular ophthalmic review is essential as it is classically asymptomatic until significant damage has occurred [20]. The type of ocular complication is related largely to the anatomical location of the inflammation and common causes include macular damage (macular edema, epiretinal membrane and macular scarring), cataract, glaucoma, and media opacities.

Treatment of non-infectious uveitis is based on local and systemic corticosteroids, together with other immunosuppression agents as needed. Recently, the anti-TNFα drug adalimumab has been licensed for the use of non-infectious non-anterior uveitis [21]. The use of infliximab and adalimumab results in extensive control of the ocular inflammation and a reduced risk of disease relapse among eyes with refractory uveitis [22]. Use of etanercept may be less effective in preventing uveitis relapses and is not advocated for use in patients with known uveitis [23–25]. The objective is to achieve zero inflammation and preserve long-term vision, while minimizing potential systemic and ocular side effects. Long-term studies demonstrate that under rigorous treatment and follow-up, visual acuity can be preserved and visual loss avoided in approximately 90% of eyes [19].

7.1.3 Cataract

Cataract is an opacification of any part of the crystalline lens: nucleus, cortex or capsule (Fig. 7.2). It is a leading cause of vision loss worldwide and its prevalence increases with age. It is estimated that 16–18 million people worldwide have visually impairing cataract. Major risk factors include genetics, exposure to ultraviolet light, uveitis, smoking, systemic diseases such as diabetes, and use of certain drugs, particularly corticosteroids [26, 27]. Cataract formation is highly associated with frequent use of topical corticosteroids, but can also result from systemic, skin, or inhaled use. Cataract associated with chronic uveitis is commonly posterior subcapsular (Fig. 7.2c) and can progress over months. Cataract surgery can be challenging due to post-inflammatory changes such as band keratopathy, small non-dilating pupils, posterior synechiae, capsular bag fibrosis, and abnormal iris bleeding, all of which increase the risk of surgical complications. Peri-operative management often includes corticosteroids (topical or systemic) to minimise inflammation and any potential flare-ups post-operatively. Accordingly, cataract surgery is only performed when the uveitis has been quiescent for at least 3–6 months.

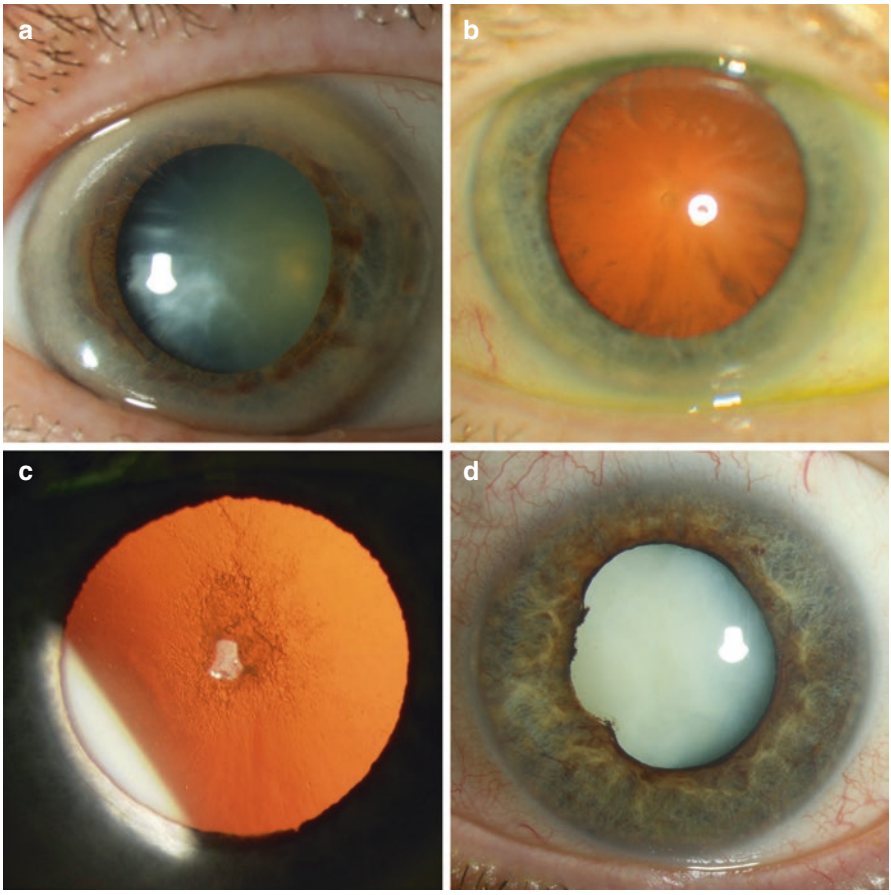

Fig. 7.2 Types of cataract. (**a**) Nuclear cataract- the center of the lens appears opaque with a yellow-green hue. (**b**) Cortical cataract involves the peripheral layers of the lens. (**c**) Posterior subcapsular cataract appears as an opacity on the posterior capsule of the lens and is a common complication of uveitis or long-term corticosteroid treatment. (**d**) Mature, white cataract with posterior synechia between the edge of the iris and the lens capsule

Symptoms caused by cataract are decreased visual acuity, glare and halos, deceased contrast sensitivity, refractive errors and monocular diplopia. Occasionally, measured visual acuity may be excellent but there are functional limitations such as blinding glare from oncoming car headlights. Surgical removal of the cataract is the mainstay of treatment and is indicated when there visually significant symptoms. Surgery is a straightforward day procedure with minimal risk [28]. The opacified lens is removed and replaced by an artificial intraocular lens. Serious sight-threatening risks such as infectious endophthalmitis are under 1 in 1–2000 [29]. Ocular comorbidities common to patients with rheumatological conditions such as dry eye, scleritis, peripheral ulcerative keratitis, uveitis, and glaucoma, increase the risk of complications however absolute relative risk is difficult to quantify.

7.1.4 Glaucoma

Glaucoma is a form of optic neuropathy where there are functional deficits with corresponding, characteristic, anatomical damage. Intraocular pressure is the predominant, and only modifiable, risk factor. Glaucoma is divided into several subtypes based on disease course (acute or chronic), etiology (primary or secondary), the intraocular pressure (ocular hypertension or normal tension) and whether the iridocorneal angle is open or closed. Chronic open angle glaucoma is the most common type. Uveitic glaucoma is a secondary glaucoma that often combines components of open-angle and angle-closure disease. Corticosteroid-induced glaucoma is an open-angle glaucoma caused by use of topical, periocular, inhaled, or oral corticosteroids. The elevated intraocular pressure is a result of increased resistance to aqueous outflow. A steroid response typically occurs within a few weeks of corticosteroid therapy, but can occur within days or after many years [30].

Optic nerve damage typically first affects the peripheral visual field, slowly moving towards the center of vision. Patients become symptomatic when the visual defect encroaches on central vision, typically in the late stages of the disease. The disease is only partially treatable and visual impairments tend to be irreversible; as such, early detection and treatment with close follow-up is essential. Diagnosis includes examination of the optic disc and visual field testing. Long-term clinical trials provide evidence that lowering intraocular pressure prevents progression of the damage to the optic nerve [31].

Treatment options include topical pressure lowering drops including beta-blockers, alpha agonists, carbonic anhydrase inhibitors and prostaglandin analogues. Oral carbonic anhydrase inhibitors can be prescribed when further lowering of intraocular pressure is required, though mostly as a temporary measure. Aside from medical treatment there are procedural options. Lasers can be used to create peripheral iridotomies in narrow or closed angles, and as a treatment option (selective laser trabeculoplasty). Glaucoma surgery typically creates a drainage pathway for aqueous, such as via a trapdoor (trabeculectomy) or tube (e.g. Baerveldt tube or Ahmed valve). Minimally invasive glaucoma surgery (MIGS) is a recent introduction and has shown promise as an adjunct to the more invasive traditional techniques.

7.2 Ocular Involvement in Common Rheumatologic Conditions

Ocular involvement is common in patients with rheumatic diseases and is almost always symptomatic, such that the eye is often the presenting organ. The most frequent form of ocular involvement is dry eye, but ocular inflammation can be a direct manifestation of the underlying autoimmune process and result in significant damage to ocular structure, leading to visual deterioration and blindness.

Furthermore while patients may already be under treatment, visual complaints should be addressed as they may reflect active ocular disease, even when the systemic condition appears quiescent. Treatment of non-infectious uveitis is based on clinical findings related to active disease. It relies on the use of local and systemic immunosuppression, and aims to achieve a state of no active inflammation, thereby preventing vision loss from ocular complications.

7.2.1 Seronegative Spondyloarthropathies (SSpAs)

Anterior uveitis (AU) is a common extraarticular manifestation of SSpAs, affecting 20–40% of SSpAs patients [32, 33], in particular males with ankylosing spondylitis (AS) [34, 35]. It may occur at any stage of the disease, may precede systemic symptoms [35], and was included by the Assessment of SpondyloArthritis Society (ASAS) into the classification criteria for axial and peripheral SSpAs with high-pooled sensitivity (73%) and specificity (88%) [36]. The mechanism behind the development of AU in SSpAs is believed to be autoimmune, with several factors involved including HLA-B27, toll-like receptors (TLRs), vitamin D and TNFα [35].

Typically, the AU in AS is acute, recurrent, unilateral, and alternates between eyes, though it can occur bilaterally in those associated with reactive arthritis, psoriatic arthritis or inflammatory bowel disease [37, 38]. Symptoms include blurry vision and photophobia that rapidly progress into a red, painful eye. Without treatment, patients experience 1–2 relapses per year. Examination reveals inflammation in the anterior chamber that can result in formation of cataract, synechiae across the pupil and iridocorneal angle, and glaucoma. In addition to AU, other ocular manifestations include conjunctivitis, which can occur in almost half of patients with reactive arthritis, characterized by bilateral mucopurulent discharge, papillary or follicular reaction, and is self-limited in most cases. Episcleritis, scleritis and keratitis have also been reported but to a lesser extent [39, 40].

Most cases of AU associated with SSpAs respond to topical ocular therapy over a 6 week period with no subsequent ocular complications. Treatment is initiated with topical corticosteroids to control the inflammation and cycloplegics, to provide pain relief and prevent the development of posterior synechiae. Complete circumferential posterior synechiae leads to angle-closure secondary to pupil block, and often requires surgical intervention. Treatment is started at a high frequency and reduced over several weeks to achieve inflammatory control and prevent relapses. In such cases, topical therapy is reintroduced and maintained for an extended period of time, and systemic immunosuppression added in refractory cases. Systemic corticosteroids are used when topical treatment is ineffective, but prolonged use may be limited by side effects including hyperglycemia, cardiovascular complications, and osteoporosis [41]. Methotrexate is used for those cases not controlled by systemic corticosteroids with relapses prevented in approximately 60% of eyes [42]. Anti-TNFα agents have been reported to induce uveitis remission in up to 60% of AU patients [43–45]. In a prospective trial of adalimumab for patients with AS, the AU relapse rate was reduced by 51% in all patients, including those with a recent history

of AU or chronic uveitis [46]. While prompt diagnosis and treatment results in resolution of AU with few complications, delayed or inadequate treatment can lead to vision-threatening problems such as cystoid macular oedema, cataract, and secondary glaucoma, and the need for prolonged or more interventional treatment.

7.2.2 Sarcoidosis

Sarcoidosis is a systemic granulomatous disease commonly seen in Asian and Afro-Caribbean patients. Multiple sites may be affected but particularly the lungs, lymph nodes, skin, liver, and eyes. Ocular inflammation can involve all structures of the eye (panuveitis) and signs are nonspecific. Systemic disease may be asymptomatic and does not rule out the diagnosis of ocular sarcoidosis. Ocular involvement is mostly bilateral with either anterior uveitis, vitritis, vasculitis or the appearance of granulomas on the iris, optic nerve or choroid (Fig. 7.3a, b). Investigations include

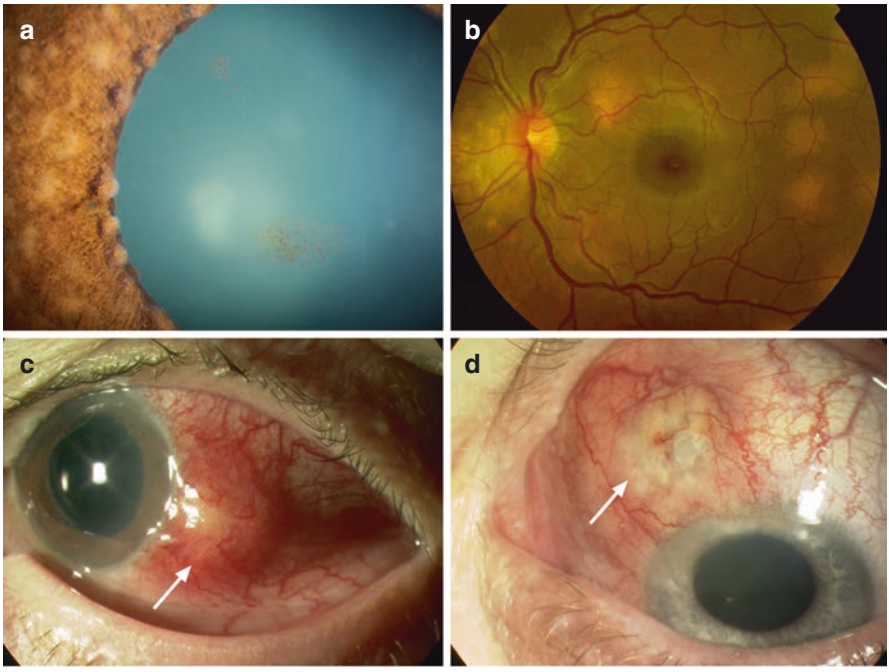

Fig. 7.3 Ocular signs of rheumatic disease. (**a**, **b**) Sarcoidosis. Granulomas can develop in the iris (**a**) or in the choroid (**b**), appearing as raised subretinal lesions. (**c**, **d**) Scleritis. Non-necrotizing nodular anterior scleritis (**c**, arrow). In necrotizing anterior scleritis (**d**) an area with regression of blood vessels can develop (**d**), leading to necrosis of the sclera. (**e**, **f**) Behçet disease. Retinal involvement with an area of retinitis (**e**, arrow) and an adjacent retinal vein occlusion with retinal hemorrhages. Anterior segment disease can appear as granulomatous anterior uveitis (**f**) with a hypopyon at the bottom of the anterior chamber, and development of posterior synechiae (arrow). (**g**, **h**) Systemic lupus erythematosus can result in occlusion and retinal vessel abnormalities (**g**, arrow) and areas of capillary non-perfusion and ischemia (**h**, arrow)

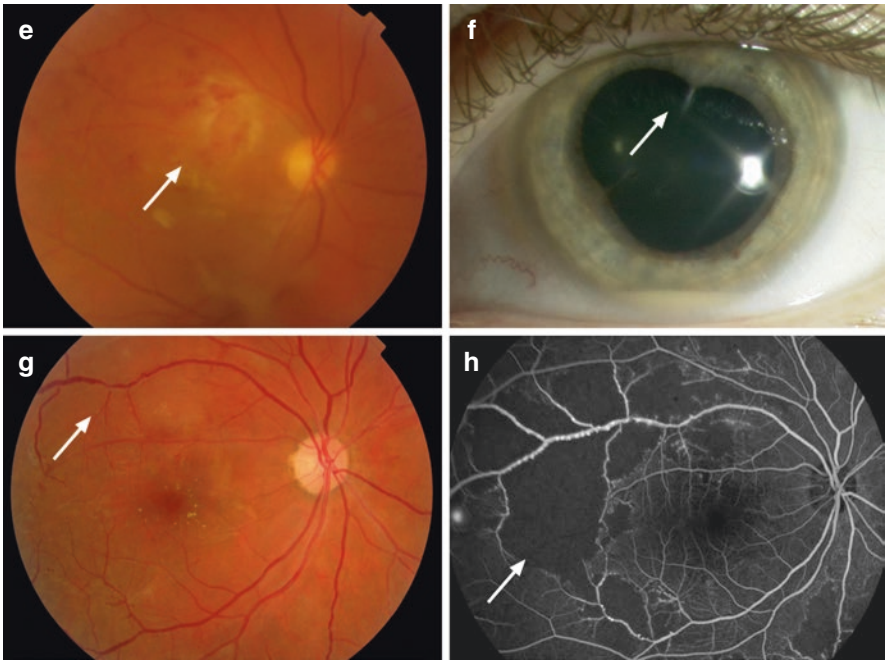

Fig. 7.3 (continued)

chest X-ray, serum angiotensin converting enzyme (ACE) levels, syphilis serology, QuantiFERON-TB Gold test or T-Spot or Mantoux. Conjunctival or skin lesions should be evaluated histologically to help confirm the diagnosis. Criteria for the diagnosis of ocular sarcoidosis have historically had low sensitivity and specificity when applied to clinical practice [47]. Serum ACE levels are commonly used for diagnosing ocular sarcoidosis. In a recent study, ACE had a sensitivity of 78% and a specificity of 90% for ocular sarcoidosis among adults, with a negative predictive value of 97% [48]. In children the test performed less well and had a sensitivity of 60% and a specificity of 78.5%, but still with a negative predictive value of 96.9%. This suggests that the greatest advantage of measuring ACE levels is in ruling out sarcoidosis when the ACE level is normal. A recent consensus on diagnostic criteria, based on a combination of ocular signs and systemic investigations, aims to improve the diagnostic classification (Table 7.2) [49].

Treatment includes topical, periocular, or systemic steroids as appropriate. Retinal neovascularization may be secondary to ischemia or inflammation and requires panretinal photocoagulation laser treatment and intraocular anti-vascular endothelial growth factor (VEGF) injections. Long-term follow-up is usually needed and while patients may go into remission, relapses are fairly common.

Table 7.2 IWOS revised diagnostic criteria for ocular sarcoidosis [49]

Clinical signs
1. Mutton-fat KPs (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Busacca)
2. Trabecular meshwork nodules and/or tent-shaped PAS
3. Snowballs/string of pearls vitreous opacities
4. Multiple chorioretinal peripheral lesions (active and atrophic)
5. Nodular and/or segmental periphlebitis (± candle wax drippings) and/or macroaneurysm in an inflamed eye
6. Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule
7. Bilaterality
Systemic investigations
1. Bilateral hilar lymphadenopathy on chest X-ray and/or chest CT scan
2. Negative tuberculin test or interferon-gamma releasing assays
3. Serum angiotensin converting enzyme elevated
4. Serum lysozyme elevated
5. Bronchoalveolar lavage fluid CD4/CD8 ratio elevated (>3.5)
6. PET positive (abnormal accumulation of gallium-67 scintigraphy or 18F-fluorodeoxyglucose)
7. Lymphopenia (<1000 cells/μL)
8. Parenchymal lung changes consistent with sarcoidosis as determined by pulmonologists or radiologists

KP keratic precipitate, *PAS* peripheral anterior synechiae, *CT* computed tomography, *PET* positron emission tomography

7.2.3 Scleritis/Episcleritis

Scleritis and episcleritis refers to inflammation of the connective tissue of the eyes. The sclera is the thick opaque white collagenous wall of the eye that provides ocular structural integrity and the attachment point for extraocular muscles. It is continuous with the cornea anteriorly and blends in with the meninges posteriorly where the optic nerve exits the globe. The episclera overlies the scleral stroma and is richly vascularized from the anterior ciliary arteries. The conjunctiva is the transparent outermost covering and lines the eyelids (palpebral or tarsal conjunctiva) and the sclera (bulbar conjunctiva).

Episcleritis is a relatively benign condition that can resolve spontaneously and is not thought to be associated with rheumatic diseases [50]. It is an adult disease typically affecting those in their fourth decade, with a female preponderance. Episcleritis presents as mild ocular discomfort and conjunctival hyperaemia; discharge and photosensitivity are uncommon, and it rarely affects vision. It is unilateral in the majority but can infrequently be bilateral. The mainstay of treatment are topical lubricants and/or a short course of topical corticosteroids.

In contrast, scleritis can be visually threatening and up to 40% may be associated with systemic disease [51]. Rheumatoid arthritis was the most common rheumatologic association (41%) followed by systemic vasculitides (24%), of which half

were granulomatosis with polyangiitis. Other associated conditions include SLE (10%), inflammatory bowel disease (8–13%), relapsing polychondritis (4–8%), and spondyloarthropathy (7%) [51, 52]. Most patients have a known systemic diagnosis at presentation, with approximately 20% diagnosed subsequently [51]. Bilateral scleritis is more common in those with rheumatic disease. Scleritis is twice as common in women and typically presents in the sixth decade.

Scleritis is classified according to anatomical site (anterior or posterior), and anterior scleritis is further sub-classified according to clinical appearance: diffuse non-necrotizing, nodular non-necrotizing, necrotizing with inflammation, or necrotizing without inflammation (scleromalacia perforans). It classically presents as a deep boring pain that can be localized to the eye, or generalized pain with radiation from the orbital margin to the temple or jaw, reflecting the trigeminal nerve distribution. The eye may have a deep red or violaceous colour, however it is usually unremarkable in posterior scleritis. Darker pigmented areas due to scleral thinning and revelation of the underlying choroid may be present. Anterior diffuse scleritis comprises the vast majority of cases (75%), followed by nodular scleritis (14%), necrotising scleritis (4%), and scleromalacia perforans (0.6%) (Fig. 7.3c, d) [53].

First-line treatment depends on whether there are signs of necrosis and relies on systemic drugs. In cases of non-necrotizing scleritis, systemic non-steroidal drugs such as ibuprofen and naproxen, and oral corticosteroids are typically used for tapering courses of up to several months [54]. More severe inflammation with imminent loss of tissue requires high dose oral or intravenous corticosteroids and may also require prompt initiation of immunosuppression. Methotrexate is the first-line therapy, while mycophenolate mofetil is considered relatively ineffective [55, 56]. Cyclosphosphamide is now rarely used in the management of uveitis, however it remains a key therapeutic option for severe necrotizing scleritis [57]. Topical corticosteroids are occasionally used as adjunctive treatment, while regional corticosteroid injections are controversial.

7.2.4 Sjögren's Syndrome

Sjögren's syndrome is a multi-organ autoimmune disease that predominantly manifests as poor lacrimal and salivary gland function. Sjögren's syndrome is classified as primary (isolated to the lacrimal and salivary glands) or secondary (associated with other rheumatologic diseases, such as systemic lupus erythematosus). It affects approximately 2% of the adult population but remains underdiagnosed. It is most common in women in their sixth decade.

Approximately 70% of patients diagnosed with Sjögren's syndrome will suffer from ocular problems, with dry eye being the most common ocular manifestation. Symptoms of dry eye may include itching, foreign body sensation, photosensitivity, increased eye fatigue, increased ocular discharge, visual disturbance, ocular discomfort and even pain. Eyes may appear normal or may be erythematous with an apparent thick discharge. Slit-lamp findings may include small superficial erosions

of the corneal epithelium, filamentary keratitis, conjunctivitis, and blepharitis due to *Staphylococcus aureus* infection. Ocular complications may include corneal ulceration, vascularization, corneal opacification, and perforation. Diagnosis is based on the American-European Consensus Committee criteria [58]. Salivary gland biopsy was previously considered the gold standard for the diagnosis, however this is no longer required. Sjögren's can result in significant discomfort, occasionally disproportionate to the clinical findings. Many patients report suffering from poor quality of life, diminished independence and even depression [59].

Treatment is based on the same principles as for dry eyes and includes the use of lubricating drops (preferably preservative-free), nocturnal use of lubrication gels and ointments (Table 7.1), and environmental optimisation [60]. Cyclosporine A 0.05% was shown to be effective treating moderate to severe Sjögren's syndrome, with improvement in symptoms and clinical signs [61]. It is currently approved for use in Sjögren's syndrome and is beneficial in controlling the symptoms [62]. In severe cases, temporary occlusion of the puncta using punctal plugs can improve dry eye symptoms by retaining the tear lake for longer periods of time. Sudden worsening of symptoms should raise suspicion of an infection (such as conjunctivitis or a corneal abscess) which should be promptly treated [63]. In particular a white opacity on the cornea, suggestive of microbial keratitis, should be urgently reviewed by an ophthalmologist.

7.2.5 Behçet Disease

Behçet disease (BD), as in most causes of systemic vasculitis, can be associated with increased risk of morbidity and mortality [64]. The disease is classically characterized by the triad of recurrent oral and genital aphthous ulcers, ocular inflammation, and skin lesions, but many patients do not present with the full set of signs and diagnosis is based on matching diagnostic criteria [65]. Ocular inflammatory features including hypopyon, superficial retinal infiltrates with retinal haemorrhages, and branch retinal vein occlusion/s with vitritis have a strong association with BD [66]. Though the signs are not specific, BD is potentially acutely blinding and treatment should not be delayed pending a formal diagnosis. Vision loss is generally related to macular ischemia, dense vitritis and macular edema [67, 68]. One study on patients with ocular BD reported a 39% risk of visual loss (Snellen visual acuity ≤6/15) and a 24% risk of severe visual loss (≤6/60) over 10 years follow-up.

Any ocular involvement related to BD should be treated immediately and is based on the use of systemic corticosteroids, followed by anti-TNFα agents [22, 69–71], to which BD is particularly responsive. Infliximab and adalimumab are both effective in achieving control of ocular inflammation, with one head-to-head multicenter study showing adalimumab to be more effective in improving visual acuity over a 1 year follow-up [72]. Interferon-α may also have a role in maintaining remission of uveitis [73], reducing the relapse rates and the requirement for high-dose systemic corticosteroids [74].

7.2.6 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a complex connective tissue disorder that involves multiple organs. Ocular involvement occurs in approximately a third of patients and can affect the orbit and all ocular structures [75, 76]. The most common ocular manifestation is dry eye, however AU, scleritis, occlusive retinal vasculitis, choroiditis, and optic neuropathy can also occur [77]. Active retinal or choroidal inflammation can reflect systemic disease [78–80], may be a presenting manifestation, and is commonly associated with vision loss [81]. Vascular involvement presents as retinal hemorrhages and small infarcts of the retinal nerve fiber layer (cotton-wool spots), but can also lead to vaso-occlusion and wide spread retinal ischemia (Fig. 7.3g, h). This in turn can result in neovascularization and vision loss through vitreous hemorrhages, retinal detachment, or neovascular glaucoma [82, 83].

Ocular evaluation of patients with known SLE includes testing for dry eyes, a thorough ocular examination and retinal dye angiography to determine any areas of peripheral retinal vaso-occlusion. Patients complaining of visual symptoms should be referred for ophthalmic examination as active ocular disease can occur even in systemically controlled patients. Treatment is primarily systemic immunosuppression but retinal laser photocoagulation and intravitreal anti-VEGF may be required for retinal non-perfusion and neovascularization.

7.3 Ocular Complications of Common Rheumatic Drugs

7.3.1 Corticosteroids

Corticosteroids remain the cornerstone of treatment for both systemic and ocular non-infectious inflammatory diseases. In patients with uveitis, corticosteroids can be given either systemically or locally in the form of topical drops, peri-ocular injections or intraocular injections and implants [84]. The choice of drug and method of delivery depends on the location of inflammation and systemic involvement. Topical corticosteroid drops are very effective in controlling anterior uveitis and ocular surface disease but are not effective for intermediate, posterior, and panuveitis uveitis. Local injections or implants are typically used in eyes with isolated ocular disease, particularly in unilateral or asymmetric inflammation. In cases of bilateral uveitis or when the disease is part of a systemic condition, use of systemic corticosteroids is warranted [85]. They work quickly and effectively for most uveitis conditions and are generally well tolerated [19]. The aim of treatment is complete control of the inflammation, while maintaining a corticosteroid dose of $\leq$7.5 mg/day, which significantly reduces the risk of systemic side effects [21, 84, 86, 87].

The main corticosteroid-related ocular complications are the development of cataract (Fig. 7.2) and raised intraocular pressure (IOP). The risk is mediated by the agent used, as well as mode of delivery [88]. Intraocular corticosteroids are more likely to result in ocular hypertension and cataract than systemic treatment and periocular injections [89, 90], while the reported risks of both cataract and raised IOP are greater for intraocular fluocinolone implants than systemic corticosteroids or intraocular dexamethasone implants [88, 89, 91]. Patients receiving long-term treatment with corticosteroids should be monitored regularly for raised IOP and referred for ophthalmic evaluation in case of reduced vision to consider cataract surgery.

7.3.2 Hydroxychloroquine and Chloroquine

Hydroxychloroquine (HCQ) is widely used in rheumatology, particularly for SLE and rheumatoid arthritis, and is increasingly being applied in dermatology and oncology. It has largely superseded chloroquine (CQ) which is now predominantly employed as an anti-malarial. Ocular side effects of HCQ/CQ include corneal changes known as vortex keratopathy and the well-recognized retinotoxicity which culminates in the stereotypical 'bull's eye maculopathy'.

Vortex keratopathy, or corneal verticillata, is a benign condition resulting from deposition of the drug in the cornea. Some patients describe haloes although it is usually asymptomatic. It is reversible with cessation of the drug and does not correlate with retinal changes.

Retinal toxicity is asymptomatic until advanced disease, whereupon patients may describe paracentral or central visual field defects, color vision and night vision difficulties. It is irreversible and may progress even after drug cessation. It is postulated that HCQ/CQ affects the photoreceptors, however the exact mechanism remains unknown [92]. Overall prevalence was 7.5% in patients who had been on treatment for over 5 years, however the risk varied according to dosage and duration of treatment [93]. Individual risk for patients on ≤5.0 mg/kg/day is <1% in the first 5 years of treatment, <2% up to 10 years, but rises to 20% after 20 years. For those on dosages >5.0 mg/kg/day, the risk increases to 10% within 10 years, and 40% after 20 years. Dosage was previously calculated by ideal body weight however this has been superseded by actual body weight which more accurately reflected the risk of retinotoxicity [93].

The American Academy of Ophthalmology and the United Kingdom Royal College of Ophthalmologists have recently published guidelines for screening [94, 95]. Screening requires specialized ophthalmic investigations (Table 7.3). Risk factors for accelerated disease include HCQ > 5.0 mg/kg/day, CQ > 2.3 mg/kg/day, renal disease with reduced glomerular filtration rate, tamoxifen use, and pre-existing macular disease [94]. Earlier screening is recommended for those at increased risk. Age and liver disease are not thought to pose additional risk.

Table 7.3 Screening schedule for hydroxychloroquine and chloroquine

	American Academy of Ophthalmology 2016	Royal College of Ophthalmologists 2018
Baseline	Within 12 months	Within 6–12 months
Recommended	Dilated retinal examination	Colour retinal photograph SD-OCT
Consider	SD-OCT and VF as required	
After 5 years	Annual screening	Annual screening
Recommended	SD-OCT Visual fields (10-2; 24-2 or 30-2 if Asian heritage)	SD-OCT Fundus autofluorescence (wide-field) Visual fields (10-2)
Consider	mfERG Fundus autofluorescence (wide-field if Asian heritage)	Visual fields (30-2) mfERG

SD-OCT spectral-domain optical coherence tomography, *mfERG* multifocal electroretinography

There are currently no treatment or preventative therapies for HCQ/CQ-induced retinopathy. HCQ is well-tolerated and efficacious, and the decision to cease or continue the drug in the setting of retinal toxicity should only be made after careful consideration of the risks and benefits.

7.3.3 Biologic Agents

Anti-TNFα agents are increasingly used for the treatment of uveitis and adalimumab has been approved by the U.S. Food and Drug Administration, European Medicines Agency, and other countries, to be used in non-infectious, non-anterior uveitis that is unresponsive to corticosteroids and an additional immunosuppressive agent. Among adults with BD, adalimumab is approved for use immediately following treatment failure with corticosteroids, and among children with JIA-related uveitis it is approved following treatment failure with methotrexate. Studies have compared the effect of treating uveitis between different anti-TNFα agents and while there is no significant difference in resolving ocular inflammation [96–99], one study found that eyes treated with adalimumab were less likely to fail treatment than those treated with infliximab [22].

Studies on tocilizumab, an IL-6 receptor antagonist, suggest that repeat infusions can result in effective control of intraocular inflammation over 6–12 months [100–104]. Treatment with tocilizumab is not licensed for uveitis and is considered only in cases that have failed anti-TNFα agents. Sarilumab, an additional IL-6 receptor antibody was less effective in controlling intraocular inflammation [105]. Secukinumab, an anti IL-17A antibody, demonstrated mixed results in controlling uveitis. Three randomized controlled studies failed to demonstrate a significant effect for subcutaneous injections [106], while a trial examining intravenous infusions resulted in improved inflammatory control and remission rates [107].

7.4 Conclusions

Ocular involvement in rheumatic diseases is common and can result directly from the underlying disease or as a result of treatment side effects. Ocular symptoms, particularly blurred vision, may be the presenting manifestation in systemic rheumatic diseases and can help navigate the investigations and diagnosis. Conversely, physicians should be aware of the potential correlation between systemic rheumatic diseases, treatments and ocular disease. Patients reporting visual symptoms should immediately be referred for ophthalmic evaluation, even when the systemic disease appears under control.

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Chapter 8
Osteoporosis, Glucocorticoid-Related Osteoporosis and Glucocorticoid Withdrawal Regimen

Leonard Saiegh and Mohammad Sheikh-Ahmad

8.1 Background

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue that leads to increased fracture risk [1]. Osteoporosis is diagnosed by the bone mineral density (BMD) criteria or by the occurrence of a fragility fracture [2].

Osteoporosis in rheumatic diseases is a very well-known complication, as systemic inflammation, circulating autoantibodies, pro-inflammatory cytokines, and glucocorticoid (GC) treatment, result in both localized and generalized bone loss [3]. Besides, as BMD decreases with age, fracture risk becomes one of the main concerns among the elderly suffering from a rheumatic disease. Osteoporotic fractures are usually followed by hospitalization, long-term care, impaired quality of life, disability, and death [4]. For that reason, it is crucial to be aware of the high risk of osteoporotic fracture in elderly patients with rheumatic diseases who can benefit from therapeutic interventions.

8.2 Bone Loss and Fracture Risk in Rheumatic Diseases

Two major forms of bone loss have been identified in patients with inflammatory rheumatic diseases [5]. The first is periarticular osteopenia with localized bone loss, and the second is generalized bone loss.

Periarticular osteopenia results from cortical bone thinning at the insertion of the inflamed synovium, the known prominent site of bone erosion in rheumatoid arthritis (RA) [5]. Radiographic periarticular osteopenia is one of the earliest radiological

L. Saiegh (✉) · M. Sheikh-Ahmad
Bnai Zion Medical Center, Institute of Endocrinology, Haifa, Israel
e-mail: leonard.saiegh@b-zion.org.il; mohammad.ahmad@b-zion.org.il

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manifestations in RA, and it may precede bone erosion or joint space narrowing [6]. The pathogenesis of local bone loss is multifactorial and pro-inflammatory cytokines are dominant players [5]. Although local cortical bone erosion revealed by radiography is commonly considered to be a hallmark of RA, it can also be observed in the spondyloarthritis group of diseases as well as in other rheumatic conditions [3, 7].

Different from periarticular osteopenia and local bone loss, systemic bone loss involving the axial and appendicular skeleton may cause a significant co-morbidity in inflammatory rheumatic diseases [5]. The prevalence of densitometric osteoporosis in RA patients is increased about two-fold compared with the general population and is responsible for both vertebral and non-vertebral fractures [8]. Systemic inflammation is the major mechanism involved in the generalized bone loss in inflammatory rheumatic diseases. Pro-inflammatory cytokines increase osteoclast activation and subsequent bone resorption in rheumatic disease, and inhibit bone formation [9, 10]. Apart from inflammation, other factors may also play a role in osteoporosis pathogenesis and fracture risk; treatment with GCs is one of the main risk factors for fragility fractures. Bone loss occurs rapidly after starting GCs treatment, and the risk for fracture is associated with the cumulative dose of GC used [11]. As GCs also affect bone health besides lowering bone mass density, increased fracture risk typically can be irrespective of densitometric findings [11]. GCs reduce bone formation, increase bone resorption and impair bone mineralization, decrease calcium absorption, increase renal calcium excretion, lead to central hypogonadism, muscle weakness and atrophy [11]. Besides GC treatment, rheumatic disease patients are frequently less physically active, which contributes to bone loss, while joint deformities increase the risk of falls and subsequent fractures as well.

Beside age-related bone loss, elderly patients suffering from a systemic disease are even more susceptible to fractures as they may suffer from frailty [12]. Frailty is defined as a dynamic clinical condition with increased vulnerability, which results from aging-related degeneration across psychological, physical and social functioning [12]. Recently, the concept of frailty in relation to osteoporosis in the elderly has been increasingly accepted, with emerging studies measuring frailty as a predictor of osteoporotic fractures [12]. Moreover, older people may suffer from sarcopenia, which is defined as a low muscle mass resulting from age-related muscle tissue loss and is often combined with osteoporosis [13].

Accordingly, the possible combination of age-related bone loss, sarcopenia, potential frailty, reduced physical activity, joint deformities and increased risk of falls, systemic inflammatory disease, and GC treatment, places elderly patients with rheumatic diseases at extremely high risk for osteoporotic fracture.

8.3 Assessment for Osteoporotic Fracture Risk

Bone densitometry utilizing dual emission X-ray absorptiometry (DXA) is the most widely used quantitative technique in clinical practice and remains the gold-standard test for osteoporosis diagnosis and quantification [2]. For adults, the WHO

definition of osteoporosis and osteopenia requires bone density of 2.5 standard deviations (SD) or lower the mean for young, healthy adult women (T-score ≤ −2.5 SD) and (T-score between −1 and −2.5 SD), respectively [2].

Elderly patients with previous fragility fracture (fracture caused by insignificant trauma), patients with DXA in the osteoporosis range, and patients with ongoing treatment with supra-physiological corticosteroid dosage, should be candidates for pharmacological treatment. However, elderly patients with DXA in the osteopenia range should be evaluated for clinical fracture risk in order to decide whether they should be treated pharmacologically. Clinical fracture risk could be evaluated by the fracture risk assessment (FRAX) tool, as proposed by the WHO [14]. The FRAX models have been developed from studying population-based cohorts from Europe, North America, Asia, and Australia and give the 10-year probability of fragility fracture. In its most sophisticated form, the FRAX tool is computer-driven and is freely available online on https://www.sheffield.ac.uk/FRAX/index.aspx. One should fill risk factors asked by the tool. Risk factors that FRAX asks for are age, sex, weight, height, previous osteoporotic fracture, a history of hip fracture in the patient's mother or father, current smoking, 3 or more alcohol units/day, actual femoral neck BMD, currently exposure to oral GCs or past exposure to oral GCs for more than 3 months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other GCs), rheumatoid arthritis, or if the patient has a disorder strongly associated with osteoporosis. These disorders include type 1 diabetes mellitus, osteogenesis imperfecta in adults, untreated, long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease.

The FRAX output is a 10-year probability of hip fracture and a 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). Patients with osteopenia and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20% should be candidates for pharmacological treatment [14].

As FRAX does not include all essential clinical risks for fractures, clinical judgment is also crucial. For example, FRAX does not include the extent and duration of the inflammatory activity of the underlying disease, and it may also underestimate fracture risk because it does not incorporate risk factors for falls, such as spine ankylosis and joint deformities. Accordingly, pharmacological treatment may be clinically indicated also in selected patients with FRAX 10-year fracture probabilities below the threshold needed for treatment. Clinical fracture risk should be assessed every year and BMD testing performed every 1–3 years, depending on the risk factors mentioned above.

8.4 Treatment of Osteoporosis

The goal of pharmacological and non-pharmacological treatment of osteoporosis is to reduce the burden of osteoporotic fractures. Non-pharmacological management includes adequate calcium and vitamin D intake, weight-bearing exercise, smoking cessation, limitation of alcohol consumption, and fall-prevention practices.

Table 8.1 Drugs for treatment of osteoporosis

Drug	Dose	Comments
Calcium	1000–1200 mg daily	Including diet and calcium supplements
Vitamin D	800–1000 IU daily	Higher daily doses may be needed in special populations
Alendronate	10 mg PO daily or 70 mg PO weekly	Bps should be used with caution in patients with reduced renal function (eGFR <30–35 mL/min per 1.73 m^2) Consider drug holiday after 3–5 years
Risedronate	5 mg PO daily or 35 mg PO weekly or 150 mg PO monthly	
Ibandronate	2.5 mg PO daily or 150 mg PO monthly or 3 mg IV every 3 months	
Zoledronic acid	5 mg IV yearly	
Denosumab	60 mg SC every 6 months	Denosumab should be used with caution in patients with reduced renal function. May be used when eGFR >15 mL/min per 1.73 m^2. Monitor calcium in these patients. Discontinuation may cause rebound effect
Raloxifene	60 mg PO daily	Be aware of increased risk for venous thromboembolic events. Reduces risk of vertebral fractures only
Teriparatide	20 mcg SC daily	Treatment approved for 2 years only
Abaloparatide	80 mcg SC daily	Treatment approved for 2 years only
Romosozumab	210 mg SC each month	Treatment approved for 1 year only

Medications to treat osteoporosis (Table 8.1) are categorized as either antiresorptive (i.e., bisphosphonates (Bps), selective estrogen receptor modulators, calcitonin, and denosumab) or anabolic (i.e., teriparatide and abaloparatide). Antiresorptive medications decrease bone resorption, while anabolic medications mainly increase bone formation.

8.5 Who Needs Treatment?

All elderly patients with rheumatic diseases, regardless of other fracture risks, should be considered for non-pharmacological interventions. Elderly patients should be considered for pharmacological treatment if (1) BMD T-score in the spine, femoral neck, total hip or radius equal to or below −2.5, or (2) they had a history of osteoporotic fracture, or (3) they had BMD in the osteopenic range (T-score between −1 and −2.5) and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20% based on FRAX score [15].

Different guidelines for the treatment of GC induced osteoporosis have been published, proposing different criteria for pharmacological treatment [16–19].

We recommend that every elderly patient with a rheumatic disease, treated by prednisone ≥5 mg/day for an anticipated period of 3 months or more, should be considered for pharmacological treatment during the period of steroid therapy. Following the cessation of steroids, continuing of the pharmacological treatment should be reconsidered by BMD and clinical risk factors.

8.6 Non-pharmacological Management (Lifestyle Modifications, Calcium and Vitamin D)

Lifestyle modifications are essential to improve musculoskeletal integrity and balance, preserve bone strength, and prevent fractures. Patients are advised to participate in weight-bearing, resistance, and balance-improving exercises to minimize falls, to avoid the use of tobacco and excessive use of alcohol, to take safety measures at home (e.g., installing support rails in the bathroom; using nightlights; not placing rugs on the floor) and to have an adequate intake of calcium and vitamin D.

Adequate intakes of calcium and vitamin D are essential for osteoporosis treatment, and for improving bone health. The recommended calcium intake for older patients, including diet and calcium supplements, is 1000–1200 mg/day. There is no evidence that daily calcium intake, more than these amounts, add a positive effect on bone strength.

The recommended intake of vitamin D is at least 800–1000 IU per day for adults aged 65 years and older [15, 20]. Adults who are vitamin D insufficient or deficient should be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week or 5000 IU daily for 8–12 weeks to achieve an adequate vitamin D level. After then, patients should continue maintenance therapy of vitamin D3 of 1000–2000 IU daily. Higher doses (up to 4000 IU daily for maintenance) may be required in patients with obesity or malabsorption and in those taking medications that may affect vitamin D metabolism (e.g., antiseizure drugs) [15]. In addition to its skeletal effects, some studies also demonstrated that treatment of vitamin D deficiency improves muscle strength, balance, and reduces fall risk [15].

8.7 Pharmacological Treatment

8.7.1 Bisphosphonates

Bps are the most commonly used drugs for treating osteoporosis. They are potent inhibitors of bone resorption that act by reducing the recruitment and activity of osteoclasts and by enhancing their apoptosis. Moreover, macrophages action is influenced by Bps. These medications reduce macrophage production of TNF-α, IL-1, nitric oxide, and induce apoptosis of monocyte-macrophage-derived cell lines.

Some of the clinical studies on Bps in chronic joint inflammatory diseases showed encouraging results both in controlling inflammation and in the reducing progression of joint and bone damage, suggesting a benefit beyond treating osteoporosis [21].

Three Bps (alendronate, risedronate, and zoledronic acid) have evidence for broad-spectrum anti-fracture efficacy (reducing 36–56% risk for vertebral, 17–20% for non-vertebral and 26–42% for hip fractures), while ibandronate has evidence only for reducing vertebral fracture risk (by 31%) [22]. Besides, oral and intravenous Bps were related to reduced mortality risk in older patients [23, 24].

Bps may cause upper gastrointestinal side effects (reflux, esophagitis, or esophageal ulcers). Contraindications to oral Bps include the inability to remain upright for 30–60 min, esophageal abnormalities that might delay tablet transit (e.g., achalasia, stricture, or dysmotility), presence of a disease or surgery that may affect malabsorption (e.g., Roux-en-Y gastric bypass), and hypocalcemia. Moreover, these drugs should be avoided in moderate to severe renal failure [15]. Intravenous zolendronic acid can induce a transient acute phase reaction of fever, bone and muscle pain that ameliorates after subsequent courses, and may also increase the risk for atrial fibrillation [24]. In post-marketing reports, some patients who were treated with oral or intravenous Bps experienced severe bone, joint, and muscle complaints [25].

Osteonecrosis of the jaw (ONJ) occurs very rarely (approximately 1 in 10,000 to 1 in 100,000 patient-years) in patients receiving osteoporosis doses of Bps. Risk factors for this complication are invasive dental procedures and poor oral hygiene. The risk for atypical femoral fracture (AFF) may become evident after 2–3 years of therapy and increases with the duration of Bps use, to about 1 in 1000 patient-years after 8–10 years of therapy [26].

8.7.2 Denosumab

Denosumab is a fully human antibody against RANKL (receptor activator of nuclear factor kappa B ligand), which prevents the interaction of RANK with its receptor, and inhibits the formation, activation, and survival of osteoclasts. The anti-fracture efficacy of 60 mg denosumab given subcutaneously every 6 months has been evaluated in postmenopausal osteoporotic women. After 3 years of treatment, there was a 68% reduction in the incidence of new vertebral fractures, a 20% reduction in non-vertebral fractures, and a 40% reduction in hip fractures [27]. During an extension phase of another 7 years, the yearly incidence of new vertebral and non-vertebral fractures remained low, similar to rates observed in the denosumab group during the first 3 years [28].

However, following cessation of denosumab treatment, and independently on treatment duration, BMD may decrease to baseline values (the rebound effect), placing patients at increased risk for developing vertebral fractures. Denosumab may cause hypocalcemia, and patients should have an adequate intake of calcium and vitamin D before initiating therapy. Denosumab is not cleared by the kidney,

and therefore it can be used in patients with renal failure. However, it should be administered with caution in these patients due to the risk of hypocalcemia. Skin infection and rash occurred more frequently with denosumab than with placebo, and sporadic cases of AFF and ONJ have been observed with long-term therapy with this drug. Some concerns have been raised about the risk of severe infections in rheumatic patients using denosumab, however, studies that examined the use of denosumab in combination with other biologic drugs have found no evidence of increased infection risk associated with concurrent treatment [29, 30].

8.7.3 Raloxifene

Raloxifene is a selective estrogen receptor modulator that mediates anti-estrogenic effects on breast and uterine tissue, and estrogenic effects on bone. It is used in a dose of 60 mg daily for prevention and treatment of postmenopausal osteoporosis, as well as for the reduction of breast cancer risk. Raloxifene is associated with an increased risk for venous thromboembolic events, although the absolute risk is low (absolute risk increase for venous thromboembolism: 1.2 per 1000 woman-years) [31]. Other side effects include menopausal symptoms (e.g., hot flashes and night sweats) and leg cramps.

Raloxifene showed a 40% reduction in the risk of vertebral fractures, but no significant effect on reduction in the risk of hip or non-vertebral fractures [32]. For patients with low BMD in the spine but not in the hip, or for patients at high risk for breast cancer, it may be an adequate initial treatment choice. When raloxifene is stopped, the skeletal benefits appear to be lost after 1 or 2 years.

8.7.4 Teriparatide and Abaloparatide

Teriparatide (PTH(1-34)) and abaloparatide (PTH-related protein analog) are anabolic agents that increase bone formation by daily subcutaneous injections. Teriparatide, compared to placebo, showed a 74% reduction in the risk of vertebral fractures and a 39% reduction in the risk of non-vertebral fractures [32]. Compared to risedronate for patients at very high risk of fracture, teriparatide reduces fractures more than risedronate [33].

Abaloparatide, compared to placebo, showed an 87% reduction in the risk of vertebral fractures and a 46% reduction in the risk of non-vertebral fractures [32]. Hip fracture risk reduction of both agents, although numerically was lower than placebo, did not reach statistical significance; however, the numbers of hip fractures in these studies were small, and the studies were inadequately powered for this endpoint [22].

Side-effects of teriparatide and abaloparatide are dizziness, leg cramps, nausea, and postural hypotension. Hypercalcemia caused by these agents was usually mild, asymptomatic, transient, and uncommon. Teriparatide caused an increased

incidence of osteosarcomas in rats but not in humans, and these drugs should not be used in patients with primary or secondary untreated or unresolved hyperparathyroidism, Paget disease of bone, a history of irradiation involving the skeleton, in patients with an unexplained elevation of alkaline phosphatase, active malignancies or bone metastasis [34].

8.7.5 Romosozumab

Romosozumab is a bone-forming monoclonal antibody that inhibits sclerostin, with a dual effect of increasing bone formation and decreasing bone resorption. A study that compared the efficacy of romosozumab to Bps in postmenopausal women with a very high risk for fractures showed that sequential treatment with monthly romosozumab during 12 months followed by weekly alendronate, resulted in a lower risk of fracture (48%, 19% and 38% lower risk of new vertebral, non-vertebral and hip fractures, respectively) than weekly treatment with alendronate alone. However, a higher number of cardiovascular events were attributed to the romosozumab group during the first year of treatment (2.5% vs. 1.9%, respectively) [35].

8.7.6 Other Drugs

Menopausal hormone therapy and tibolone are optional drugs for treatment, mainly for patients under the age of 60 years or less than 10 years after menopause. Calcitonin is recommended only for patients not tolerating or have contraindications for other drugs [22], and this drug may be used for vertebral fracture pain relief. Strontium ranelate is rarely used due to the evidence of increased cardiovascular risk and the occurrence of severe Stevens-Johnson reactions and is not recommended for use by the American association of clinical endocrinologists [15].

8.8 Approach to Treatment

A decision regarding the choice of appropriate therapy must take into consideration the availability of the various drugs, preferences of the patient, and costs.

Each treatment plan should include lifestyle modifications, calcium, vitamin D, and one of the pharmacological therapies if indicated. Because of the lower costs and the extensive experience with Bps, they are often the first-line pharmacological treatment choice for osteoporosis in most countries [22]. For severe cases (T-score of ≤ -3.5 even in the absence of fractures, or T-score of ≤ -2.5 plus a fragility fracture), teriparatide, abaloparatide or romosozumab may be considered to be the first choice of treatment [36]. In patients with vertebral osteoporosis and high risk for

breast cancer, raloxifene may be the first choice. Patients with contraindication to oral Bps, may be treated with zoledronic acid or denosumab.

The definition of treatment failure is a matter of debate. According to the Endocrine Society [22] failure is defined as loss of BMD greater than the least significant change (usually 5% in the lumbar spine, 4% in the total hip, and 5% in the femoral neck) after 2 years of treatment, or bone turnover marker decrease less than the least significant change. Moreover, having two or more fractures while on therapy, especially vertebral ones, is usually considered as a treatment failure. In cases of treatment failure, one can replace an antiresorptive drug with a more potent one, replace an oral drug by an injected one, or replace an antiresorptive drug with an anabolic drug [37]. Switching from an antiresorptive to an anabolic therapy may also be considered in patients suffering from ONJ or AFF [22].

The duration of treatment is another issue that should be considered carefully. For Bps, one should reconsider the need for continuing therapy after 5 years of oral Bps, or 3 years of IV Bps. One should continue treatment beyond this period or switch to another treatment only in high-risk patients. Otherwise, a drug holiday for up to 5 years should be considered. High-risk patients are those who had a prior spine or hip fracture, have BMD T-score at the hip or spine of ≤ -2.5, or have a 10-year risk $\geq 3\%$ and $\geq 20\%$ for hip and major osteoporotic fracture, respectively [22]. Denosumab may be used for a period of 5–10 years, while following the cessation of denosumab, Bps should be considered in its place in order to prevent the rebound effect. Teriparatide and abaloparatide should be used only for 2 years. The effect of all non-Bp therapies usually fades with the discontinuation of therapy, and the gain in BMD is lost rapidly. Accordingly, when a non-Bp drug is stopped, one should consider switching to a different therapy for high-risk patients or reassessing fracture risk in 1–3 years and restart treatment when indicated (i.e., bone loss or a patient becomes high-risk for fracture) [22].

For patients with GC-induced osteoporosis, the first-line therapy is usually oral Bps, while second-line therapies can be intravenous Bps, teriparatide, denosumab, or raloxifene [38].

8.9 Glucocorticoid Withdrawal Regimen

GCs are widely used in the treatment of the rheumatic diseases due to their powerful anti-inflammatory action. However, GC side effects require dosage tapering down and drug cessation once possible. Long-standing GC treatment may lead to hypothalamic-pituitary-adrenal (HPA) suppression, making patients steroid-dependent, and GC cessation in these patients may lead to adrenal insufficiency [39]. The degree of HPA suppression depends on GC potency, dosage and duration of treatment. HPA suppression can also be caused by topical steroid treatment; however, this is much less frequent [39].

When an indication to suspend steroid treatment exists, usually, a gradual tapering down regimen is used, in order to avoid a flare of the underlying rheumatic

disease, as well as adrenal insufficiency-like symptoms, and to provide time for the suppressed HPA axis to restore normal function [40].

GC treatment even with high doses, given for a duration of less than or equal to 3 weeks, usually does not lead to HPA suppression, and abrupt steroid cessation can be done with a very low risk for subsequent adrenal insufficiency. However, patients treated with supra-physiologic doses of GCs for periods of more than 3 weeks, may be at increased risk for adrenal insufficiency when steroids are stopped abruptly, and tapering down regimen should be used.

There is a paucity of studies that address GC tapering regimens, and there is no evidence to support any particular regimen [41]. Here we propose a practical and simplified regimen for steroid withdrawal, which is primarily based upon clinical experience.

As long-acting GCs and GCs given in the evening are more capable of suppressing morning cortisol secretion, they may have a more negative effect on HPA function. Therefore, during steroid withdrawal, we recommend that long-acting GC preparations be converted to the equivalent-strength dose of prednisone, and given in the morning as a single dose. In the regimen we propose for steroid withdrawal, we will discuss prednisone as the GC formula being used (Fig. 8.1).

Patients treated with a daily dose of ≤5 prednisone given as a single dose in the morning, most probably will not suffer from HPA suppression, and steroids can be stopped safely. In patients using prednisone at a daily dose of more than 5 mg, for a period of more than 3 weeks but less than or equal to 2 months, total prednisone dose should be given in the morning and decreased at a rate of 30–50% every 2 weeks, to reach a daily dose of 5 mg. After 4 weeks of 5 mg daily dose, prednisone may be safely stopped. Following the cessation of steroids, if the patient develops

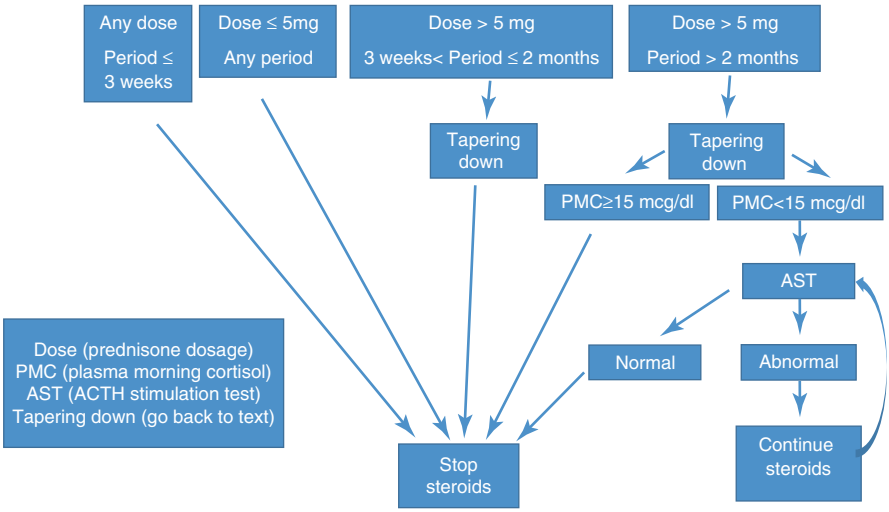

Fig. 8.1 GC withdrawal regimen

any symptoms suspected for adrenal insufficiency, we recommend restoring treatment with ≥5 mg prednisone and proceeding to the ACTH stimulation test. Also, if the patient is about to undergo major surgery, we recommend the ACTH stimulation test before steroids are stopped.

Patients using prednisone at a daily dose of more than 5 mg for more than 2 months, should practice the same tapering down regimen. In these patients, at the end of the 4 weeks of the 5 mg prednisone and before steroid cessation, we recommend testing morning plasma cortisol concentration (before taking prednisone). If plasma cortisol concentration is higher or equal to 15 mcg/dl (414 nmol/L), then prednisone can be stopped safely. Otherwise, HPA axis evaluation by the ACTH stimulation test should be done.

In cases when ACTH stimulation test is abnormal, steroids should be continued at a daily dose of 5 mg prednisone, and stimulation test repeated after 1–3 months.

In all scenarios mentioned earlier, where steroids could have been stopped without the need for the ACTH stimulation test, we recommend short term supportive treatment with GCs through acute illnesses or stressful events that occur during the 6 months following steroid cessation.

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Chapter 9
Vaccination of Geriatric Population with Rheumatic Conditions

Alona Paz

9.1 Introduction

Patients with chronic rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or vasculitides suffer higher morbidity and mortality from infectious diseases, compared to the general population [1]. Known risk factors include age older than 60 years, comorbidities, the severity of the underlying autoimmune disease activity and immunosuppressive therapy including corticosteroids, non-biological Disease-Modifying Antirheumatic Drugs (DMARDs) such as methotrexate (MTX) and biologic DMARDs such as tumor necrosis factor (TNF) blockers, B-cell depleting therapy (rituximab), and others [2]. Vaccines are effective in preventing infections by inducing protective immunity, and therefore play a major role in the management of patients with chronic inflammatory disorders [3, 4].

9.2 General Principles

1. **The vaccination status of the patient should be assessed as soon as the diagnosis of a rheumatic disease is made**. There are three main reasons for assessing the vaccination status: (1) Some rheumatic diseases per se confer an increased risk of infection, and vaccinations should be updated as soon as possible after diagnosis. (2) Many patients do not immediately receive immunosuppressive treatment, and thus, vaccines can be administered when the immunogenicity of vaccination is not compromised by the immunosuppression. (3) Live vaccines can be safely administered at this point.

A. Paz (✉)
Infectious Diseases Unit, Bnai Zion Medical Center, Haifa, Israel
e-mail: Alona.paz@b-zion.org.il

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2. **Vaccinations should be performed whenever possible before immunosuppressive treatment**. The timing of vaccination should be considered in order to ensure an optimal response to vaccines [5]. This should be emphasized especially with B cell depleting therapy (rituximab): vaccination should be given at least six months after the administration and four weeks before the next course of anti B cell monoclonal antibodies [6].
3. **Inactivated (non-live) vaccines can be administered during immunosuppressive therapy**. If vaccines cannot be administered before the initiation of immunosuppressive therapy, they can be administered safely during treatment [7]. Their administration was not associated with a higher risk of vaccine reactions, nor with a worsening or reactivation of the underlying disease. Studies regarding the immunogenicity of seasonal influenza, pandemic influenza (H1N1), pneumococcal polysaccharide, pneumococcal conjugate, hepatitis A, hepatitis B, tetanus toxoid, Haemophilus influenza B, and human papillomavirus vaccinations during immunosuppressive therapy showed slightly reduced, but sufficient immune responses following vaccination, supporting the administration of inactivated vaccines to patients with chronic rheumatic diseases under immunosuppressive therapy [8].
4. **Live-attenuated vaccines should be avoided in patients under immunosuppressive therapy**. In general live-attenuated vaccines are contraindicated in patients receiving immunosuppressive treatment, because of the risk of infection in the immunocompromised host. If live attenuated vaccines are administered, the start of immunosuppressive therapy should be delayed for at least four weeks [9].
5. **Household contacts of immunocompromised patients should be vaccinated according to the usual recommendation for the general population**. Immunocompetent individuals, who live in a household with immunosuppressed patients, should receive inactivated vaccines as well as live-attenuated vaccines such as MMR, rotavirus, varicella, and zoster vaccine, according to national guidelines. Oral polio vaccine should be avoided due to a risk of transmission to household members, with a small risk of vaccine-associated paralytic poliomyelitis in immunosuppressed household members. Highly immunocompromised patients should avoid handling diapers of infants vaccinated against rotavirus for at least 4 weeks following the administration of the vaccine. Contact with persons developing skin lesions after varicella or zoster vaccines should be avoided [10]. The live influenza vaccine should be avoided in contacts of severely immunocompromised patient groups.
6. **Consultation in a travel clinic before traveling is recommended, especially for immunocompromised patients**.

9.3 Recommendations

1. **Influenza vaccine**

   Inactivated influenza vaccine is recommended yearly for all patients with chronic rheumatic diseases. Like other immunocompromised hosts, patients

with chronic rheumatic diseases are at higher risk of contracting influenza compared with the general population. Influenza vaccine was found to be immunogenic in most patients, although the responses tend to be lower as compared to healthy controls, and correlated with the intensity of immunosuppressive therapy [11]. Significantly reduced responses were found in rituximab treated patients, but this should not preclude administration of influenza vaccine [12]. Adverse events of influenza vaccines in patients with chronic rheumatic diseases are comparable to those in healthy controls. There was no increased rate of flare-ups in the disease activity of SLE, RA, and other rheumatology disorders [8].

2. **Pneumococcal vaccines**

   Pneumococcal vaccines for patients with chronic rheumatic diseases are recommended according to the CDC schedule for immunocompromised patients [13]. The burden of pulmonary infections is high in patients with chronic rheumatic diseases [1]. The incidence of severe pneumococcal infections is increased 13-fold in patients with SLE. Two pneumococcal vaccines are currently available: the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV-13). The current recommendation for immunocompromised patients by CDC and ESCMID is a protocol with PCV13 first and PPSV23 boost strategy, with an interval of at least eight weeks between the two vaccinations. A randomized controlled study in RA patients evaluated the serological response to PCV13 followed by PPSV23 after 16–24 weeks. The study demonstrated an adequate response (87% and 94% in RA patients on biologics and non-biologics DMARDS, respectively). A significantly decreased response was observed in patients treated with rituximab. No disease flares or significant side effects have been reported after pneunococcal vaccines [8].

3. **Tetanus Toxoid vaccine**

   Patients with chronic rheumatic diseases should receive tetanus toxoid vaccination in accordance with recommendations for the general population. Patients with RA and SLE, regardless of immunosuppressive therapy, show satisfactory immunogenicity for tetanus toxoid vaccination comparable with healthy controls [14]. In patients treated with anti-B cell therapy, passive immunization with tetanus immunoglobulins should be considered in case of high-risk exposure to tetanus [15].

4. **Hepatitis B virus (HBV) vaccine**

   In adults, HBV immunization is usually recommended for individuals at high risk of exposure, such as healthcare professionals, close contact with persons with chronic HBV infections, and HBV-seronegative travelers to endemic regions [15].

5. **Hepatitis A virus (HAV) vaccine**

   Hepatitis A vaccine should be considered for patients at risk, such as travelers to endemic areas. In immunocompromised patients, two doses of the vaccine (at least six months apart) are usually needed to create sufficient protection [16].

6. **Herpes Zoster vaccine**

   Herpes zoster (HZ) (shingles) is caused by reactivation of varicella zoster virus (VZV) that remains dormant after primary infection (chickenpox). Key risk factors for HZ reactivation are increasing age and immunosuppression. Shingles may cause significant morbidities such as postherpetic neuralgia (PHN), disseminated infection, and even mortality [17]. Patients with chronic rheumatic diseases are at increased risk of HZ compared to the general population, with the highest risk of infection in patients with SLE. Currently, there are two HZ vaccines available. The live-attenuated HZ vaccine (Zostavax), which contains the Oka strain of live-attenuated VZV. Zostavax has been shown by randomized controlled trials (RCTs) to be safe and protective in immunocompetent subjects >60 years and between 50 and 59 years of age in reducing HZ reactivation and PHN by two-third. However, as the vaccine is live-attenuated, it is contraindicated for patients receiving intense immunosuppression. The second vaccine is a new non-live recombinant subunit adjuvant zoster vaccine called Shingrix that was recently licensed in the USA and Europe and is available in some countries. The vaccine is recommended for adults 50 years and older, including immunosuppressed patients, and is administered in two intramuscular doses 2–6 months apart. Shingrix is safe and more efficacious compared with the live-attenuated vaccine in elderly adults [18]. The efficacy and safety of the subunit HZ vaccine in immunocompromised subjects are being investigated. Preliminary data have confirmed the immunogenicity and safety of the non-live HZ vaccine in patients with HIV infection and hemopoietic stem cell transplant recipients [19]. Based on the fact that Shingrix is a non-live vaccine, it may replace the live-attenuated vaccine in patients with chronic rheumatic diseases.

7. **Yellow fever**

   The yellow fever vaccine is a live attenuated vaccine. The vaccine is recommended for people who are traveling to or living in areas endemic for yellow fever virus in Africa and South America. Yellow fever vaccine is contraindicated in immunosuppressed patients as they may develop severe reactions. Personal consultation at a travel clinic is recommended before traveling. For patients traveling to endemic countries, withholding immunosuppressive therapy to allow a safe vaccination may be considered [15].

9.4 Future Directions

The number of immunosuppressed patients is continuously increasing and new immunosuppressive agents are being introduced. On the other hand, new vaccines against CMV, varicella, influenza and additional pathogens are in development. Future prospective clinical trials will evaluate the safety, immunogenicity, and efficacy of new vaccinations in various cohorts of patients with rheumatic disease.

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Chapter 10
Interpretation of Laboratory Tests in a Geriatric Patient with Rheumatic Disease

Sergey V. Lapin

10.1 General Considerations on Immunological Biomarkers in Laboratory Diagnostics

Starting with the Jones Criteria for the Diagnosis of Acute Rheumatic Fever (1944), the diagnosis of most autoimmune diseases (AID) was based on clinical and laboratory data, and the value and weight of laboratory criteria are continuing to increase [1]. Nowadays, criteria for most rheumatic AID generally include laboratory tests.

Autoantibodies are immunoglobulins of G, A, and M (IgG, IgM, IgA) classes that bind to antigenic epitopes of the human organism's molecules. Self-epitopes of molecules of the human organism become targets of autoantibodies due to antigenic similarity with exogenous structures [2]. Thus, it is difficult to accurately separate the pathological autoimmune response from the natural reaction of the human immune system.

Sometimes, identification of autoantibodies in patients with AID indicates their involvement in the mechanisms of the pathogenic autoimmune reaction. However, autoantibodies do not always contribute to the development of processes that are characteristic of AID. In such cases, autoantibodies are thought to be "witnesses" of immunological reactions. On the other hand, autoantibodies can carry an independent immune function, for example, participate in the clearance of tissue antigens. Antinuclear antibodies (ANA) are often observed in "graft versus host disease" and in cases of solid tumors, which can be explained by an alloimmune response or antitumor immunity [3]. In these examples, autoantibodies are components of the natural immune response. The induction of autoantibodies synthesis is a normal biological phenomenon, and the binding of immunoglobulins to their self-antigens can be detected in the blood serum of any person. The spectrum of antigenic stimuli

S. V. Lapin (✉)
Laboratory for Diagnosis of Autoimmune Diseases, Center for Molecular Medicine, Pavlov First Saint Petersburg State Medical University,
Leo Tolstoy str. 6/8, Saint-Petersburg, Russian Federation

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affecting a person is continually changing, which leads to the formation of low-affinity non-pathogenic autoantibodies. Low titers of low-affinity autoantibodies with multiple reactivities can be detected almost in every individual. Clinically significant levels of autoantibodies may be an accidental finding in clinically healthy adult individuals. As such, ANA can be detected in 3–5% of the population (mostly women), rheumatoid factor (RF)—in 3%, antibodies to thyroperoxidase—in 4%, antibodies to cardiolipin—in 1–5%, antibodies to myocardium—in 5%, and antibodies to skeletal muscle—in 3% (mainly in the elderly). This phenomenon is called "natural autoantibodies", and its biological significance is not well understood [4]. The role of these autoantibodies is not entirely clear, but this phenomenon probably reflects the contribution of the immune system to a process that is commonly called immune surveillance [5].

Aging is associated with the formation of a large number of autoantibodies [6]. The leading cause of increased autoantibody production in elderly persons is believed to be the involution of thymic tissue after the age of 50 years and, therefore, termination of several processes that are important for the formation of immunological tolerance of T cells. There are several other changes in the biology of T and B cells at an older age that are described elsewhere [7].

The frequency of detection of different autoantibodies in elderly persons is presented in Table 10.1. There is some variation in frequencies of autoantibodies detection among scientific reports. That discrepancy is easily explained by differences in test performance, reference ranges, and comorbidities in the tested cohorts, but the average incidence of many autoantibodies in older people is 5–10 times higher than in a healthy young population.

The possibility to utilize specific autoantibodies as a diagnostic marker is determined by their frequency in AID. The prevalence of those autoantibodies that are used for clinical diagnosis of AID is usually more than in 60–80% of patients with the

Table 10.1 Relative frequency of antibodies in older adults without evident autoimmune disease

Autoantibody	Relative frequency in elderly vs. adult	Clinical significance
ANA HEp-2 IIF	11.4% in elderly vs. 3.8% in adults (high titers) [8]	Seropositivity in elderly is related to female gender [9], vitamin D deficiency [10], *HLA* genotype [8]
Anticardiolipin antibodies	12% in elderly vs. 2% in adults (high titers) [11]	Seropositivity in elderly is related to ANA positivity [11], CVD in elderly group [12]
Rheumatoid factor	16.6% in elderly vs. 3.6% in adults [13]	Risk of RA development depends on initial levels of RF and its increase in titer during the time [14]
Gastric parietal cell antibodies	18% in elderly vs. autoantibodies absent in adults [15]	Seropositivity was related to *H.pylori* seropositivity and presence of thyroid diseases
Antibodies to thyroid antigens	26% in elderly vs. 4% in adults [15]	Subclinical hypothyroidism in 4.70% of European population [16]

ANA antinuclear antibodies, *CVD* cerebrovascular disease, *RA* rheumatoid arthritis, *IIF* indirect immunofluorescence, *RF* rheumatoid factor

specific disorder and, optimally, less than 5% in healthy controls and relatively rare in patients with other diseases. The proper clinical and laboratory parameters of many autoantibodies allow us to consider them as laboratory markers of AID with exceptional diagnostic information. Specific serological markers are those autoantibodies that are found exclusively in studied disease. As such, highly-specific serological markers include antibodies to double-stranded DNA (anti-dsDNA) and anti-Sm antibodies, that are used for diagnosis of systemic lupus erythematosus (SLE), and antibodies to the Scl-70 antigen, that are used for systemic sclerosis (SSc) diagnosis.

The identification of specific autoantibodies in AID can predict the characteristic features of the clinical course of the disorder. The best example of that phenomenon is the presence of specific autoantibodies in inflammatory myopathies that readily characterize unique features of muscle involvement, rate of progression, and occurrence non-muscular symptoms. Even low-prevalent autoantibodies typically specify some peculiar disease manifestation valuable for clinical classification and prognosis. So-called disease phenotypes are generally characterized by the presence of a specific set (or spectrum) of antibodies. Antibody profiling, which means the investigation of a wide range of autoantibodies, is an essential tool for personalized medicine in the field of autoimmunity. Furthermore, during differential diagnosis, a combination of positive antibody test results makes the final diagnosis more convincing. Therefore, the determination of some autoantibodies allows the physician not only to predict, but sometimes also to prevent the development of complications.

In AID, specific antibodies are synthesized in high concentration and usually have high affinity. However, high concentrations of low-affinity autoantibodies can sometimes give a more reliable signal than a low concentration of high-affinity specific autoantibodies. The detection of nonspecific binding of autoantibodies in some immunological tests and the detection of low titers of autoantibodies often require the creation of a “gray zone”, or a range of doubtful results. Low titers are not considered disease-specific like, for example, in the cases of low titers of antibodies against cardiolipin in APS, low titers of RF, and ACPA in RA. From a clinical point of view, at low concentrations, the interpretation of the result of autoantibodies low concentration depends on the clinical risk of AID.

Despite specific difficulties in interpreting the results of the immunological tests, as well as a large amount of information that must be taken into account analyzing the results of the test, the clinical significance of immunological tests is very high.

10.2 Antinuclear Antibodies Testing in Systemic Autoimmune Rheumatic Diseases

ANA is a family of autoantibodies directed against various cellular structures, including the nucleus, nuclear membrane, mitotic apparatus, components of the cytoplasm and organelles of the cell, as well as cell membranes. Since ANA antigens are not only found in the nucleus, the term ANA may be misleading and outdated.

There was an attempt to re-name the ANA into “anti-cellular” antibodies; however, the term ANA is presented in a large number of specialized literature and recommendations for many medical specialties, and therefore it is not easy to replace it. The detection of ANA represents an indispensable approach for early diagnosis of the main systemic AID, autoimmune liver diseases, rheumatic diseases in pediatrics, and other conditions.

Because of the diversity of antigenic targets of ANA, there is no universal method for the detection of all clinically significant autoantibodies. A sequence of tests should be performed to determine the spectrum of antibodies and to confirm the diagnosis. The screening laboratory test for ANA detection is based on the binding of the antibodies to internal antigens of the HEp-2 cell line. HEp-2 cells are epithelial in origin, have a relatively large polyploid nucleus, several nucleoli rich in the cytoplasm, and are characterized by a high division rate. Because of these characteristics, they represent the best substrate for detection ANA with indirect immunofluorescence (IIF). The sensitivity of the HEp-2 IIF ANA test is up to 100% in the diagnosis of classical autoimmune systemic diseases like SLE and SSc. In novel ACR/EULAR criteria of SLE of the 2019 year HEp-2 IIF ANA test is considered to be an initial diagnostic test for SLE confirmation, so negative result virtually excludes SLE. The specificity of the test dramatically depends on the upper reference range (cut-off) that are used. International recommendations for ANA testing suggest that the initial screening at the dilution of serum at 1:160 is optimal for the adult population. On the other hand, the ACR / EULAR SLE classification criteria recommend an initial dilution of 1:80 to exclude the diagnosis of SLE. It should be noted that at low dilution, the specificity of ANA IIF testing is very low. If low dilutions of serum (1:40–1:80) would be used, up to 25% of sera from apparently healthy individuals can be ANA positive [17]. The ability to diagnose a systemic autoimmune rheumatic disease substantially depends on the level of positivity of the ANA IIF test. Low positive titers (1:80–1:160) are usually not associated with any AID, and, usually, it is impossible to determine the antigenic specificity of ANA at these concentrations. At medium positive titers (1:320–640), the probability of detecting an AID, and a specific antigenic target ANA increases to 30%. With high titers of more than 1:1280 (up to 1:1,000,000 in some cases), the probability of systemic rheumatic disease is over 50%, and there is a high probability of detecting specific autoantigens of antibodies.

The antigens of ANA are distributed across different cellular structures, and 30 patterns of ANA immunofluorescence patterns were described. New nomenclature of ANA patterns links them with the antigenic targets and diseases, dramatically increasing the clinical value of ANA IIF testing [18]. There are up to 100 described targets of ANA that are commonly called antibodies to the extractable nuclear antigen (ENA). Historically, many of antigens of ANA were described using crude called ENA. Although ENA is not currently used to detect ANA antibodies, the term has been retained and has become the general name used to describe ANA antigens.

Due to unknown clinical significance, low frequency, and methodological problems, only a limited number of anti-ENA antibodies are tested in clinical laboratories. Although the presumable spectrum of autoantibodies can be predicted from clinical symptoms and ANA IIF screening results, the patient’s serum is usually

tested on a panel of specific autoantigens. The so-called "multiplex approach" for detecting anti-ENA and other autoantibodies has become a valuable tool for immunological testing. It can increase diagnostic "hit rate" because many reactions are carried out in a single test, and can also help to capture rare autoantibodies important for the classification and prognosis of the disease.

Typically, anti-ENA antibodies are tested if initial ANA IIF screening is positive. However, sometimes the result of ANA IIF testing can be false-negative, especially in the presence of several particular ENAs, that may be lost from the nucleus of HEp-2 cells during the fixation process (e.g., SSA, or Ro-52). Also, an ANA directed to cytoplasmic antigens or antigens, expressed only on mitotic cells, can be easily missed during IIF testing even by an experienced laboratory specialist. In cases when clinical suspicion is high, it is recommended to order the ENA multiplex test even in cases of ANA negative IIF result. This is especially true for ANAs associated with inflammatory myopathies when special detection of myositis-specific antibodies should be performed regardless of the results of ANA IIF [19].

Anti-dsDNA autoantibodies are very important for the diagnosis of SLE. Antibodies against dsDNA formally do not belong to antibodies against ENA and should be separately ordered in patients with symptoms of SLE. Several methods are recommended for their laboratory detection: ELISA, immunofluorescent test on protozoan Crithidia Lucilia (CLIFT), and radioimmune Farr assay. Among all of these methods, ELISA is the less specific, but the most sensitive one. Antibody levels against dsDNA measured with ELISA that exceed twice the threshold value are considered highly positive and are important for the diagnosis and prognosis of SLE [20]. To confirm the specificity of the ELISA test-results in a controversial clinical situation, other anti-dsDNA detection methods can be used, namely the CLIFT and Farr assays [21].

10.3 Interpretation of Antinuclear Antibodies Testing in Geriatric Patients with Systemic Autoimmune Rheumatic Diseases

The assessment of the diagnostic value of ANA in elderly patients is challenged by the fact that ANA is relatively prevalent in healthy older adults. A gradual increase in the incidence of ANA from 5.6% in persons under 60 to 24% in people aged 71–80 years has been demonstrated [13]. Incidence of positive ANA IIF >1:50 was 23% in a large cohort of older people over 85 years old without AID [9]. The prevalence of positive results of ANA tests in older people with other prevalent AIDs, such as autoimmune thyroiditis or RA, is even higher.

Other factors contributing to the higher prevalence of ANA positivity in older people include female gender, vitamin D deficiency [10], and malignancy [22]. The reported frequency of ANA titer ≥1:160 in the elderly was approximately 5–10%. In most patients with ANA titer more than 1:200, researchers were unable to detect antigenic specificity of autoantibodies [9], although some authors detected anti-ssDNA and anti-histone antibodies in older people without the AID [8]. Other

authors reported that fine speckled pattern of ANA IIF can be associated with anti-DFS-70 antigen antibodies not related to any of AID. In general, ANA is found in older people more often, but frequently is not associated with any particular antigen, particularly if detected in low and medium titers.

The importance of ANA testing is supported by recently published 2019 EULAR/ACR classification criteria for SLE [23]. In accordance with recommendations, the diagnosis of SLE is based on a set of 11 criteria, which includes five laboratory and six clinical or morphological findings, which are evaluated in accordance with their diagnostic weight. To fulfill the criteria, the score should be equal to or bigger than ten. A new feature of these criteria is that the ANA HEp-2 IIF test results are used as the entry criterion for the initial patient selection. The titer ANA HEp-2 IIF test used for initial screening remains highly controversial, especially in the elderly population. The ANA titer of 1:80 had 97.8% sensitivity with 74.7% specificity, while after the increase in the level of titer to 1:160, meta-regression analysis showed a 95.8% sensitivity and an 86.2% specificity. The authors evaluated the diagnostic value of 1:80 titer of ANA in juvenile-onset SLE; however, the analysis of diagnostic parameters in the late-onset SLE was not reported to date [24].

Late-onset SLE diagnosed after 50 years of age is not a rare disease and represents approximately one-tenth of all cases of SLE [25]. Late-onset SLE patients have a specific autoantibody spectrum with significantly lower prevalence of anti-dsDNA antibodies, anti-Sm and anti-RNP autoantibodies, normal complement levels, but relatively more prevalent SSA and SSB antibodies, and RF [26]. The prevalence of ANA was not related to the age of onset of SLE, but the total number of all serological findings in late SLE, including anti-ENA, anti-dsDNA, and aPLA, is lower than that of SLE, which starts earlier [27].

The differential diagnosis of SLE in older adults comprises other systemic inflammatory rheumatic diseases, including Sjogren syndrome (SjS), SSc, and idiopathic inflammatory myopathies (IIM). Among them, SjS is the most common, affecting up to 6% of adults over 65. Anti-SSA 60 kDa antibodies that belong to the ANA family are frequently found in SjS. The positive result of SSA testing is used in ACR-EULAR 2016 classification criteria of the SjS. Anti-SSA antibodies are typically found together with anti-SSB antibodies, while isolated anti-SSB positivity is rare and is not considered a disease-related marker. Several other autoantibodies are frequently found in SjS, including RF, anticentromere antibodies, antimitochondrial antibodies [28]. SjS can be associated with the presence of polyclonal RF and type III cryoglobulinemia as well. Extra glandular manifestations of SjS and the development of lymphoma correlate with anti-SSA positivity and the presence of RF and IgG class hypergammaglobulinemia. Sometimes, loss of autoantibodies and a decrease in the level of hypergammaglobulinemia can precede the progress to malignant lymphoma. Anticentromere antibodies are increasingly described as specific SjS markers, with molecular targets presumably different from CENP-A/B antigens, found in limited forms of SSc. Low incidence of SSA antibodies and RF is characteristic in patients, positive for anticentromere antibodies.

Antiphospholipid antibodies (aPLA) can also be found in patients with SjS and are associated with increased thrombotic risk and other symptoms of antiphospholipid syndrome (APS). Relatively low frequency of anti-SSA antibodies and RF have been reported in patients, diagnosed with SjS after the age of 70. On the contrary, patients diagnosed with SjS before 45 years of age, had a higher rate of positivity of the autoantibodies, and higher incidence of lymphomas.

Scleroderma or SSc is frequently associated with old age. There are several scleroderma specific autoantibodies, including anti-Scl-70, anti-centromere, and anti-RNA polymerase III. The clinical specificity of their detection is high; that's why they were used in ACR-EULAR 2013 classification of the disease. Anti-Scl-70 antibodies are almost never co-occur together with the anti-centromere antibodies and the anti-RNA polymerase III antibodies. The prevalence of the anti-U1RNP and the anti-PM-Scl antibodies is significantly lower among older patients. These autoantibodies are detected mainly in juvenile or young-onset forms of SSc with a higher frequency of muscle involvement. A higher incidence of lung cancer was reported in Scl-70 positive patients. The close temporal relationship between the onset of cancer and scleroderma in patients with anti-RNA polymerase III antibodies has been reported as well.

The IIM are a heterogeneous group of muscle diseases associated with certain pathomorphological signs, the presence of muscle inflammation, and frequent relationship with systemic AID and cancer. Polymyositis, dermatomyositis, autoimmune necrotizing myopathy, and inclusion body myositis can be found in an elderly patient. Currently, only anti-Jo-1 antibody positivity is used in the 2017 EULAR/ACR classification criteria. Despite this fact, over a dozen myositis specific antibodies and myositis-associated antibodies are widely used for the diagnosis, classification, and prognosis in patients with symptoms of IIM. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, and ferritin levels are higher in the elderly patients with IIM, as compared to their younger IIM counterparts.

10.4 Laboratory Diagnostics in Geriatric Patients with Inflammatory and Non-inflammatory Arthropathies

The prevalence of RA in the general adult population is between 0.2 and 1% with the peak age of disease onset between 40 and 60 years of age. The reported prevalence of RA in persons older than 60 is up to 2% and can be even higher in the age of 85 [29, 30]. The lifetime risk of developing RA in adults is 3.6% for women and 1.7% for men [31].

There are several clinical variants of RA in the elderly population. The first one is elderly-onset RA (EORA) that starts after the age of 60. Classic RA that presents before 60 years of age and persists into the older age is commonly called young-onset RA or YORA. Older patients can have polymyalgia rheumatica

(PMR)-like EORA that is associated with predominant involvement of the axial joints. The PRM-like disease EORA is typically RF negative, has an acute onset, does not cause joint erosions, and has a good prognosis [32].

The 2010 ACR/EULAR diagnostic criteria for RA emphasize the significance of laboratory findings. Most patients who have RA have a positive test for RF and ACPA antibodies, as well as an elevated ESR and CRP. Highly elevated concentration of ACPA or RF together with raised ESR and CRP can provide four out of six points necessary for a diagnosis of RA.

In 60% of EORA patients, ACPA can be determined at the beginning of the disease, and in most of them, the aggressive phenotype of the disease and frequent bone erosions are found. The results of cohort studies revealed a lower incidence of ACPAs in patients with EORA, with reported ACPA positivity in about 60% in RA patients who started their disease at the age of 50–60 years old, 50% in EORA patients at the age of 60–70 years, 40% when the disease started at 70–80 years, and only 30% in very late RA, starting after 80 years [33]. The ACPAs were not different with respect to the titer, isotype distribution, specificity, and avidity index with increasing age of disease onset. Similar observations were made for RF that showed a decrease in frequency with increasing age of onset of the disease [34]. Anti-modified citrullinated vimentin (anti-MCV) antibodies and high sensitive anti-CCP (hsCCP) based on citrullinated vimentine peptides are the other types of ACPAs in RA. They are not as specific as antibodies to cyclic citrullinated peptide (anti-CCP) in the diagnosis of early RA, but in patients positive for anti-CCP, together with anti-MCV (or hsCCP) faster progression of bone destruction was noted.

A pronounced inflammatory response, accompanied by high levels of ESR and CRP is usually observed in patients with EORA. These markers of inflammation, however, are commonly found in other rheumatic diseases as well.

Osteoarthritis (OA) is the most prevalent form of non-inflammatory arthritis in the elderly population. Basic laboratory evaluation is normal in OA and the finding of autoantibodies (like RF or ACPA), alevated inflammatory markers (e.g., CRP) or specific metabolites (e.g., high uric acid) usually indicate another diagnosis.

10.5 Laboratory Diagnostics in Patients with Polymyalgia Rheumatica, Systemic Vasculitis, and Antiphospholipid Syndrome in the Advanced Age

Systemic vasculitis is a heterogeneous group of diseases associated with inflammation in the wall of blood vessels. Among them, several diseases are commonly found in older persons and deserve mention in this chapter. PMR and giant cell arteritis (GCA), or temporal arteritis, are closely related diseases of the elderly. Both diseases often coexist together and are characterized by a dramatic inflammatory

response [35]. Systemic inflammation is a common denominator for PMR and GCA, and in almost 80–90% of patients, ESR is higher than 50 mm/h, and the level of CRP is over 50 mg/L. Other laboratory markers of acute-phase response that are associated with the effects of IL-6 include hypoalbuminemia, hypergammaglobulinemia, thrombocytosis higher than 400,000/μL, mild normocytic anemia, and hyperfibrinogenemia. Autoantibodies directed to anti-N-terminal peptides of the ferritin heavy chain can be found in up to 90% of GCA cases, but they are not specific for the disease. Since the diagnosis of PMR is based on the exclusion of other rheumatic diseases with systemic inflammation, many other tests such as ACPA, RF, ANA, creatine kinase, alkaline phosphatase, and other analyses of bone and liver metabolism should be performed.

ANCAs are associated with small-vessel vasculitis, commonly found in old age. The group of ANCA-associated vasculitis (AAV) consists of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Pauci-immune rapidly progressive necrotizing crescentic glomerulonephritis (RPGN) is also classified as a kidney-limited form of AAV. ANCA is a family of autoantibodies directed against antigens of azurophilic and specific granules of neutrophil cytoplasm. About ten molecular targets of ANCAs have been described; among them proteinase-3 (PR3), and myeloperoxidase (MPO) appear to be the most clinically significant. Non-specific ANCAs that do not target PR3 or MPO antigens have been noted in many chronic inflammatory conditions [36]. Anti-PR3 and anti-MPO ANCAs are characteristic for AAV, and are related to different clinical syndromes. Anti-PR3 antibodies are primary biomarkers of GPA and are essential for the pathogenesis of the disease. Anti-PR3 can be found in both localized and systemic forms of the disease, manifested by granuloma in the airways, and lung damage. Glomerulonephritis is found in about 30% of the anti-PR3-positive GPA. Also, anti-PR3-positive patients have a more recurrent nature of the disease. Anti-PR3 antibody titers frequently change in parallel with the disease activity. Isolated RPGN is more frequent in MPO-positive patients, and kidney involvement is found in 50–90% of MPO-positive MPA. All patients with clinical suspicion of AAV should be tested with a sensitive ELISA method for the detection of anti-PR3 and anti-MPO antibodies. Goodpasture syndrome or anti-glomerular basement membrane disease (anti-GBM disease) is another example of small vessel vasculitis associated with ANCA-positivity that can manifest in older patients. Detection of anti-GBM antibodies directed against the non-collagenous domain of type IV collagen expressed in kidney and lung have 95% sensitivity and specificity in this disease.

Another kind of small vessel vasculitis is so called immune complex-mediated vasculitis. Immune complexes (IC) are formed in the slow bloodstream of small vessels and deposited in the walls of blood vessels of the skin and kidneys. Cryoglobulinemic vasculitis is the most common IC-mediated disease of old age. Cryoglobulins are IC consisting of aggregated immunoglobulin molecules that can reversibly precipitate at temperatures lower than body core temperature (e.g., below

35 °C). The defect in the solubility of IC is attributed to impaired glycosylation of the Fc fragment of immunoglobulin molecules. There are several types of cryoglobulins with slightly variable clinical presentations. Type I cryoglobulinemia consists of monoclonal immunoglobulins (paraprotein) of IgG or IgM classes highly prone to precipitation. Type I disease is manifested with high serum cryocrite levels and severe skin lesions with ulcers in almost half of patients and, in contrast, the decreased incidence of glomerulonephritis. Type II essential mixed cryoglobulinemia is typically related to chronic HCV infection. Cryoglobulins in type II cryoglobulinemia represent a monoclonal RF of the IgM class. Cryoglobulins in type II CSs cryoglobulinemia can be detected almost in 30% of HCV-infected patients, but clinical signs of vasculitis can only be found in 5–15% of patients. Cryoglobulins in type III cryoglobulinemia are polyclonal RF, which bind to self IgG. This is the most clinically indolent type of disease related to joint involvement, myalgia, and Raynaud's phenomenon. RA, SjS, or SLE are the leading causes of type III cryoglobulinemia, and a high prevalence of secondary lymphoma has been noted in cryoglobulin-positive patients with rheumatic diseases [37]. Tests for RF and monoclonal paraprotein are valuable tools for the diagnosis of cryoglobulinemic vasculitis.

Antiphospholipid syndrome (APS) is an antibody-mediated AID that is characterized by hypercoagulation, recurrent miscarriages and obstetric pathology. There are several clinical manifestations closely related to APS and potentially mediated by aPLA; however, the pathogenic mechanisms have not been fully elucidated. The diagnosis of APS can be suspected after receiving positive results of a laboratory panel of serological and coagulation tests, including lupus anticoagulant (LAC), antibodies of IgG and IgM subclasses directed to cardiolipin (aCL) or β-2 glycoprotein I (anti-b2GPI). According to the 2006 classification criteria for APS, persistently elevated levels of these antibodies in medium or high titers and/or presence of LAC, determined by re-evaluation after 12 weeks, are necessary for the confirmation of the diagnosis. Higher titers of aPLA are usually found before the development of thrombosis and slightly decrease immediately after thrombotic events.

At the same time, aCL antibodies are commonly found clinically healthy individuals. The prevalence of aPLA in the general population ranges between 1 and 5%, and goes up to 12% in elderly people. Low titers of aPLA are detected in many diseases, but they are not considered as risk factors for thrombosis [38]. Therefore, the diagnosis of APS in old age can be puzzling because of the high frequency of low positive aPLA, and the presence of other coexisting factors of acquired thrombotic risk. These risk factors for thrombosis include older age (>55 in men, >65 in women), all established risk factors for cardiovascular diseases and atherosclerosis, such as hypertension, diabetes, high LDL cholesterol or low HDL cholesterol, smoking, early onset of cardiovascular diseases in the family, body mass index over 30 kg m^2, as well as microalbuminuria, decreased glomerular filtration rate, congenital thrombophilia, oral contraceptives, nephritic syndrome, tumors, immobilization, and surgery.

Several attempts have been made in order to recognize the individual risk of thrombosis in patients positive for aPLA. Published EULAR guidelines for

the management of APS in adults specially address the issue of so-called “high-risk aPLA profile”, defined as any of the following: multiple (double or triple) aPLA positivity, persistently positive LAC or high aPLA titers, high aPLA score and Global Anti-Phospholipid Syndrome (GAPSS) Score [39, 40]. Additional risk factors for recurrent APS manifestations are coexistence with other systemic AID, especially SLE, a history of thrombotic and/or obstetric APS, and the presence of traditional cardiovascular risk factors including smoking, hypertension, dyslipidemia, diabetes, surgery, hospitalization, prolonged immobilization and the postnatal period. All but the latter factors are highly relevant in older age, so elderly patients with APS almost universally are classified as high-risk patients with more active treatment strategies.

10.6 Conclusion

Immunological laboratory testing is the basis for the diagnosis of most autoimmune and inflammatory rheumatic diseases. The substantial characteristics of the immune system at the older age include a higher frequency of autoantibodies, a predisposition to the inflammatory reactions, and a shift towards the monoclonal production of immunoglobulins. Interpretation of laboratory tests in geriatric patients should consider the unique characteristics of the immune response in older individuals.

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Chapter 11
Radiography in the Diagnosis of Rheumatic Disease in the Elderly

Iris Eshed

11.1 Osteoarthritis

Degenerative joint disease, or osteoarthritis (OA), represents the most frequently diagnosed condition of the musculoskeletal system and accounts for a high amount of direct and indirect socioeconomic costs worldwide [1]. It is characterized by focal areas of damage to the cartilage surfaces of synovial joints and is associated with remodeling of the underlying bone, and mild synovitis. Clinical features include pain, bony tenderness, and crepitus. The main feature of OA is progressive cartilage degradation though pathologic changes in other intra-articular tissues characterize OA as "a whole joint disease". Articular cartilage wear and tear is considered the result of repetitive microtrauma that occurs throughout life combined with intra-articular inflammatory processes [1]. Contributing factors to the development of OA may be body habitus, physical activity level, preexisting articular disease as well as genetic, hereditary, nutritional and metabolic factors [1, 2]. Primary OA, the most common form of OA usually seen in weight-bearing joints, typically involves the hands, hips, knees and feet.

The diagnosis of OA is often suggested on physical examination, however radiographs are usually used for initial evaluation, diagnosis confirmation and disease severity assessment. Two orthogonal planes views of the involved joint are generally required, with exception of the sacroiliac joints and the pelvis.

The typical radiographic appearance of OA is characterized by non-uniform joint space narrowing, the formation of bony spurs at the joint margin (osteophytes) and subchondral bone sclerosis and cysts (Fig. 11.1). Marginal osteophytes are typically used for OA detection while joint space narrowing, bone sclerosis, and subchondral cysts are used to assess severity [3]. Radiographic joint space narrowing serves as a

I. Eshed (✉)
Department of Diagnostic Imaging, Sheba Medical Center, Tel Hashomer, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

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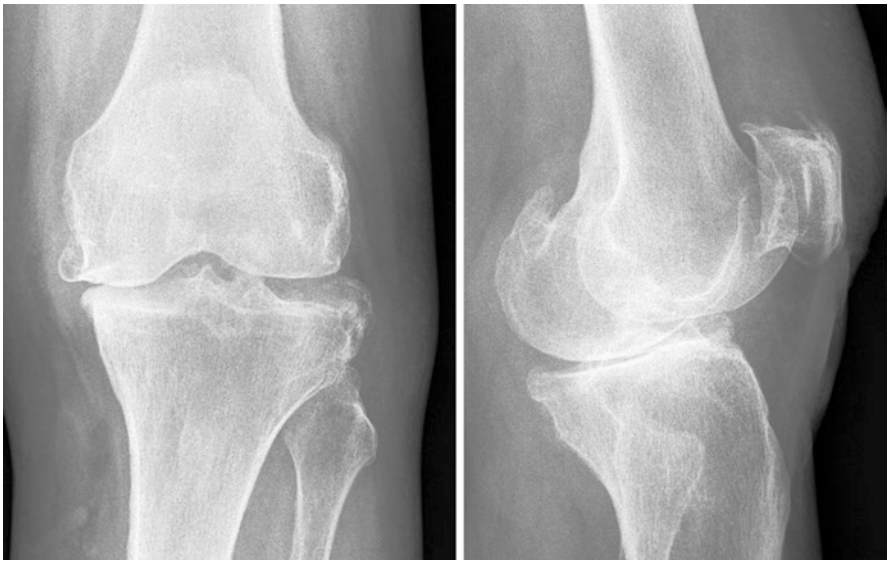

Fig. 11.1 AP and lateral radiographs of the knee of a 69 years old male demonstrating osteoarthritis of the knee affecting mainly the medial compartment with joint space narrowing and peripheral osteophytes

surrogate marker for joint's hyaline cartilage loss. As the joint space narrows, osteophytes develop and become larger, bone sclerosis increases, and subchondral cysts may be detected. Subchondral sclerosis corresponds to new bone deposition and trabecular microfractures and is located at sites of maximum stress in the subchondral bone [4]. The initial radiographs may not show all of these findings. At first, only minimal, non-uniform joint space narrowing may be present. With disease progression, subluxation, osteophytes and subchondral cysts may form [5]. Subchondral sclerosis or subchondral bone formation occurs as cartilage loss increases. In advanced stages, severe joint space narrowing with "bone on bone" appearance may occur, however without intra-articular bony bridging or ankylosis [5].

The most frequently radiographic scale used to identify and quantify OA is the Kellgren and Lawrence scale. This scale ranges from 0 to 4: 0 corresponding to absence of OA features and 4 to severe OA. The radiological features usually examined are: marginal osteophytes, periarticular ossicles, joint space narrowing associated with subchondral sclerosis, subchondral cysts and altered shape of the bone ends [6].

11.1.1 Knee

Knee OA affects about 10% of adults aged over 60 years, with increased risk in obese patients or patients with joint damage or abnormalities [7]. Weight bearing anterior-posterior (AP) and lateral radiographs are warranted for adequate

evaluation of the three knee compartments (medial, lateral and patellofemoral). Radiographic OA findings include medial tibio-femoral and patellofemoral joint space narrowing and subchondral sclerosis [8, 9] followed by tibial lateral subluxation and medial osteophyte formation (Fig. 11.2). Prominent lateral joint space narrowing can be seen due to altered joint alignment. Osteophytes are seen anteriorly and medially at the distal femur and proximal tibia, and posteriorly at the patella and the tibia (Fig. 11.3) [5].

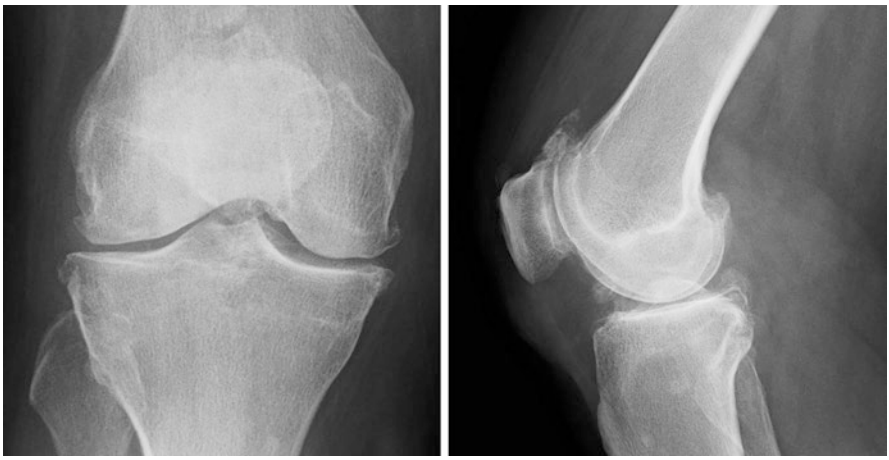

Fig. 11.2 AP and lateral radiographs of the knee of a 66 years old female demonstrating medial tibio-femoral and patellofemoral joint space narrowing and marginal and central osteophytes

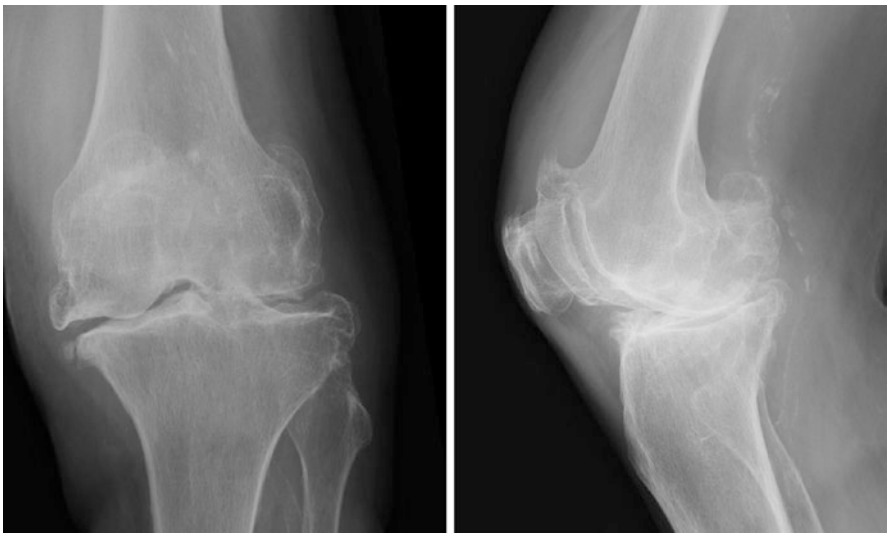

Fig. 11.3 AP and lateral radiographs of the knee of a 69 years old female demonstrating advanced osteoarthritis with diffuse joint space narrowing, osteophytes subchondral sclerosis and mild subluxation

11.1.2 Hip

Hip OA is rare below the age of 45 years and the prevalence increases substantially afterwards, with a peak incidence around the age 75 years [10]. AP and axial, or frog views of the hip are advised for assessment of hip arthritic changes. A suspected subtype of hip OA is related to an abnormal shape of the hip joint (e.g. resulting from acetabular dysplasia, Perthes disease and more) with subsequent femoral head malformation [11, 12].

Degenerative hip radiographic changes include supero-lateral joint space narrowing (as opposed to medial joint space narrowing seen in rheumatoid arthritis) with osteophytes and subchondral sclerosis and cysts (Fig. 11.4). Osteophytes are thought to precede joint space narrowing and can be either marginal or central. While central osteophytes produce an irregular contour of the articular surface, marginal osteophytes grow at the joint margins, increasing the femoral head coverage and reducing the joint stress [4].

Rapidly destructive osteoarthritis of the hip is a unique subtype of OA usually seen in elderly women of which pathogenesis remains unclear. It is characterized by rapid chondrolysis with no evidence of infection or crystal induced joint disease (Fig. 11.5). On consecutive radiographs erosions, osteophytes, sclerosis, subchondral cysts, subluxation and joint space narrowing develop within a few months [13].

11.1.3 Hands

An estimated 70% of the population over age 65 is affected by hand OA [14].

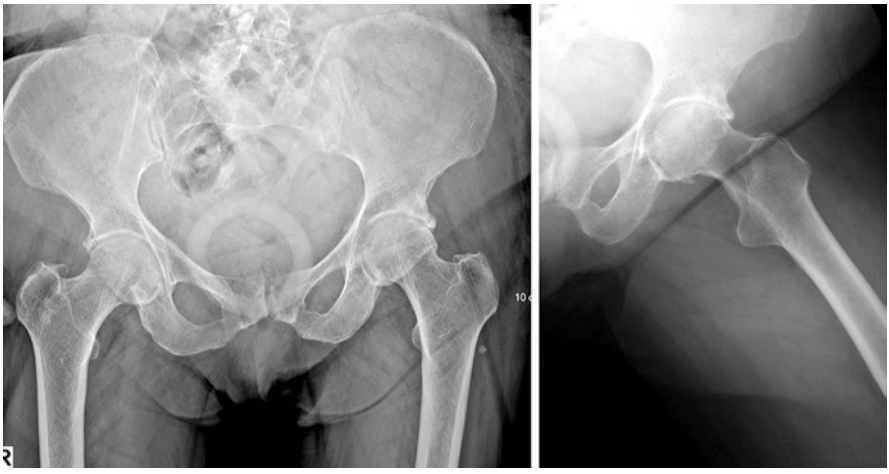

Fig. 11.4 AP and axial radiographs of the pelvis and left hip of a 79 years old female demonstrating osteoarthritis with supero-lateral joint space narrowing, osteophytes and subchondral sclerosis

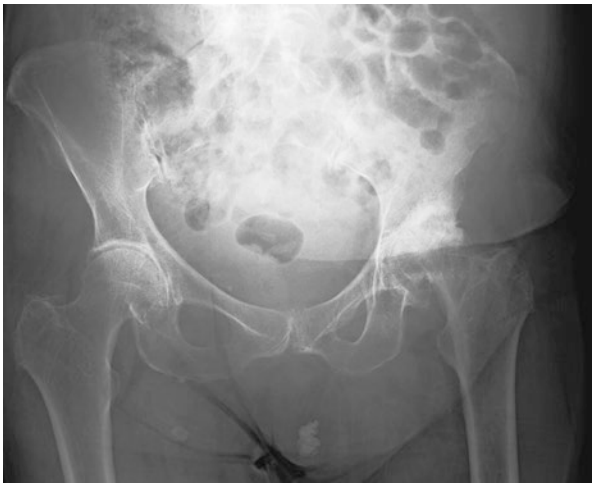

Fig. 11.5 AP radiograph of the pelvis a 89 years old female demonstrating advanced destructive osteoarthritis of the left hip with supero-lateral joint space narrowing, osteophytes and subchondral sclerosis

The most commonly involved joints in the hand and wrist are the first carpometacarpal (CMC) joints and distal interphalangeal joints [5]. AP and oblique views are used for radiographic evaluation of the hand however, oblique and magnified views of the entire hand or of a specific joint are used for targeted evaluation. Joint space narrowing of the interphalangeal and metacarpophalangeal joints may be symmetric or asymmetric and is accompanied by characteristic marginal osteophytes and subchondral sclerosis and cysts. Erosive changes are not evident in primary OA.

The first carpometacarpal joint, or trapeziometacarpal joint OA can be classified into various stages according to OA severity [15];

- Stage I. includes mild joint narrowing or subchondral sclerosis, mild joint effusion, or ligament laxity. No subluxation or osteophyte formation are present.
- Stage II. In addition to joint narrowing and subchondral sclerosis, there is osteophyte formation at the ulnar side of the distal trapezial articular surface (Fig. 11.6). In addition, mild to moderate radial and dorsal subluxation of the base of the first metacarpal may be present.
- Stage III. Further joint space narrowing with cystic changes, bone sclerosis and prominent osteophytes at the ulnar border of the distal trapezium are seen. The first metacarpal is moderately radially and dorsally displaced (Fig. 11.7).
- Stage IV. Similar destruction of the CMC joint to that in stage III in addition to scaphotrapezial joint destruction and CMC joint immobility.

Distal interphalangeal (DIP) joint's OA is detected in 65% of individuals 65 years and older while approximately 50% of these patients also have involvement of the proximal interphalangeal (PIP) joints [16] (Fig. 11.8).

Erosive osteoarthritis (EOA) is a relatively uncommon clinical subset of hand OA marked by a greater degree of inflammation which unlike primary, or nodal OA is characterized by the presence of erosions on plain radiographs. While EOA is considered to be a variant of OA by most, controversy remains as to whether it is a

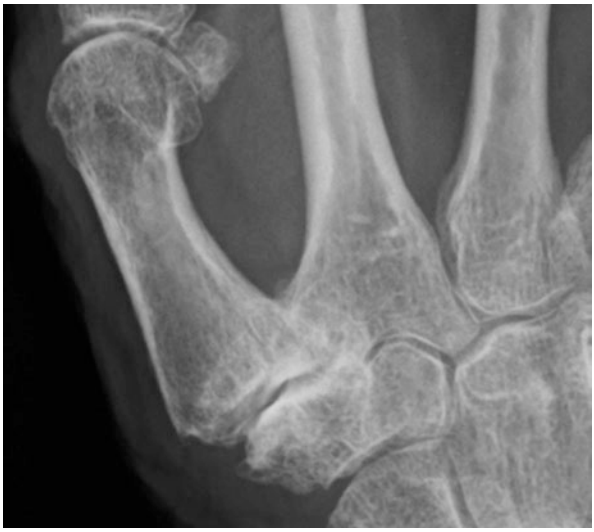

Fig. 11.6 An AP radiograph of the first carpometacarpal joint of an 87 years old male demonstrating a stage II osteoarthritis with joint space narrowing, cystic changes, bone sclerosis and osteophytes at the ulnar border of the distal trapezium and base of the first metacarpal bone

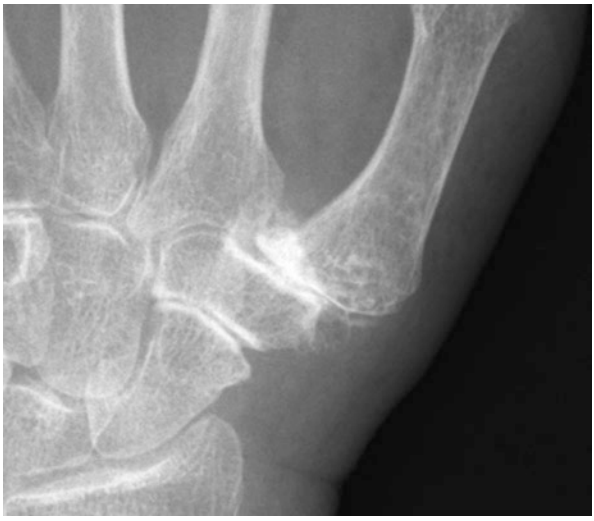

Fig. 11.7 An AP radiograph of the first carpometacarpal joint of an 82 years old female demonstrating a stage III osteoarthritis with joint space narrowing, cystic changes, bone sclerosis and osteophytes. The first metacarpal is moderately radially and dorsally displaced

distinct entity or a phase of nodal OA. EOA predominantly affects postmenopausal women with a typical age of onset between 50 and 55 years [17, 18]. Pain, swelling and warmth of the DIP and PIP joints are the most common symptoms. Pain is often of abrupt onset and is followed in most cases by intermittent inflammatory episodes with progressive joint destruction [19].

EOA is characterized by DIPs and PIPs central erosions often in combination with bony proliferation, collapse of the subchondral bone, and interosseous bone fusion [20]. The combination of central erosion with marginal osteophytes often lead to the hallmark “gull-wing” deformity [21]. Another type of lesion, the saw tooth erosion often eventually leads to ankylosis [17] (Fig. 11.9).

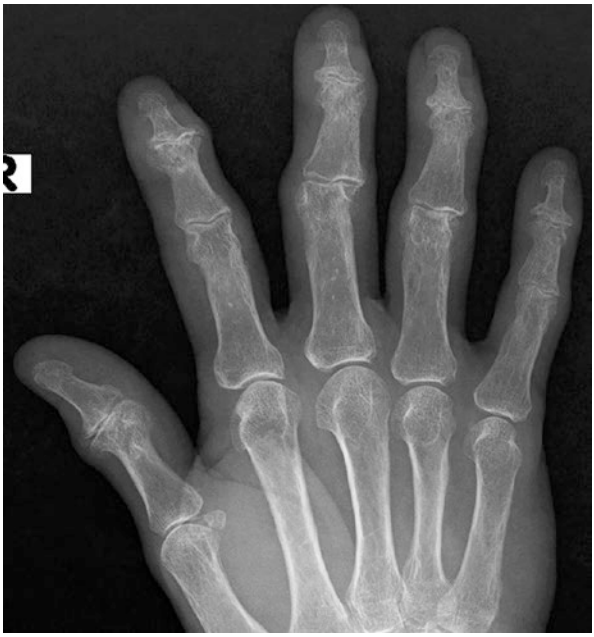

Fig. 11.8 An AP radiograph of the right hand of a 68 years old female demonstrating osteoarthritis of the proximal and distal interphalangeal joints including joint space narrowing, subchondral sclerosis, marginal osteophytes and mild subluxation

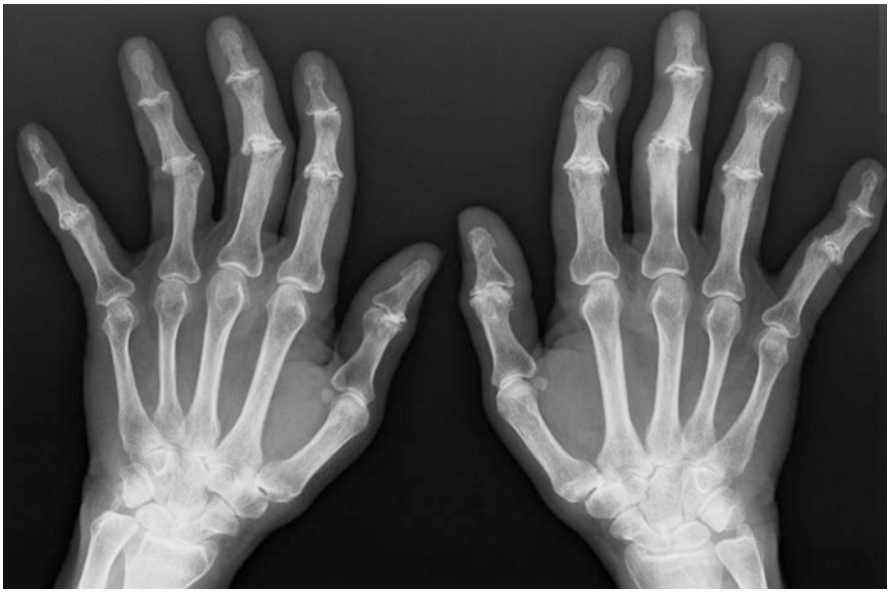

Fig. 11.9 An AP radiograph of the hands joint of a 90 years old female demonstrating advanced erosive osteoarthritis involving mainly the proximal and distal interphalangeal joints with central erosions leading to the characteristic gull-wing and saw tooth deformities

11.1.4 Feet

The foot is involved with a variable frequency according to the joint sites of which the first metatarsophalangeal (MTP) joint is most commonly involved in OA while hindfoot OA is quite uncommon [22]. Weight-bearing dorso-plantar and lateral radiographic projections are advised to best appreciate the feet [23]. Radiographic first MTP joint OA most commonly occur in isolation from the other joints in the affected foot, whereas OA in the midfoot joints tend to co-occur with OA in other joints in the same foot [24]. In addition to the general OA presentation, first MTP OA is accompanied by lateral subluxation of the first toe resulting in a hallux valgus deformity (Fig. 11.10).

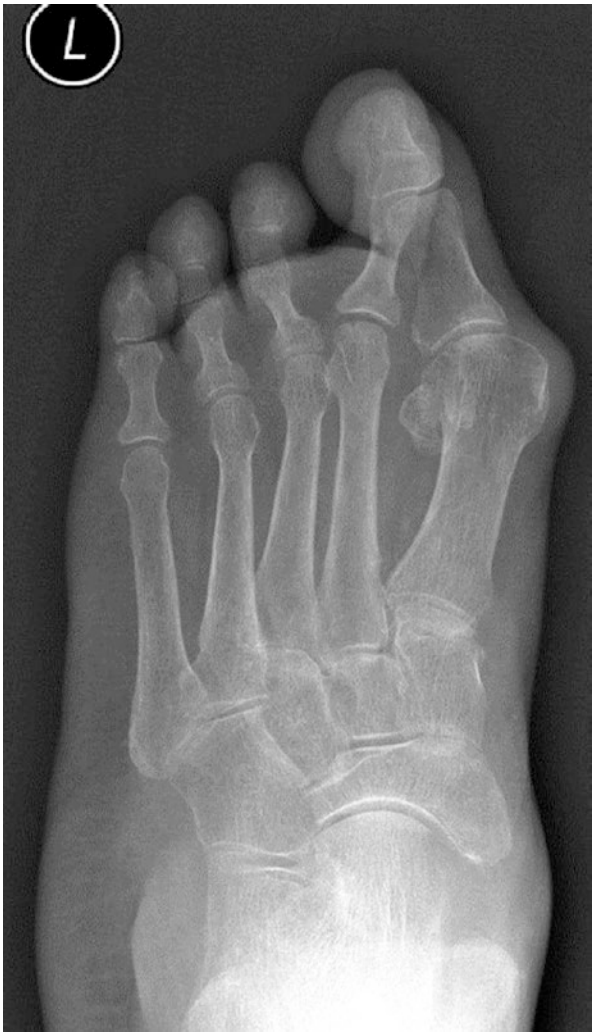

Fig. 11.10 An AP radiograph of the left foot of an 81 years old female demonstrating moderated hallux valgus

11.1.5 Spine

Degenerative changes of the spine are a part of normal aging, starting in late adolescence and progressing with age not necessarily clinically manifested. Degenerative disease is most often located in the lumbar spine, followed by the cervical and thoracic spine, with the lower parts of the lumbar spine (L4–S1) and cervical spine (C4–C7) most commonly involved [25].

Degenerative spinal disease, also called spondylosis or spondylosis deformans involves the whole disco-vertebral unit (consisting the intervertebral disc, adjacent vertebral endplates, facet joints, ligamentum flava and longitudinal ligaments) at a given level. All these components may be affected by degenerative spinal disease to varying degrees. Spondyloarthrosis is one type of degenerative spine disease that mainly affects the facet joints and causes facet degeneration while degenerative disc disease (DDD) is another type, mainly affecting intervertebral discs. Unlike spondyloarthrosis that is best appreciated by CT, DDD can be appreciated on AP and lateral radiographs.

The first stage of DDD disease is usually dehydration of the nucleus pulpous of the intervertebral disc, combined with fissures in the adjacent annulus fibrosus (annular tears) and endplate cartilage microfractures. These of course cannot be radiographically detected, however as the processes progresses intervertebral space narrowing occurs and is evident on radiographs along with anterior and posterior osteophytes and endplate subchondral sclerosis and cysts [25] (Figs. 11.11 and 11.12). Other forms of disc degeneration evident on radiographs are vacuum phenomenon (gas collections, mostly nitrogen) and calcifications.

Facet joint degeneration involves mainly hypertrophy and osteophytes of the articular processes, with narrowing of the joint space. Facet degeneration along with disc degeneration can lead to degenerative spondylolisthesis due to vertebral instability [25] (Fig. 11.13).

11.2 Crystal Induced Arthropathies

The Crystal induced arthropathies are a spectrum of inflammatory arthritides, in which deposition of a variety of microcrystals induce an inflammatory response. The main common diseases in this group include gout, calcium pyrophosphate deposition disease (CPPD) and calcium hydroxyapatite deposition disease (HADD). Clinical presentation, deposited crystal, and radiographic appearance may be somewhat similar and on the other hand may differ between the three diseases. Imaging plays an important role in diagnosis and follow up of the crystal induces arthropathies.

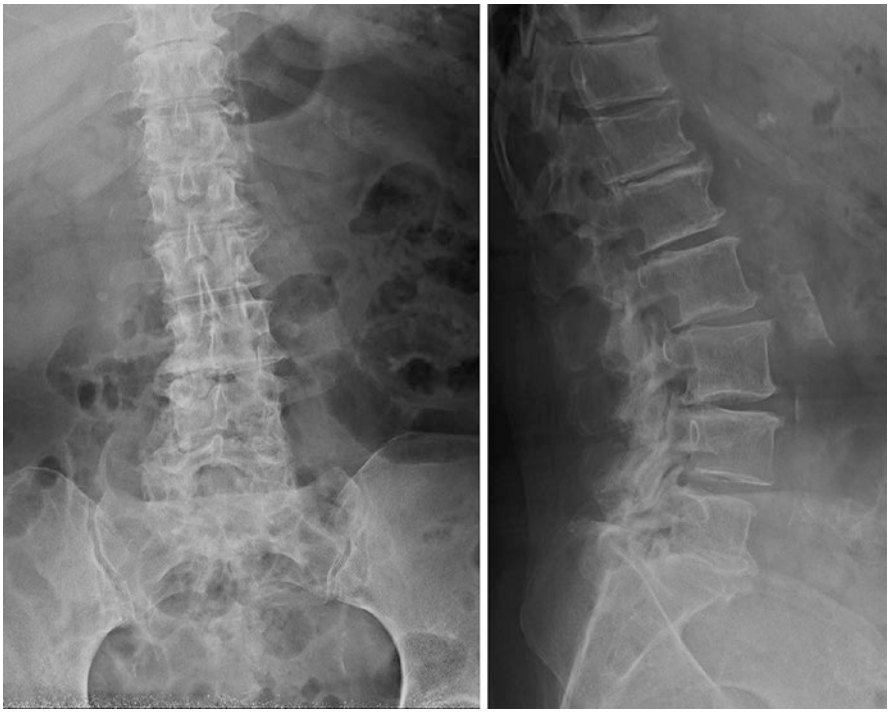

Fig. 11.11 An AP and lateral radiographs of the lumbar spine of a 82 years old male demonstrating mild spinal osteoarthritis with reduced intervertebral disc height, mild subchondral sclerosis of the endplates and anterior osteophytes

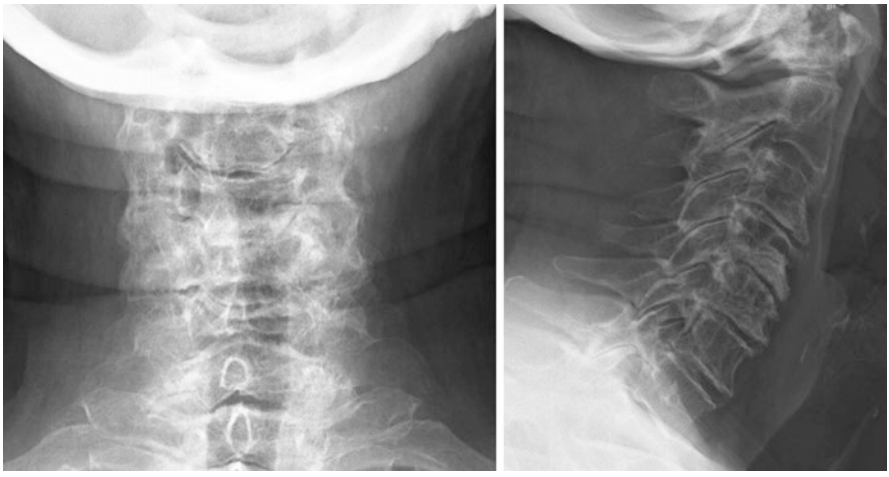

Fig. 11.12 An AP and lateral radiographs of the cervical spine of an 80 years old female demonstrating spinal degenerative disc disease with reduced intervertebral disc height, subchondral sclerosis of the endplates as well as anterior and posterior osteophytes. Mild facet joints osteoarthritis is also present

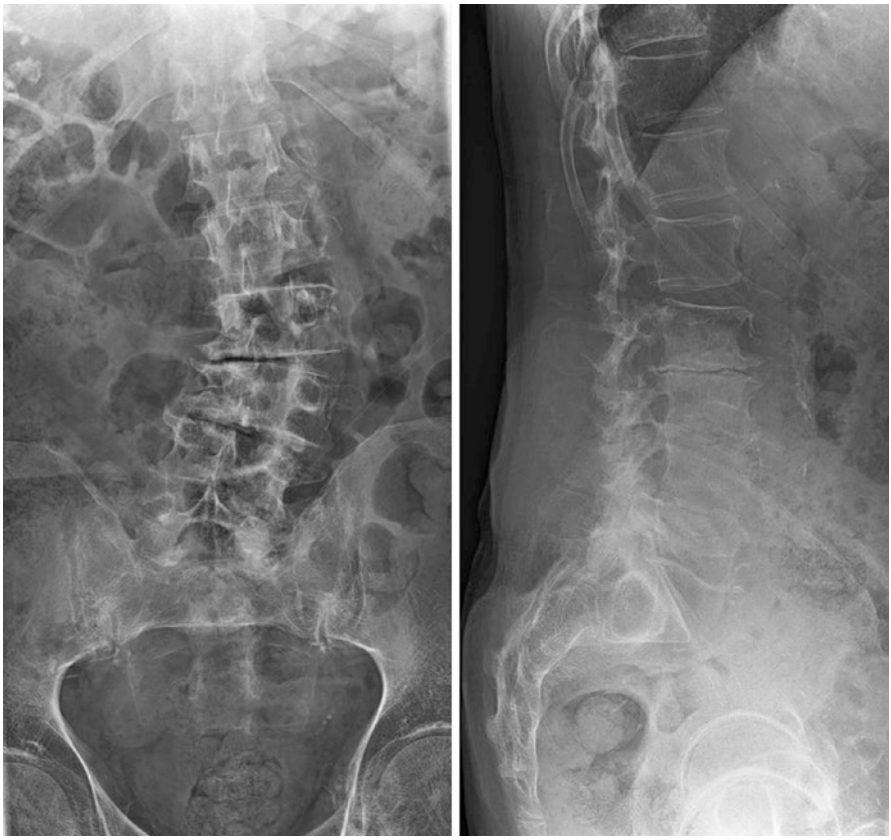

Fig. 11.13 An AP and lateral radiographs of the lumbar spine of a 78 years old male with scoliosis, advanced degenerative disc disease as well as advanced degenerative facet joints disease

11.2.1 Gout

Gout is caused by uric acid overproduction or under excretion resulting in deposition of monosodium urate monohydrate crystals that induce acute episodes and chronic joint's inflammation. The key to the diagnosis is joint aspiration with synovial fluid analysis depicting negatively birefringent urate crystals on polarized light microscopy, or classic radiographic findings [26].

Classically, the disease begins in men between the ages of 30 and 60 years with the sudden onset of acute and severe pain with a predilection for the metatarsophalangeal (MTP) joint of the first toe (Podagra) [27]. The first MTP joint is involved in approximately 50% of patients at onset, and eventually in 90% of patients with untreated gout.

In early stages of gout, either no radiographic findings are present or nonspecific soft tissue swelling is seen. The hallmark of chronic gout is the presence tophi deposits. Tophus is a mixture of monosodium monohydrate crystals in a matrix of

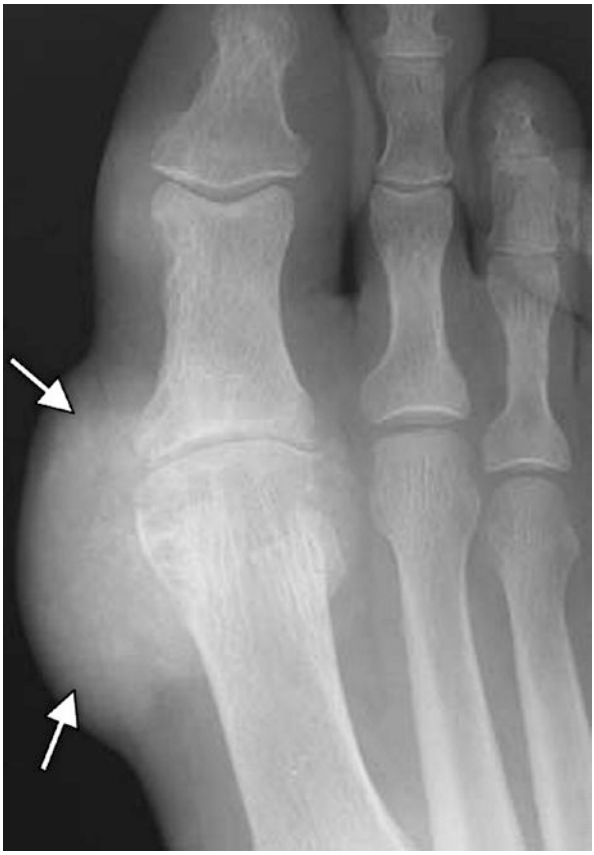

Fig. 11.14 An AP radiograph of the first toe of a 55 years old male with gout demonstrating soft tissue swelling around the first metatarsophalangeal joint and periarticular hyperdense mass corresponding to tophus deposits

amorphous debris containing urate, proteinaceous deposits, and lipids with a surrounding foreign body reaction [28]. In chronic disease, tophi can be seen on radiographs as periarticular or intraosseous soft-tissue hyperdense masses (Fig. 11.14). Generally, they are ovoid and asymmetric and in up to 50% of tophi, faint calcification may occur [27].

Erosions in gout, can be intra-articular but unlike the other erosive arthropathies (e.g. rheumatoid arthritis and psoriatic arthritis) can be also seen outside the joint, possibly resulting from chronic pressure of a nearby tophus deposit. Radiographic erosions are a late feature of chronic gout, occurring 15 years after disease onset, and is always present in association with subcutaneous tophi [29].

Frequently, erosions are eccentric, round or oval in shape, well circumscribed, and oriented along the long axis of bone (Fig. 11.15). A characteristic feature is the 'punched out' erosion, often with osteophytes producing an "overhanging edge" that is, an elevated margin of bone that extends over the expected confines of the cortex [30]. Erosions may coalesce to present a honeycomb appearance and may be associated with subchondral collapse [31]. In some patients, extensive erosions produce a mutilating arthritis mimicking the arthritis mutilans commonly associated with psoriatic arthritis [32].

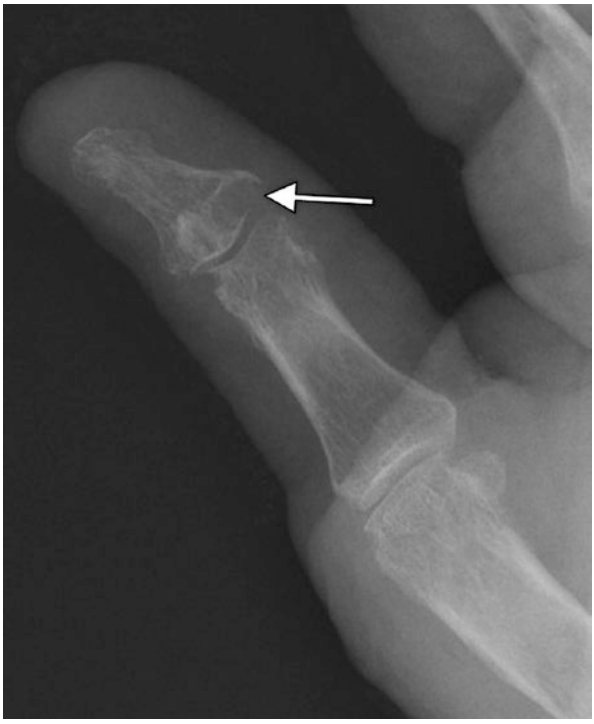

Fig. 11.15 An AP radiograph of the first finger of a 60 years old male with gout demonstrating characteristic eccentric, well circumscribed erosion at the base of the distal phalange

New bone formation occurs adjacent to erosions or within them. Overhanging margins is another radiographic feature of longstanding tophaceous gout [13] (Fig. 11.16).

Osteopenia is usually not evident in the involved joints and the joint space is usually preserved.

Gout tends to affect the lower extremities more often than the upper extremities and the small joints more often than the large joints [33]. An asymmetric and monoarticular distribution is characteristic though bilateral and symmetric polyarticular involvement may be present. All compartments of the hand and wrist, knee, shoulder, hip, and sacroiliac joint are favored sites [31]. Bilateral olecranon bursitis (Fig. 11.17) and bilateral swelling at the dorsum of the foot and calcaneus are characteristic of gout.

11.2.2 Calcium Pyrophosphate Deposition Disease

Calcium pyrophosphate deposition disease (CPPD) is a relatively common arthritic disorder caused by the deposition of calcium pyrophosphate (CPP) crystals in and around articular tissues. CPPD crystals elicit an inflammatory response that results in arthritis, synovitis, or tendonitis. CPPD occurs most often in elderly patients

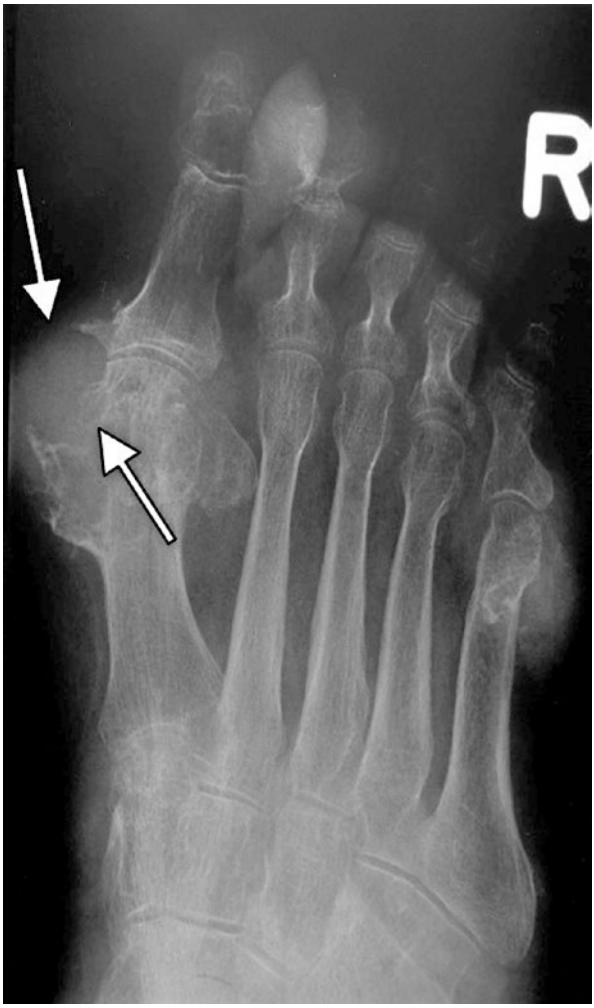

Fig. 11.16 An AP radiograph of the right foot of a 75 years old male with gout demonstrating periarticular hyperdense tophus deposit at the first metatarsophalangeal joint as well as characteristic erosion that is eccentric, well circumscribed and with overhanging margins. Tophus is also seen around the fifth metatarsophalangeal joint

affecting 4–7% of the adult population in Europe and US [34, 35]. CPPD is a heterogeneous group ranging from an acute inflammatory mono-articular arthritis, (pseudogout) to chronic polyarticular degenerative processes with or without features of inflammation. It is characterized by joint inflammation and a typical pattern of structural joint damage that may occur with or without radiographic chondrocalcinosis.

Advanced age is the major risk factor for sporadic CPPD, however several metabolic diseases such as hemochromatosis and hyperparathyroidism, are associated with an increased prevalence of CPPD.

Currently, the most specific test for the presence of CPPD is visualization of weakly birefringent rhomboid CPPD crystals in synovial fluid aspirates from the affected joint.

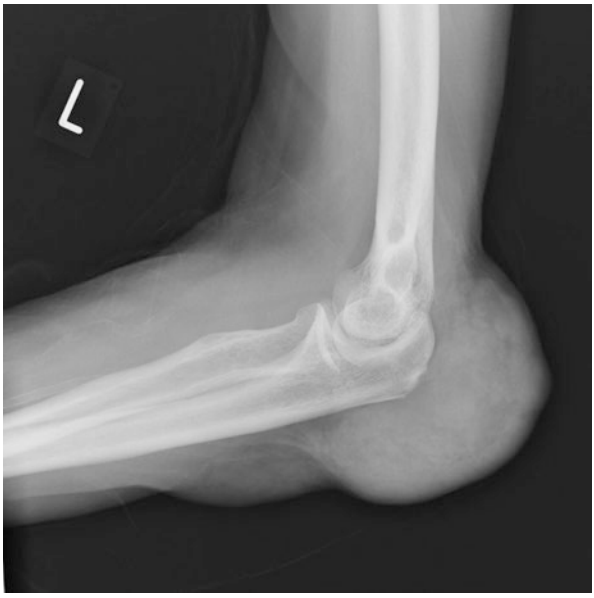

Fig. 11.17 A lateral radiograph of the left elbow of a 63 years old male with gouty olecranon bursitis demonstrated as a massive dorsal hyperdense mass resulting from tophus deposition

However, the smallest and most inflammatory crystals can be easily missed and crystals may not always be detected in a single synovial aspirate [36]. The presence of cartilaginous linear calcification (chondrocalcinosis) on x-ray is often used to confirm the diagnosis of CPPD. However, it is neither highly sensitive nor specific for this diagnosis [37]. Nowadays, the presence of radiographic chondrocalcinosis along with positively birefringent crystals in synovial fluid suffice to establish a diagnosis of CPPD [38], however the mere presence pf chondrocalcinosis on its own does not imply clinical arthritis.

It is important to note that chondrocalcinosis is not synonym with CPPD. Calcium can be deposited in soft tissues including cartilage in various forms of calcium phosphates, including calcium hydroxyapatite and basic calcium phosphate. Typical chondrocalcinosis involvement in CPPD include the fibrocartilage of the wrist's triangular cartilage, of the pubic symphysis, and of the knee's meniscus leading to the suggested inclusion of these three locations in radiologic screening of CPPD [39]. While calcium in CPPD is indeed most commonly deposited on fibrocartilage, it may also be found in the mid-zone of articular cartilage following the articular surface contour or also in capsular and peri-articular locations. CPPD is often found in the context of osteoarthritis. There is overlap in the clinical presentations of CPPD and osteoarthritis. Osteoarthritis and CPPD are both relatively common with advanced age, and thus co-occurrence by chance might explain the association. However, CPP crystals worsen cartilage damage and likely have a role in initiating the OA process [40].

Characteristic radiographic features of CPDD include in addition to soft tissue calcification, joint space narrowing, bone sclerosis, subchondral cyst

formation and large/giant intraosseous geodes [41, 42]. Cysts in CPPD tend to have sclerotic margins and vary in shape and size. Variable osteophyte formation is commonly seen with CPPD in which large, irregular bony excrescences are sometimes present [27].

11.2.2.1 Knee

Chondrocalcinosis of the knee involves mainly the menisci but also the hyaline cartilage and capsular calcinosis (Fig. 11.18). The location of structural damage in the knee helps to distinguish CPPD from OA. As with OA, CPPD tends to be bilateral and asymmetric, however, advanced, asymmetric, or isolated involvement of the patellofemoral compartment should raise the possibility of CPPD [27]. Tricompartmental (medial, lateral, patellofemoral) involvement on the other hand is infrequent [39].

11.2.2.2 Wrist and Hand

Chondrocalcinosis of the triangular fibrocartilage ligamentous complex is a common presentation in CPPD of the wrist, however calcium deposition in the intercarpal ligaments is quite as well common (Fig. 11.19). CPPD favors the radiocarpal compartment and trapezio-scaphoid joints of the wrist.

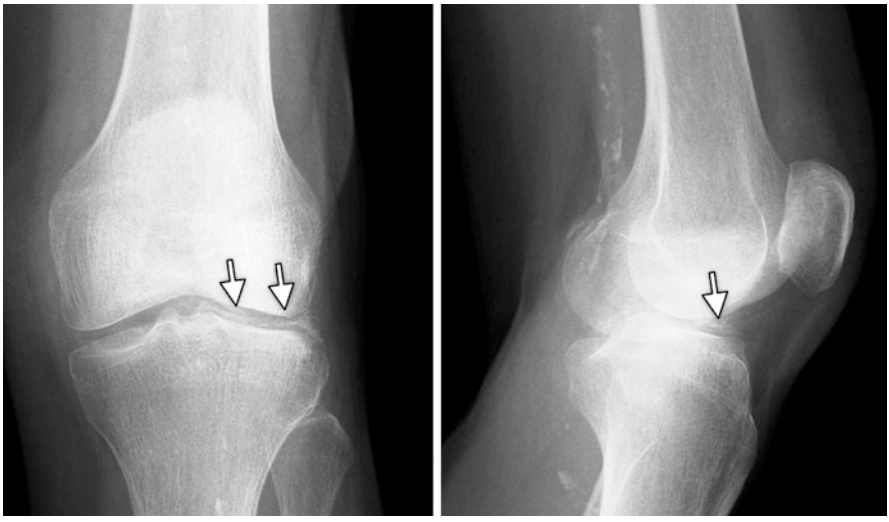

Fig. 11.18 An AP and lateral radiographs of the knee of an 87 years old female demonstrating chondrocalcinosis of the lateral meniscus due to calcium pyrophosphate deposits

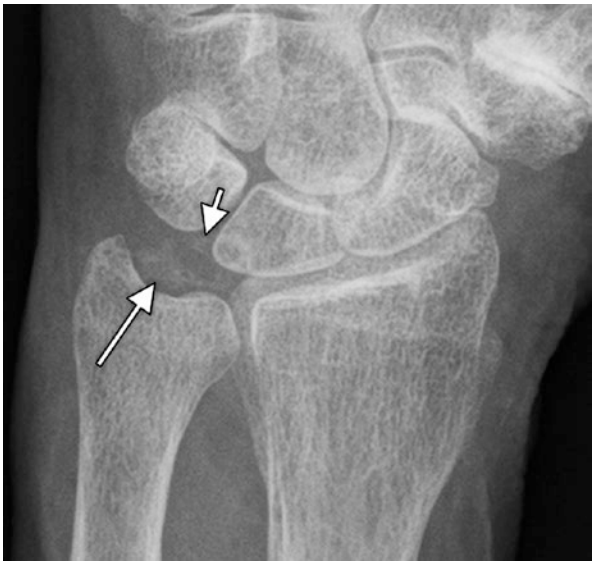

Fig. 11.19 An AP radiograph of the wrist of an 86 years old female demonstrating chondrocalcinosis of the triangular fibrocartilage ligamentous complex as well as chondrocalcinosis of the lunate-triquetal ligament. A subchondral cyst in the lunate is also seen on its proximal ulnar side. These findings are all characteristic of CPPD

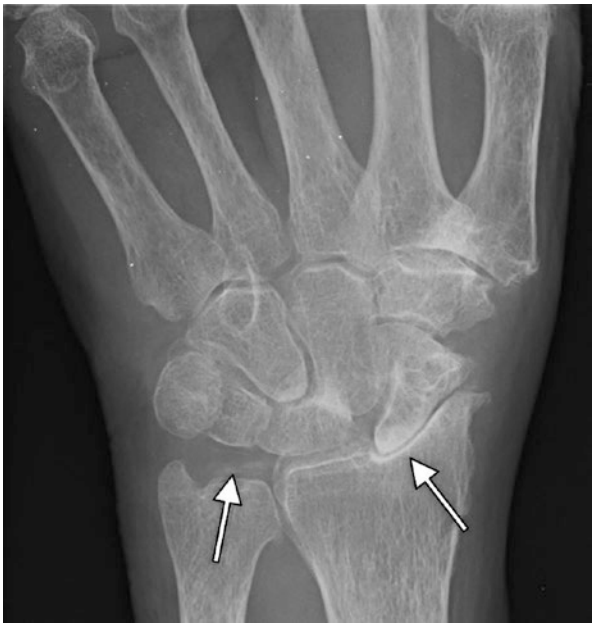

Fig. 11.20 An AP radiograph of the wrist of a 93 years old male demonstrating chondrocalcinosis of the triangular fibrocartilage ligamentous complex as well as proximal migration of the scaphoid bone with advanced osteoarthritis changes with the adjacent radius resulting from a tear of the scapho-lunate ligament. These findings are all characteristic of CPPD

CPPD crystal deposition in the scapho-lunate ligament predisposes to disruption of the joint with subsequent scapho-lunate collapse [43]. The result is proximal migration of the scaphoid bone and advanced osteoarthritis changes with the adjacent radius (Fig. 11.20).

11.2.3 Hydroxyapatite Deposition Disease (Calcific Tendinitis)

Calcium hydroxyapatite (HA) crystals deposits in periarticular soft tissues and tendons and bursa results hydroxyapatite deposition disease (HADD). The calcium deposition stage is a chronic phase which is typically asymptomatic. During this silent phase HA is contained within tendon and on radiographs calcium is well defined. However, once inflamed, liquefaction and enlargement of the calcium within the tendon occurs, with Increased pressure within and around the tendon. The end result is complete or partial rupture of calcium into or under the adjacent bursa which reacts with recurrent bouts of bursitis. During this mechanical and inflamed stage calcium is less well defined on radiographs. The onset of symptoms in the inflamed phase is acute with severe pain, tenderness, associated with restrictive motion. The disease typically occurs between the ages of 40 and 70 years with gender predilection.

The typical radiographic features of periarticular HADD during the acute phase are cloudlike, poorly defined calcific deposits that initially blend into the surrounding soft tissues. With time calcification appear denser, homogenous, and more sharply delineated [27]. Calcified deposits may remain static for a long time, however they may also change in size over time and become larger, smaller, or disappear [27].

11.2.3.1 Shoulder

HADD is usually a monoarticular disease affecting the shoulder most frequently.

Crystal deposition in the shoulder most commonly involve the supraspinatus tendon, but the rest of the rotator cuff tendons as well as the biceps tendon may also be involved (Fig. 11.21).

Osseous erosions may be located adjacent to tendon.

11.2.3.2 Milwaukee Shoulder Syndrome

Milwaukee syndrome is another basic calcium phosphate crystal associated syndrome. It is characterized by the gradual onset shoulder pain that is often unilateral but could be bilateral, worsen at night and is sometimes associated with renal disease [44]. This rare destructive arthropathy occurs predominantly in elderly women and is characterized by intra-articular or periarticular hydroxyapatite crystals and rapid destruction of the rotator cuff and the glenohumeral joint [45]. Calcium pyrophosphate or apatite crystal deposition involving other peripheral joints is sometimes described [46].

Milwaukee syndrome results in a radiographic characteristics similar to neuropathic joint. There is joint space loss, subchondral sclerosis, osseous debris, joint disorganization and deformity (Fig. 11.22). These are associated with large effusion and with rotator cuff disruption.

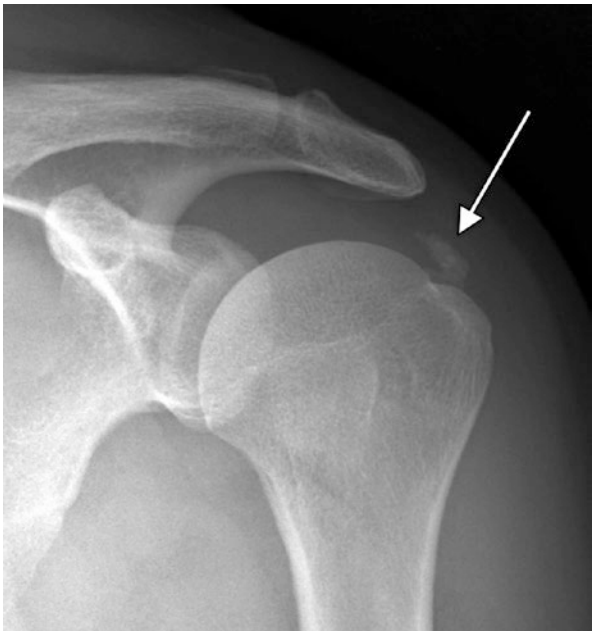

Fig. 11.21 An AP radiograph of the left shoulder of a 65 years old female with calcium deposition at the distal end of the supraspinatus tendon near its insertion to the humeral head (calcific tendinitis). This finding is characteristic of calcium hydroxyapatite deposition disease

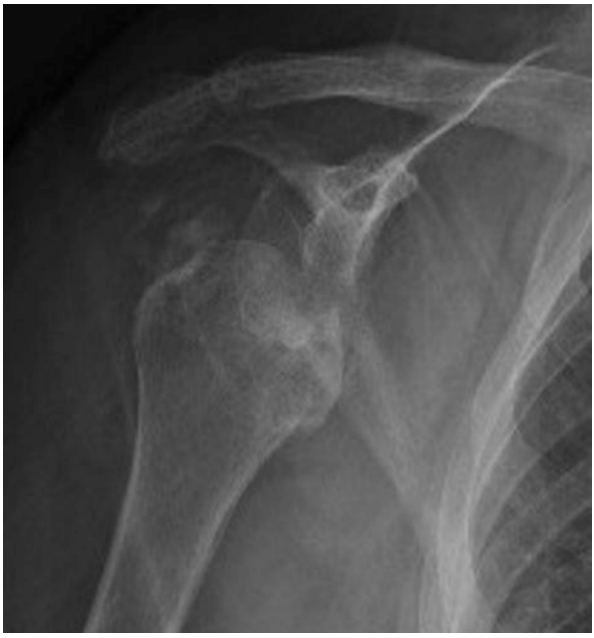

Fig. 11.22 An AP radiograph of the right shoulder of an 86 years old female with Milwaukee shoulder demonstrating joint antero-inferior subluxation and space loss, subchondral sclerosis, and joint disorganization and deformity. Calcium deposits within and above the joint are also detected corresponding to calcium hydroxyapatite deposition

11.3 Diffuse Idiopathic Skeletal Hyperostosis (DISH)

DISH is characterized by ligamentous ossification of the anterolateral spine and involves the calcification and ossification of soft tissue, in particular ligaments and entheses of the axial and appendicular skeleton [47, 48]. It is more common in males, and usually diagnosed after the age of 40 years [49]. The pathogenesis of DISH is poorly understood, however, it is clear that entheseal and ligamentous ossification, osteophyte formation and finally bone bridging and ankylosis are a continuum, somewhat similar to the process in the inflammatory counterpart of DISH—ankylosing spondylitis. Diagnosis is currently based solely on radiographic abnormalities defined using the criteria of Resnick and Niwayama [50]. These include flowing osteophytes in at least four contiguous vertebras of the thoracic spine with absence of other degenerative changes (Fig. 11.23) in these vertebral segments or

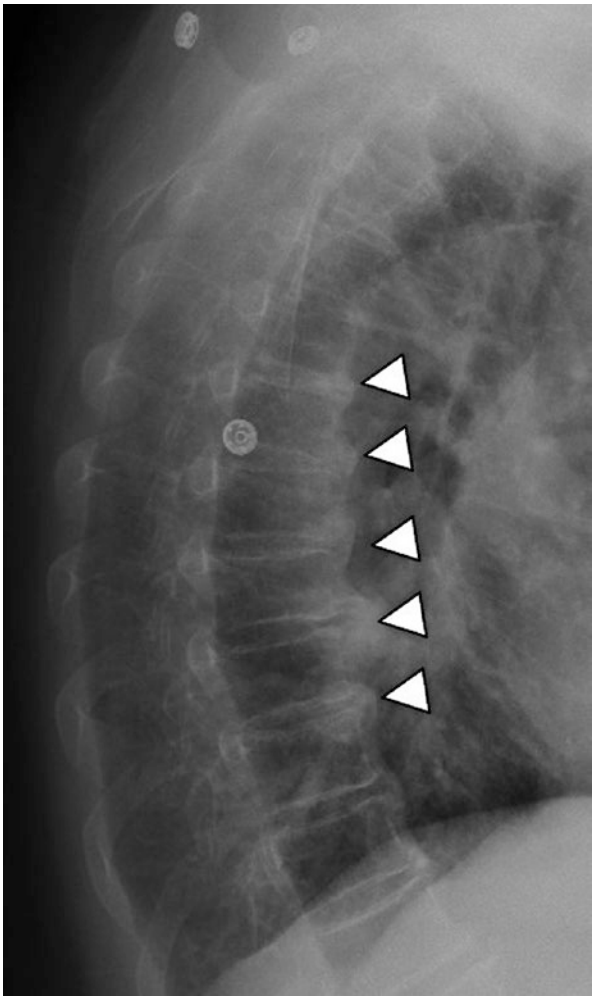

Fig. 11.23 A lateral thoracic spine radiograph of a 73 years old male with diffuse idiopathic skeletal hyperostosis (DISH) demonstrating multiple flowing osteophytes in the anterior aspect of the vertebras with relative preservation of the intervertebral disc space in these vertebral segments

inflammation in the sacroiliac joints [50]. However, a decade may pass from onset of radiographic changes to formation of the characteristic bridging osteophytes [51]. Although DISH was initially considered a radiographic rather than a clinical entity, clinical complaints are prevalent among affected individuals. These may range from nonspecific back pain to severe limitation of spinal motion as well as dysphagia [52].

11.3.1 Spine and Sacroiliac Joints

Ossification of the anterior longitudinal spinal ligament with flowing osteophytes on the right side of the spine and intervertebral disc space preservation are the hallmark of DISH [53]. These involve mainly the thoracic spine but vigorous flowing osteophytes of the anterior cervical spine are commonly seen in DISH (Fig. 11.24). The bony bridges in DISH may cause extensive morbidity such as neck pain, dysphagia and stridor, spinal stenosis and myelopathy. Specifically enthesopathy of the stylohyoid ligament results in an elongated and protruded styloid process that may cause dysphagia—an entity called Eagle syndrome [54]. Indeed such thick styloid process is characteristic in DISH [55].

The characterized flowing osteophytes of DISH are thick and more horizontal in orientation on lateral radiographs contrary to the thin, vertically oriented syndesmophytes seen in ankylosing spondylitis. DISH patients are thus prone to unstable spinal fractures resulting from the rigid spinal structure, unable to withstand bending forces [56].

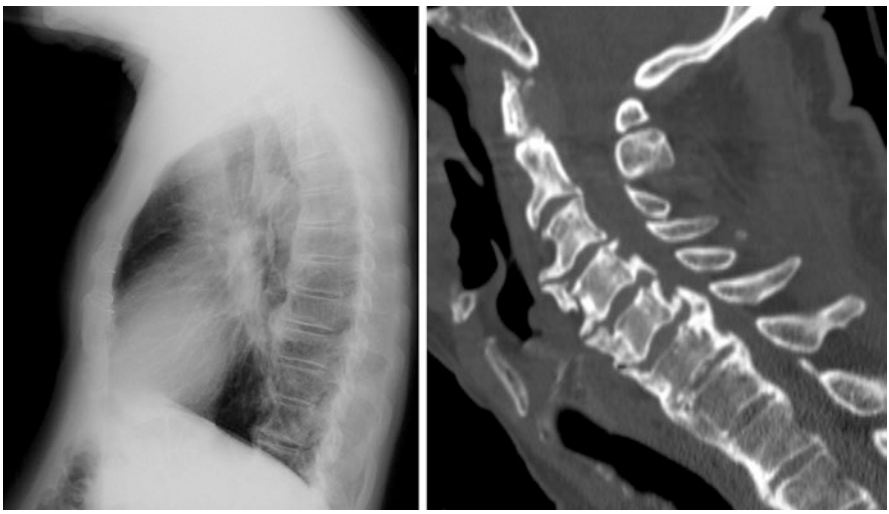

Fig. 11.24 A lateral thoracic spine radiograph (left panel) and a sagittal CT reconstruction of the cervical spine (right panel) of an 83 years old male with diffuse idiopathic skeletal hyperostosis (DISH) demonstrating multiple flowing osteophytes in the anterior aspect of the vertebras of the thoracic and cervical spine with relative preservation of the intervertebral disc space in these vertebral segments

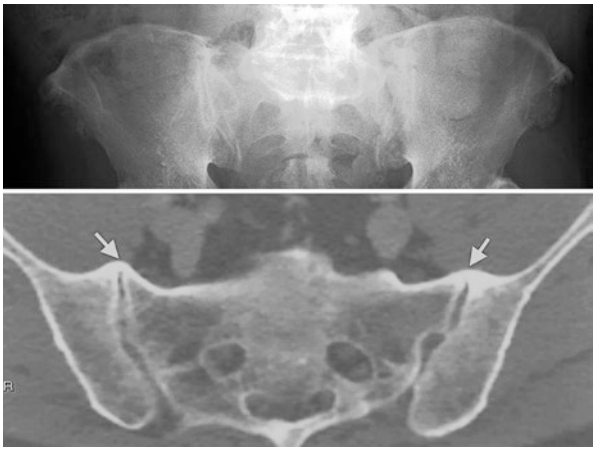

Fig. 11.25 An AP radiograph (upper panel) and an axial CT slice (lower panel) of the sacroiliac joints of a 73 years old male with diffuse idiopathic skeletal hyperostosis (DISH). The joint space of both sacroiliac joints on the radiographs is hardly detected and the joints are erroneously perceived as ankylosed. On the CT, anterior thick osteophytes connecting between the iliac and sacral sides of the joints are seen. These osteophytes cause the erroneous perception of ankylosed joints on AP radiographs

In contrast to the exclusion criterion of the Resnick and Niwayama DISH classification criteria, sacroiliac joints' (SIJ) fusion, anterior and posterior bridging, and entheseal bridging characterize subjects with DISH and distinguish them from patients who do not have DISH [57]. These indeed involve mainly the anterior and posterior entheses of the sacroiliac joints but are also commonly detected within the joint. On pelvic radiographs SIJ anterior bridging and ankylosis in DISH may mimic an ankylosed joint in spondyloarthritis (SpA) (Fig. 11.25). Erosions however are rare in DISH and the presence of such erosions on radiographs may help in differentiating between DISH and SpA [57].

11.3.2 DISH Peripheral Enthesopathy

The pathogenesis of DISH is poorly understood, however it is clear that entheseal and ligamentous ossification, osteophyte formation and finally bone bridging and ankylosis are a continuum [51]. Pelvic enthesopathies are considered highly characteristic of DISH, and include enthesopathy of the sacrotuberous and iliolumbar ligaments as well as insertional enthesopathy of tendons such as the iliopsoas on the hips' lesser trochanter, the gluteus medius along the iliac crest and its insertion at the greater trochanter [48, 58]. Characteristic pelvic enthesophytes are thick and prominent just like the ones seen on the spine (Fig. 11.26).

Peripheral enthesopathy in other locations have been commonly described including the anterior chest wall joints and the elbows [59, 60].

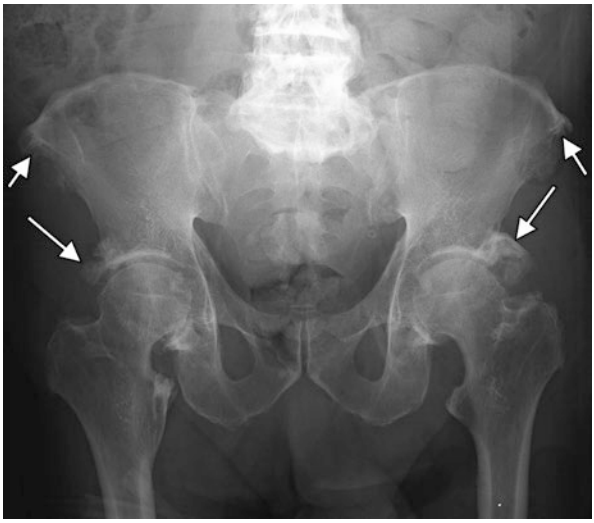

Fig. 11.26 An AP pelvic radiograph of a 73 years old male with diffuse idiopathic skeletal hyperostosis (DISH) demonstrating multiple thick enthesophytes characteristic of DISH

11.4 Psoriatic Arthritis and Rheumatoid Arthritis

Psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are of course not limited to the elderly. However, since they are commonly seen in the elderly and need to be differentiated from other erosive diseases in this age group we have decided to elaborate on them in the current chapter.

In both diseases intra-articular synovial inflammation and hyperplasia is an important pathologic process. However, in PsA ethesopathy has also a major pathogenetic role.

The joints of the hands and feet are commonly affected in both diseases thus their imaging has a significant role in the assessment and diagnosis [61, 62].

Both diseases present radiographically with joint space narrowing, periarticular erosions and joint destruction as well as joint subluxations and potentially ankylosis. However, despite the similar basic mechanism of synovial hypertrophy leading to these erosions, the two diseases have quite distinctive and different radiographic characteristics in the hands and feet. While RA affects mainly the proximal joints (e.g. intercarpal/intertarsal- and metacarpal/metatarsal joints), PsA affects the distal joints (e.g. proximal and distal interphalangeal joints) (Fig. 11.27). Also, unlike RA, joint involvement in PsA is often asymmetrical and may be oligoarticular.

In RA there is an associated periarticular osteopenia with no reactive bone formation (e.g. osteophytes) while PsA present with reactive osteophytes and periostitis with minimal if any periarticular osteopenia. Though RA is considered a more destructive disease, some forms of PsA may lead to extreme destruction and mutilation of the joints. These changes in PsA can affect the entire digit leading to dactilitis, or sausage finger.

Hip involvement may occur in both diseases. In both there is characteristic medial displacement of the femoral head leading to concentric and symmetric joint

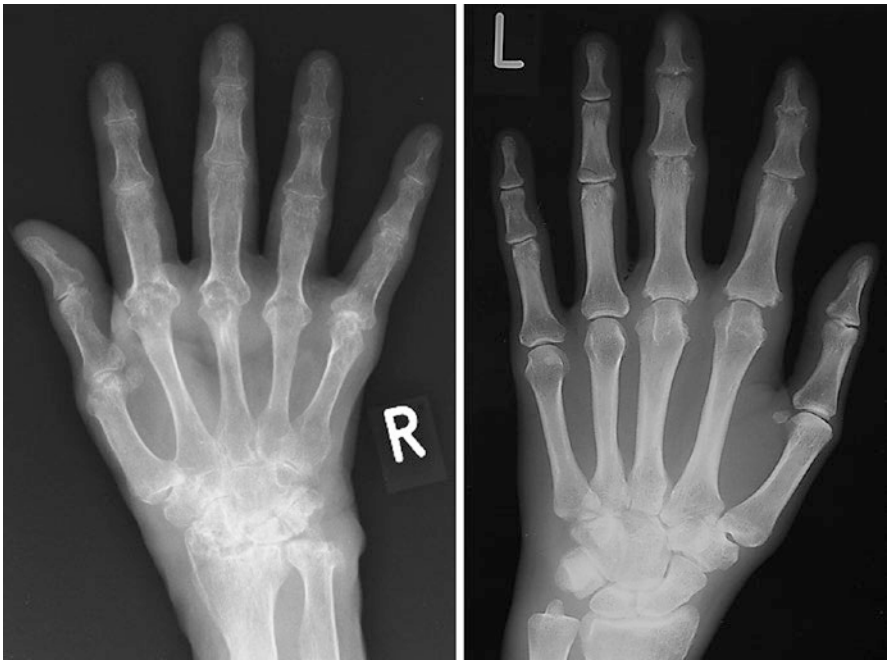

Fig. 11.27 An AP radiograph of the right hand of a 66 years old female with rheumatoid arthritis (left panel) and the left hand of a 68 years old male with psoriatic arthritis (right panel). The patient with rheumatoid arthritis has multiple proximal erosions involving the radius and ulna as well as the carpal bones and metacarpophalangeal joints. The patient with psoriatic arthritis have distal involvement with erosions of the metacarpophalangeal, proximal and distal interphalangeal joints of the second and third fingers as well as some mild periostitis

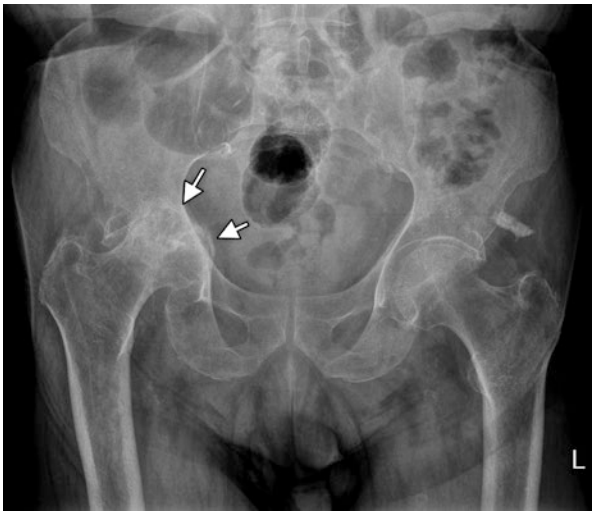

Fig. 11.28 An AP pelvic radiograph of a 60 years old female with rheumatoid arthritis demonstrating concentric and symmetric joint space loss in the right hip with remodeling of the acetabular roof resulting in the characteristic image of "protrusio acetabulum"

space loss (Fig. 11.28). This is in contrast to the characteristic osteoarthritic joint space narrowing that results in a superior migration of the femoral head with an asymmetric joint space narrowing. This concentric joint space narrowing can lead to medial acetabular displacement, or protrusio acetabulum, that is known to affect RA but was also described in PsA.

The axial skeleton can be involved in both diseases, however with completely different characteristics. Subjects with PsA that have axial involvement of the sacroiliac joints (SIJs) and spine and are part of the spondyloarthritides while the SIJs in RA are not characteristically affected. Sacroiliac inflammation in PsA results in erosions, subchondral sclerosis, narrowing or pseudo-widening of the joints and ankylosis. It is important to know that these structural lesions are detected on X rays relatively long time after the beginning of joint inflammation, while MRI enables the detection of inflammation in its early stages. Sacroiliitis in PsA can be either symmetric or asymmetric differentiating it from ankylosing spondylitis that is usually symmetric disease.

Spine involvement in PsA results in the development of bulky lateral osteophytes, that grow asymmetrically along the spine, also known as parasyndesmophytes.

Synovial involvement of the cervical spine is a characteristic of RA. Synovitis in the cervical first and second vertebras' joint may lead to ligamentous tear and spinal instability. Flexion and extension cervical spine radiographs may help in detection such instability.

11.5 Neuropathic Foot

Neuropathic arthropathy was first described in 1868 by Jean-Martin Charcot related to tabes dorsalis [63]. It refers to progressive degeneration of a weight bearing joint, marked by bone destruction and resorption leading to eventual deformity due to loss of sensation. Onset is usually insidious. Although neuropathic joints can be seen in a variety of diseases other than tabes dorsalis, today diabetic polyneuropathy is the most common cause of neuropathic arthropathy [64, 65]. The majority of the patients with neuropathic feet present between the fifth and sixth decades and most have had diabetes mellitus for a minimum of 10 years [65]. Acute presentation is characterized by a warm, red, and swollen foot and ankle. These of course may also be seen in presence of infection. In the chronic stage, a warm and red foot is no longer present but edema may persist.

The midfoot is usually the first to be affected and the earliest finding on radiographs is demineralization, or osteopenia. Radiographs of neuropathic foot in the chronic stage can be summarized with rule of "6 D's" that is representing joint distention, destruction, dislocation, disorganization, debris and increased bone density [66] (Fig. 11.29). Metatarsophalangeal joint involvement with pencil and cup appearance can be seen. The involvement of tarsometatarsal joints lead to the collapse of the longitudinal arch, which results in increased load bearing on the cuboid

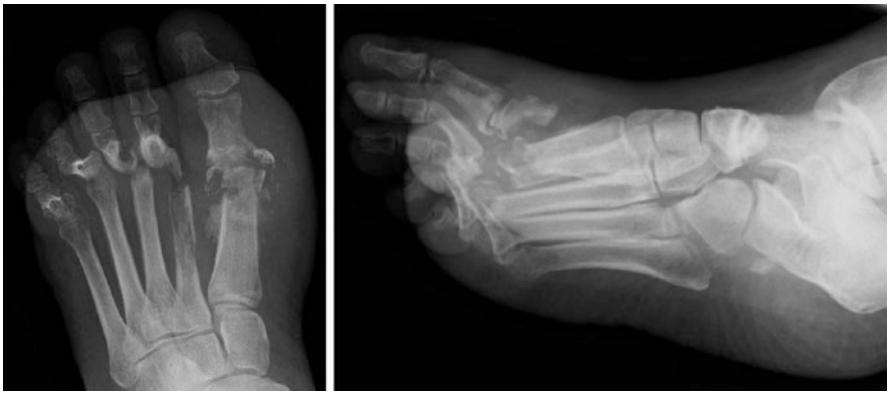

Fig. 11.29 An AP and lateral radiographs of the left foot of a 71 years old diabetic male demonstrating characteristic findings of neuropathic foot involving mainly the metatarsophalangeal joints. These include bone and joint, destruction, dislocation, disorganization, debris and increased bone density

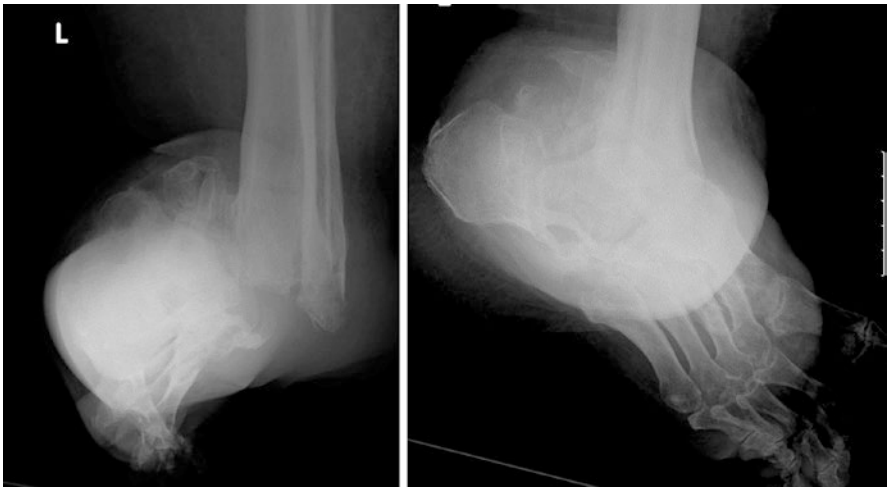

Fig. 11.30 An AP and lateral radiographs of the left foot of a 64 years old diabetic female with advanced neuropathic foot changes involving mainly the hindfoot. These include severe tibio-talar joint dislocation as well as bone and joint destruction, disorganization, debris and increased bone density

and rocker-bottom deformity. Talocalcaneal dislocation, talar collapse, atypical calcaneal fractures might be seen in hindfoot [66] (Fig. 11.30). Differentiating between infection and neuropathic joint is challenging using radiographs alone and usually more advanced imaging techniques such as CT and MRI are necessary to distinguish between the two.

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Chapter 12
Musculoskeletal Ultrasound in the Diagnosis of Rheumatic Disease in the Elderly

Amir Haddad, Tal Gazitt, and Devy Zisman

12.1 Use of Ultrasonography in Rheumatology

Over the years, ultrasound (US) has become an important tool in the diagnosis, assessment, and management of rheumatic diseases.

Unlike other imaging modalities, ultrasonography provides real-time dynamic imaging and can be performed in the clinical setting by a rheumatologist, allowing rapid decision making in the evaluation and management of patients. Compared to other imaging modalities, it is inexpensive, better tolerated, and more readily available.

Using US, multiple joints can be assessed in a short period of time, allowing for the simultaneous analysis of tissue morphology and function, the detection of synovitis, tenosynovitis, enthesitis, and bone erosions, as well as detection of other rheumatologic pathologies including vasculitis, nerve entrapments, and salivary gland and skin abnormalities. Moreover, US is also used for guidance of joint aspirations and intra-articular joint injections by allowing accurate needle placement.

A. Haddad (✉) · T. Gazitt
Rheumatology Unit, Carmel Medical Center, Haifa, Israel

D. Zisman
Rheumatology Unit, Carmel Medical Center, Haifa, Israel

The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel

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12.2 Ultrasound Imaging in Rheumatoid Arthritis

Rheumatoid arthritis (RA) manifests as symmetrical polyarthritis, most commonly affecting the hands. The synovium of the joint proliferates and becomes thickened, and increased blood flow is seen on power or color Doppler ultrasonography indicating the presence of active inflammation. Synovial hyperplasia is a distinctive feature of RA, appearing on gray-scale ultrasonography as frond-like projections of the synovium which are abnormally hypoechoic (but which may also be isoechoic or hyperechoic) relative to subdermal fat. This intra-articular tissue is non-displaceable and poorly compressible and may exhibit Doppler signal [1] (Fig. 12.1).

Both color and power Doppler imaging enable in-depth assessment of disease activity in the joints. Indeed, recent studies show that ultrasonography has an added value compared to the use of clinical and laboratory evaluation alone in the diagnosis of RA [2]. For instance, a study by Salaffi et al. reported an odds ratio of 9.9 for likelihood of progression to RA if a Doppler signal was documented in one joint and 48.7 whenever more than three joints were involved in comparison to 10.9 in patients with high titers of anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF) [3]. Another added advantage of Doppler ultrasonography lies in its ability to detect subclinical synovitis in cases where joint swelling is subtle.

Aside from synovitis, tenosynovitis is another common clinical feature of RA. Normal tendons have a characteristic "fibrillary" appearance which exhibits isotropic echogenicity with respect to the angle of insonation by the US beam. Tenosynovitis is defined as hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit Doppler signal [1]. The documentation of tendonitis is supportive of RA; however, the documentation of paratendonitis and enthesitis would be less supportive of the diagnosis of RA but rather suggesting other etiologies such as psoriatic arthritis [4, 5].

The presence of bone erosions, another characteristic feature of RA, is a poor prognostic sign. In RA, erosions are commonly found at the proximal bone ends just at the edge of the hyaline cartilage. US imaging has been shown to be superior to standard imaging in detecting bone erosions, showing definite early erosions that are not yet visible on standard radiography [6]. In ultrasonographic terminology,

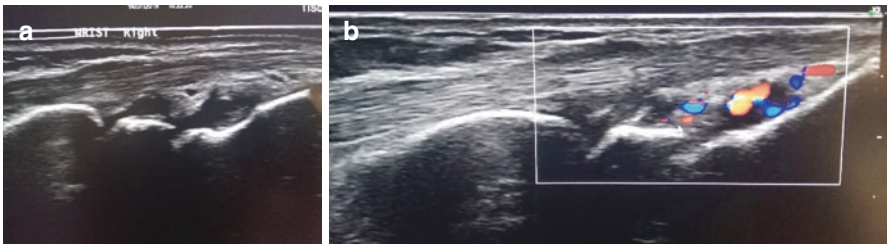

Fig. 12.1 (**a**) Gray scale synovitis of the radiolunate and lunucapitate joints. (**b**) Presence of Doppler signal

erosions are defined as an intraarticular discontinuity of the bone surface that is visible in two perpendicular planes [1].

In RA, the use of US is not only limited to disease diagnosis but may also be used for monitoring of disease activity and musculoskeletal tissue function. For instance, the dynamic assessment of joint and tendon movement aids in the detection of structural abnormalities. Also, repeated ultrasonographic assessment of joints over time may point to subclinically active disease. Importantly, however, unlike the consensus which exists regarding the role of US use in RA diagnosis, the use of US in day-to-day clinical management of RA is still controversial given recent studies showing increased risk of overtreatment of RA based on subclinical ultrasonographic findings. In these studies, patients whose disease activity was monitored by ultrasonography experienced more frequent medication changes which were not associated with better clinical or imaging outcomes [7, 8]. On the other hand, in patients in clinical remission, US has been shown to predict maintenance of remission, as patients with US-detected residual synovitis are at higher risk of flareup and often had a shorter duration of remission than patients in sonographic remission [9, 10].

12.3 Spondyloarthritis

Seronegative spondyloarthritis (SpA) represents a group of diseases that share certain genetic, clinical, and radiographic features, with spondylitis, enthesitis, dactylitis, and peripheral oligoarthritis considered the hallmark musculoskeletal clinical features of this group of arthritides. Enthesitis is defined as inflammation at the site of tendon insertion into the bone, whereas dactylitis is defined as diffuse swelling of a entire digit in the hand or foot to the extent that the individual, independent small joint swelling in the digit can no longer be recognized. US is a sensitive tool which allows for the detection of these types of soft tissue inflammation.

Ultrasonographic enthesitis is defined as an abnormally hypoechoic and/or thickened tendon or ligament with loss of its normal fibrillar architecture at its bony attachment site, seen in two perpendicular planes, and which may occasionally contain hyperechoic foci consistent with calcifications, and/or may exhibit Doppler signal and/or bony changes including enthesophytes, erosions or irregularity at the insertion site [1]. US assessment of the entheses, particularly using power Doppler, may assist in early diagnosis and correct classification of patients with non-specific symptoms suggestive of SpA [11]. In psoriatic arthritis (PsA), several indices to assess active enthesitis exist; however, none of them have been validated. In this group of patients in particular, where obesity and mechanical injury commonly affect the entheses and are thus known confounders of entheseal pathology, any entheseal abnormality should be interpreted with caution [12]. Notably, however, a recent study aimed at validation of the realibility of ultrasonographic entheseal findings confirmed that hypoechogenicity, increased thickness of tendon insertion, calcifications, enthesophytes, erosions, and Doppler activity are suggestive of ‘true’ enthesitis [13] (Fig. 12.2).

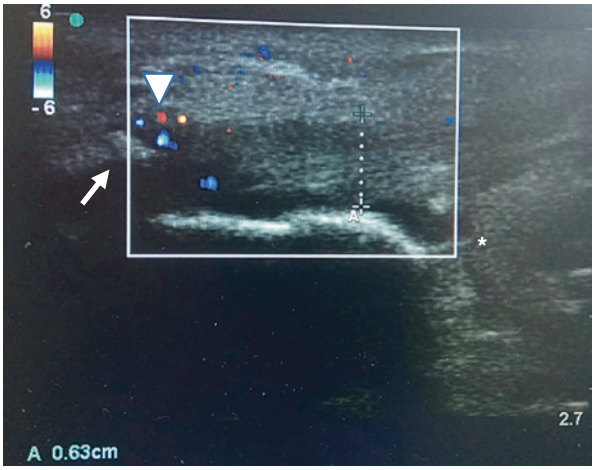

Fig. 12.2 Active enthesitis of the Achilles tendon (arrowhead) with calcaneal spur (arrow) and expansion of the retrocalcaneal bursa (asterisk)

In the case of dactylitis, ultrasonographic imaging studies have revealed that it is a highly heterogeneous, mainly pandigital disease involving tenosynovitis (with flexor tendons being more frequently affected than the extensor tendons), joint synovitis, soft-tissue and bone marrow edema, and erosive bone damage [14].

12.4 Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease of the elderly characterized by proximal muscle pain and stiffness that affects the neck, shoulder, and pelvic girdles. PMR can occur independently or in association with giant cell arteritis (GCA), which is the most common form of primary vasculitis. The diagnosis of PMR is usually based on clinical disease presentation in the presence of acute phase inflammatory marker elevation. Because no pathognomonic findings exist which can confirm the diagnosis, different imaging techniques, especially ultrasonography, can assist in the diagnosis. The most prominent ultrasonographic findings are subdeltoid subacromial bursitis, bicipital tenosynovitis, and glenohumeral joint synovitis and less commonly hip synovitis and trochanteric bursitis [15, 16] (For 2012 EULAR/ACR Provisional Classification Criteria for PMR see chapter 19 on PMR). US is considered an easily accessible tool, which is able to rapidly reveal the presence of fluid accumulation in the aforementioned bursae, aiding in the diagnosis of PMR (See Fig. 1a, b in the Chapter 19 on PMR). Moreover, the detection of such findings on US has increased the sensitivity and specificity for the diagnosis of PMR, helping to discriminate it from non-rheumatoid shoulder conditions though unfortunately not to the extent where US findings can distinguish between PMR and RA.

In PMR, US can be used not only for diagnosis and for exclusion of other shoulder conditions, but also for monitoring treatment response or relapse on tapering of

glucocorticosteroids (GC). Some experts even suggest to examine the axillary artery bilaterally in all patients with PMR who require higher doses of GC and in cases of PMR disease relapse to rule out clinically silent large vessel vasculitis [17].

12.5 Giant Cell Arteritis (GCA)

Giant cell arteritis is a form of large vessel vasculitis affecting older adults. This type of vasculitis preferentially targets the branches of the common and external carotid arteries, the subclavian and vertebral arteries, as well as the aorta. Typical clinical features include new-onset headaches, scalp tenderness, jaw claudication, polymyalgic symptoms, fever, malaise, anorexia and weight loss. When panarteritis is intense, it can lead to luminal occlusion, manifesting as vision loss, stroke and ischemia of the upper extremities [18, 19].

All patients presenting with signs and symptoms suggestive of GCA should be urgently referred to a specialist for further multidisciplinary diagnostic work-up and management (preferentially through a 'Fast Track' evaluation process [19]) as untreated active GCA is an emergency that carries a substantial risk of permanent vision loss and other ischemic complications. Early GCA management recommendations advised on obtaining a temporal artery biopsy in every case of suspected GCA. However, accumulating evidence from good-quality data supports the use of imaging modalities, especially ultrasonography, as an alternative to tissue diagnosis [19].

A non-compressible 'halo' sign is the US finding most suggestive of GCA [20]. It is defined as a homogenous, hypoechoic wall thickening that is well delineated toward the luminal side and that is visible both in longitudinal and transverse planes, and is most commonly concentric in transverse scans [21] (Fig. 12.3). This sign has a sensitivity of 77% and a specificity of 96% as compared with the clinical diagnosis of GCA. The persistence of a hypoechoic swelling despite the compression of the artery lumen with the ultrasound probe (termed 'compression' sign) is a variant of

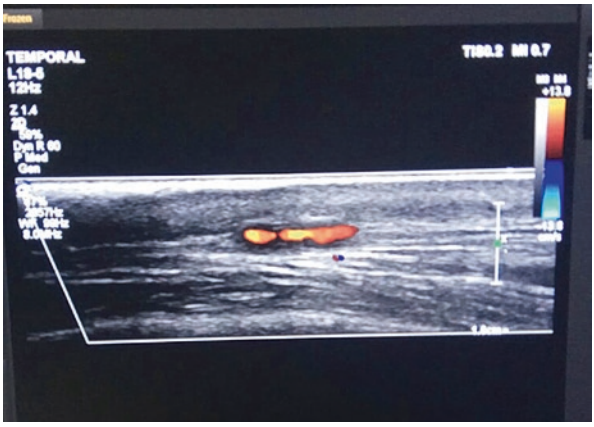

Fig. 12.3 'Halo' sign

the ‘halo’ sign with a sensitivity of 77–79% and a specificity of 100% [22]. The detection of temporal artery stenosis or occlusion is also supportive of the diagnosis but does not increase the diagnostic yield over the ‘halo’ sign alone [21].

Of note, because vasculitis lesions may affect only parts of the affected artery (appearing as skipped lesions), the common superficial temporal artery and its frontal and parietal branches should be scanned as completely as possible. According to expert opinion, examination of both axillary arteries is particularly helpful in patients with suspected GCA with negative or inconclusive temporal artery ultrasound.

Current recommendations [19] suggest that, given that imaging and temporal artery biopsy have similar diagnostic value whenever assessors are proficient in these techniques, and neither imaging nor temporal artery biopsy are 100% sensitive in diagnosing GCA, it is reasonable to perform both tests (US and temporal artery biopsy) whenever there is a high pre-test clinical suspicion of GCA and one of these diagnostic tests is negative. However, in patients with a low clinical pre-test probability of GCA and a negative US imaging result, the diagnosis of GCA can be considered unlikely. In all other situations, additional efforts toward a diagnosis are necessary.

Importantly, US studies in GCA report the disappearance of the ‘halo’ sign in temporal arteries in the majority of patients after 2–4 weeks of GC therapy. Current data also shows that the sensitivity of US rapidly decreases from 88% to 50% even as early as 4 days following initiation of GC treatment [23]. Therefore, imaging of patients with suspected GCA should be performed as soon as possible, preferably within the first days of treatment. Nonetheless, imaging should not defer starting GC treatment.

US may be used not only for diagnosis of GCA, but also for long-term monitoring of structural damage, particularly in the detection of stenosis, occlusion, dilatation and/or aneurysms of large vessels in GCA patients.

12.6 Crystal-Induced Arthropathies

12.6.1 Gout

Gout is the most common form of inflammatory arthritis, occurring secondary to the deposition of monosodium urate (MSU) crystals in the articular and periarticular tissues. In the elderly, the diagnosis of gout is more challenging since it has a more equal gender distribution, frequent polyarticular presentation with involvement of the joints of the upper extremities, fewer acute gouty episodes, a more indolent chronic clinical course, and an increased incidence of tophi.

The gold standard for diagnosis of gout is the demonstration of MSU crystals (negatively birefringent needle-shaped crystals) from synovial fluid, tissue, or tophi, on polarizing microscopy. Unfortunately, however, even in diagnostic studies of gout where the gold standard used was MSU crystal identification in synovial fluid or nodule aspirate among individuals with a broad range of diagnoses, the sensitivity for diagnosis of gout has ranged from 57.6 to 100% (i.e., with 100% sensitivity

considered MSU crystal identification), and with specificity ranging from 34.3 to 86.4% [24] mostly due to technical difficulties such as aspiration of insufficient amount of synovial fluid for crystal analysis and difficulty in crystal identification under polarizing microscopy. In this regard, the new 2015 ACR/EULAR Classification Criteria for Gout represent an advancement over the previous sets of criteria with the incorporation of newer imaging modalities including US with the sonographic demonstration of the 'double contour' (DC) sign [25].

The physics of US makes it an ideal tool to detect crystalline material in soft tissues. MSU crystal deposition can be detected on ultrasonography in several ways. First, crystals may deposit on the surface of the articular cartilage manifesting as a hyperechoic enhancement, i.e. the DC sign. This irregular or regular linear enhancement lies over the surface of the hyaline cartilage, and can be either continuous or intermittent and is independent of the angle of insonation of the ultrasound beam. Importantly, this linear enhancement should be differentiated from a false positive DC sign which may appear at the cartilage surface but which disappears with a change in the insonation angle of the probe ('cartilage interface' sign). Second, crystals may be found within the joint space as floating heterogeneous hyperechoic foci resembling the appearance of a snowstorm. These aggregates may be either intra-articular or intra-tendinous, and should maintain their high degree of reflectivity even when the gain setting is minimized or the insonation angle is changed. Occasionally, these hyperechoic foci may generate posterior acoustic shadowing; may appear as a circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (which may or may not generate a posterior acoustic shadow); and may be surrounded by a small anechoic rim, suggesting tophi within the joint or along tendons (Fig. 12.4). Gout erosions are defined as an intra- and/or extra-articular discontinuity of the bone surface (visible in two perpendicular planes [1]).

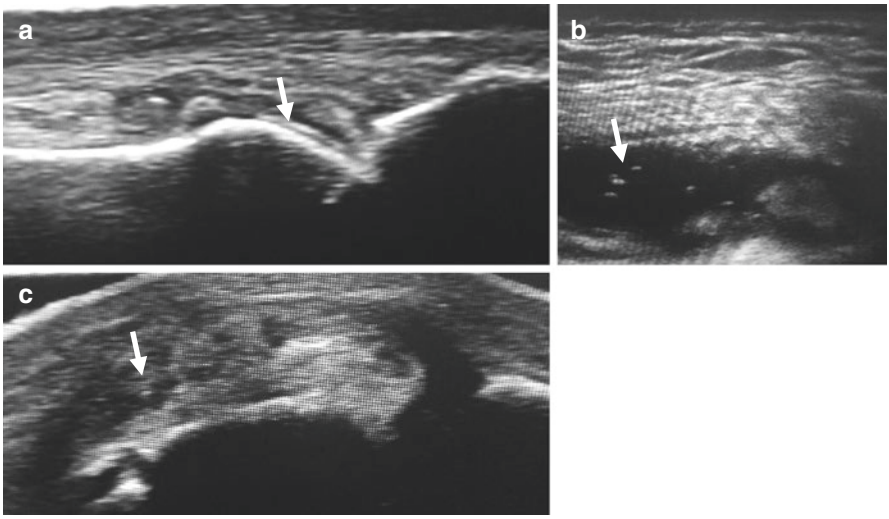

Fig. 12.4 (**a**) DC sign (arrow) (**b**) snowstorm MSU aggregates (arrow) (**c**) with hyperechoiec aggregates suggestive of toph aceous material (arrow)

Data from the largest US study on gout show that these ultrasonographic features have high specificity (84%) and that the DC sign and ultrasonographic imaging of tophi perform better than the snowstorm appearance in the diagnosis of gout [26]. However, recent studies show that ultrasonography cannot reliably distinguish between gout and calcium pyrophosphate deposition disease (CPPD) in everyday clinical practice, in which 'atypical' (punctate) forms of DC sign are described [27]. Moreover, in patients with asymptomatic hyperuricemia, both hyperechoic, cloudy foci and 'DC signs' were found in the joints of some individuals who had never had any symptoms of gout [28]. Despite these limitations, a recent study was able to show that combining the DC sign with hypervascularization (Doppler signal ≥ grade 2) and elevated serum uric acid levels were highly associated with gout as opposed to CPPD, thus increasing the diagnostic value of the DC sign [27].

12.6.2 Calcium Pyrophosphate Deposition Disease (CPPD)-Induced Arthropathy ('Pseudogout')

Calcium pyrophosphate (CPP) crystals may deposit in both articular tissues (predominantly hyaline cartilage and fibrocartilage) and periarticular soft tissues. CPPD may be asymptomatic or be associated with a spectrum of clinical syndromes, including both acute and chronic inflammatory arthritis, sometimes even mimicking PMR, RA, and diffuse idiopathic skeletal hyperostosis (DISH).

Accurate diagnosis of CPPD is achieved on the basis of the clinical picture and demonstration of CPP crystals in synovial fluid or tissue by compensated polarized light microscopy. The advent of musculoskeletal US, however, has enabled us to visualize crystal deposits within the joint structures, the hyaline cartilage, and/or fibrocartilage, thus aiding in the diagnosis of CPPD [29, 30]. The presence of hyperechoic deposits or bands within the intermediate layer of hyaline cartilage that do not create posterior shadowing is supportive of the presence of CPP crystals, as opposed to MSU crystal deposits that lie on the surface of the cartilage. Hyperechoic, nodular, amorphous shaped foci, often found with acoustic shadowing and most commonly located in the fibrocartilage of the wrist or the acromioclavicular joint, are also consistent with CPP crystal deposition. CPP crystals can also present as nodular, hyperechoic deposits in the bursae and joints, as well as in the form of multiple hyperechoic linear deposits running in parallel to tendon fibers that maintain their echogenicity even at very low levels of gain and are not affected by anisotropy as the surrounding tendon. In addition, CPP crystals can also be detected on US as a thin hyperechoic band paralleling the bone cortex within the cartilage resembling a DC sign initially described in gout (see discussion of DC sign in section on gout above), but often exhibiting a stippled appearance rather than the smooth pattern characteristic of gout [30]. Such ultrasonographic findings in patients presenting with inflammatory hypertrophic osteoarthrpathy favor the diagnosis of CPPD as opposed to gout based on the characteristics of the crystal aggregates and their preferential localization in different anatomical areas (Fig. 12.5).

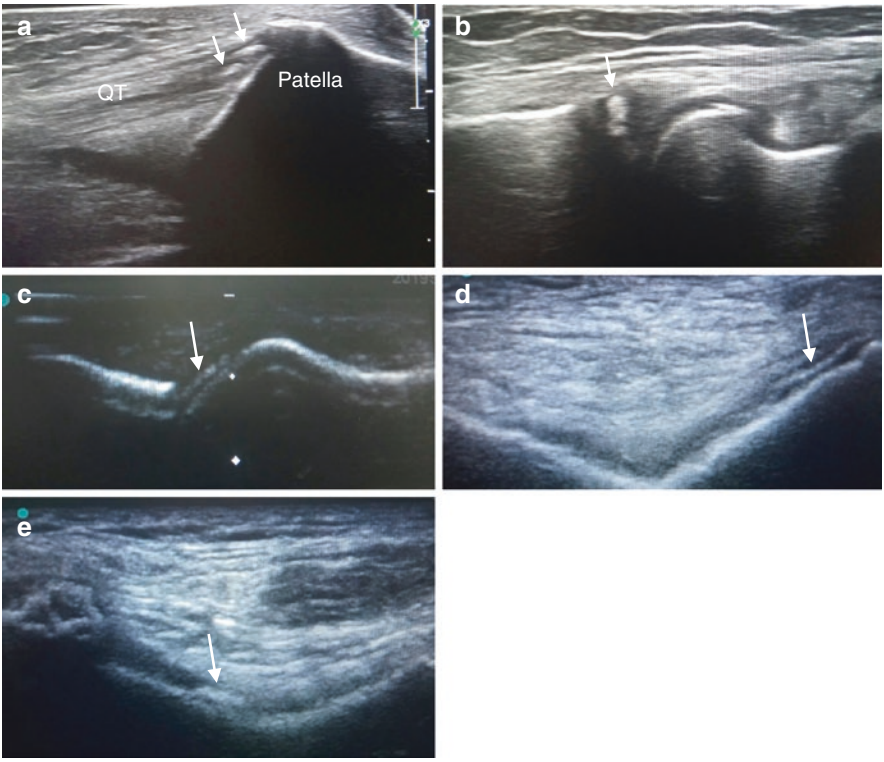

Fig. 12.5 (**a**) CPP deposits in the quadriceps tendon (QT) (arrows) (**b**) intrameniscal CPP Deposits (arrow) (**c**) CPP deposits resembling DC sign (arrow) (**d**, **e**) CPP deposits within the cartilage (arrow)

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Part II
Rheumatic Disease in Geriatrics

Chapter 13
Rheumatoid Arthritis

Gleb Slobodin

Rheumatoid arthritis (RA) is one of the most prevalent rheumatic diseases in the elderly and affects at least 2% of the population of ≥60 years of age in the US [1]. The peak age of the RA onset has become older worldwide, being gradually shifted from the fourth decade of life in the 1930s to the sixth and even to the seventh decade of life in 2010s [2]. Thus, plenty of patients in their 70s, 80s, and even 90s are developing new RA, called late-onset or elderly-onset RA, nowadays. The studies show that late-onset RA may represent up to 30% of all new RA cases nowadays. On the other hand, persons who have acquired RA at an earlier age, keep carrying this chronic disease throughout their elderly, being always subjects for disease flares, adverse effects of treatment, and related disability.

In the elderly patients, both new-onset RA or flare of the established disease, if not diagnosed fast and treated properly, can rapidly lead to sometimes grave consequences including functional deterioration, physical dependence, and depression [3–5]. Hence, the importance of the timely diagnosis and treatment of RA in the elderly population, the cornerstone of which is the knowledge of a variety of clinical presentations of late-onset RA by a primary care provider.

13.1 Diagnosis and Differential Diagnosis

Late-onset RA is a heterogeneous disease. While the majority of elderly patients with RA have signs and symptoms of a prototypical classic RA, seen in all ages, unusual presentations, including polymyalgia-like late-onset RA and Remitting Symmetric Seronegative Synovitis with Pitting Edema are common and should be recognized by primary care providers.

G. Slobodin (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel
e-mail: gleb.slobodin@b-zion.org.il

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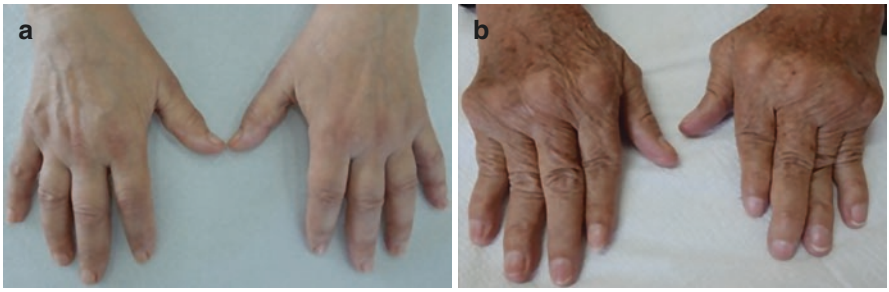

Fig. 13.1 Hand in rheumatoid arthritis. (**a**) Early disease with a typical pattern of joint involvement. Mild swelling of second to fifth PIP, second to third MCP joints, and both wrists are present. (**b**) Advanced erosive disease with permanent damage to the majority of PIP and MCP joints

Classic RA. RA, being an autoimmune disease, affects females predominantly and is characterized by insidious onset and symmetrical joint involvement, most frequently starts in proximal interphalangeal (PIP), metacarpophalangeal (MCP) joints and wrists, usually sparing distal interphalangeal (DIP) and first carpometacarpal (CMC) joints (Fig. 13.1a). At first, however, only several joints can be involved, sometimes in an asymmetric pattern. With time, a typical pattern of articular involvement becomes evident in the majority of the patients. The disease manifests with joint pain, morning stiffness and tenderness and swelling of the affected joints on examination, called synovitis. Elbows, metatarsophalangeal (MTP) joints, ankles, and knees can be involved from the early disease stage, while shoulders and hips are usually spared at the beginning. Laboratory investigation can support the diagnosis of classic RA by the elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and as well by the positive tests for rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (ACPAs). However, some patients with undoubtful clinical picture of RA can have unambiguously normal laboratory work up. Thus, negative laboratory studies, both measurement of inflammatory mediators and immune markers, do not exclude RA in a patient with characteristic clinical presentation. Anemia of chronic disease can be seen in patients with more severe arthritis and reflects the systemic nature of RA. Imaging data, contributing to the diagnosis of RA, can be very scanty at the first stage of the disease. Periarticular soft tissue swelling may be the only radiographic finding on the first evaluation, while articular bony erosions usually show up later. Eventually, erosions lead to joint deformities and impaired function (Fig. 13.1b). Comparing to conventional radiography, ultrasonography (US) can detect synovitis and even erosions in much earlier disease stage and is a preferred imaging tool for the diagnostics of the early RA.

Extra-articular manifestations of RA include rheumatoid nodules, seen usually in the seropositive RA, interstitial lung disease and other pulmonary syndromes, sicca syndrome and, rarely, vasculitis.

Late-onset RA. The demographics of late-onset RA differs from the classic disease by moderately decreased female dominance with female to male ratio of about

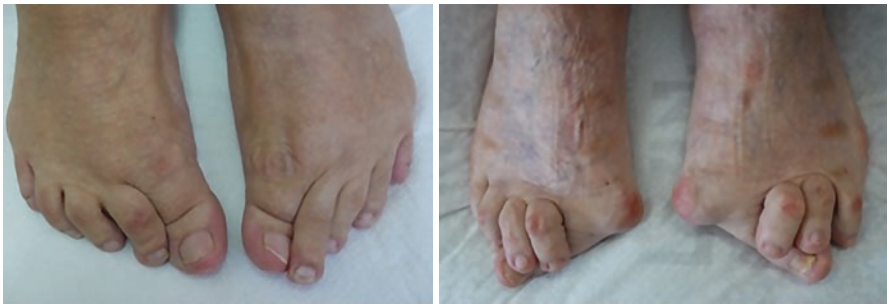

Fig. 13.2 Feet in advanced rheumatoid arthritis

2 to 3:1 in the majority of reports, and as well by the reduced prevalence of ACPAs in new RA patients, with some large-scale cohorts reporting majority of late-onset RA patients being seronegative [3, 6, 7].

The most common clinical presentation of the late-onset RA is analogous to the classic RA. Both clinical activity of the disease, judged by the counts of tender and swollen joints and elevated levels of CRP/ESR and structural damage, measured by articular erosions, have been reported in the elderly at least as bad as in younger persons [8–10]. Insidious beginning of joint pain and morning stiffness involving PIP, MCP joints, and wrists in a symmetric pattern is typical. The most commonly involved, tender or swollen, are second and third PIP and MCP joints, while synovitis in the wrists can be more evident in the proximity to the ulnar styloid. Ankles and metatarsophalangeal (MTP) joints are frequently involved in the disease process as well and should always be examined in any patient with suspected RA. In some elderly patients, feet affected by arthritis, which manifests by painful swelling or typical deformities can be a single or utmost factor in RA-related disability (Fig. 13.2). Larger joints, including knees, elbows, and shoulders can be affected as well, sometimes in the asymmetric order, already in the early disease stage. While, as already mentioned, DIP joints are usually spared by RA, these joints may be occasionally already affected by the preceding osteoarthritis in an elderly patient. Thus, the finding of affected DIP joints in an aged patient with recent inflammatory joint symptoms should not lead to the exclusion of RA at all. Systemic symptoms of late-onset RA are common, and many patients complain of concomitant weakness, tiredness and decreased activity. ACPAs can be found relatively more frequently in this subset of late-onset RA comparing to others, and, because of its high specificity, can be diagnostic. Besides, anemia of chronic disease can emerge, and CRP and ESR elevate in many, but not all patients. Extra-articular manifestations, such as rheumatoid nodules or vasculitis are rarely seen in late-onset RA; however, some elderly patients with the long-standing seropositive disease and seemingly "burnt out" inflammation have been reported to develop small vessel vasculitis with resulting rashes, neuropathy or digital gangrene [11].

Differential diagnosis of this subset of late-onset RA includes inflammatory osteoarthritis and crystal-related arthropathies above all. Tests for the serum levels

of uric acid, calcium, liver, and kidney function studies, RF and ACPAs, CRP, ESR, complete blood count (CBC) are a must. Radiography of the affected joints is always recommended and can detect calcium deposits, hooked osteophytes or, for example, punched out erosions of gout, leading to the alternative diagnosis. On the other hand, scattered entheseal calcifications not related to clinical symptoms are common in the elderly, and caution should be employed while interpreting the random appearance of those on X-rays performed in a patient with clinical RA. Similarly, radiographic signs of osteoarthritis should not serve exclusion criteria for clinically suspected RA, as both entities can co-exist in the elderly. Ultrasonography of the affected joints is useful for confirmation of clinically indistinct synovitis in some persons, and differentiation of RA from, for example, crystal-related arthropathies.

The second frequent presentation of RA in the elderly is a polymyalgia rheumatica (PMR)-like. This presentation is seen in about 25% of all late-onset RA, and its clinical features include acute onset, the involvement of both shoulders and, sometimes, hip joints, severe myalgia, and profound morning stiffness [12]. Weakness, fatigue, anemia of chronic disease, and significantly elevated CRP/ESR are very prevalent in this subset of late-onset RA. Low-grade fever can be present. Many such patients are first diagnosed with PMR, start treatment with glucocorticoids and, not surprising, improve within days. Then, RA becomes evident much later, sometimes during a flare in a patient with a presumed diagnosis of PMR, when previously undetected peripheral synovitis shows up, disclosing late-onset PMR-like RA. Thus, the keys to the diagnosis of this subtype of RA are often hidden at the first encounter, while the high level of suspicion and focused quest are frequently the decisive factors, leading to the right judgment. Concomitant synovitis of peripheral joints, such as wrists, ankles, or knees is an essential clinical feature in favor of RA but sometimes requires a thorough physical examination to be disclosed. Elevated CRP and ESR are seen in both PMR and PMR-like RA, but a positive test for ACPAs, although not very sensitive in this setting, can be diagnostic for late-onset RA. Sometimes, less than expected in genuine PMR clinical and laboratory improvement under treatment with glucocorticoids can lead to the reevaluation of the whole clinical picture and the alternative diagnosis of RA. It has been reported that up to 20% of late-onset RA presenting with bilateral girdle pain and elevated CRP and ESR were diagnosed by a rheumatologist as having PMR on the first encounter [13, 14]. In this regard, ultrasonography and magnetic resonance imaging (MRI) modalities, able to localize the disease process as articular versus periarticular, have been suggested as potential tools for differentiation of seronegative PMR-like late-onset RA from PMR. However, their practical use is still limited by current research data, which shows that shoulder synovitis has similar prevalence in both PMR and late-onset PMR-like RA, and only existing extracapsular inflammation, such as subacromial and subdeltoid bursitis or pelvic tendonitis, is thought to be more typical for PMR [15, 16].

Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE) is another presentation of RA, which occurs in the elderly in up to 10% of all patients with late-onset RA. Patients complain of acute onset of joint pain and stiffness, while physical examination reveals severe synovitis and tenosynovitis of hands, wrists, feet, and ankles with massive surrounding pitting edema. Large joints can be

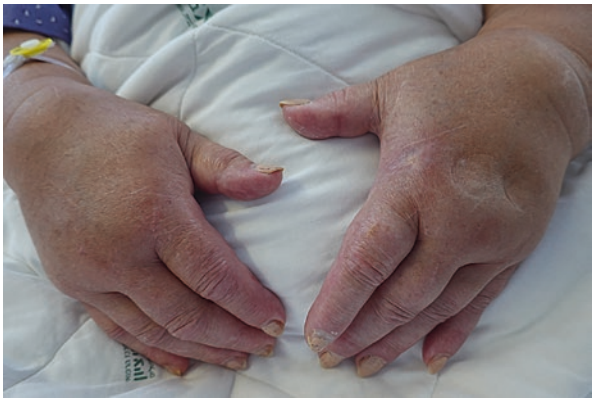

Fig. 13.3 Patient with RS3PE syndrome. Synovitis of both wrists and metacarpophalangeal joints of both hands is present. Pitting edema is a hallmark of this syndrome

frequently involved as well; however, the swollen hands and feet are a hallmark of this syndrome (Fig. 13.3). Fatigue, low-grade fever, and weight loss have been repeatedly reported in patients with RS3PE as well. Serum inflammatory markers are consistently elevated, and anemia of chronic disease is commonly seen. Tests for RF and ACPA are usually negative. The clinical presentation of RS3PE syndrome is straightforward, but differential diagnosis exists and includes malignant disorders, both solid and hematologic. It was suggested that up to 30% of RS3PE syndrome might be related to known or hidden neoplasia. Thus, relevant malignancy workup should be considered in every patient presenting with RS3PE [17]. On the other hand, RS3PE, if not related to malignancy, usually carry a favorable prognosis, is not accompanied by erosion formation and responds well to treatment [17, 18].

13.2 Principles of the Pharmacological Treatment

13.2.1 Treatment at the disease start or during the flare

The main goal of treatment during the acute phase of RA is to achieve the state of low activity of the disease as fast as possible to prevent deconditioning of the elderly patient. Waiting for the positive effect of therapy for 2 or 3 months can be unwise in an aged patient who suspends his activities and can rapidly progress to frailty due to the active disease. Thus, the first goal of treatment is to reduce joint pain and stiffness, preferably within days.

Selective as well as non-selective non-steroidal anti-inflammatory drugs (NSAIDs) are used relatively rarely in the elderly in this setting due to their potential side effects in the prone for comorbidities population. Arterial hypertension, heart failure, renal insufficiency, upper gastrointestinal problems, and concomitant anticoagulation therapy are the most important, but not the only contraindications for continuous NSAIDs administration. An aged person, even without evident contraindications, may be put in substantial risk for NSAIDs-related side effects by daily treatment with NSAIDs in the full dose even for a short period [19].

Thus, glucocorticoids stay frequently a drug of choice to suppress RA activity in the short-term and prevent disease-related frailty, and are used in this population more commonly comparing to younger persons in this setting [10, 20]. Usually, the daily quantity of 20 mg prednisone is a sufficient dosage to suppress the inflammatory process within days in late-onset RA, and it can be tapered down to daily 15 mg already the next week. Further tapering of the dosage down depends on the well-being of a patient, with daily 10 mg or even 5 mg of prednisone be enough to allow the acceptable quality of life while waiting for the benefits of disease-modifying anti-rheumatic drugs (DMARDs). In patients with significant comorbidities, the initial dose of prednisone can be reduced to 10 mg a day. The entire course of glucocorticoids can last up to 6–8 weeks until the simultaneously administered DMARDs start acting. These relatively short courses of glucocorticoids, used in limited quantities, are generally safe even in the aged patients but may necessitate adjustment of the intensity of anti-hypertensive or anti-diabetic therapies as well as the use of proton pump inhibitors. Concomitant treatment with calcium, vitamin D, and bisphosphonates is not usually required during these restricted in time and dosage glucocorticoid courses. The larger dosages of glucocorticoids are rarely required in elderly RA patients. In any patient with late-onset RA, a single morning dose of drug administered after breakfast should be a preferred scheme of glucocorticoid treatment, primarily because of decreased rate of potential side effects, including adrenal insufficiency. In general, well-planned glucocorticoid treatment can significantly benefit elderly patients with RA during periods of disease activity even in the presence of significant comorbidities. On the other hand, prolonged administration of glucocorticoids, even in tiny doses, is highly undesirable in the elderly because of the burden of side effects, including increased rate of infections, osteoporosis, glaucoma, cataract, diabetes, arterial hypertension, adrenal insufficiency, and others.

13.2.2 Maintenance Treatment

Synthetic DMARDs (sDMARDs). All patients with RA should start treatment with sDMARDs promptly after the diagnosis of RA was made [21]. The goals of DMARD administration include the change in the natural disease course and prevention of erosion formation, avoidance of disease flares and a decrease in cumulative glucocorticoid dosage with resulting improvement of the functional status of patients and their well-being.

Methotrexate has been accepted worldwide as a mainstay of long-term therapy for patients with RA. Usually used in a weekly dose range between 7.5 and 25 mg, methotrexate has distinct advantages as well as caveats when used in elderly patients. The once-weekly administration of methotrexate may be more convenient for an aged person, typically taking multiple medications for a variety of medical disorders. It also has little reported interactions with other drugs and is available in injections, which have less gastrointestinal side effects, such as nausea, and better bioavailability as well, when compared to pills. On the other hand, as the decreased renal function can lead to methotrexate accumulation and toxicity, adjustment of

methotrexate dosage by creatinine clearance rate is advised in every aged patient. The initial weekly dosage of methotrexate in the range of 7.5–12.5 mg is commonly used in the elderly and can be tapered up after 2 months if necessary and safe. The benefits of methotrexate are usually seen after 6–8 weeks of treatment. In any case, blood tests for complete blood count and liver function should be performed every 6–12 weeks, and any change in the level of hemoglobin or liver enzymes should not be missed. Folic acid is usually added to methotrexate to decrease its toxicity. Contraindications for methotrexate use include primarily renal failure, liver dysfunction, and bone marrow maladies, such as myelodysplastic syndromes.

Leflunomide is an alternative to methotrexate drug in patients with RA. It has comparable to methotrexate efficacy, is used as a daily 10 or 20 mg pill, and its onset of action is seen after about 6 weeks of administration. A spectrum of relevant for the elderly potential side effects of leflunomide includes loss of appetite and weight loss with or without diarrhea and the possible deterioration of liver function, which should be monitored every 4–6 weeks at first and every 6–12 weeks after that.

Hydroxychloroquine is less potent medicine for RA and is used in mild cases or as an addition to methotrexate treatment in a dosage of up to 5 mg/kg/day. Examination by an ophthalmologist is advised before and periodically during the hydroxychloroquine treatment because of its potential ocular toxicity.

Sulfasalazine, while generally recommended as an alternative sDMARD for RA patients, is rarely used in the elderly because of its inconvenient way of administration as up to 4 daily pills and relatively frequent gastrointestinal and neurological, such as dizziness or headache, side effects.

Biologic DMARDs (bDMARDs) and small molecules. The emergence of biologic medicines has led to the blooming of rheumatology as a field of medicine in recent decades. These medicines, intentionally targeted against pathogenic cytokines or cell surface-linked particles, have cardinally changed the battlefield with some major rheumatic conditions, including RA. Small molecules are a relatively new group of medicines, targeting molecules of intracellular inflammatory pathways, which possess comparable to biologic medicines efficacy and safety. The ability of bDMARDs and small molecules to improve symptoms and signs of RA as well as to shut down the process of erosion formation in the majority of RA patients resistant to sDMARDs, have led to the growing popularity of this class of medicines worldwide. More than 30% of all RA patients are being treated with one of the biologic medicines or small molecules in developed countries nowadays [22]. The administration of these medicines is a subject of local health regulations due to the high cost, and their accessibility varies in different countries. Both bDMARDs and small molecules are indicated for patients with moderately severe and severe RA and synovitis, resistant to one or several sDMARDs [21]. Available nowadays bDMARDs include inhibitors of tumor necrosis factor-alpha (TNF-a), inhibitors of interleukin-6 (IL-6), co-stimulation (CTLA-4) antagonists, and anti-B cell (anti-CD-20) agents. Small molecules, indicated for RA, encompass non-selective and selective for JAK-1 JAK inhibitors (Table 13.1). The unequivocal efficacy of all bDMARDs and small molecules in RA patients has been demonstrated in multiple clinical trials, in the majority of which elderly patients showed clinical efficacy, radiographic stability, safety and drug survival rate comparable to their younger

Table 13.1 bDMARDs and small molecules approved for the treatment of RA

TNF-α inhibitors	IL-6 inhibitors	CTLA-4 inhibitors	B cell therapy	Non-selective JAK inhibitors	Selective JAK-1 inhibitors
Infliximab	Tocilizumab	Abatacept	Rituximab	Tofacitinib	Upadacitinib
Etanercept	Sarilumab			Baricitinib	
Adalimumab					
Golimumab					
Certalizumab					

counterparts [10, 23–27]. However, some other reports have mentioned moderately decreased efficacy or slightly increased percentages of side effects of biologics and small molecules in the aged population [28–31]. A systematic review of the efficacy and safety of biologic agents in the older RA patients was recently published [32]. Notably, all bDMARDs and small molecules have shown approximately similar rates of efficacy and safety in clinical studies involving patients with RA; thus the choice of medicine for an individual patient depends nowadays mostly on this patient's medical background and preferences. In the elderly population, the choice of drug is particularly influenced by existing comorbidities. It is believed that comorbidities are probably the main limiting factor and cause of low, less than 10% utilization rates of bDMARDs and small molecules in the elderly patients with RA [3, 20, 33, 34].

Tests for latent tuberculosis, PPD or quantiferon blood testing, are strongly advised for all candidates for treatment with bDMARDs and small molecules. In patients with positive tests, the beginning of biologics should be delayed for at least 1 month since the prophylaxis of tuberculosis has been started. The onset of action differs in various bDMARDs and small molecules, being generally shorter in the latter. In the beginning, biologics are usually added to the current treatment regimen with sDMARD due to the better efficacy of the combined treatment, but monotherapy is often possible and is frequently preferred by patients. Commonly, at least 3–6 months of treatment by a bDMARDs or small molecule are allowed before stating drug inefficacy and switching to another module of treatment. It is essential to remember and to share with a patient as well, that no tool predicting the efficacy and safety of a particular bDMARDs or a small molecule in a particular RA patient exists at this time. Thus, recurrent switching to alternative biologic medicine, while seeking a state of remission or low activity disease in an RA patient is a common practice in modern rheumatology.

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Chapter 14
Treating Rheumatoid Arthritis Through the Life Course

Lina Serhal, May N. Lwin, and Christopher J. Edwards

14.1 Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects patients at different ages [1]. The onset of RA varies from young age of 14 to elderly age of 60 or more [2]. The incidence of RA increases with age [3]. The elderly RA population constitute the third of the general RA population and include elderly onset RA and patients with a history of young onset RA who aged naturally [2]. There is a good body of evidence that the immune system undergoes age related changes in RA regardless of the age of onset and disease duration [3]. These changes, although similar to the physiological aging process, are more accelerated and premature in RA [4]. Elderly RA patients seem to be particularly at risk of infections and associated comorbidities, perhaps due to the effect of both age and RA on the immune system [4, 5]. It seems that elderly onset RA displays a characteristic clinical and biological pattern and is associated with worse long-term outcomes than young patients [6]. Nevertheless, this age group is not well presented in clinical trials due to restrictions on age or the presence of comorbidities, and hence evidence on the efficacy and safety of RA therapy is lacking [7]. We reviewed the literature to determine whether age may influence the treatment of elderly RA patients in real practice, and whether elderly patients may have particular benefit-risk profile that would suggest specific therapeutic strategies.

L. Serhal · M. N. Lwin · C. J. Edwards (✉)
Department of Rheumatology and NIHR Clinical Research Facility,
University Hospital Southampton NHS Foundation Trust, Southampton, UK
e-mail: cedwards@soton.ac.uk

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14.2 Immunosenescence

The immune system undergoes changes with age known as immunosenescence [5]. There is good evidence demonstrating a strong association between immune aging changes and increased susceptibility of infections, cancer and autoimmune diseases, such as RA [5, 8].

14.2.1 Immunosenescence: A Physiological Aging of the Immune System

The aging of the immune system is a physiological process commonly observed in healthy individuals as they naturally age [4]. With age, the innate immunity increases whereas the adaptive immunity declines [3]. Since the innate response is non-specific, its overactivity in the elderly leads to tissue damage and eventually to chronic tissue inflammation, known as 'inflammaging' [5]. This might contribute to the increased susceptibly to cancer and infections in the elderly [5, 8]. Hence, it would be important to consider the likely increased infectious risk with RA therapy in elderly patients.

Moreover, it seems likely that the aging of the immune system could be directly involved in the pathogenesis of some comorbidities that are increased with age [9–11]. In fact, the aging immune system becomes defective in response to injury, where it favours the proinflammatory cells, such as CD4+ T cells and M1 macrophages [9, 12]. This is supported by the increased level of proinflammatory cytokines in the elderly, which play a direct role in the pathogenesis of atherosclerosis, type diabetes mellitus, Alzheimer's and thromboembolic events [9, 10]. This makes it complicated when often a complex therapy is considered in elderly RA patients.

At a cellular level, T cells appear to be the most affected immune cells with age [3]. The emergence of senescent T cells is an aging hallmark demonstrated in healthy elderly individuals [4]. This results from an age associated decline in the generation of new T cells. Consequently, the peripheral T cells proliferate continuously to try and compensate for this decline [4]. The peripheral T cells become exhausted and senescent by undergoing characteristic molecular changes [4]. These changes might contribute to the breakdown to the immune tolerance, which could explain the increased susceptibility to autoimmune diseases in the elderly [4]. Interestingly, similar features are observed in RA patients regardless of the age of onset [3].

14.2.2 Immunosenescence and RA

It is well demonstrated that RA patients show accelerated and premature immunosenescence [4]. Similar features of the physiological immune aging at both cellular and molecular levels exist early in the disease course of RA and regardless of

the disease duration [3]. However, these features are premature by 20–30 years in RA patients compared to age matched non-RA individuals [4].

The cause-effect relationship between RA and immunosenescence has been extensively studied but it is yet to be fully elucidated. It is not clear whether RA may develop as a consequence of the primary immune aging process or whether immune aging is secondary to chronic inflammation in RA [3]. However, premature aging of both naïve and mature T cells in RA patients and the existence of similar immune aging features at a molecular level in healthy individuals who share HLA-DR4 with RA patients might raise the possibility of primary immunosenescence in RA [13].

It seems that the premature appearance of senescent T cells is a fundamental finding in RA [4]. Despite the fact that all immune cells are affected by the aging process, T cells might play a pivotal role in the development of RA and perhaps its systemic complications [3]. This is likely to be independent of the age of onset or the duration of RA [3]. The senescent T cells have characteristic features: (1) Premature shortening of the chromosomal telomeres with each cell division that leads to cell cycle arrest, senescence and cellular dysfunction [11, 14]; (2) Defective DNA repair that causes an accumulation of DNA damage, resulting in premature cellular senescence or apoptosis that possibly contributes to lymphopenia [11]; (3) Loss of CD28 that breaks immune tolerance [3]. This subsequently contributes to the development of autoimmune RA and perhaps its extra-articular complications where CD28 negative (CD28−) T cells are markedly increased [4]. For instance, CD28− T cells are found to be associated with atherosclerosis in RA [4]; (4) Disturbed induction of regulatory T cells and metabolic restructuring of the senescent T cells that result in a proliferation bias towards proinflammatory effector T cells [5, 12]. This could suggest the need for future studies to evaluate the possibility of rejuvenating the immune system of RA patients with young and adaptable T cells [14].

14.3 Characteristics of Elderly Onset RA

The prevalence of elderly onset RA is increasing gradually, occupying almost one third of the general RA population. Over the last decade, the average age of RA onset increased from 50 to 60 years according to one of the studies from US [2]. It is likely that the current elderly population were exposed to different environmental factors than younger generation; For instance, smoking being one of the important risk factors in the occurrence of RA, its consumption has extensively reduced over the years in the UK from 50% in 1970 to 25% in 1998 and to 14.4% in 2018 [15–17].

There is a growing body of evidence that elderly onset and young onset RA are different in terms of characteristic features, presenting symptoms, biomarkers and exposure to environmental risk factors [15, 18]. Elderly onset RA seems to have a male dominant prevalence pattern, an acute onset presentation, more large joint involvement, systemic and polymyalgia rheumatica (PMR)-like symptoms, more seronegative disease and poorer outcomes [6]. A higher level of IL-6 causes an

increased level of CRP and more PMR-like symptoms in elderly onset RA, whereas TNF-α level is much lower in this group than the young onset RA [19]. Moreover, the age-related increase in ESR could interfere with the assessment of RA remission (DAS28-ESR < 3.1) in the elderly population, although DAS28-ESR score is proved to be reliable in moderate to severe RA regardless of age and sex [20].

14.4 Risk Profile in Elderly RA Patients

The risk profile varies markedly between elderly patients. This reflects the degree of physical and mental dysfunction of the elderly when compared to chronologically aged individuals, also known as biological age [11]. We have classified the elderly RA patients as low and high risk depending on the presence of several risk factors, including geriatric syndrome, comorbidities and polypharmacy. This is crucial to consider when treating elderly RA patients to try and reduce the side effects and long-term complications of RA therapy.

14.4.1 Geriatric Syndrome and RA

Geriatric syndrome is a well-known term in geriatrics and reflects the degree of vulnerability to health and social difficulties that contribute to the degree of frailty of the elderly [21]. Multiple and interrelated factors contribute to this syndrome, including cognitive impairment, depression, fall, incontinence, sensory dysfunctions and malnutrition [22].

It seems that geriatric syndrome and RA are two strongly interrelated conditions. In fact, arthritis constitutes a risk factor for the development of cognitive impairment, depression and functional disability [23, 24]. In addition, elderly RA patients with high disease activity and long disease duration are found to be at increased risk of developing geriatric syndrome [22]. Moreover, elderly RA patients with geriatric syndrome tend to frequently experience anaemia of chronic disease that would further promote cognitive impairment, functional disability and depression [22, 25]. Alternatively, geriatric syndrome worsens RA activity, perhaps via subsequent malnutrition [26]. This could suggest that effective RA therapy might improve mental and physical outcomes in elderly RA patients.

14.4.1.1 Cognitive Impairment in RA

Systemic inflammation is a well-established risk factor for cognitive impairment, which is found to be a strong predictor of poor physical and mental outcomes in RA patients [23, 27]. while RA is associated with an increased risk of Alzheimer's disease and vascular dementia, elderly RA patients are at a particular risk due to

increased cardiovascular morbidity [28, 29]. It has been suggested that RA therapy might have a protective effect on cognitive function, further supported by a German study where effective treatment significantly improves the mental component of the Short Form 36 (vitality, social functioning, role-emotional and emotional well-being) [28, 30]. However, cognitive impairment in RA could be underestimated in clinical practice and might therefore undermine the efficacy of RA therapy in the elderly by affecting their compliance to therapy [22].

14.4.2 Comorbidities

Both RA and increased age are associated with increased comorbidities, partly attributable to the aging of the immune system [11, 31]. Understandably, elderly onset RA patients are at higher risk of developing comorbidities than young onset RA, perhaps due to the effects of both RA and increased age [32, 33]. In addition, it is thought that RA and some associated comorbidities might share a similar underlying inflammatory mechanism [4]. In fact, the higher the number of comorbidities in RA patients, the lower the response to RA therapy and the greater is the mortality [34].

14.4.2.1 Cardiovascular Diseases

Cardiovascular morbidity and mortality are increased in RA [31]. Congestive heart failure and ischaemic heart disease are the main contributors to overall increased mortality in RA [35]. This is important to consider in elderly RA patients, since increased age together with chronic inflammation constitute cardiovascular risk factors [11]. In addition, it is suggested that inflammation and atherosclerosis have a similar underlying autoimmune mechanism in RA [36]. This might suggest that tight control of RA would reduce the cardiovascular morbidity, which was demonstrated in a population-based study [37]. Furthermore, the use of steroids and non-steroidal anti-inflammatory drugs contribute to the increased cardiovascular risk in elderly RA patients [31]. Thus, it is important to weigh the risk and benefits of RA therapy against comorbidities in elderly RA patients.

14.4.2.2 Infections

Rheumatoid arthritis is associated with increased risk of infection, where serious infections remain a major concern that lead to premature death in RA [38]. Elderly RA patients are at particular infectious risk due to a combination of factors. Age in itself is an independent risk factor for serious infections, likely due to the decline of the immune system over the years [39]. Additionally, associated immune compromising conditions such as comorbidities and drug use including RA therapy can

further increase the risk in the elderly RA population [33, 40]. Furthermore, elderly onset RA often presents with high disease activity leading to increased early disability and eventually immobility [32, 41]. The reduced mobility constitutes an additional risk for infections, in particular respiratory and urogenital infections [41]. Hence, the infectious risk of elderly RA patients should be carefully assessed to help decide the best RA therapy individually for each patient.

14.4.2.3 Cancers

Cancer is one of the leading causes of increased mortality in RA patients [42]. Increasing age is a known risk for increased cancer, partly due to the aging process with subsequent chronic inflammation and impairment of DNA repair mechanisms [11, 43]. In addition, RA seems to be another independent cancer risk factor [44]. The cancer risk is slightly increased in the RA compared to the general population, particularly for lymphoma and lung cancer [45]. Besides, the cancer risk of RA therapy is debatable [40]. Nevertheless, RA therapy is overall safe, apart perhaps from a slight increased risk of melanoma [40]. Therefore, a cancer history is important to consider in practice when treating elderly RA patients.

14.4.2.4 Lung Diseases

Lung disease is commonly encountered in RA patients [46]. This could be related to one or more factors, for instance comorbidities, RA and drug therapy [46]. Chronic infections and smoking are established contributing factors to RA-related lung disease in genetically predisposed individuals [46]. Interstitial lung disease (ILD) is increased in RA and is associated with increased mortality compared to RA patients without ILD [47, 48]. Besides, it is likely that the risk of chronic obstructive pulmonary disease (COPD) is increased in RA patients, though smoking is an established contributing factor to RA and might have contributed to this association [49]. Thus, lung disease constitutes a complex condition in RA which can affect the choice of RA therapy in elderly patients.

14.4.3 Polypharmacy

The use of multiple drugs is common in the elderly due to associated comorbidities [11]. This makes it complicated to achieve a treat-to-target approach in elderly RA patients, where the risk of drug interactions, adverse events and contraindications due to liver and or renal diseases is likely to be increased. However, it is important to notice that effective RA therapy would reduce the long-term steroid use, thus risk and benefits must be carefully balanced on an individual basis [50].

14.5 Treatment of Elderly RA Patients in Clinical Practice

It seems likely that the physicians are usually cautious in clinical practice when treating elderly RA patients, perhaps due to uncertainty regarding the efficacy and safety of RA therapy in this age group. Less aggressive therapy is often preferred in elderly RA patients regardless of their risk profiles [51]. Age appears to be a significant predictor of failure to initiate any conventional drugs or biologics within the first year, where less than half of patients aged more than 65 received therapy in a population-based study [52]. However, data from a large cohort of early arthritis network (ERAN) showed an absence of delay to first visit or to initiate therapy within 3 months in elderly RA [53].

Monotherapy with methotrexate seems to be the most common approach used in elderly patients, though the weekly dose is considerably lower than that received by the young patients [33]. On the other hand, the use of multiple conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs) or the switch between bDMARDs are less frequent in the elderly RA when compared to young patients, independent of the disease activity, disease duration, comorbidities or bDMARD class when bDMARDs are used [33, 34, 54, 55]. Interestingly, it appears that the short and long term use of high doses of steroids is a common practice in treating elderly RA patients [34, 50, 53]. Nevertheless, the risk of steroids must be balanced against that of the other RA therapies, in view of the increased risk of cardiovascular diseases and mortality with steroid use in the elderly in a dose dependent manner [50].

14.6 Efficacy of RA Therapy in Elderly Patients

It seems likely that RA therapy is similarly effective in elderly and young RA patients. This applies to csDMARDs and bDMARDs.

14.6.1 Conventional Synthetic Disease-Modifying Anti-rheumatic Drugs

The available data, yet limited, suggest that conventional drugs have similar efficacy among all age groups [56]. Nonetheless, a lower maintenance dose of Methotrexate might be required in the elderly patients [57]. In fact, important changes in drug pharmacokinetics with age lead to a decline in renal clearance, partly contributing to an increased incidence of side effects with some csDMARDs in elderly RA patients [56]. Therefore, it is fundamental to recognise the need for appropriate dose adjustment or the use of the lowest possible effective dose of csDMARDs in elderly RA patients.

14.6.2 Biologic Disease-Modifying Anti-rheumatic Drugs

The bDMARDs seem to display similar efficacy among all age groups. In fact, a large Japanese cohort of RA patients showed similar clinical improvement at 48 weeks and drug maintenance rates after the initiation of bDMARDs in elderly and young patients [58]. The data is mainly available for tumour necrosis factor inhibitors (TNFi), and is limited for the other bDMARD classes.

14.6.2.1 Tumour Necrosis Factor Inhibitors

Data from the real-world has shown that TNFi's are likely effective in both elderly and young RA patients (British, Swiss and US registries) [59–61]. Nevertheless, some other data showed slightly reduced efficacy in the elderly. For instance, the therapeutic response was slightly less significant in elderly patients from the Dutch RA monitoring registry, whereas patients from Swiss registry over 70 years had clinical but not functional improvement, possibly due to associated comorbidities and osteoarthritis [60, 62].

Etanercept has been particularly analysed in elderly RA in various large cohorts. Etanercept showed a similar efficacy profile among all age groups following analysis of a large cohort of patients from five open-label and four double-blind randomised controlled trials [63]. Likewise, the pattern of clinical and radiological response to Etanercept was similar although it tends to be less robust in elderly compared to young patients, in a post-hoc analysis of four controlled and two long extension studies in early and late stage RA [64–67]. Furthermore, it seems that combined therapy of Etanercept with Methotrexate displayed a greater efficacy than either therapy alone in elderly with late stage RA, whereas all arms were equally effective in elderly with early RA [67–69]. Interestingly, elderly RA patients tend to have a greater disability at baseline than young patients but had greater functional improvement with etanercept [67].

Besides, TNFi monotherapy was analysed in a large British cohort of elderly of more than 75 years [70]. It showed that elderly patients are less likely to discontinue monotherapy due to inefficacy than due to adverse events, maybe owing to reduced immunogenicity associated with immunity decline with age [70].

14.6.2.2 Other Biologic Disease-Modifying Anti-rheumatic Drugs

Abatacept had a good efficacy profile in the elderly in two RA population-based cohorts. Abatacept had the highest retention rate among other biologics for its clinical efficacy and tolerability in a Japanese cohort [71]. Likewise, elderly patients of more than 75 years with higher disease activity at baseline than that of young patients tend to have slightly better response with Abatacept over 2 years [72].

Tocilizumab showed a less significant clinical response and remission in elderly compared to young patients in a small French study, yet data is limited [73].

Rituximab's efficacy seems likely to be similar among all age groups, yet elderly of more than 75 years might be better responders than those aged between 65 and 75 years over 1-year follow-up period, though data is limited to a small French study [74].

Oral Janus Kinase inhibitors (JAKi), namely Tofacitinib and Baricitinib were analysed in clinical trials that showed a comparable efficacy in elderly and young patients [75, 76]. Nevertheless, larger real-world studies are needed to make conclusions on the efficacy of the above-mentioned bDMARDs in the elderly RA patients.

14.7 Effect of RA Therapy on Comorbidities

The cardiovascular risk in RA patients is accelerated due to a possible inflammatory mechanism underlying RA-associated atherosclerosis [77]. An anti-atherogenic effect of RA therapy was demonstrated in vitro, in addition to its anti-inflammatory effect [78]. This might explain the protective effect of an effective treatment against ischaemic heart disease in RA patients [31, 50]. In fact, Methotrexate, TNFi and Rituximab are shown to reduce cardiovascular risk and overall mortality in RA patients [37, 79]. Nevertheless, the effect of bDAMRDs on congestive heart failure in RA patients remains unclear [80]. Unlike ischaemic heart disease, congestive heart failure in RA is not only related to traditional cardiovascular risk factors but also seems to occur more frequently with rheumatoid factor positive RA [81]. Furthermore, steroid use in elderly RA patients was shown to increase cardiovascular diseases and mortality [50]. Therefore, an effective RA therapy might further reduce cardiovascular risk in the elderly via reducing the need of steroids.

14.8 Safety of RA Therapy in Elderly RA Patients

There is no evidence of specific safety alerts for RA therapy based on increased age, apart perhaps form an increased likelihood of infections risk with age, associated comorbidities and steroid use [41].

14.8.1 Conventional Synthetic Disease-Modifying Anti-rheumatic Drugs

Hydroxychloroquine remains the safest conventional drugs where age is not shown to be an independent risk for retinopathy [82]. The other csDMARDs could have slightly increased toxicity with age, perhaps via age-related changes in pharmacokinetics leading to reduced renal clearance [56]. Methotrexate seems to be better

tolerated than sulfasalazine in elderly RA patients [83]. Nonetheless, csDMARD-sare generally safe where the dose need to be appropriately adjusted to renal function and possibly with associated comorbidities and polypharmacy [45].

14.8.2 Biologic Disease-Modifying Anti-rheumatic Drugs

It seems that bDMARDs in the elderly RA patients are overall safe. Most evidence exists for TNFi and Abatacept whereas the data for other bDMARDs are limited.

14.8.2.1 Tumour Necrosis Factor Inhibitors and Abatacept

The safety profile of TNFi appears likely comparable among all age groups (Dutch and Swiss Registries) [60, 62]. Nonetheless, it is difficult to establish the risk of adverse events of TNFi imposed by the age against that related to the risk profile of individual elderly RA patients. In fact, the risk of serious infections of elderly RA patients treated with TNFi from a German cohort was increased with age of more than 60, active disease, high steroid use and comorbidities such as renal and liver diseases [41]. Likewise, the presence of comorbidities at baseline is shown to be strong predictor to develop adverse events with biologics in the elderly [84]. Etanercept is a TNFi that was particularly studied by clinical trials to assess its safety in the elderly. This showed that the increased risk of serious adverse events, serious infections and cancer was appropriate for age and associated with comorbidities [63, 67]. Besides, Infliximab displayed a slightly increased incidence of cervical cancer in women aged more than 60 years when compared to biologic naïve patients and the general population in a large Swedish cohort, thus routine cervical screening with Infliximab is suggested [85].

Abatacept was associated with the lowest discontinuation rates for adverse events among other biologics in a Japanese cohort of elderly RA patients, perhaps via steroid sparing effect [71, 72].

When risk of subsequent infection is assessed in RA patients with biologic exposure at mean age of 64–69 years and history of infection with TNFi, Etanercept and Abatacept displayed a lower risk than Infliximab [86]. One could therefore suggest that the risk-benefit profile of RA therapy in the elderly needs to be balanced against the risk profile of the patients.

14.8.2.2 Other Biologic Disease-Modifying Anti-rheumatic Drugs

The data for safety of other bDMARDs in the elderly RA patients is limited. Rituximab seems to be associated with an increased number of infections in elderly RA patients (French cohort) [74]. Similarly, Baricitinib and Tofacitinib displayed a higher risk of serious infections and herpes zoster infections in elderly than young

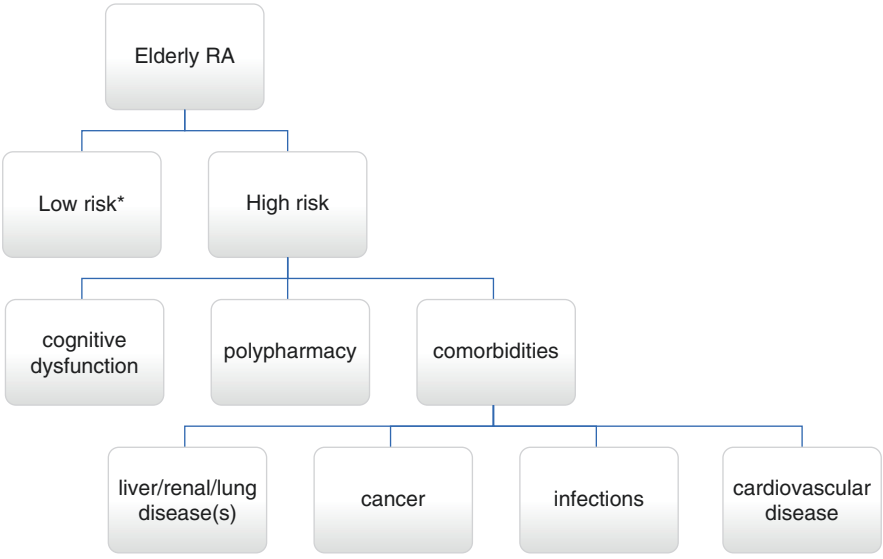
RA patients in the clinical trials [75, 76]. Hence, it is recommended in the summary of product characteristics (SmPC) to reduce the dose of Baricitinib from 4 to 2 mg daily for patients aged more than 75 years.

14.9 Suggested Clinical Approach in Elderly RA Patients

The management of elderly RA patients is challenging due to commonly associated comorbidities, polypharmacy and cognitive impairment. Hence, there is no unique approach to adopt though one could suggest a tailored therapy to the risk profile of the individual elderly patients. We suggested a flow chart of considerations when treating elderly RA patients (Fig. 14.1). We then attempted to suggest a clinical approach to match the risk profile of the elderly patients (Table 14.1).

14.10 Conclusion

To sum up, it seems that overall RA therapy is effective and safe in elderly RA patients. The treatment of elderly patients is vital although it often remains unsatisfactory in clinical practice. The management of RA in this age group is often complicated due to commonly associated comorbidities and polypharmacy.



* Low risk profile reflects elderly patients with no comorbidities, cognitive dysfunction or polypharmacy

Fig. 14.1 Suggested flow chart of considerations when treating elderly RA patients

Table 14.1 Suggested clinical approach in elderly RA patients

Elderly risk profile	Considerations	Treatment suggestions
1. General	ESR increases with age	Care when using DAS28(ESR)
	CV risk and mortality increase with steroid use	Balance risk of steroids against other therapies
	Infectious risk likely to be increased	Vaccination as per guidelines
	Biologic adverse events associated with increased comorbidities	Weigh benefits and risks of biologics vs. comorbidities
2. Low risk[a]	General, as above	Treat-to-target approach
3. Cardiovascular disease	Traditional CV risk factors and accelerated atherosclerosis	Encourage smoking cessation, healthy lifestyle and regular gentle exercises and consider statins (have anti-inflammatory effect)
	CV risk increased with doses of >5 mg/day in dose-dependent manner	Avoid high dose steroids
	RA therapies have a protective effect on IHD but effect on cardiac function controversial	RA therapies generally safe
4. Renal, liver and/or lung disease	Lower maintenance doses of Methotrexate commonly required	Start low dose Methotrexate and increase slowly
	Age-related changes in drug pharmacokinetics and reduced renal clearance	Adjust dose; i.e. Baricitinib 2 mg daily for elderly more than 75 years
5. History of infection with TNFi	Etanercept and Abatacept displayed lower risk of subsequent infection compared to Infliximab	Consider biologics with short half-life
6. History of cancer	Increased reported cervical cancer in patients on Infliximab compared to biologic naïve	Cervical screening for female patients on TNFi may be advisable
7. Cognitive dysfunction	Protective effect of RA therapies on cognitive function	Support elderly patients to improve adherence
8. Polypharmacy	Drug interactions	Consider dose adjustment

RA rheumatoid arthritis, *DAS(ESR)* Disease Activity Score (erythrocyte sedimentation rate), *CV* cardiovascular, *IHD* ischaemic heart disease, *TNFi* tumour necrosis factor inhibitors
[a]Low risk profile reflects elderly patients with no comorbidities, cognitive dysfunction or polypharmacy

Nevertheless, RA therapy can be tailored to the risk profile of every elderly patient where careful selection of the drug, adjustment of the dose and monitoring of the disease is required.

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Chapter 15
Systemic Lupus Erythematosus in Geriatrics

Hagit Peleg and Oshrat E. Tayer-Shifman

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by heterogeneous multisystem involvement and the production of autoantibodies to nuclear and cytoplasmic antigens. The main systems involved are the skin, musculoskeletal, pleura\pericardium, hematologic, renal and neurological system. Manifestations include various rashes and photosensitivity, arthralgia\arthritis, serositis, autoimmune hemolytic anemia, thrombocytopenia, leukopenia, glomerulonephritis, nephrotic syndrome, psychosis and seizures. Clinical features in individual patients can be variable and the disease is characterized by acute or chronic relapses and periods of remission. The most common autoantibody in SLE is ANA, which is positive in 96–98% in large series. ANA negative lupus is currently very rare and the 2019 ACR/EULAR classification criteria for SLE actually require an ANA titer of at least 1:80 (or an equivalent positive ANA test) for classification of SLE. Other antibodies include anti-dsDNA, anti-Smith and antiphospholipid antibodies (which are included in the 2019 classification criteria) as well as anti-Ro, anti-La, anti-histone and anti-ribosomal P [1, 2].

The diagnosis of SLE relies on the constellation of characteristic symptoms, signs and laboratory findings in the appropriate clinical context and after excluding other reasonable diagnoses. Various classification criteria for SLE were developed over the years including the 1997 ACR criteria [3, 4], the 2012 SLICC criteria [5] and the 2019 ACR/EULAR classification criteria [1]. These criteria were developed primarily for clinical research and not for the diagnosis of an individual patient but can be used as a guide in clinical practice.

Differential diagnosis is wide and depends on the clinical and laboratory presentations. It includes other autoimmune diseases (such as mixed connective tissue

H. Peleg (✉) · O. E. Tayer-Shifman
Rheumatology Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel

Department of Internal Medicine B, Meir Medical Center, Kfar Saba, Israel
e-mail: hagitp@hadassah.org.il

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disease, Rheumatoid arthritis), infectious, neoplastic, medication related (including drug induced SLE) or vaccine related diseases [6, 7].

Although SLE is most prevalent among women of childbearing age, it may present at any age and in either gender. Clinical manifestations are similar at all ages but incidence and severity differ.

15.1 Late Onset SLE

Late onset SLE is defined as age of onset of 50 years and above and presents with a frequency of 2.9–18% cases of adult onset SLE [2, 8–13].

There is scarce data on the incidence or prevalence of SLE in elderly patients since most published series of late onset SLE do not give information on how many patients were diagnosed at age 65 or above. The mean age reported in published series is usually 55–58 years ±5–7 years. A single center Korean series encountered 21 SLE patients with disease onset at 65 years and older during a 10 year period. The ratio of lupus patients below age 65 years to patients over 65 years was more than 300 to 1 in these 10 years [14]. In the Eurolupus cohort of a 1000 SLE patients about 3% were diagnosed after the age of 60 and less than 1% over the age of 70 [11].

Epidemiologic, clinical and laboratory features differ between late onset and adult onset SLE (onset at ages 18–50 years) probably due to immune senescence, hormonal differences and differences in genetic predisposition. Non Caucasian predominance decreases with age of diagnosis [13, 15, 16]. Female to male ratio is less pronounced in some series 2.5–11:1 in late onset lupus compared to 9–14:1 in adult onset SLE, and only 3:1 and 1.1:1 for patients presenting with SLE over the age of 60 and 65 respectively [9, 10, 14, 15, 17, 18]. This supports the role of estrogen in the pathogenesis of SLE.

Diagnosis of SLE in older adult patients is often delayed due to its insidious onset, lower number of cumulative SLE criteria, nonspecific presentation and lack of awareness [13, 19, 20].

Clinically, late onset SLE patients are less likely to have SLE associated major organ involvement, have less mean ACR criteria met at diagnosis and less hospitalization due to disease flare [13, 21]. Pulmonary manifestations are more common in late onset SLE including serositis (odds ratio (OR) 1.31 (95% CI: 1.05–1.65)), pleuritis (OR 1.53 (95% CI: 1.19–1.96)) and interstitial lung disease (ILD) (OR 2.56 (95% CI: 1.27–5.16)), as was shown in a meta-analysis of 1656 patients with late onset SLE [22]. Sicca symptoms are more common in late onset SLE at disease onset, although there is no difference in the prevalence of anti-Ro and anti-La antibodies which are associated with Sjogren syndrome. Therefore sicca symptoms may be a manifestation of increased age and not Sjogren's disease per se [10, 11, 16, 22, 23].

On the other hand, Lupus related neuropsychiatric manifestations, renal and mucocutaneous manifestations (in particular, malar rash, photosensitivity, livedo reticularis and alopecia) are less common in late onset SLE patients [9, 10, 13, 18, 20, 24].

Comorbidities are higher in patients with late onset SLE and include hypertension, arterial thrombotic events, osteoporosis and hypertriglyceridemia, probably reflecting the association of these manifestations with age or long term medication [12, 13, 16, 20, 23, 25, 26].

Whether the type and frequency of autoantibodies differ between late and early onset lupus is unclear due to inconsistent findings. In some studies the incidence of positive anti Sm, anti-RNP, dsDNA or reduced C3 are lower in late onset SLE. The serological differences may reflect the difference in disease activity and renal involvement [8, 9, 11, 13, 15, 21, 23].

Even though SLE tends to be less active in older patients (lower SLEDAI scores) [8, 23], age is a factor for poor outcome due to higher damage accrual and mortality [8, 13, 16, 27].

Damage in SLE is measured by the SDI (SLICC/ACR damage index) which describes the accumulation of damage that occurred since the onset of SLE but not necessarily attributed to SLE. The score includes cataract, atherosclerosis (CVA, IHD, PVD), diabetes, malignancies and more [2]. The older the patient is at diagnosis, the greater the cumulative damage. Damage occurs more often in elderly patients even in patients with mildly active disease, suggesting that damage is not due to a different disease phenotype but to additional causes of morbidity and damage such as age and co-morbidities. SDI scores in adult onset SLE are generated mostly by cataracts, muscle weakness, osteoporosis with vertebral fractures, skin atrophy, malignancy and myocardial infarction [8, 27].

Treatement of SLE is aimed at remission or low disease activity, prevention of flares and minimizing damage accrual. Hydroxychloroquine is recommended for all patients at a dose not exceeding 5 mg/kg. Glucocorticoids are used in doses that depend on type and severity of organ involvement and in chronic use should be minimized to less than 7.5 mg\day and when possible withdrawn. Additional Immunumodulating/Immunosuppresive agents are used according to the type and severity of organ involvement and may include azathioprine, methotrexate, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide, belimumab and rituximab. Patients with SLE and high risk antiphospholipid profile may receive antiplatelet agents especially if other atherosclerotic/thrombophilic factors are present and after balancing bleeding risk [28]. Patient medication does not differ in late onset SLE in most studies except for lower use of cyclophosphamide in some studies probably reflecting less renal involvement [8–10, 20, 26, 29].

Survival of patients with late onset SLE is reduced: multivariate adjusted HR for 10 year risk of death is 4.96 (95% CI: 1.75–14.08) compared to adult onset SLE patients in one cohort [18] and OR of death compared to younger SLE patients was 2.61 (CI 1.2–5.6) in another cohort [10]. Mortality in late onset SLE is higher than in age matched non SLE patients (HR 3.44 (CI 2.76–4.28) and higher relative to the increased risk of death in adult onset SLE compared to age matched non SLE patients (OR 1.75) [25]. Causes of death include infections, cardiovascular events (MI, stroke) and malignancy [12, 16, 18, 25]. The increased risk of damage accrual and death in late onset SLE patients occurs

despite the fact that late onset SLE patients show more adequate illness related behavior [16].

15.2 Elderly SLE Patients

Since the diagnosis of new onset SLE in an elderly patient (above 65) is rare, and the survival of SLE patients is high, most elderly patients with SLE are probably those diagnosed before the age of 65 and even patients diagnosed in childhood.

Elderly patients, especially those diagnosed at a young age, are subject to long term toxicities of medication. For example, retinal abnormalities due to hydroxychloroquine treatment exceed 10% after 20 years of continuous use. Major risk factors include duration of therapy, dose and chronic kidney disease. Long-term prednisone therapy poses a significant risk of morbidity due to permanent organ damage. Daily dosages above 6 mg have been shown to increase the risk of future organ damage by 50%. Glucocorticoid use carries a higher risk of opportunistic infections, iatrogenic osteoporosis and avascular necrosis, and an increased risk of cardiovascular events, cataracts and glaucoma [19]. Minimizing side effects from glucocorticoids and other immune-modulating therapies is especially relevant in the elderly patients who are more prone to infections and suffer from comorbidities. Immunizations according to the EULAR recommendations for vaccination of patients with autoimmune rheumatic diseases and early recognition and treatment of infection is needed. SLE is an independent risk factor for cardiovascular disease due to both traditional and disease related factors. Regular assessment for these factors and preventive strategies as in the general population are needed [28].

In conclusion, late onset SLE is characterized by an insidious onset, lower number of cumulative SLE criteria, more pulmonary involvement and sicca symptoms and less mucocutaneous, renal or neurologic involvement. Patients have more comorbidities, higher damage accrual and reduced survival. Therefore elderly SLE patients need to be closely followed in order to reduce the occurrence of damage and morbidity such of infections, cardiovascular disease and osteoporosis.

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Chapter 16
Systemic Sclerosis in the Elderly

Doron Rimar

16.1 Systemic Sclerosis Overview

Systemic sclerosis (SSc) is a rare autoimmune disease in which autoantibodies, vasculopathy and tissue fibrosis serve as the cornerstones of its pathogenesis [1].

16.1.1 Autoantibodies

Autoantibodies may appear years before clinical disease is apparent [2]. The three common targets for antibodies in the nucleus include the centromere (associated with limited disease and PHT), topoisomerase 1 (scl-70) (associated with diffuse disease and lung involvement) and RNA polymerase III (associated with diffuse disease and renal crisis) [1].

16.1.2 Vasculopathy

Vasculopathy is usually the first clinical sign of disease manifesting with Raynaud's phenomenon (RP) in 95% of patients and may result in DU or critical ischemia (in about 30–50% of patients more in the diffuse subset) [3, 4]. Pulmonary arterial hypertension (PHT) is the second and, sometimes, disastrous manifestation of vasculopathy related to SSc. PHT is the second most common cause of disease related

D. Rimar (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel

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mortality in SSc, accounting for 26% of deaths [5, 6]. Scleroderma renal crisis (SRC) is the most severe manifestation of SSc vasculopathy, which occurs in about 2% of patients.

16.1.3 Fibrosis

Fibrosis in target organs is the hallmark of SSc. Skin involvement is the most prominent characteristic of SSc. The extension and degree of skin sclerosis is quantified using the modified Rodnan skin score (mRSS) [1]. Patients with proximal involvement above the elbow and knees are considered to have a diffuse disease and frequently present with a higher mRSS and involvement of internal organs, as heart and lungs. Lung fibrosis is the second commonly involved target organ (about 60% in patients with diffuse disease), result in great morbidity and is the most common cause of mortality [5]. Another important target organ of fibrosis is the heart. Cardiac manifestations include pericardial disease, dilated cardiomyopathy, autonomic neuropathy, arrhythmias and left ventricular (LV) or right ventricular (RV) diastolic dysfunction. Cardiac complications account for 26% of SSc related deaths according to EUSTAR database and is the third most common cause of death in patients with SSc [5, 6]. Finally, the gastrointestinal tract may be involved from the oropharynx to the anus.

16.1.4 Morbidity and Mortality in SSc

Disease related mortality in SSc is dependent on the clinical characteristics of disease, the age and the sex. In a recent French cohort including 625 patients, overall 5 years survival was 85% yet several risk factors predicted higher mortality: Age at diagnosis >60 years, dcSSc subtype, telangiectasia, scleroderma renal crisis, severe dyspnea, NYHA functional classes III and IV, a shorter distance at the six minute walk distance (6MWD), forced vital capacity (FVC) < 70% predicted, DLCO < 70% predicted, PHT, valvular disease, anemia, CRP > 8 mg/L, and cancer [7]. The most comprehensive analysis of EUSTAR database included 11,193 patients, using the SCOpE score with 15 domains that categorize patients to four prognostic quartiles. Patients in the high-risk quartile were found to have a 3 years survival of 53% compared to 98% in the low risk quartile [8].

16.2 Systemic Sclerosis in the Elderly

In order to be precise in the discussion of SSc in the elderly two different groups of patients should be regarded:

(a) Elderly patients with long standing SSc

This group includes elderly patients with SSc who were diagnosed in an earlier age (usually around 40–50 years of age). This group can be further divided into two main subsets, the diffuse and the limited SSc. Progressive diffuse disease is commonly characterized with internal organ damage, namely lung fibrosis or cardiac involvement, DU, contractures of joints and anti scl-70 or RNA POL III antibodies. In this subset most of the damage is accumulated within the first 3–5 years in an accelerated phase that may subside in most but not all patients [9]. Indeed, in one study lung disease progressed even after 10 years after diagnosis in 31.7% of patients with diffuse disease [10]. The second subset with limited disease is usually characterized by less prominent skin fibrosis and internal organ damage, but more commonly with calcinosis, telangiectasia and late complications of PHT and primary biliary cirrhosis that progress slowly or appear at late stage of the disease. Patients should be evaluated and treatment and follow up should be tailored to the disease subset and the anticipated progression.

(b)Late onset systemic sclerosis—definition

The definition of elderly or late onset systemic sclerosis (LOSSc) has not been defined in the literature and different authors use different age criteria varying between 50 and 75 [11–20]. The reported age of onset of SSc is generally increasing in the last 30 years and is now approximately 56, thus in this chapter we have decided to include only reports of LOSSc that was diagnosed after the age of 60 [21, 22]. Differences between these reports, other than the age criteria should be accounted, mainly the inclusion criteria. The diagnosis of SSc was based until 2013 on the 1980 ACR classification criteria, which were very rigid and had low sensitivity, precluding the ability to diagnose early systemic sclerosis. Thus, studies that were published before 2013 include patients with a straightforward diagnosis of SSc. The current 2013 Eular guidelines, are based on a score that includes skin changes, vascular involvement, lung involvement, PHT and specific autoantibodies. These classification criteria have a higher sensitivity, that enables classifying “missed” early SSc patients manifesting with milder disease and even patients without skin involvement.

16.2.1 Late Onset Systemic Sclerosis Demographics and Clinical Characteristics

Table 16.1 compares the relevant studies regarding clinical and laboratory manifestations of LOSSc [11–20]. The female percentage in LOSSc is similar to the data in SSc, approximately 80%. The proportion of patients with anti-centromere antibodies (ACA) is higher than in younger SSc patients in most studies and varies between 40 and 87%, while anti topoisomerase 1 (ATA) is reported to be less prevalent 3–32%. Accordingly, the prevalent clinical manifestation of LOSSc is limited

Table 16.1 Characteristics of late onset systemic sclerosis

Study (first author and reference)	L. Czirjak [14]	C T. Derk [15]	C. Perez Baocanegra [19]	T. Hugle [16]	R. L. Manno [18]	M. Alba [12]	A. Achille [11]	M. Luis (117)	P. E. Carreira [13]	P. E. Carreira [13]
Year of publication	1992	2006	2010	2011	2011	2014	2018	2018	2019	2019
Number of patients	9/105 (8.5%)	12/769 (1.5%)	67/319 (21%)	123/855 (14%)	216/2300 (9%) (>75 years old 1.8%)	191/1037 (18%)	27/246 (8%)	35/178 (20%)	126 **Very early SSc**	296 **early SSc**
Female (%)		83	91	89	85	88	89	83	78	
Age criteria	60	75	65	75	65	60	70	65	60	60
Mean age	72.2 ± 7.3	77.5 ± 1.2		79.6 (78.2–81.7)		67 ± 5.9	78 ± 4.5	71.4 ± 4.7		
ANA (%)		100	96	94	97	85		100		
ACA (%)		9	40	54	42	47	69	87	38	39
ATA (%)		27	21	23	17	20		3	32	30
RNA POL III										
mRSS		14.4 ± 8.4 vs. 14.4 ± 9.4		7	4				11 ± 10	11.8 ± 11
Diffuse SSc (%)	77.8	58	23	18	32	21	12	13	36	34
Limited SSc (%)	22.2	42	54	74	68 (79% in >75 years old)	67	88	42	64	58
Sine sclerosis (%)			16							
Early SSc (%)								26		

Pulmonary fibrosis (%)	66 vs. 16		43	30	57	57	29	27	35	36
Pulmonary hypertension (%)			17	35	3% RHC	14	11% RHC	30	39	30
Cardiac abnormalities (%)	55.6 vs. 31.4	58 vs. 4		57	37	36		48	48	47
Digital ulcers (%)			40	22	37	34	22	30	25	25
SRC (%)				0.8		2.9			2	3
Telangiectasia (%)	22.2 vs. 61		74			63	63			
Malignancies (%)		30 vs. 4	5.6				11			
Mortality	55% in 2 years	50% in 42 months	36% 10 years	22% 49 months			33% 3 years			
Mortality cause	3 cardiac	3 cardiac								
Mortality due to SRC	2 (22%)	2(16%)								
SMR			1.2			1.78				
Median survival				49 months		12.2 months				
Time from non-Raynaud's phenomenon		9.2 ± 3.8 months			6 ± 28 months				11.5 ± 2	18.7 ± 6.1
Time from Raynaud's phenomenon		50 months	139	2.1	72 months	28 ± 3.6 months				

ANA antinuclear antibody, *ACA* anti centromere antibody, *ATA* anti topoisomerase antibody, *mRSS* modified Rodnan Skin Score, *SSc* Systemic sclerosis, *SRC* Scleroderma renal crisis, *SMR* standardized mortality ratio

(42–88%) and looking only at the recent case series of LOSSc onset with age criteria of above 70 years of age, the proportion of limited disease is even higher, 74–88% [11, 16]. In this respect the skin disease is usually mild in LOSSc with reported mRSS of 7–14 [13, 15, 16]. Considering the atherosclerosis and tendency to vasculopathy in older age, it is not clear why vascular disease is much milder in LOSSc with a very consistent reporting of lower than expected rate of DU (DU), 22–40% [11–13, 16–19]. Low frequency of DU may have to do with more frequent limited disease with ACA. Indeed, a study from EUSTAR data base reports higher frequency of DU in patients with Scl-70 antibodies, 44.8% versus 31.2% in patients with ACA [3].

Lungs are not commonly involved in LOSSc 27–43% [11–13, 16–19]. Heart complications, on the other hand, are far more common in LOSSc and are reported in 37–58% of patients [12–19]. Age is probably an important factor with regard to heart complications and indeed high proportion of LOSSc patients have essential hypertension and diastolic dysfunction that may aggravate disease related cardiac abnormalities including cardiomyopathy, conduction abnormalities and diastolic dysfunction due to fibrosis. PHT is far more common in LOSSc than is the general population of SSc (14–35%) [11–13, 16–19] in line with the high proportion of limited disease in LOSSc, a risk factor for PHT. Moreover, cardiac abnormalities may contribute to mixed PHT in LOSSc patients. PHT is considered a late complication in patients with limited SSc (usually appears more than 3 years after disease onset), yet in LOSSc it is reported earlier and in high proportion and thus may reflect mixed or post capillary PHT due to diastolic dysfunction or left heart failure. Indeed, Hugle et al. reported high rates of systemic hypertension in LOSSc compared to younger patients with SSc (40.6% vs. 20.2% $p < 0.001$), more diastolic dysfunction (29% vs. 16% $p < 0.001$), more conduction abnormalities (21.8% vs. 9.7% $p < 0.001$) and more PHT in 35% vs. 20% $p < 0.001$), yet no difference in the lung carbon dioxide diffusing capacity (DLCO) or dyspnea, implying cardiomyopathy is a contributing factor [16]. Moreover, reduced LV function, diastolic dysfunction and conduction blocks were found to be independent risk factors for PHT in that study, which implies that PHT is left sided in many case (post capillary) [16]. In studies reporting pure precapillary PHT diagnosed by right heart catheterization the proportion of PHT in LOSSc was much lower and similar to SSc younger patients, 3–11% [11, 18].

16.2.2 Mortality

Age is an independent risk factor for mortality in SSc and specifically an age older than 60 confers one of the most important risk factors for mortality with an odds ratio of 5.9 [5, 7]. LOSSc studies indeed report high mortality reaching 55% in 2 years in old studies [14]. LOSSc portends poor survival in most series, yet looking at a report from the Spanish RESCLE Registry it appears that although age at diagnosis was an independent predictor of increased mortality, the standardized

mortality ratio (SMR) was higher in younger SSc patients aged ≤30 years (26.22; 95% CI, 14.43–38.01), compared to older patients ≥60 years (1.78; 95% CI, 1.17–2.39) [12]. Perez Bocanegra et al. reported similar results with a reduced 10 year survival in LOSSc, 64% vs. 81% in the whole cohort, yet SMR of 2.6 in young patients and only 1.2 in LOSSc [19]. A possible explanation for the low SMR in LOSSc may be related to the clinical manifestation that include mostly limited disease with less pulmonary involvement.

16.2.3 Malignancy

Malignancies are evident in SSc in higher proportion than the general population, the most common of which are lung and breast cancer [23]. Cancer has become a leading cause of mortality in SSc disease (third cause), resulting in about 11% of deaths according to EUSTAR database [5]. Age and specific autoantibodies are the main independent risk factor for malignancy in SSc patients. The antibodies that have been described to be related to malignancy in SSc are anti RNA POL III, that enhances the risk of malignancy in SSc fivefold and a more recently described, anti RNPC 3 (RNPC-3 is a protein member of the minor spliceosome, ribonucleoprotein complex that participates in the splicing of pre-messenger RNAs), that carries a fourfold risk of malignancy [24, 25]. LOSSc patients, however, have not been found to have a higher proportion of malignancies than expected in SSc and this may be due to the high rate of limited disease and anticentromere antibodies that characterize these patients. RNA POL III and RNPC 3 antibodies have not been reported in studies of LOSSc. Achille found 11% of synchronous malignancy with the diagnosis of LOSSc and Perez-Bocanegra et al. have reported twice the rate of malignancies in LOSSc patients in a 13 years follow-up (10.4% vs. 5.6%), yet this difference was not statistically significant [19].

The interplay of malignancy and autoimmunity is complex. Some immunosuppressant drugs as azathioprine have been associated with malignancies, yet on the other hand chemotherapy agents, as docetaxel gemcitabine and bleomycin, may result in SSc like disease. Chronic inflammation and fibrosis in target organs like the lungs may predispose to dysplasia and lead to malignancy. A predilection to esophageal carcinoma in SSc has to do with chronic gastroesophageal reflux disease due to widening and incompetence of the lower esophageal sphincter. Recently, cases of SSc has been reported with the checkpoint inhibitors, which emphasizes the relations between autoimmunity and cancer [26]. On that note, it has been suggested that in some cases autoimmunity in SSc is the result of the immune system that is triggered against malignancies. Somatic mutations of RNA POL III antigen in several tissues like the lung may trigger a protective immune response, that enables abolishing the malignancy through direct antitumor activity of activated T cells and NK cells at the price of activation of autoreactive B cells that produce antibodies to the wildtype RNA POL III, resulting in an autoimmune response, and SSc phenotype.

16.2.4 The Approach to SSc in the Elderly

16.2.4.1 Diagnosis

Raynaud's Phenomenon

RP is characterized by sensitivity to cold temperatures associated with either triphasic, biphasic or uniphasic change in color of the digits. RP may precede SSc by many years. New onset primary RP is rare in the elderly and secondary reasons should be evaluated [27].

Evaluation should begin with a careful physical examination and history taking. DU, continuous symptoms through the summer, skin fibrosis and telangiectasia will direct the diagnosis of SSc that may be further investigated by blood tests for specific autoantibodies, inflammation markers and nailfold videocapillaroscopy (Figs. 16.1 and 16.2). Atherosclerosis is one of the most common reasons for secondary RP in the elderly. Careful evaluation of radial and ulnar pulses including an

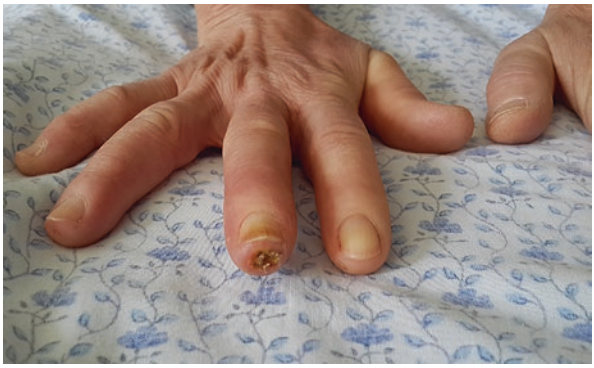

Fig. 16.1 A digital ulcer in systemic sclerosis patients

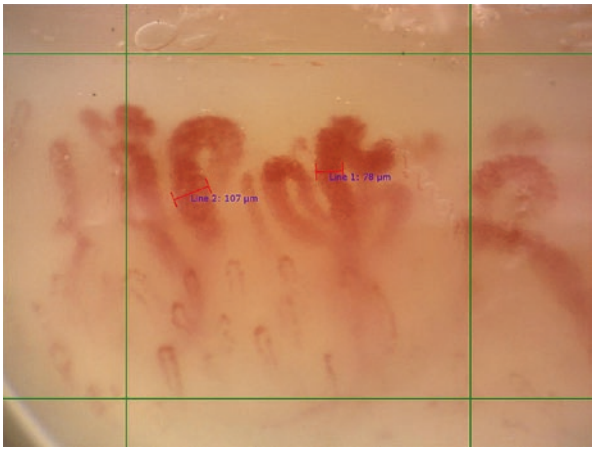

Fig. 16.2 Nailfold videocapillaroscoy, using Optilia video capillaroscope (magnification ×200) showing 4reduced number of capillaries and a giant capillary with width of 100 µm—a systemic sclerosis pattern

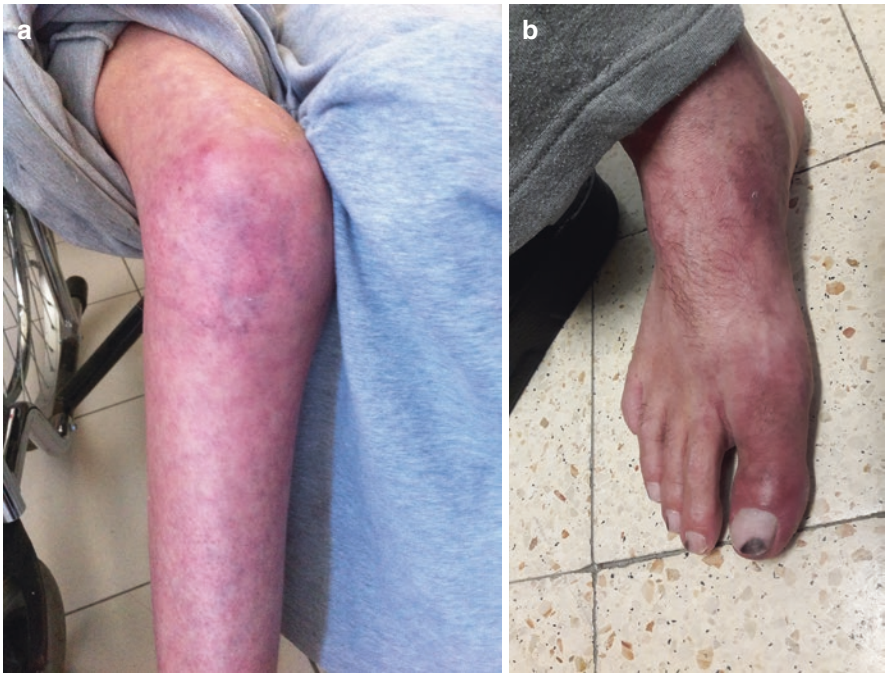

Fig. 16.3 (**a**) Acrocyanosis due to atherosclerosis in a 67-year-old patient manifesting a fixed diffuse purple hue distal to the knee. (**b**) Fixed ischemia of first toe with skin purple color changes in a patient with atheroemboli

Allen test should be undertaken. A history of metabolic risk factors as smoking, diabetes or known vasculopathy including a heart disease, peripheral artery disease, prior CVA or carotid artery stenosis should be elucidated. Atherosclerotic vasculopathy may result in a RP, yet more classically it is manifested with more prolonged, fixed ischemia that do not resolve with warming, either of the whole limb (acrocyanosis) or of a finger (Fig. 16.3a). Atheroemboli may result in areas of purple hue at the fingertips mimicking RP (Fig. 16.3b). High blood pressure and acute kidney injury will favor and direct to a diagnosis of atheroemboli in this setting, yet SRC should be ruled out. Evaluation of radial, ulnar, brachial and subclavian arteries by ultrasound doppler, CT angiography or formal angiography may be rewarding, revealing occlusive atheroma as the culprit or a complicating factor that should be treated. Hypercoagulability is not rare in SSc and should be evaluated in cases of severe RP or ischemia. Other conditions that may result in secondary RP include blood dyscrasia, Polycythemia and cryoglobulinemia, drugs (mostly beta blockers in the elderly), infections (Fig. 16.4), malignancy, occupational reasons and anatomical Shoulder girdle compression syndromes (Fig. 16.5).

Capillaroscopy has become a standard tool in the evaluation of RP. Several capillaroscopic red flags may help the clinician diagnose SSc, including low density of capillaries per 1 mm, widened capillaries, bizarre or bushy capillaries, capillary loss

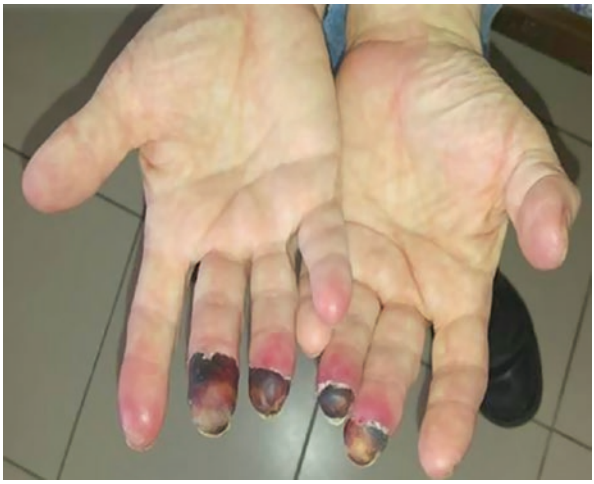

Fig. 16.4 An elderly patient 2 weeks after mycoplasma pneumonia presenting cold agglutinin related fixed ischemia of the fingers

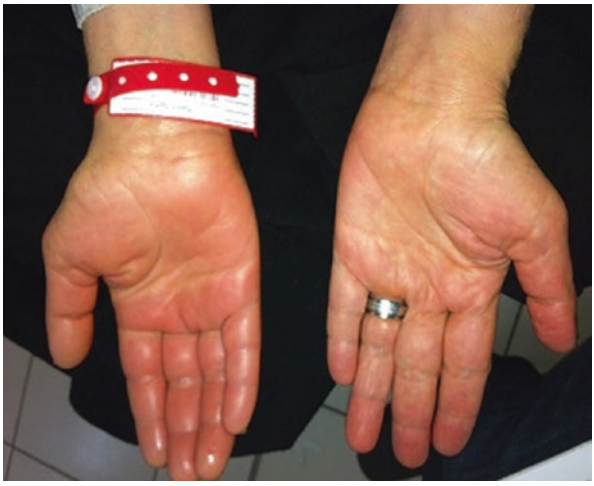

Fig. 16.5 Anatomical shoulder girdle compression syndromes due to cevical rib may present with color change in one hand and mimic Raynaud's Phenomenon

and microhemorrhages, but the pathognomonic evidence, that should be noted, is the presence of giant capillaries measuring more than 50 μm in width or even with greater specificity above 100 μm (Fig. 16.1).

Skin Examination

DU, pits, fissures, telangiectasia and skin thickening (Fig. 16.6) are important clues for SSc, though dermatomyositis and overlap syndrome may appear very similar but usually lack skin fibrosis. Puffy fingers are common in early disease and later on sclerodactyly evolve with more generalized distal or diffuse skin thickening

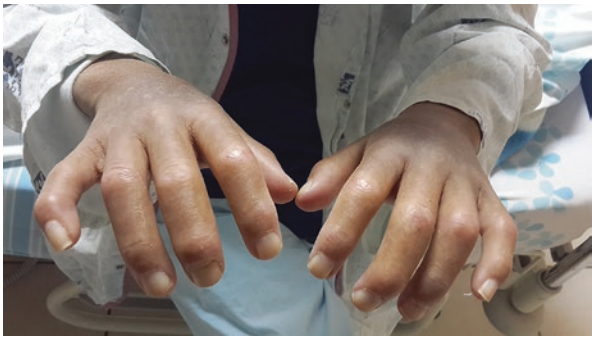

Fig. 16.6 Skin thickening with contractures, classic manifestations of systemic sclerosis

(Fig. 16.6). A whole 17 sites examination using the modified Rodnan Skin Score (mRSS), should be accomplished for each patient in order to quantify the disease distribution and severity. Early SSc or SSc sine sclerosis have been described in the LOSSc in up to 26% in one series, thus the diagnosis should not be dismissed in cases without skin involvement [17].

A thickened skin without RP should alert the clinician to look for conditions mimicking systemic sclerosis. In the elderly osteoarthritis may falsely give a tense feeling of the skin on the distal area and thus fingers should not be examined distal to the proximal interphalangeal joint (PIP). The site of thickening is important and may hint for mimicking conditions. Paraproteinemia associated scleromyxedema and scleredema associated with infections or diabetes mellitus, will usually affect the neck, the face, the back and spread to the shins sparing the fingers (reverse scleroderma). In the proper clinical context other rare mimickers may include nephrogenic systemic fibrosis, eosinophilic fasciitis, POEMS syndrome, graft versus host disease, radiation injury and drug related fibrosis.

16.2.4.2 Systematic Work-Up

Patients diagnosed with SSc should undergo a systematic work up in order to tailor therapy and rule out malignancy. The suggested workup, detailed below, should be considered as a framework screening that should be modified according to clinical manifestations in each individual patient.

Laboratory Tests

A suggested laboratory workup should include a comprehensive chemistry panel including inflammatory markers, complete blood count, TSH, urine examintion and viral serologies. The specific laboratory workup should include routinely autoantibodies tests: antinuclear antibodies (immunofluorescence pattern), anti-topoisomerase 1 (SCL-70), anti-centromere, and RNA POL III, SSA, SSB, RNP, ANCA, ACLA, B2glycoproten 1, lupus anti-coagulant, rheumatoid factor, ACPA, C3 and C4. In

cases of accompanied myositis, a myositis panel should be evaluated as well. Cardiac markers, troponin and NT-pro BNP should be evaluated. Finally, a screening of tumor markers including CEA, CA 15-3, CA 125, AFP, PSA, HCG, B2-microglobulin and protein electrophoresis is suggested.

Lungs—Auscultation of the lung is important as a simple mean of follow up, but simple auscultation do not preclude the need for a chest CT scan that is more sensitive in evaluation of lung involvement. CT may help quantify the percent of the lung involved and the pattern on CT carries important prognostic information from worse to best, usual interstitial pneumonia, nonspecific interstitial pneumonia or ground glass opacities. Ct scan is important to rule out a neoplasm and accompanying conditions as emphysema. Lung function test is an important noninvasive diagnostic tool. The forced vital capacity is a measure of the lung volume and the DLCO measures the carbon monoxide diffusing capacity which quantifies the lung function. The DLCO is a sensitive marker that may predict lung involvement before actual volume loss is evident and moreover, a disproportionally high FVC to DLCO ratio of more than 1.6 is a useful marker for PHT [28]. Bio markers of lung fibrosis like KL-6 are not in wide clinical practice but may be useful as a follow-up. Carbohydrate antigen 15-3 (CA 15-3), a biomarker for breast carcinoma and carcinoembryonic antigen (CEA) a biomarker of colon cancer, are overexpressed in patients with lung fibrosis, inversely correlate with FVC and predict future lung damage [29].

Gastrointestinal Tract

Gastroesophageal reflux disease (GERD) is almost universal in SSc patients. Upper gastrointestinal (GI) series and CT scan may demonstrate widening of lower esophagus and associated reflux. Involvement of the rest of the GI tract is common and is sometimes overlooked. Gastric antral vascular ectasia (GAVE) that tend to ooze and bleed is the parallel of telangiectasia in the stomach and appears as red longitudinal stripes that stretch from the pylorus, or as dots. Biopsies normally show capillary dilation with focal intravascular thrombi and muscular hyperplasia of the lamina propria and multiple tortuous submucosal capillaries [30]. GAVE is not rare and have been reported in 5–22% of SSc patients and up-to 78% in patients with early (within the first 18 months) diffuse disease who have RNA POL III antibodies [30, 31]. LOSSc have mostly limited disease, which is also a risk factor for GAVE, but mostly as a late complication. Another common GI complication is small intestine bacterial overgrowth (SIBO) due to impaired peristalsis resulting in chronic diarrhea.

Finally, weight should be monitored closely as weight loss, is frequent due to several causes that needs to be addressed. In early diffuse disease weight loss may precede other symptoms while in more progressive disease it may be related to difficulty in eating due to impaired mouth opening, dysphagia, SIBO or on the other hand accompanying depressive disorder. Our approach is to evaluate gastrointestinal tract by an abdominal CT, gastroscopy and colonoscopy in any case of weight loss, anemia or reduced albumin level.

Cardiac and Pulmonary Hypertension Workup

Cardiac involvement in SSc is common and may be aggravated by non SSc related cardiac conditions that are common in elderly patients as essential hypertension, valvulopathies and diastolic dysfunction. A routine workup should include an ECG, Echocardiography, troponin serum level and NT pro-BNP. In case there is evidence or suspicion of arrhythmia, a 24 h holter monitoring should be done. Cardiovascular magnetic resonance (CMR) is becoming a standard tool in the evaluation of SSc. It is the gold standard technique to assess ventricular volumes, ejection fraction, and is very useful to reliably and non-invasively detect myocardial inflammation, early perfusion defects, and myocardial fibrosis. Alas, in our opinion CMR is a very sensitive tool that have more a prognostic than clinical implication and we do not suggest the routine use of it yet [32, 33]. LOSSc patients have high rate of primary or mixed PHT that should be screened for by a yearly echocardiography [13, 19]. The DETECT score may be a useful tool in the decision of right heart catheterization of patients with suspected PHT by echocardiography. As mixed conditions due to diastolic dysfunction and valvopathies are common in older age and have a practical implication on treatment decisions we tend to be more liberal with regard to right heart catheterization decision in LOSSc patients. Our approach is to proceed to a right heart catheterization in patients with estimated echocardiographic systolic pulmonary artery pressure (sPAP) above 40 mmHg who have elevated NT pro BNP above 300 pg/mL or DLCO < 60% predicted and FVC/DLCO ratio > 1.6.

16.2.4.3 A Paraneoplastic Workup

SSc is a risk factor for malignancies, most common of which are lung and breast cancer. Special attention should be taken in LOSSc group [34]. Red flags that should alert a more meticulous workup are weight loss, seronegative patients without ANA antibodies, patients who do not have a RP and patients with anemia, low albumin, high ESR or LDH. The workup should include the screening tests that are appropriate to the age group in general including: mammography, gynecological examination and colonoscopy. We suggest a lung, abdomen and pelvic CT scan in all LOSSc patients at onset. Tumor markers should be evaluated. CA 15-3 and CEA have been described to correlate with lung fibrosis, but even in the setting of lung disease their value in screening for malignancy should not be dismissed. A trend of increase in a tumor marker or the combined elevation of three tumor markers in this setting, has been found to predict malignancy and therefore serial follow up of tumor markers is warranted [29].

PET CT is becoming an important diagnostic tool in the evaluation of paraneoplastic phenomena and may be helpful in SSc to rule out malignancy and at the same time to evaluate the activity of lung disease [35, 36].

16.2.4.4 Treatment

SSc is a complex disease and although guidelines for the treatment of SSc have been published, treatment is still most often tailored for specific manifestations of the disease trying to reduce damage and not to cure the disease [37]. An exception is autologous stem cell transplantation, an aggressive treatment that "restarts" the immune system and may result in complete remission and seroconversion, yet this treatment carries risks and is not recommended for patients over 65 years of age and therefor will not be discussed further here [38]. Treatment is tailored for each patient considering disease stage, anticipated progression, target organ involvement, prognostic factors, the health condition of the patient, his needs and his expectations. A thorough investigation of the involved target organs is therefore the base for a personalized therapy that combines treatments directed at various systems. In contrast to other rheumatic diseases in which monotherapy is favored in order to achieve high adherence, the evolving concept in SSc is "combination therapy". Although each treatment is directed mostly at one organ, almost any treatment has been found to benefit other aspects of disease. Understanding the pathophysiology of SSc helps understanding this approach. Treating GERD for instance is beneficial not only for dyspepsia but also for the lung disease as micro-aspirations aggravate lung fibrosis [39]. Treating vascular disease is also helpful for the fibrotic part as vascular damage induces uncontrolled fibrosis [40]. Finally treating autoimmunity that drives the whole pathophysiology of disease may be beneficial in most aspects including microvascular [41]. SSc is a disease with a high mortality rate, hence treating SSc is not only about improving quality of life, but about improving survival. The question is therefore, why not treat every patient with all modalities? Theoretically a combination therapy of immune suppression, antifibrotic therapy and vasodilation, should indeed be considered in all patients, yet some patients have passed the progressive phase of disease, or are very debilitated and need less aggressive therapy since risk of treatment may overweigh the chance of improving their quality of life. Therapy, hence, should be tailored with respect to symptoms, target organ involved and prognosis.

Skin

Skin thickening, the hallmark of disease, is not only an esthetic problem. Skin thickening may rapidly result in contractures limiting activity mostly in the fingers, wrists and shoulders. Rapidly progressive skin thickening usually with an mRSS above 15, heralds a severe disease with multiorgan involvement and therefore should be treated aggressively and promptly. Methotrexate is graded A for the treatment of skin fibrosis, yet the evidence is weak with a trend of improvement in one study of 29 patients and a modest response in another study of 79 patients in whom a reduction of 4.3 in mRSS was achieved [37]. MTX has not been found to benefit lung disease. It is a safe treatment which is reasonable to use in limited disease where skin is not a major problem or in the geriatric population if general state

precludes more aggressive therapy. Mycophenolate mofetil (MMF) is graded B by the EULAR guidelines based on small studies, yet the Scleroderma lung study II (SLSII) has shown MMF to have a positive effect on skin and lung and therefore this treatment is considered the standard of care today for patients with diffuse disease [42]. Rituximab has gained evidence of being an efficient and safe treatment for skin and lung disease in retrospective studies, prospective analysis of the EUSATR data bases, several open label trials and two randomized controlled trials (RCT) versus cyclophosphamide [43–50].

IV immunoglobulins (IVIG) is an interesting option in the geriatric population as it is the only immunotherapy that does not increase the risk for infections. Several small open label trials have found beneficial effect for the skin in SSc [51–54]. We find it a safe and efficacious treatment for skin fibrosis but advise careful screening for hypercoagulability before the use of IVIG, as cases of arterial ischemic events mainly, cerebrovascular accident (CVA) have been described. It is suggested to prophylactically use enoxaparin 40 mg at the day of treatment.

Lung Disease

Lung fibrosis is still the main cause of mortality in SSc and should be treated vigorously at an early stage before irreversible damage occur. In the past, when cyclophosphamide was the only treatment for lung fibrosis, a scheme of treatment only of patients with severe disease of more than 20% fibrosis of the lung volume or less than 70% FVC, have been suggested [55]. Nowadays the paradigm is changing as safer and more efficacious treatments are available. The dynamics of disease progression are a more important consideration then the absolute numbers. For instance, a 70 years old patient with a mRSS of 7, 20% lung fibrosis and a FVC of 65%, that is stable over 10 years, may not need aggressive therapy as progression is not anticipated, while a patient at the same age with new onset SSc, RNA pol III positive, and only 10% lung fibrosis and an FVC 75% predicted, should be treated promptly as he is expected to worsen in the near future. The standard of therapy today for lung disease is MMF, that has been found to be mildly efficacious for lung and skin fibrosis in the SLS II study [42]. In cases of progression on MMF, treatment can be switched to rituximab that has gained a lot of evidence in the literature in retrospective studies open label trials, and even RCT [43, 44, 46, 47, 56, 57]. It has been suggested in the EUSTAR prospective trial that rituximab is more efficacious in combination with MMF and this has been our experience as well (manuscript in press) [45]. Other suggested therapies include tocilizimab that was found to slow disease progression in inflammatory early progressive SSc in recent studies [58, 59]. New generation antifibrotic agents as pirfenidone, nintedanib and lenabasum are at the spotlight of literature these days [60]. Nintedanib was recently found to slow lung fibrosis and thus became the first specific drug with an FDA indication for SSc lung disease [61]. The future of SSc lung treatment is in combination therapy and ongoing trials evaluate numerous possible combinations including rituximab and belimumab or MMF and pirfenidone (SLSIII study).

Vasculopathy

Vasculopathy is an important aspect of the pathophysiology of SSc in all target organs the spectrum of manifestations of which, include RP, DU, critical ischemia, PHT and SRC. Ischemia drives fibrosis, thus we suggest treating vasculopathy universally in all SSc patients and to modify treatment according to clinical manifestation.

RP is almost universal in SSc. Patients should be educated about warming their hands with gloves. Possible treatments include calcium channel blockers and serotonin uptake inhibitors, which have an additive beneficial effect if depressive signs occur. We use iloprost, a prostacyclin analogue (that is not available in the US), at least once monthly in all patients that tolerate it well even if only RP is evident and increase frequency of treatment if DU occur.

DU are the unwanted result of a RP. Patients should be counselled regarding the importance of smoking cessation. Wound care include cleaning, debridement, topical and if needed systemic antibiotic and suitable dressings, if the DU is dry then attempt to wet it (alginates and antimicrobials, e.g. Suprasorb and Aquacel Ag, respectively) and vice versa for wet DUs (hydrogel and hydocolloids, e.g. Intrasite gel and Duoderm, respectively) [62]. Iloprost and phosphodiesterase 5 inhibitors (PDE5i) (sildenafil, tadalafil) have been found to improve digital ulcer healing [37, 63]. In case of recurrent ulcers, endothelin receptor antagonists (ERA) have been found to be useful in reducing recurrence rate and can be combined with PDE5i [37].

Other treatments that have been suggested, but have not been confirmed in trials, include botulinum injections at the base of the fingers and stellate ganglion block (Fig. 16.7) [62]. A non-healing ulcer with pain at night or pulsating pain should raise suspicion of underlying osteomyelitis that should be diagnosed and treated. Combination therapy (iloprost, PDE5i and ERA) is helpful and warranted in case of non-healing ulcers. Critical ischemia may result in amputation and thus warrants maximal vasodilation by triple therapy. We find hyperbaric oxygen therapy useful as an additive treatment in cases of critical ischemia with impending amputation [64].

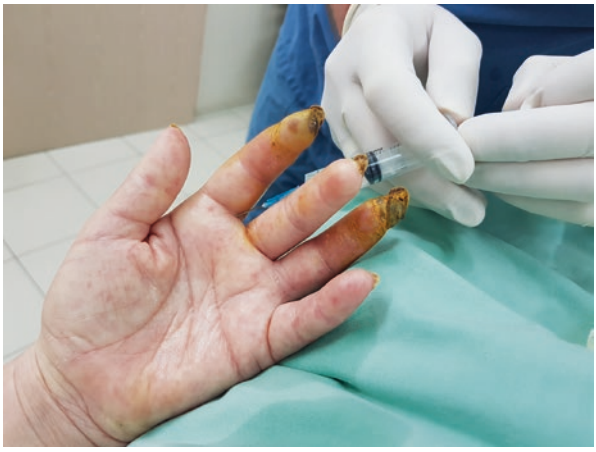

Fig. 16.7 Botulinum injection at the base of second phalanx in a patient with digital critical ischemia

PHT is probably the most important vascular manifestation of SSc in LOSSC, as it is not infrequent, heralds poor prognosis and high mortality and therefore should be systematically evaluated by echocardiography and lung function tests. PHT is usually a late complication in SSc and if occurs at the first 3 years since diagnosis, a mixed etiology should be suspected. A high percentage of cardiac comorbidities in the geriatric population warrants right heart catheterization in cases with suspected PHT in order to rule out post capillary PHT. Treatment of primary PHT in patients with functional class (FC) II–III should include two vasodilating agents (ERA and PDE5 inhibitors), but we suggest additive strategy in the elderly, starting with one drug (usually PDE5i) monitoring blood pressure and adverse reactions and then adding an ERA [65]. Although the recommended combination today for primary PHT is ambrisentan with tadalafil, we advocate the use of bosentan in SSc patients with DU because of its efficacy on DU in contrast to macitentan. Selexipag, an oral prostacyclin receptor agonist received FDA approval in 2015 and may also be added to dual therapy or replace an agent that is not tolerated and may improve 6-min walk, yet its up titration is not convenient in the elderly patient. Recently a new agent has been approved for PHT, riociguat, a stimulator of soluble guanylate cyclase that activates cGMP-dependent protein kinase (protein kinase G) to regulate cytosolic calcium ion concentration. This changes the actin–myosin contractility, which results in vasodilation. If PDE5 inhibitors are not tolerated it may be exchanged for Riociguat in symptomatic patient with FC II. Although riociguat was not found to improve skin fibrosis in the RISE-SSc study, it may have a trend for additive value in prevention of lung function decline in patients with lung fibrosis and reduction of DU in long extension studies [66–68]. In patients with FC class IV subcutaneous continues treprostinil treatment has largely substituted IV epoprostenol as it is safer and equivalently efficacious [65].

Gastrointestinal Tract

GERD is the most common GI manifestation of SSc and occurs in most patients. As GERD results in local gastric and esophageal damage that may lead to esophageal strictures, dysplasia and malignancy, and on the other hand aggravation of lung disease due to micro aspirations, all patients should be treated by protein pump inhibitors with up titration until symptoms are controlled [39]. We use most often esomeprazole 40 mg twice daily. In case of anemia gastroscopy may help evaluate and treat bleeding from GAVE for which recurrent treatment of argon plasma coagulation may be needed [30]. Dysphagia and regurgitation due gastroparesis and lower esophageal dysmotility are treated by Diet modifications including eating smaller meals more frequently, not eating for several hours before lying down, and avoiding high fiber and high fat foods [69]. Pharmacotherapy is a second line treatment and we tend to use metoclopramide 10 mg twice or thrice daily. We suggest avoiding the use of domperidone in the elderly because of high tendency for cardiac arrythmia that have been reported. Impaired motility may result in small

intestine bacterial overgrowth (SIBO) which is a common complication and results in chronic diarrhea. Many antibiotic regimens have been reported to be beneficial most of which are prolonged and may risk the elderly patient with clostridium infection. We favor the use of rifaximin, a nonabsorbable antibiotic with bactericidal activity, that have been found to have a good effectiveness with complete cessation of diarrhea and other abdominal symptoms and normalization of lactulose hydrogen breathing tests in 73.3% of treated SSc patients in one study [70]. We use a short course of 400 mg X3/day for 7 days. The involvement of gastrointestinal tract in SSc may be life threatening and sometime may be diagnosed too late. In refractory cases with partial small bowel obstructions either subcutaneous octreotide, 0.1 mg twice daily, or intramuscular octreotide LAR (long-acting-release), 20 mg/mo was found efficatious. Attention to weight loss, diarrhea and albumin level should be paid at every visit. An additional optional safe treatment that have been demonstrated to be beneficial in several aspects of GI involvement by validated Gastrointestinal Tract score is IVIG [71]. A beneficial effect of IVIG to other aspects of disease as skin fibrosis or myopathy may be taken as a consideration for the use of IVIG. In case of weight loss that is not improved with adjustment of nutritional caloric intake, total parenteral feeding can be a bridging therapy until gastric feeding or in case of severe GERD jejunal feeding is used.

Other Treatment Considerations in Geriatric Patients with Systemic Sclerosis

Systemic sclerosis is a complex and challenging disease that may carry increased morbidity and mortality and therfore needs a dedicated rheumatologist that specializes in SSc along with a multidisciplinary team of a cardiologist, pulmonologist, gastroenterologist, dietitian and physiotherapist. SSc in the elderly is challenging due to the frailty of the patients, polypharmacy and special considerations due to the age of the patients. It is advised to try and wisely choose treatments with dual effects that can help avoid polypharmacy, for example if a patient receives ERA for PHT bosentan that can decrease DU recurrence should be chosen or if a patient has a myositis, skin fibrosis and GI involvement, IVIG may be helpful for all indications. Special attention should be given for mental state as the severe disease with physical and cosmetic impairment may frequently be complicated by depression and weight loss that could be aided by selective serotonin reuptake inhibitors (SSRI) that may also improve RP. Routine Dietitian counselling is important in view of the common GI involvement. Physiotherapy is important for improving range of motion and avoiding skin contracture in the fingers and other areas, which limit function and are easier to avoid than to repair. Osteoporosis is common in geriatric population and specifically in SSc due to inflammation, malnutrition, impairment in absorption and weight loss and should be diagnosed and treated. Vaccinations for pneumococci (prevenar 13 and pneumovax 23) and influenza vaccine are highly recommended due to immune suppression as part of the disease and because of the therapy. Finally, vigilance and a malignancy workup cannot be overemphasized in the population of LOSSc.

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Chapter 17
Crystal Arthropathy in the Elderly Population

Lisa Kaly

Crystal arthropathy and periarticular syndrome are the results of inflammation due to the local deposition of crystals. The two best-recognized forms of crystal-induced joint disease in the elderly are related to the deposition of monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPPD).

A recently renewed interest in these diseases resulted in progress both in the field of imaging and treatment of crystal arthropathies, especially in gout.

CPPD, sometimes also named pseudogout, shares many common features with gout, and extrapolations have been made between the two diseases in terms of diagnosis means and new treatment.

Hydroxyapatite crystals deposition disease is responsible mainly for shoulder periarticular syndrome, while lack of specific and widely available diagnostic tools and efficient treatment make its management paricularly difficult.

17.1 Gout

17.1.1 Epidemiology

Gout arthropathy is the most common inflammatory arthropathy. Gout has a strong correlation with age; as the population ages, its prevalence rises from 3% in the general population to 5–8% in the males older than 75 years [1–3]. As the population ages, the gender disparity of gout narrows. Gout prevalence can reach up to 2% in women over 80 years old, while it is rarely seen in the premenopausal period [4].

L. Kaly (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel

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17.1.2 Risk Factors for Gout

The risk of gout increases dramatically with the rise of serum uric acid (SUA) levels. Risk factors for gout that are manageable are, in fact, risk factors for hyperuricemia. However, it is well-known that hyperuricemia is far more common than gout, implying that additional factors are involved in the mechanisms of clinical disease.

Hyperuricemia can result from an exogenous or endogenous source. Exogenous sources of hyperuricemia come from rich purine diets, including some beverages, such as alcohol or fructose sweeteners and food. Endogenous resource of hyperuricemia is found in two situations: in uric acid under-excreter patients and in uric acid over-producers. Uric acid underexcretion is by far the most prevalent condition, especially in elderly people. Underexcretion of uric acid can be seen in individuals with acute or chronic renal failure or be related to various medications, such as diuretics, low dose aspirin, L-Dopa, or calcineurin inhibitors on uric acid renal tubule transporters.

Uric acid overproduction can be related to high cell turn-over, for example in the course of Paget disease, hemolytic anemia, hematologic cancers, or solid tumors.

17.1.3 Clinical Picture

Gout arthropathy is the consequence of progressive and primarily asymptomatic monosodium urate crystals deposition in the cartilage, synovia, tendons, ligaments, and bones over the years.

In older people, the clinical presentation of gout can be challenging. According to the last EULAR recommendations, gout diagnosis relies on the presence of arthritis, hyperuricemia and, detection of MSU crystals by fluid aspiration or through suggestive imaging including plain radiographs, ultrasound (US), or dual-energy computed tomography (DECT) [5].

Hyperuricemia is determined by uric acid blood level higher than 6.8 mg/dL, which is its solubility threshold. Interestingly, not every patient with hyperuricemia will develop gout. So, it is essential to keep in mind that monoarthritis or polyarthritis in a patient with hyperuricemia is not gout arthritis for granted. On the other hand, hyperuricemia is not necessarily present in a patient with acute arthritis. For incompletely clear reasons, uric acid can be found at normal serum levels during an acute attack of gout, whether because of sudden precipitation into crystals with consequent engulfment by macrophages or increased adaptive urinary UA excretion [6, 7].

Further, the sudden decrease or increase of UA serum level for any reason, including high purine intake, acute renal failure, drug-induced hyperuricemia, or new uricosuric treatment, is often a trigger for an acute gout attack or a cause of delayed attack cessation.

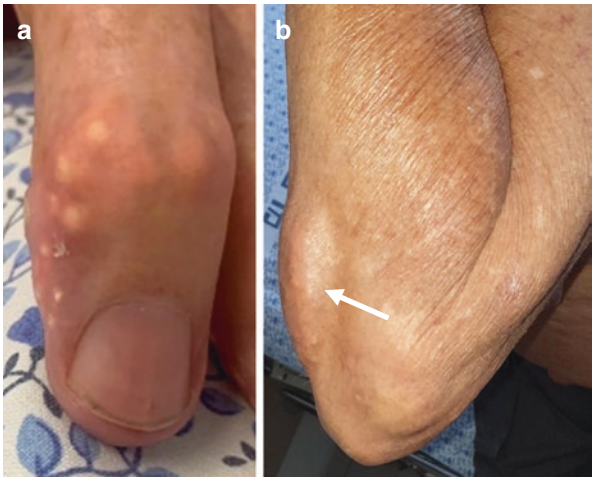

Fig. 17.1 Tophaceous gout. (**a**) Multiple tophi over distorted distal interphalangeal joint, or Heberden node. (**b**) A large tophus over the elbow region (arrow)

While the classic clinical picture of the first episode of gout is monoarticular and involves the first metatarsal-phalangeal joint (MTP) in the majority of middle-age patients, the clinical presentation of gout in elderly is frequently atypical.

The polyarticular tophaceous disease is a relatively common atypical presentation of gout in the elderly population [8]. Up to 39% of patients aged between 60 and 64 years have a history of polyarticular gout already at its onset. This higher frequency of polyarticular gout onset is thought to be multifactorial, due to chronic co-morbidities, particularly chronic renal failure, and contributing to the development of hyperuricemia medications [9–11]. Joints already damaged by osteoarthritis, such as knees or distal interphalangeal joints with classical Heberden nodes, are more prone to develop gout (Fig. 17.1). The other misleading manifestion of gout in elderly people is chronic hyperuricemia with asymptomatic arthropathy and tophi accumulation as it has been reported in case reports and small case series [11]. Asymptomatic chronic tophaceous gout affects predominantly elderly women with chronic renal failure, partricularly those on diuretic treatment. The hands are involved most often.

17.1.4 Diagnosis

Because of the particular atypical presentation of gout arthritis in older people, identification of monosodium urate (MSU) crystals in synovial fluid or from tophi, to confirm the diagnosis, becomes essential. MSU crystals are typically needle-shaped and different from rhomboid CPPD crystals; however, in some case of long-standing gout exacerbation, examination of the synovial fluid can exhibit crystals with broken edges and the MSU crystals become more rectangular and similar to the crystals of CPPD. For this reason, the use of a compensated polarizing

microscope, showing a typical strongly negative birefringence of MSU crystals, is recommended. MSU crystals can be found in the synovial fluid during the attack but also in the inter-critical gout stage. The finding of MSU crystals engulfed by neutrophils supports the diagnosis of the acute gout attack.

In acute gout, the synovial fluid reveals white blood cell (WBC) counts range typically from 5000 to 25,000 cells/μL; however, higher WBC counts of up to 100,000/mL are occasionally seen.

Nevertheless, the aspiration of the synovial fluid or tophi is not always possible or successful. Conventional radiography has historically been the initial investigation of choice in patients presenting with the gout-like clinical picture. However, radiographs in the acute phase usually demonstrate non-specific soft tissue swelling or joint fluid only. At the later stage, radiographic abnormalities demonstrate more specific osseous changes, but those may take more than 10 years from the onset of disease to manifest [12]. In these cases, radiographs show a non-demineralizing erosive arthropathy characterized by well-defined 'punched out' juxta-articular or intra-articular erosions with overhanging and sclerotic margins [13, 14]. The radiographic appearance of the soft tissue tophi is usually ill-defined, with attenuated mass lesions of different sizes (Fig. 17.2). Notably, tophi are usually radiographically occult if less than 5–10 mm [15].

In the past decade, additional imaging techniques evolved tremendously, giving new opportunities to confirm the diagnosis of gout.

The use of ultrasound (US) in the assessment of rheumatic conditions is increasing due to its availability, relatively low cost, lack of ionizing radiation, dynamic and multiplanar imaging capability, and high soft-tissue resolution. The MSU

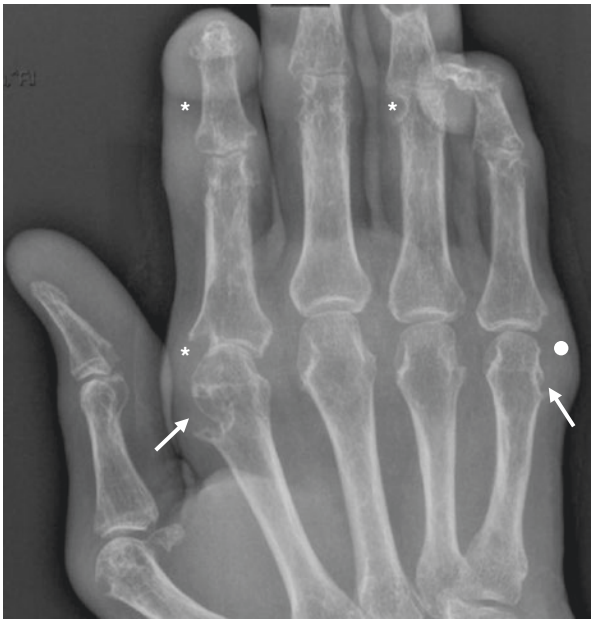

Fig. 17.2 A hand radiogram of a patient with advanced gout. Overhanging erosions (arrows), tophus (white spot) and marginal erosions with sclerotic borders (asterixis) are seen

crystals, precipitating on the surface of hyaline cartilage, produce an echogenic line that parallels the osseous margin. This double-contour sign, consisting of two dense hyperechoic bands, separated by a hypoechoic structure of normal articular cartilage, has been shown to have a very high specificity in patients with gout or asymptomatic hyperuricemia, as compared with controls. Still, the sensitivity of the double-contour sign is low [16]. Other sonographic signs, including tophi or gouty synovitis, have as well specific features that help for the diagnosis of acute attack or chronic disease (Figs. 17.3 and 17.4). According to a multicenter study on the US versus arthrocentesis for the diagnosis of gout, US features of MSU crystal deposition, including double-contour sign, tophus, and 'snowstorm' appearance, have

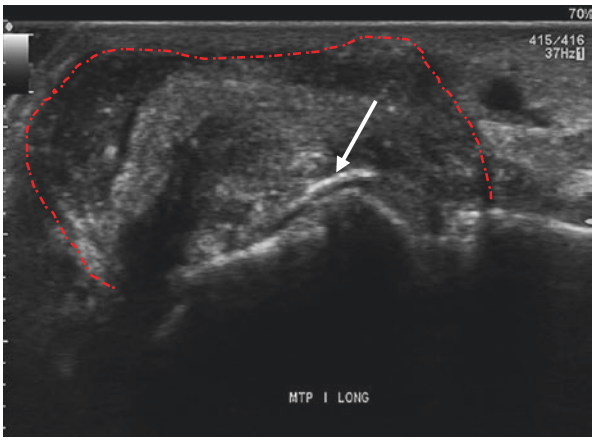

Fig. 17.3 Ultrasonography of the first MTP joint of a patient with gout. A hyperechoic double contour sign (arrow) is seen, surrounded by a large tophus (outlined by the red line)

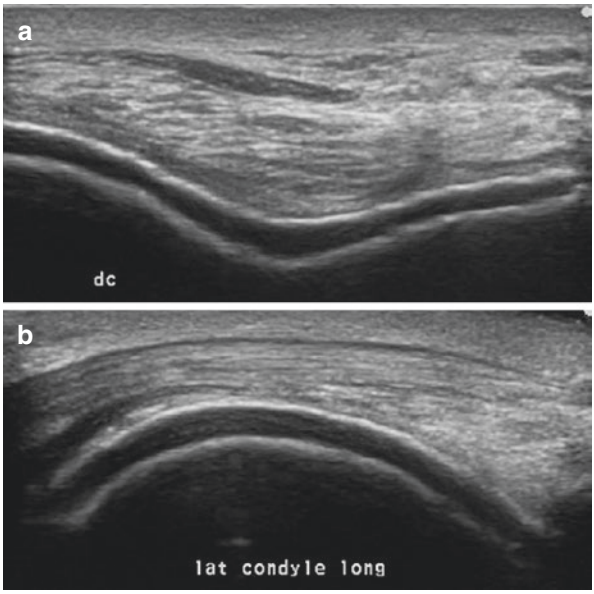

Fig. 17.4 Ultrasonography of the knee joint of a patient with gout. Trochlea cartilage (**a**) and the lateral femoral condyle cartilage (**b**) with a double-contour sign (thickened hyperechoic cartilage border)

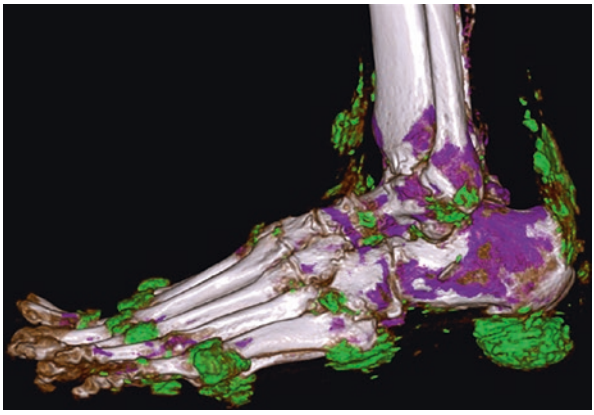

Fig. 17.5 Dual energy computed tomography in a patient with gout. Numerous green-coloured tophi are seen over MTP joints and foot entheses (Achilles tendon, digits extensor tendons and plantar fascia)

excellent specificity and diagnostic value when present, but have somewhat limited sensitivity in early gout [17].

Dual-energy computed tomography (DECT) has been used in cardiology for years as a means to image calcifications within coronary artery plaques and, as well, in renal medicine for the identification of uric acid calculi [18, 19]. It has also been recently investigated in tophaceous gout [20]. DECT scanning involves the use of two x-ray tubes positioned at 90° to each other and two corresponding detectors, acquiring the images simultaneously at two different energy levels, providing two data sets. Further, a 3D material decomposition algorithm allows the characterization of uric acid deposits, colored differently from calcium and soft tissue (Fig. 17.5).

A recent meta-analysis, which summarized data of seven studies including in total 417 patients with acute, inter-critical, and chronic tophaceous gout, found that both pooled sensitivity and specificity of DECT for the detection of gout was 84% [21]. The diagnostic accuracy of DECT was comparable with a 'composite gold standard' test comprised of a combination of both joint aspiration or ACR clinical-radiographic criteria. DECT was also compared with and far outperformed both conventional radiography and non-contrast CT, which showed significantly lower sensitivities of 15% and 26%, respectively. Notably, the threshold for DECT detection requires a tophus to be at least 2 mm in size and composed of at least 15–20% MSU by volume [22, 23]. Another study investigated the prevalence of monosodium urate (MSU) crystal deposits, indicative for gout, in patients with rheumatoid arthritis (RA) and concomitant hyperuricemia [24]. Hyperuricemic RA patients were mostly males over 60 years of age and had established mildly to moderately active RA. Surprisingly, the MSU crystal deposits on DECT were seen in 20 of 100 RA patients, while 70% of these RA patients positive for MSU crystal deposits, had a seronegative disease. Hence, this study raised a question whether in these cases, chronic polyarticular gout could be misdiagnosed as a seronegative RA.

DECT has its limitations and can demonstrate false-positive results due to the artifacts. MSU may be falsely displayed in up to 90% of studies, but these artifacts are easily identified by the location in joints with significant osteoarthritis, on the

surface of arthroplasties and in the skin and nail beds [25]. MSU deposits have also been demonstrated in the costal cartilages and intervertebral discs in healthy, normouricemic older adults, but not in younger control patients, suggesting urate deposition in these locations may be physiological in aging [26]. DECT is as well associated with increased radiation load comparing to radiography, US, or MRI and may become a concern if it has to be used repeatedly, particularly in younger patients. US and MRI demonstrate the non-crystalline tophus components with higher resolution, comparing to DECT [27]. However, DECT and ultrasound have similar sensitivities for the detection of the tophus, while DECT has the undeniable advantage of improved visualization in certain, inaccessible for the US anatomical regions or sites with poor acoustic windows [28]. Additionally, DECT can distinguish urate from other crystal arthropathies, such as CPPD [29].

The performance of MRI for the diagnosis of gout remains uncertain due to a lack of data, and the relative lack of specific imaging findings and MRI findings have not been included in the diagnostic criteria published by the ACR or EULAR.

17.1.5 Treatment

Management of gout in older people is influenced by polypharmacy, co-morbidities, and patients' susceptibility to developing side effects. Treatment of acute attacks of gout differs from preventive treatment in the long term.

In acute gout arthritis, the goal is to stop the current attack as fast as possible. Although flares are usually self-limited with a mean duration of 10 days, pain intensity is usually quite unbearable, and, in some patients, acute attacks can last for weeks.

The treatment of choice for monoarticular gout flare in older people should be a local injection of a glucocorticosteroid, because of limited side effects of this treatment. However, when the flare involves more than two joints, simultaneous steroid intra-articular injections can cause systemic effects, similar to oral glucocorticosteroid treatment or intramuscular injection, including the deterioration in control of serum glucose levels, blood pressure or congestive heart failure in predisposed patients. Systemic glucocorticosteroid treatment, when chosen, should be administered as 30 mg of prednisone a day.

Colchicine at the dosage of 1 or 1.2 mg a day is another treatment possibility in elderly patients with normal renal function. Notably, a loading dose of colchicine is no longer recommended for the treatment of acute gout [29]. Dosage of colchicine has to be reduced in patients with compromised renal function. Co-administration of colchicine with some medicines, *i.e.*, clarithromycin, is not recommended because of the risk of toxicity.

Non-steroidal anti-inflammatory drugs (NSAID) can be used for a short period of several days to relieve an acute attack but are contraindicated in the presence of renal failure, uncontrolled hypertension, recent upper gastrointestinal bleeding or unstable ischemic heart disease.

Anakinra, an interleukin-1 inhibitor, can be useful in those patients in whom standard anti-inflammatory agents failed [30]. Few daily doses of anakinra subside most gout attacks rapidly, but the treatment is still off label. Canakinumab, a longer-acting anti-interleukin-1 inhibitor, is now approved in some countries for treatment of gout flares for patients in whom other anti-inflammatory drugs are ineffective or contraindicated [31, 32]. Any treatment of flares should be accompanied and followed by colchicine in prophylactic doses, if not contraindicated, to avoid rebound flares, especially in a patient with severe gout [33].

***Preventive treatment*:** The concept of treat-to-target (T2T) in gout emerged in 2012 [34, 35]. The T2T therapeutic strategy has been accepted in various clinical practices and has been implemented in several diseases, such as hypertension, diabetes, and hyperlipidemia. T2T has been proposed for other rheumatic diseases such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, and lately gout. According to the last EULAR guidelines for gout treatment, serum uric acid (SUA) level should be maintained under 6 mg/dL for gout arthritis without tophi and under 5 mg/dL for patients with severe gout, characterized by tophi, polyarticular involvement, and frequent attacks, until total crystal dissolution and resolution of gout. The compliance with these thresholds is of primary importance and leads to better disease control and patients' wellbeing. SUA level under 3 mg/dL is not recommended in the long term because of the controversial data about the possible neurologic impact of chronic hypouricemia. In the elderly population, the preventing treatment for gout should be considered after the first episode, because of more severe disease and associated comorbidities, in compliance with the EULAR recommendation to start chronic treatment at the first attack in patients with UA level more than 8.0 mg/dL or those with associated renal impairment, hypertension, ischemic heart disease, or heart failure [36]. In order to achieve the targeted SUA level, non-pharmacologic and pharmacologic strategies have been developed.

Non-pharmacologic recommendations are basic but usually not sufficient or challenging to perform in the long term. It includes a low purine diet, weight loss for obese patients, and depends on the compliance of the patient to change habits. Dairy food, vitamin C, and cherries have been shown to have a partial but potential effect on lowering the SUA level [37, 38].

The pharmacologic management of gout is thought to be a lifelong treatment and should not be stopped during attacks, as based on SUA lowering strategy. However, the initiation of a uric acid lowering drug during an acute attack is not recommended because of possible attack aggravation, and 2 weeks of delay of preventive treatment is instead advised.

Allopurinol is the first-line treatment of uric acid lowering agent. It is a xanthine oxidase inhibitor (XOI) that prevents the conversion of hypoxanthine, a soluble product of nucleotide degradation, to uric acid. Allopurinol should be started at a daily dose of 100 mg and gradually increased, according to the SUA target. The maximal daily approved allopurinol dose is 900 mg. In patients with chronic renal failure, allopurinol is not contraindicated, but the starting dose should be lowered according to a dedicated study (Table 17.1) [39]. The rather slow increasing

Table 17.1 Proposed starting dosage of allopurinol according to GFR ([39] with permission)

Proposed starting dosage of allopurinol based on 1.5 mg per estimated GFR[a]	
Estimated GFR mL/min/1.73m^2	Allopurinol starting dosage
>5	50 mg/week
5–15	50 mg twice a week
16–30	50 mg every 2 days
31–45	50 mg/day
46–60	50 mg/100 mg on alternate days
61–90	100 mg/day
91–130	150 mg/day
>130	200 mg/day

Consideration should be given to starting allopurinol at even lower doses in patients at high risk of developing allopurinol hypersensitivity syndrome such as those with HLA-B5801
[a]Estimated GFR-estimated glomerular filtration rate

allopurinol dose is preventive for both gout exacerbation, which can develop secondary to the sharp fluctuation of SUA, and allopurinol hypersensitivity syndrome (AHS). AHS is characterized by a skin rash, elevated liver transaminase, and eosinophilia with risk mortality around 25%. AHS, being a delayed-type hypersensitivity reaction, develops within weeks after starting allopurinol. For this reason, monitoring of blood count and liver enzymes during the first month after allopurinol administration is strongly recommended. If pruritus occurs, allopurinol has to be stopped. Ethnicity, particularly of Asian ancestry and presence of HLA B5801, have been suggested as risk factors for developing AHS.

There is a critical interaction to know between allopurinol and azathioprine. Azathioprine has an active metabolite, the 6-mercaptopurine, that is partially inactivated by xanthine oxidase, the same enzyme that allopurinol inhibits. So, inhibition of xanthine oxidase enzyme can lead to an increase of 6-mercaptopurine concentrations resulting in pancytopenia [40]. A less recognized but quite relevant in the older people interaction has been reported between furosemide and allopurinol. It seems that furosemide attenuates the hypouricemic effects of allopurinol, and a higher dose of allopurinol is needed to achieve the target [41].

Several observations have been recorded concerning the pleiotropic effects of allopurinol on the common in patients with gout co-morbidities, among them hypertension, cardiovascular disease, and renal impairment. Accordingly, allopurinol has been reported to slow progression of renal function [42], to reduce cardiovascular death rate [43] and improve exercise capacity in chronic stable angina [44], and reduce blood pressure [45].

Febuxostat is a non-purine selective XOI. The hepatic metabolism of febuxostat is a significant advantage for many patients with mild to moderate chronic kidney failure (CKD), as the dose of drug does not need to be adjusted. However, patients with severe CKD (eGFR < 30 mL/min/1.73 m^2) were excluded from febuxostat phase 3 clinical trials, and caution has been recommended in those with cardiovascular disease or heart failure [46]. Febuxostat can be a useful alternative

urate-lowering drug in those who are allopurinol intolerant [47], although the risk of skin reactions or elevated liver enzymes with febuxostat still exists [48]. Febuxostat is available in the dosages of 40 mg, 80 mg, and 120 mg. Febuxostat seems to be a more potent drug than allopurinol, achieving the SUA target faster. A cohort of 762 patients with gout and hyperuricemia above 8 mg/dL was randomized to receive allopurinol 300 mg, febuxostat 80 mg, or febuxostat 120 mg. After 3 weeks of treatment, 21%, 53%, and 62% of each group, respectively, had achieved the goal of SUA under 6 mg/dL [49].

Uricosurics act by reducing urate reabsorption at the renal tubules through different uric acid transporters. They are usually used as adjuvant therapy to XOI when the target SUA levels are not achieved on monotherapy [49, 50]. Probenecid and benzbromarone belong to the first generation of uricosurics and are available in a limited number of countries. The improving of uric acid renal clearance results in the reduction of tissue burden of monosodium urate crystals, SUA levels and, consequently, better patient's status. Benzbromarone needs careful liver enzyme monitoring, and probenecid is not recommended in patient with hyperuricosuria over 800 mg/day, history of uric acid nephrolithiasis or chronic renal failure. Another uricosuric agent lenisurad, which inhibits URAT1 transporter, has recently been approved for use in gout in combination with an XOI [51]. Some other drugs like losartan, high dose salicylates, and fenofibrate have some uricosuric activity as well, with mild to moderate range of SUA level reduction between 10 and 20%.

Recombinant uricase is indicated for patients resistant to uric acid-lowering therapy (ULT), or those with multiple tophi. Uricase is an enzyme that exists in most mammalian animals and fungus. It catalyzes the utilization of urate into allantoin, which is highly soluble and easily excreted through the kidney [52]. This enzyme does not exist in humans. However molecular engineering has developed several recombinant uricase therapies, which are administered parenterally.

Rasburicase is a recombinant fungal uricase with a half-life of 16–20 h. It is indicated for short-term treatment of tumor lysis syndrome. Although few case reports and a small cohort study have shown fast response regarding the reduction of SUA level, gout attacks, and tophi size in patients with severe gout intolerant or resistant to XOI, rasburicase has not been approved for the management of chronic gout [53]. The principal limitation of the usage of rasburicase as a long-term treatment for gout is hypersensitivity reaction.

Pegloticase is a chimera of porcine and baboon liver uricases and is designed for the continuous treatment of refractory gout [54]. Pegloticase has a half-life of 3–7 days and is given in the dosage of 8 mg every 2 weeks for 6 months. According to previous studies, repeated administration of pegloticase can cause an immune response in 20% of the patients, so a premedication with glucocorticosteroids is given before each treatment [55]. Anti-pegloticase antibodies, present in 41% of patients, increase pegloticase clearance but do not neutralize uricase activity [56]. The most frequent adverse event of pegloticase is infusion reaction, which is seen in as much as 25% of the patients [57].

17.2 Pseudogout

17.2.1 Epidemiology

Chondrocalcinosis is the radiologic description of CPPD deposition in the cartilage, whereas pseudogout is the clinical consequence of this deposition. There are no clear estimates on the prevalence of pseudogout in population. A French study revealed that the number of hospitalizations for pseudogout attacks was approximately the same as for the attacks of gout [58]. On the other hand, the prevalence of chondrocalcinosis, an imaging substrate of CPPD disease, can fluctuate between 7% and 14% in adults, increasing with age and affecting up to 80% of people over 80 years old [59–61]. Both genders are affected similarly by pseudogout.

17.2.2 Clinical Manifestations

Acute CPPD arthritis is seen in 25% of all CPPD patients [62] and usually manifests as monoarthritis or oligoarthritis, affecting most frequently the knee or wrist; however, any joint can be involved. Flares can be similar to gout with typical pain, erythema, warmness and swelling, and even can occur in the first MTP, which led to its name 'pseudogout'. Trauma, acute illness, or surgery can precipitate an attack of pseudogout [63].

Chronic CPPD-related arthritis can sometimes be difficult to distinguish from the so-called inflammatory osteoarthritis or rheumatoid arthritis. CPPD can also involve vertebral junctions, and the transverse ligament of atlas, resulting in the crowned dens syndrome, manifesting with acute neck pain, headache, sometimes low-grade fever, and elevated C-reactive protein, a clinical picture that can sometimes be mistaken for giant cell arteritis or even meningitis (Fig. 17.6). Other CPPD patients can have an aggressive monoarthritis radiographically resembling neuropathic arthropathy, however, without neurologic pathology [64].

17.2.3 Diagnosis

The gold-standard diagnosis is based on the analysis of the synovial fluid by a compensated polarizing microscope, showing typical positively birefringent rhomboid or rectangular shaped crystals. The capacity for crystals to reflect the light in its way allows using the technic of polarized light to distinguish between different types of crystals irrespectively to their shape. As CPPD crystals can differ by both shape and size, the use of polarized light is critical for their identification.

The synovial fluid is inflammatory, opaque, sometimes hemorrhagic, with the WBC counts ranging from 5000 to 25,000 cells/μL. Lower WBC counts can be seen

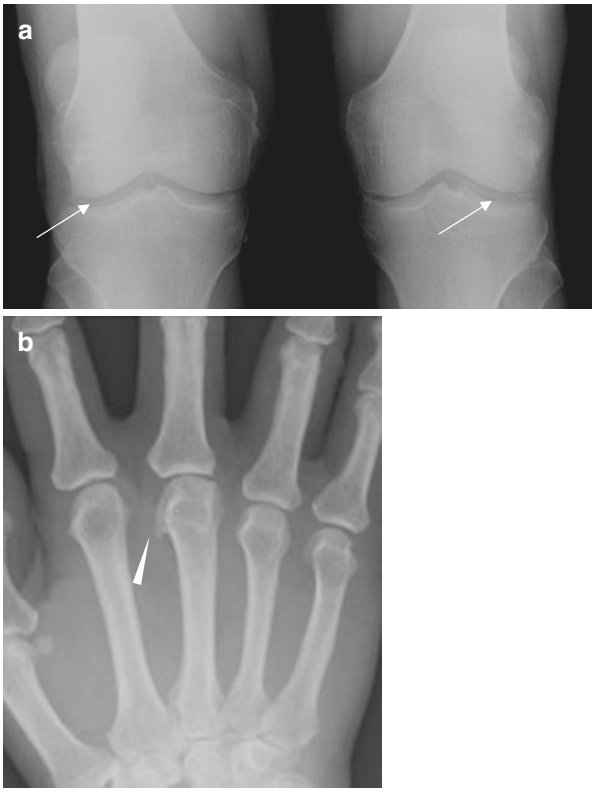

Fig. 17.6 Radiograms of a patient with calcium pyrophosphate dihydrate deposition disease: (**a**) Chondrocalcinosis within the hyaline cartilage of the knees (arrows). (**b**) Hooked osteophyte of the third MCP head (arrowhead)

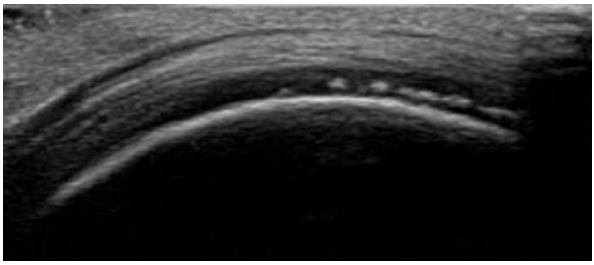

Fig. 17.7 Ultrasonography of the femoral condyle of a patient with pseudogout. Dot line within the cartilage is typical for the calcium pyrophosphate dihydrate deposition disease

in patients with a chronic pattern of the disease, while up to 100,000 WBC/μL are possible in patients with pseudo-septic CPPD arthritis. Elevated serum CRP and ESR are typical.

The sensitivity of conventional radiography to detect CPPD is 50%–70% in proven disease [61, 65]. Chondrocalcinosis is most commonly seen in the knee articular cartilage and menisci, the acetabular labrum, the fibrocartilage of the symphysis pubis, the triangular fibrocartilage of the wrist and the annulus fibrosus of the intervertebral discs (Fig. 17.7) [59]. Hook-like osteophytes located at the medial

aspects of the second and third metacarpophalangeal joints are very suggestive of a CPPD disease, particularly of hemochromatosis-associated CPPD (Fig. 17.6).

US has recently become a major tool in the diagnosis of CPPD, and it has better, comparing to the conventional radiography, sensitivity, and specificity, both being in the range of 90% [65].

CT is the best tool for the imaging of CPPD deposition at the spine, especially around the dens (Fig. 17.6). The use of DECT for the diagnosis of CPPD is promising [66].

17.2.4 Treatment

The lack of randomized studies on CPPD treatment has been replenished by expert-derived recommendations, most of them inspired by guidelines on the management of gout [67]. Different from gout, however, we still do not know how to dissolve CPPD crystals, thus targeting only the secondary inflammation [68]. Three major goals to achieve while treating a patient with CPPD include limitation of the duration of acute attacks, prevention of further attacks or chronic disease manifestations, and treatment of secondary arthrosis.

The pharmacologic management of acute CPPD arthritis relies on colchicine, NSAIDs, and glucocorticosteroids [67, 68]. Patient's comorbidities usually dictate the choice of treatment. NSAIDs should be used very cauciously in the elderly population. For colchicine, no loading dose is needed to avoid side effects for no proven additional efficacy. Intraarticular glucocorticosteroid is preferred over systemic glucocorticosteroid treatment in monoarticular arthritis. Prednisone, if chosen, is usually started at the daily dosage of 30–40 mg and tapered gradually down over up to 2 weeks. In the case of contraindication to all of the above, off label treatment with anakinra can be considered in selected patients [69].

The data on preventive pharmacologic management for recurrent attacks and other chronic manifestations are quite disappointing [68]. Formerly, the concept of immunomodulatory treatment with hydroxychloroquine was examined in a pilot study, which demonstrated encouraging results versus placebo. However, no confirmative studies have been published since, and results of using hydroxychloroquine in daily practice are disappointing in the majority of CPPD patients [70]. Further, a 3 months pilot study with methotrexate in the weekly dosage of 15 mg versus placebo was negative as well [71]. However, despite the lack of direct evidence of efficacy methotrexate in CPPD, it is still considered as an option in the absence of more efficacious therapy. Continuous oral colchicine is another alternative for preventive treatment in CPPD patients, but dose adjustment should be implemented for those with impaired renal function [72–74]. Magnesium supplementation in the long term is occasionally recommended as an adjuvant treatment in the hope that it can inhibit the formation of new CPPD crystals [75].

17.3 Hydroxyapatite Periarticular and Articular Deposition Disease

Hydroxyapatite is part of basic calcium phosphate (BCP) crystals. In the musculoskeletal system, hydroxyapatite crystals can be found in various tissues, including synovium, tendons, bursae, cartilage, and intervertebral discs.

Often responsible for shoulder pain or acute calcified tendinitis, hydroxyapatite crystals seem to be also involved in osteoarthritis. Epidemiologic data on the prevalence of the hydroxyapatite-related rheumatic disease lack, however.

17.3.1 Clinical Manifestations

Hydroxyapatite crystals are believed to be involved in osteoarthritis as at least an aggravation element [76]. The typical presentation is a recurrent knee monoarthritis in an older patient with the background diagnosis of osteoarthritis, while the synovial fluid is hypocellular and no crystals are seen on the standard microscopic analysis of the synovial fluid. The diagnosis of hydroxyapatite arthritis is frequently missed in these cases, as the radiograms are usually do not show specific findings, and special staining with alizarin red is necessary for the detection of tiny crystals in the synovial fluid [77]. Also, acute calcific periarthritis can result from hydroxyapatite crystal deposition in the periarticular soft tissues, particularly in the tendons, and although deposition can occur in almost any joint, the shoulder is most commonly affected. As such, shoulder calcifications can be detected in 7.8% and 42% of asymptomatic and symptomatic patients, respectively [78]. Acute calcific periarthritis due to hydroxyapatite crystal deposition is usually self-limiting and tends to resolve within 2–3 weeks; treatment with NSAIDs can further shorten the clinical course [79]. Commonly, trauma or overuse of the joint can trigger the attack onset, which is believed to be related to the rupture of pre-existing calcific deposits and their transport into an adjacent soft tissue space, which in turn drives an acute inflammatory reaction [80].

An extreme clinical manifestation of hydroxyapatite arthritis is Milwaukee shoulder syndrome. It is rapidly destructive arthritis that typically affects the shoulder but can also affect the hip joint. Patients with Milwaukee shoulder syndrome have characteristic large, non-inflammatory synovial effusions, massive rotator cuff tears, restricted motion, and advanced articular surface destruction. Bone-on-bone crepitus on joint movement is also typical. The synovial fluid can be hemorrhagic but contain low numbers of WBCs [81].

Hydroxyapatite crystals can also precipitate in the skin and manifest with skin calcinosis, as happen in the course of systemic sclerosis or tumoral calcinosis. Tumoral calcinosis is a rare condition characterized by the progressive deposition of calcified masses in cutaneous and subcutaneous tissue. It is typically associated with chronic renal failure with secondary hyperparathyroidism.

Familial tumoral calcinosis is a heritable disorder that combines hyperphosphatemia, normal or elevated 1,25 dihydroxy vitamin D, and often severe ectopic calcification.

17.3.2 Hydroxyapatite Detection Means

Hydroxyapatite deposition is characterized by dense, homogeneous and amorphous calcium deposits, usually of a round or oval shape, from 2 to 10 mm in size, without cortex or internal trabeculae, typically located periarticular or in proximity to tendons or ligaments [82]. The characteristic cloudy-like appearance on imaging, frequently without an underlying disorder, distinguishes the hydroxyapatite deposition disease. CT is a preferred method for delineating intra-tendinous calcifications. The US is another useful diagnostic tool, showing hyper-echogenic calcifications with or without acoustic shadow, tendon thickening, and increased color Doppler vascularization [83, 84].

BCP crystals are small, being only 20–100 nm in size, as compared with the maximal resolution capacity of light microscopy of 1 μm, and non-birefringent, and thus usually undetectable by conventional or polarized light microscopy. However, when present in large amounts, BCP crystals tend to clump into aggregates, large enough to be visualized. Microscopy with alizarin red staining is quite sensitive for BCP crystals, but its specificity is low, and dye preparation is laborious. Thus, a simple, reliable, and inexpensive methods for BCP crystal identification are absent.

17.3.3 Management

Patients with acute calcific periarthritis or BCP-related arthritis should be treated with NSAID or colchicine. Local corticosteroid injections will help resolve the acute symptoms as well. Proposed treatment modalities in chronic calcific tendinitis include very safe short-wave ultrasound, phonophoresis with EDTA, as well as more invasive treatment by local steroid injections, barbotage, high-energy extracorporeal shockwave therapy or arthroscopic surgery [85–87]. Our experience supports the long-term colchicine administration as an alternative, both efficacious and safe therapy for patients with chronic hydroxyapatite crystals-related arthritis and periarthritis. Finally, a recent case study reported promising results with the anti-IL1 blockade in these patients, suggesting that BCP-related disease is driven by inflammasome activation [88]. In Milwaukee shoulder (or hip) syndrome, the treatment includes recurrent aspiration of the synovial fluid, accompanied by local glucocorticosteroid injection, continuous use of colchicine and short courses of NSAID. In advanced arthritis, joint replacement can be considered, while postoperative complications, including the heterotopic ossification are frequent [89].

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Chapter 18
Osteoarthritis

Itzhak Rosner

18.1 Introduction

Osteoarthritis (OA) is by far the most common form of arthritis, probably affecting more people than all other forms of arthritis combined. It is largely viewed as age related. Thus, in the minds of most of the lay public as well as many health professionals, it seems to define arthritis in general, and possibly all of rheumatology, as age related.

Osteoarthritis is commonly held to be a chronic degenerative disease, thought by many to be an inevitable consequence of growing old. The general perception is that osteoarthritic joints suffer from "wear and tear" that comes with prolonged use.

Aside from the opening statement that OA is the most common form of arthritis, there are major problems with all of the above 'understandings' as will be detailed below.

18.2 Definition

Osteoarthritis defies succinct definition. Clinically, it is an articular ailment recognized by typical radiographic changes: asymmetric joint space narrowing across the breadth of a joint, accompanied by bony reaction, so called sclerosis, in the subchondral bone, and marginal bony spurs or osteophytes, frequently with resultant joint mal-alignment. These structural changes are manifest clinically as joint pain, more prominent with joint use and receding with rest, typically in the absence of

I. Rosner (✉)
Bnai Zion Medical Center, Technion-Israel Institute of Technology, Haifa, Israel
e-mail: itzhak.rosner@b-zion.org.il

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classical signs of inflammation such as prolonged ‘morning stiffness’, joint redness or heat. Accordingly, conventional blood indices of systemic inflammation, c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are usually within normal limits, and there is no reliable diagnostic biomarker to confirm the diagnosis. Besides pain, the condition is clinically apparent in characteristic joint deformities and limitation of joint motion.

To complicate matters of ascertainment and diagnosis of osteoarthritis, there is poor correlation between the obligatory radiographic findings and patients’ symptoms. On the one hand, many more individuals have radiographic findings of osteoarthritis—as noted in population surveys or incidentally during investigations for non-articular ailments—than actually ‘suffer’ from osteoarthritis; and, on the other hand, patients may manifest such radiographic changes and yet their relevant active joint disease may be secondary to one of the many inflammatory or autoimmune arthropathies, independent of the imaging findings. While in theory there must exist a pre-radiographic state of osteoarthritis, one if we could recognize and treat may enable us to prevent irreversible joint changes, our present state of knowledge defies our ability to define it with any confidence.

Osteoarthritis may be further classified as primary or idiopathic—with no notable predisposing condition driving the osteoarthritic process and occurring in specific typical joints—or secondary, possibly due to joint mal-alignment, trauma, crystal deposition, metabolic disorder, etc. Primary osteoarthritis may develop in the distal inter-phalangeal (DIP), proximal inter-phalangeal (PIP) finger joints and first carpo-metacarpal (CMC) joints, yet spare the metacarpo-phalangeal (MCP) and wrist joints in the hands. Also, in primary osteoarthritis, while hips and knees are involved, the ankles are not, though technically they bear more weight than knees and hips.

To confuse matters more, some forms of secondary osteoarthritis may include a prominent inflammatory component.

Further, though osteoarthritis is typically recognized/diagnosed in the joints of hands, knees, hips and spine, it appears that the condition in each of these locations may represent a separate entity or subset, not necessarily related to its appearance in any of the other locations in any given individual.

Curiously, the pathology/histology of osteoarthritis, typically occurring in elderly individuals, is shared with chondromalacia patella, a non-progressive condition occurring frequently in the knees of adolescents. The existence of this latter subset of OA tends to argue against the necessarily ‘degenerative’ nature of OA. In fact, in support of this latter assertion, is the observation that OA, once diagnosed by standard clinical and radiographic criteria, advances toward worsening symptoms and loss of joint integrity in only a minority of individuals, roughly 20%, on 5 year follow-up [1]. Those who do worsen structurally appear to be those individuals who are more painful and have evidence of active inflammation, such as warm joints with excess joint fluid and elevated blood indices of inflammation. Again, such observations from studies in OA tend to belie the common wisdom that OA is inevitably progressive and destructive, intractably advancing, with aging, toward maximal joint damage.

Pathophysiologically, osteoarthritis is unique among the arthritides in that it is restricted to the joints, having no systemic component. Further, its major structural/

pathologic lesions are located in the cartilage and bone rather than the synovium and synovial fluid of a joint. Emphasizing its relative absence of inflammation, OA is also known as ‘osteoarthrosis’ or ‘degenerative joint disease’.

18.3 Epidemiology

While osteoarthritis (OA) is the most prevalent form of arthritis, actively involving 10% of the adult population and 20% of those above the age of 60, its most striking feature is its increasing presence with age [2]. And yet, epidemiologically, there appears to be a levelling off its incidence in the seventh decade, with an apparent decreased prevalence in the ninth decade of life [3, 4] (Fig. 18.1). These observations challenge the assumption that it is age related and an inevitable consequence of getting old. While OA is viewed as a benign condition, its associated comorbidities, especially obesity, are associated with a shortened lifespan [5]. But while mortality is minimally affected directly [6], osteoarthritis is the leading cause of disability in older individuals, impacting heavily on ‘quality of life’ and entailing heavy societal costs including those of medical care. Surveys in the US have determined it to be the most expensive medical condition in terms of hospitalization costs and insurance companies’ outlays, especially the costs surrounding joint replacements [7].

The overall prevalence of the condition is equal between sexes, but multi-joint involvement—prominently including fingers and toes—is more typical in women, becoming more symptomatic post menopause. A more oligo-articular presentation, favoring knees and hip joints, is more frequent in males.

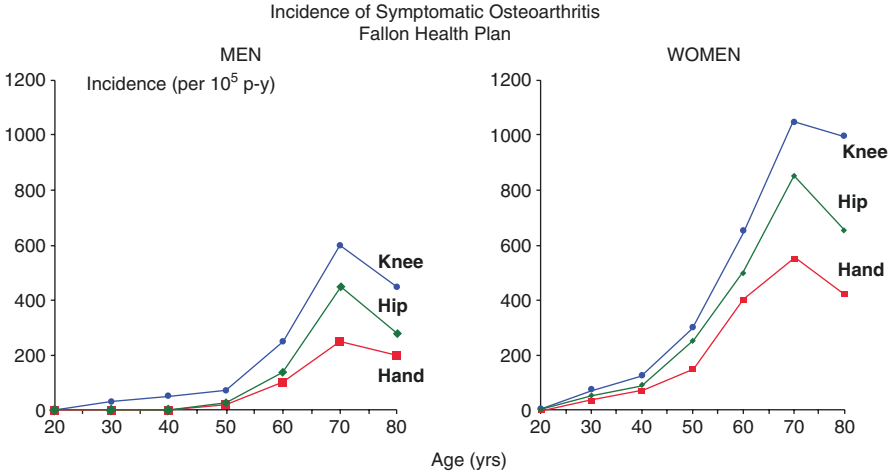

Fig. 18.1 Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Reprinted with permission from: Oliveria SA, et al. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis & Rheumatol 1995; 38: 1134–41

Despite radiographic findings of joint changes consistent with OA in 85% of individuals in their eighth decade of life, only an eighth to fifth of them complain of symptoms relating to these structural changes. Women tend to be more symptomatic with their arthritis than men.

Studies on the role of obesity in inducing the disease have been unclear, though it appears to correlate with symptoms. Interestingly, this correlation in not simply mechanical, as it holds not only for weight bearing joints, such as knees and hips, but also for sternoclavicular and DIP joints in the hands. Some studies have suggested a somewhat protective effect of osteoporosis on the initiation of OA and yet it may act as an aggravating factor on its progression once present. Also the impact of exogenous elements, such as repetitive professional or avocational use of certain joints, may promote expression of the disease at those locations of heavy use in predisposed individuals. This apparent connection of osteoarthritis' development with mechanical factors has been supported by studies demonstrating statistical correlation between work-related and recreational repetitive use of certain joints and the presence of OA. The structural features of use-driven OA involve prominent osteophyte formation and less so joint space narrowing, leading some to question the significance of these findings. Further caution should be exercised in assigning undue importance to these work-pathology associations as correlations of this sort are not unique to OA and may hold true for all forms of arthritis.

Endocrine disturbances and metabolic diseases such as diabetes, hemochromatosis, and others also appear to drive the osteoarthritic process (Table 18.1).

Table 18.1 Classification of osteoarthritis

Primary
Idiopathic
Generalized osteoarthritis
Inflammatory erosive osteoarthritis
Chondromalacia patella
Secondary
Local determinants
Acute trauma (fracture, torn meniscus)
Chronic trauma (occupational, avocational)
Developmental (joint dysplasia, osteochondrosis)
Septic arthritis
Avascular necrosis
Hemarthrosis (hemophilia)
Inflammatory arthritis
Steroid Injections
Frostbite
Bone disease (Paget's disease)
Neuropathic arthropathy (diabetes mellitus, syphilis)
Systemic determinants
Endocrine (acromegaly, hyperpararthyroidism)
Metabolic (ochronosis, pseudogout/CPPD)
Joint hypermobility
Hereditary

While osteoarthritis is universal, occurring in all geographic locations and all cultures and races, there are apparent differences between certain population groups. For example, the relative infrequent involvement of hip joints among the Chinese is notable as well as reduced occurrence of hand finger joint OA among American Blacks. An extreme example of this observation is the Kashin-Beck syndrome of osteoarthritis-like changes in children and young adults in a defined geographic region in certain provinces of China bordering on mid-Siberia.

18.4 Pathogenesis

As the name OA implies, the earliest understanding of this condition, favored by orthopedists in the first half of the twentieth century, was that the primary lesion in the development of this disorder is in the bone of the joints [8]. It was felt that local factors relating to bone physiology and structure and response to undue stress resulted in subchondral fractures and consequent abnormal joint pressures that led, in turn, to damage of articular cartilage—which was viewed as a passive player in the process [9] In the second half of the twentieth century, the realization that cartilage, though a tissue of low cellularity, avascular, devoid of nerves or lymph channels, and with a low basal cellular turnover, is indeed a metabolically active and biologically dynamic tissue brought about a revolution that viewed OA largely as a 'cartilage disease.' It should be emphasized in this regard that the joint cartilage of elderly individuals indeed shows signs of "aging" relative to cartilage of the young, but is distinctively different from osteoarthritic cartilage. This has raised the issue of whether "aging" of the cartilage doesn't make it more susceptible to the development of OA, thus suggesting a structural basis for the notable age-disease correlation [10].

The notion that OA is a "cartilage disease" has been challenged and subsequently further modified in the twenty-first century, especially with insights gained from MRI studies. These have demonstrated elements of inflammation and involvement of the joint capsule—tendons and ligaments encompassing the joint [10]—as well as subchondral bony edema at the earliest stages of OA development and not only secondarily. This has advanced the current view that OA pathogenesis involves all tissues of the joint equally.

A separate but very relevant issue in OA pathogenesis relates to the source of pain in joints affected by this pathologic process. On the one hand, as noted earlier, cartilage itself is a-neural and can be damaged without incurring pain, and, on the other hand, inflammation is not a prominent feature of this condition. The derived understanding is that pain sensors in the synovium, capsule and bone of the joint must somehow be responsible for the resultant pain accompanying the process. This relationship must be complex, keeping in mind the lack of correlation between structural changes seen on joint imaging and the clinical picture.

Certainly genetics may plays a role in OA development, with familial predisposition to the presence of hand DIP/PIP hand involvement noted many years ago. On the other hand, it is difficult to narrow down genetics in such a common condition

and especially in a condition which is typically manifest only after many decades after birth and in several different subsets.

In the final analysis, without a single focused unifying concept of OA pathogenesis, and—unlike other forms of arthritis—without inflammation as a major player, OA may be viewed simply as a state of joint failure. The problem with this dismal state of affairs in understanding OA pathogenesis is that it does not suggest nor point to notable targets for therapy and therefore has not led as yet to novel revolutionary therapies of major impact on disease development.

18.5 Clinical Aspects

The pain of OA is characteristically of 'toothache'-like quality and often referred to the surrounding musculoskeletal structures. It is referred to as a 'use pain', crescendoing with motion. In contrast with inflammatory arthritis, in OA the accompanying stiffness is easily relieved with minimal motion. As the disease advances, there is frequently pain at rest, this representing end stage disease, correlating pathologically with major joint structural damage. Also there may be acute flares with evidence of inflammation—soft tissue swelling, local heat and joint fluid accumulation—possibly in response to previously accumulated calcium based microcrystalline deposits.

On examination, enlargement of the OA affected joint is readily noted. This may occur secondary to marginal spur formation or reactive synovial proliferation. The enlargement is described as rubbery in character, to be distinguished from the bogginess of markedly inflamed tissues. With further disease progression, joint motion limitation assumes a greater role in the clinical syndrome, with accompanying periarticular muscle spasm, reflecting the irreversible structural damage produced by the osteoarthritic process. At later stages of the disease this joint enlargement may progress to gross joint deformity with subluxation, as cartilage degenerates unevenly throughout the joint; the subchondral bone may collapse, with bony cyst formation and gross reactive bony overgrowth. As the patient gets still worse, the pain on passive motion and restricted range of joint motion are prominent findings. Chronic restriction of joint motion is frequently manifest in joint contractures.

18.5.1 Hands

The most common and readily recognizable manifestations of primary OA are Heberden's nodes, defined by firm enlargement of DIP joints of the digits, often with associated flexion and medial or lateral deviation of the distal phalanx. In some cases, they are associated with small gelatinous cysts along the dorsal aspects of the joints. Similar finding in the PIP joints are known as Bouchard's nodes. While generally these develop insidiously, occasionally these lesions appear

suddenly with prominent manifestations of local/focal inflammation. The roentgenograms in such cases may show evidence of erosive destructive disease. This combination of findings is known as 'inflammatory erosive osteoarthritis.' Actually, the first carpo-metacarpal (CMC) joint, at the base of the thumb, is the single most affected joint in OA. As almost all activity of the hand includes the thumb, in apposition as well as exertion of power, this joint's involvement has major impact on hand function.

18.5.2 Knees

Knee OA results in impaired walking and special difficulty in negotiating stairs. Disproportionate involvement of the medial compartment of the joint leads to medial deviation of the joint (genu varus) associated with instability; prominent involvement of the patello-femoral compartment results in disturbed bending, all functions of flexion-extension of the knee with concomitant muscular exertion, progressing to flexion contracture and functional shortening of the extremity. This, in turn, results in total disruption of normal gait with secondary low back and hip pain due to abnormal compensatory stresses.

Because of the pain associated with joint motion relative disuse of the joint follows and is accompanied by muscle atrophy about the knee, most prominently the quadriceps—important in stabilizing the knee and important in straightening the knee and bearing the brunt of weight bearing with a flexed knee.

18.5.3 Hip Joints

Hip OA typically is of insidious onset, frequently initially presenting with a limp rather than pain. The accompanying pain is typically in the groin radiating along the inner thigh to the knee or in the buttock. Examination is usually required to localize the problem to the hip joint itself. The cardinal finding is limitation of internal rotation and flexion of the joint, frequently with flexion contracture of the joint. The progression of hip OA is associated with major problems in ambulation, arising from a sitting position, and night symptoms/disturbed sleep with pain on turning in bed.

18.5.4 Spine

OA of vertebral articulations is referred to as spondylosis. These OA manifestations appear most frequently in regions of maximal spine motion at the apices of the normal lordotic/kyphotic curves—about C5 in the neck, T8 in the thoracic spine and

L3–4 in the low back region. In addition to the facet/apophysial joints and joints of Lushka, much of the clinical and radiographic picture here is dominated by changes in the intervertebral fibrocartilage discs interposed between the vertebral bodies' end plates. The pain resulting from these osteoarthritic changes is of uncertain origin—whether from para-spinal ligaments, joint capsules, periosteum at the articulations of the spine or secondary muscular spasm. This last is a major clinical factor, such that dealing successfully with the reactive muscle spasm can improve symptoms and function while the OA persists.

Another feature of OA at the spinal location is the occasional radicular syndrome due to nerve root pressure and irritation secondary to projecting osteophytes and bulging discs. In these cases neuropathic pain, accompanied by numbness, and paresthesias—burning or tingling in character—may be present along a dermatome, enabling anatomic localization of the spinal lesion. In severe cases, nerve reflexes and motor muscle changes in the dermatomal distribution are affected, with impaired reflexes and muscle weakness.

A major clinical syndrome associated with these OA changes, typically in more than one intervertebral space, in the lumbar spine in the elderly is lumbar spinal stenosis. This is typically the result of the anatomic confluence of bulging discs, prominent ligamentous hypertrophy, bony osteophytes from facet joints and spondylolisthesis which combine to narrow considerably the space available to lumbar nerve roots in the spinal canal. In this condition, in addition to the back pain there is pain or "heaviness", a sense that the legs are not responsive to commands, with a characteristic neurogenic claudication limiting the ability of the elderly to walk distances without requiring rest. Whereas in the radicular syndrome of a herniated disc the pain usually is unilateral, lumbar spinal stenosis is typically distinguished by its bilateral presentation.

Spondylosis of the cervical spine is manifest in neck pain, frequently radiating in dermatomal distribution to the upper extremity, as well as referred pain to the anterior/posterior upper chest and occiput, in association with limited neck rotation. Typically, anterior/posterior neck flexion is preserved. Osteophyte compression of the extra-articular structures is responsible for the clinical syndrome, many times without concomitant neck pain. In these cases, the constellation of pain in a number of regions along the same upper extremity without clear findings localizing lesions to a particular joint along with possible accompanying neuropathic features should alert the physician to focus on the neck as the source. Not only radicular syndrome but myelopathy or vascular compromise may be associated with cervical spondylosis. Posterior spurs and bulging discs may result in direct compression of the spinal cord or may indirectly produce a cord syndrome via impingement and restriction of blood flow through the anterior spinal artery. Similarly, basilar artery insufficiency may result from compromise of the vertebral arteries as these vessels course through the cervical vertebral foramina to the brain. An uncommon syndrome of osteoarthritis of the atlanto-axial joint has also been described. This condition may be present with symptoms of occipital pain, stiffness of the shoulder and paresthesias of the fingers.

18.6 Laboratory Findings

OA is distinguished from other arthropathies by the absence of associated laboratory abnormalities. The major reason to perform laboratory studies is to exclude the presence of other rheumatic diseases as well as to assess the general health of the patient, noting comorbidities as well other factors that may impact on treatment. While the diagnosis of OA is primarily based on clinical findings, that is a consistent history and physical examination as well as supportive imaging data, laboratory studies may be useful. For example, evidence of primary hyperparathyroidism with its associated calcium pyrophosphate dehydrate crystal deposition disease or Paget's disease of bone, two causes of secondary OA, may be obtained via screening blood studies. Measurement of acute phase reactants also may be useful to exclude the presence of systemic inflammation which would tend to indicate the presence of a primary inflammatory disorder.

The performance of arthrocentesis, the aspiration of excessive joint fluid and subsequent fluid analysis is performed with the same rationale as other laboratory studies. That is, an effort is made to exclude other primary inflammatory arthropathies. This is practical only in the knee which is readily accessible and therefore technically convenient to perform. The typical joint fluid is non-inflammatory characterized by a minimal increase in cells, good viscosity and low protein. As associated crystal deposition is not uncommon, especially in advanced cases, calcium pyrophosphate dihydrate or calcium hydroxyapatite crystals are sometimes seen. Synovial histology in primary OA is non-diagnostic, being essentially normal in early disease and only demonstrating nonspecific inflammation in advanced disease.

Because of the lack of an objective laboratory parameter which is pathognomonic or highly diagnostic of the disease, research efforts have been made to arrive at a disease marker. While cartilage degradation products and other candidate biomarkers have been identified, none of these have clinical applicability.

18.7 Imaging

Since characteristic X-ray findings are usually the only objective support for the diagnosis of OA, these studies are frequently performed to corroborate the diagnosis. The roentgenographic appearance of a joint consistent with OA is supportive but not sufficient evidence for the diagnosis of OA as the cause of the patient's joint symptoms. Hence, as a general principle X-RAY evidence of osteoarthritic disease may be extensive and yet bear little relationship to a given patient's symptoms. On the other hand, severe symptoms may develop, especially in the spine, with relatively minor spur formation, facet joint changes or disc bulges in certain critical locations to account for these symptoms. In peripheral joints, the X-ray appearance of OA may be virtually normal with relatively mild pathology leading to symptoms.

In these situations, MRI may reveal subchondral bone edema—a nonspecific finding—and cartilage damage that may not as yet be appreciated on plain radiography, as well as evidence of joint capsule stress. Efforts to identify MRI cartilage lesions diagnostic of OA have not arrived at a practical/reliable level where they would be available for general clinical use.

As such, when it comes to imaging, most physicians rely on the more easily appreciated osteophytes, well-defined projections of radio-opaque density beyond the normal contours of bone, as these are most obvious on X-ray, to support the diagnosis. But while these osteophytes are usually regarded as manifestations of OA, the use of this feature alone in diagnosis has been questioned, as they correlate with aging but less so with the presence of clinical OA. Thus the diagnosis should be based more on structural abnormalities of the articular cartage, usually appreciated as asymmetric radiographic joint space narrowing or changes in subchondral bone such as eburnation ('sclerosis') and cysts. Further, OA may be differentiated from inflammatory arthropathies by the relative absence of juxtaarticular osteopenia.

In many peripheral joints routine anterior-posterior and lateral views are sufficient to demonstrate the findings. In the cervical and lumbar spine where nerve root irritation is a frequent clinical problem, structural changes involving the intervertebral neural foramina are best evaluated via the use of additional oblique views. These same views also profile the apophysial/facet joints and thus aid in their evaluation. In the spine, CT and MRI have superceded plain radiography with improved resolution and ability to assess soft tissues better. This is particularly true in evaluating spinal stenosis and facet joint disease.

In assessing the hands, plain radiography is particularly revealing in defining the pattern of OA joint involvement, classically the DIPs, PIPS and first CMCs. The finding of OA changes in wrists and MCPs immediately suggest a secondary type of OA, most likely secondary to a systemic or metabolic disease. Interestingly, although Heberden's nodes feel quite hard on physical examination, only minimal spur formation may be evident on X-ray evaluation, suggesting the enlargement noted clinically consists of soft tissue and cartilage.

Evaluation of the hip joint is typically accomplished with anterior-posterior X-ray views of the pelvis which profile the femoral-acetabular articulation and also offers information on the sacroiliac joints, symphysis pubis and pelvic bones. In OA of the hip, focal loss of articular cartilage frequently leads to superior-lateral migration of the femoral head in relation to the acetabulum. This differentiates it from primary inflammatory disease of the hip or secondary OA where the femoral head migrates medially due to diffuse circumferential loss of cartilage. In advanced disease, the entire floor of the acetabulum may be displaced medially by the head of the femur so that it bulges into the pelvis, referred to as protrusio acetabuli. CT and especially MRI show a great deal more detail of the osteoarthritic process leading to interpretation that tends to "exaggerate" clinical severity. As such, these modalities frequently raise the question of osteonecrosis of the femoral head. Caution should be exercised in drawing far reaching conclusions based on imaging alone, again remembering the frequent lack of correlation with the clinical state.

18.8 Secondary Osteoarthritis

The term ‘secondary osteoarthritis’ may be applied whenever OA joint changes occur secondarily or concomitantly with a clearly identifiable primary disorder, whether local or systemic. This diagnosis is particularly considered when the disease appears at a relatively younger age or in locations not usually involved in primary OA such as shoulder, elbows, wrists and MCP joints as well as ankles. This should also be considered when there is an atypical presentation in joints that are involved in primary OA, for example concentric narrowing of the osteoarthritic hip joint, rather than the classical dorso-lateral narrowing, or predominantly lateral knee compartment narrowing in this process rather than the conventional initial medial femoral-tibial narrowing.

The most common local factor associated with subsequent development of OA is antecendent joint trauma. The trauma may occur as a single specific event such as fracture, osteonecrosis or meniscal tear. Repeated microtrauma has also been suggested as a primary event in vocational or recreational associated OA, but as noted above this assertion is controversial. Another type of chronic local trauma may be that imposed by developmental abnormalities such as hip dysplasia.

Systemic metabolic and endocrine disorders, possibly through their effects on cartilage metabolism, are associated with OA. Many of these tend to predispose to the deposition of calcium pyrophosphate dehydrate (CPPD) crystals in the cartilage. Similarly, in metabolic disease where there is excessive accumulation of minerals and by-products of intermediate metabolism, this may lead to an osteoarthritic process: homogentisic acid may accumulate in the fibrocartilage discs of the spine promoting spondylosis; excess iron deposits in mesechymal tissues in hemochromatosis may drive OA in joints; copper deposition in Wilson’s disease is marked by OA development, etc. The endocrinopathies are also generally associated with an increased incidence of OA. The most common are hypothyroidism and diabetes mellitus, even when these are well controlled therapeutically. Also hyperparathyroidism, whether primary or secondary, and acromegaly are associated. Some of the OA in these conditions may relate to heightened subclinical calcium pyrophosphate dehydrate crystal deposition in these illnesses. In diabetes, chronic low grade damage to peripheral nerves may also drive instability and joint damage manifest as OA. Acromegaly, a pituitary disorder of growth hormone hypersecretion results in excessive growth of articular cartilage and subsequent development of peripheral and spinal OA. The characteristic finding on X-rays is unusually wide joint spaces, reflecting the thickened cartilage, in the setting of OA. Probably it is the poor quality of the excessive cartilage that drives the OA process in this setting,

Secondary OA as a manifestation of a condition which may be associated with increased CPPD deposition tends also to be more inflammatory in its clinical manifestations than the general run of the mill OA.

Some have suggested that adequately searched for, most OA will be found to be secondary in nature [11].

18.9 Treatment

An important issue in the treatment of OA is under-treatment of this condition by rheumatologists and primary care physicians, possibly due to lack of knowledge sustained by the belief that there is little to be done. All too often these specialists abandon OA patients to the care of orthopedists—who are naturally surgically oriented, physiotherapists—who are rarely supervised by physicians—and healers dealing in alternative or complementary medicine. All this results in poor quality medicine.

An important element of the management program of any patient with OA is education as to the nature of his/her disease. Simple reassurance as to the benign nature of the condition—distinguishing it from inflammatory, autoimmune disease—along with emphasis on the absence of systemic components and prominence given to its relative non-progressive course, may be sufficient for many to deal with it without requiring special treatment. Furthermore, an understanding by the patient of the pathology, prognosis and goals of treatment in OA may enhance the patient's compliance with the therapeutic program especially where it involves changes in lifestyle. Specifically, presenting OA as a natural consequence of getting old is both counterproductive and scientifically untrue.

There are general principles useful in the management of OA: The program of treatment of OA needs take into account the concerns of the patient: pain, functional disability, body image, disease progression, effect on general health; The treatment program also needs take into account comorbidities, reduced function of various organ systems and altered metabolism which are common to the older population most effected by OA; In the absence of drug therapy with dramatic effect on the pathologic process, the focus has been justly placed on non-pharmacologic measures; Further, it should be emphasized that while OA is a chronic disease with potential for progression/deterioration of joints, most of the time its course is of a waxing and waning pattern, so that measures undertaken may focus on relief for a short or intermediate time period; Also, the therapeutic approach should vary with the joints specifically most involved [12].

While in the past much emphasis was placed on rest of affected joints involved in OA, the importance of continuing mild to moderate activity of affected joint has come to be appreciated due to its beneficial effect on long term pain reduction, maintenance of function and muscle strengthening serving to unload the joint. Certainly during acute flares, rest—including immobilization via splinting—and heat applications to relax secondary muscle spasm afford significant symptomatic relief. In the cervical spine a soft neck collar may provide a mild form of immobilization and a splint of the first CMC may assist in reducing pain. The use of a cane in the contralateral hand to share some of the load-bearing function of involved hip or knee joints may provide relative rest to affected joints. In this situation, similar to others, there is a need to overcome patient resistance to 'appearing old' in the use of these aids. Stressing the multidisciplinary approach to OA management, occupational therapist may advise the patient on the use of long handled tools in everyday

activities so as to avoid stress of lumbar spine or knees when these are involved and advise, in general, on more ergonomic alternatives in the patient's home and work environment.

And yet for long term advantage from active therapy, appropriate exercises guided by physical therapists are to be preferred [13], with attention given to promoting the patient's self-management rather than dependence on others. Pelvic tilt exercises along with abdominal flexion exercises may aid alleviate symptoms of lumbar facet arthritis as well as spinal stenosis. Hydrotherapy, exercising while immersed in a pool of slightly warmed water, is to be highly recommended. Most patients let loose of protective inhibitions to motions on land when in the water, less concerned about falling; and yet the water's resistance to motions protects the patients from overly sharp motions, on the one hand, while providing some opposition to motion requiring muscular effort. The warmth of the heated pool can allow for these activities to take place with the muscles more relaxed and less painful. In the knees, where a major component of the pain is of patello-femoral origin, isometric exercises to strengthen quadriceps muscles—basically straight leg raising while supine, one leg at a time—are the cornerstone of therapy. The gradual strengthening of these muscles has major impact on improving knee function and pain, stabilizing the joint and tightening the extensor mechanism with readjustment of the balance between flexion—extension mechanisms' contributions to knee motion.

Hand OA, while particularly resistant to all forms of therapy, may be ameliorated by paraffin baths, which are best performed at home at the patient's convenience as frequently as needed. Hip joint OA may also be ameliorated by physiotherapy, hydrotherapy and exercises aimed at relieving the adduction and flexion contractures which complicate this condition.

Aside from physical measures, there is evidence that weight loss reduces knee and hip OA symptoms. Unfortunately, all are aware of the difficulty in achieving prescribed weight loss and yet this goal should not be easily abandoned in the context of OA management. For example it may be one of the factors to be considered when considering bariatric surgery. The efforts at weight loss in the context of knee and hip OA is of particular importance when considering joint replacement for end stage disease as there is data correlating success of such surgery with the patients' weight.

In the absence of clear cut and compelling evidence for disease modification by any modality, the emphasis of OA management is on pain relief [14]. To approach this successfully, one should clarify the nature of the pain. For example, while some may view this cynically, for many patients, especially women with hand OA, the disfigurement of PIP and DIP joint OA is the primary issue of 'pain'. The same line of thought may be brought to understanding of why knee or hip OA starts hurting an individual who's had the characteristic structural joint changes for some time and yet suffered no pain until a certain point [15]. Especially in older individuals, attention should be given in this context to the presence of mild depression with its associated somatization as the background for the joint pain. On the other hand, the persistent pain and secondary limitation on function in OA may its result in a depressive reaction which then, in turn, worsens the prognosis and complicates OA

management. Thus, depression and the patient's general sense of wellbeing needs to be addressed in the management program [16].

At all levels of therapy the use of pharmaceuticals in OA is controversial. In most studies the end points measured include pain relief, patients' function (which almost always perfectly parallels pain relief!) and structural joint deterioration over time. It may be summarized that to date there is no generally accepted evidence for drug therapy modifying disease progress in OA. As such most efforts have concentrated on pain relief.

Some agents considered have focused on long term effects. This category includes diacerein, glucosamine/chondroitin sulfate, colchicine and so called 'nutraceuticals'. While there are quality studies that demonstrated long term benefit of diacerein in knee and hip OA [17], the improvement measured was small, and cannot be generalized to benefit to OA at other sites. This drug was never approved for use in the USA and therefore its studied use there is lacking. The use of glucosamine sulfate and or chondroitin sulfate in ameliorating OA is highly controversial with little quality controlled trials showing benefit. Nevertheless, because there is some evidence favoring their use, in the absence of evidence for major side effects, a supervised trial of treatment for 3–4 months may be attempted. If no significant benefit is demonstrated this should be stopped and not continued as if it is a "food supplement" with its attendant drain on patient resources and possible interactions with other drugs—an area not well studied. Because of the demonstrated benefit of colchicine in preventing flairs of pseudogout, one of the manifestations of CPPD deposition, some have championed its use in secondary osteoarthritis as well primary OA where subclinical CPPD may play an aggravating role [18]. As this agent works slowly, a 3–5 month trial of two tablets a day is warranted.

For more immediate monoarticular OA relief, intraarticular injections of corticosteroids have been used for decades, on the assumption that there may be a significant inflammatory component to the pain. The utility of this treatment has been the subject of many studies and controversy. What is clear is that while there may be some short term benefit, which needs be weighed against complications and side effect, there is no evidence for long term benefit and frequent repeated injections are contraindicated due to clear evidence of accrued cartilage damage with this treatment [19]. Equally controversial is the utility of hyaluronic acid injections, particularly in knee OA. Overall there may be benefit, but it is relatively small and short term, but may be worth a trial. It appears to work somewhat less well in those older than 65, with a lower benefit/risk ratio. There is much less published experience of this treatment in other joints. In the past some trials of tidal irrigation of the knee joint, putatively to remove phlogistic material and debris from knees with OA, also showed benefit, but this procedure is technically very cumbersome and time consuming and has been abandoned.

Systemic treatment focusing on reduction of inflammation has not been successful in the treatment of OA. Systemic corticosteroids are contraindicated, with a negative risk benefit ratio. Treatment with biologic agents, anti TNF and anti IL1, has not been found useful, again with risk outweighing benefit [20]. There remains the issue of polyarticular inflammatory-type of osteoarthritis which may be difficult

to differentiate from psoriatic arthritis and appears to respond to methotrexate or leflunomide.

The treatment of OA pain with oral analgesics has become much more complicated in recent years. Non-steroidal anti-inflammatory drugs (NSAIDs) have proven utility in OA, preferable to simple analgesics. Their use, which was known for decades to increase the risk of gastrointestinal bleeding, as a major issue in their chronic use, especially in elderly individuals, has been severely curtailed, due to evidence for elevation of blood pressure, increase cardiovascular risk, decompensation of mild renal insufficiency—all issues of heightened importance in a geriatric population. Nevertheless, it appears that not using these effective agents totally is unjustified, as they may be used with safety for immediate short term relief, possibly cycling courses of therapy with intervals of 'drug holidays'. Paracetamol has become the drug of choice for OA analgesia, but is frequently underdosed and thus judged ineffective. A dose of 1–2 g a day is to be recommended. However, the long term use of these doses of paracetamol is also attended by hepatic, gastrointestinal and vascular side effects and requires monitoring. The use of tramolol as well as paracetamol/low dose narcotic combinations is at times a more potent alternative. The use of narcotics for intermediate and long term analgesia is to be discouraged in general. Firstly, narcotics have not been shown to be more effective than paracetamol for chronic pain. Secondly, their use is attendant with side effects of major impact on a geriatric population, especially constipation, nausea, depression and dizziness—with drug dependence being a secondary issue in this population. Other drugs used in the treatment of chronic pain, especially of a neuropathic origin, have been found to be effective in OA, but their use is frequently associated with unacceptable side effects-weight gain, dizziness. There have been trials of agents aimed at neutralizing nerve growth factor. These have been found to afford good pain relief but their use has not been approved as yet due to concerns of occasional rapid acceleration of OA joint deterioration associated with their use. This effect is reminiscent of findings that use of indomethacin, a potent NSAID used frequently in the past, was associated with more OA progression than use of the milder NSAID nabumetone. It should be mentioned as an aside, that for all of its media hype, cannabis—at this point more a recreational agent than a medicinal formulary drug—has not been found to be an useful analgesic, its risk far outweighing its benefit.

Much underappreciated and underused, despite a great deal of scientific evidence as to their utility in OA, are topical NSAIDs. For best effect, these should be applied to effected joints on a regular schedule when indicated and not simply on a needs basis. The total systemic dose absorbed of these drugs is very small and should allay the concerns that accompany the use of systemic NSAIDs.

While degenerative lumbar spinal stenosis is a growing problem in an elderly population there is no good drug treatment that has been demonstrated to be of benefit in controlled trials. Treatment with a series of monthly intravenous pamidronate infusions has been described to benefit many patients [21]. Enthusiasm for a surgical solution to spinal stenosis has waned in time due to the multilevel intervertebral involvement with resultant protracted rehabilitation proving difficult in the elderly population effected.

When OA pain is unmanageable, including rest pain—especially night pain with resultant sleep deprivation, and appears to require use of narcotics, all this usually in the presence of major joint damage, surgery to replace the joints is an option. Knee and hip total joint replacements are the most successful of these with age of the patient not being a barrier to good results. Knee arthroscopy, for irrigation and removal of debris 'cleaning out' the joint in OA has been shown to be ineffective in two major controlled trials and is nor to be recommended. Spine surgery, in the absence of a neurologic indication, is not to be recommended for spondylosis due to poor results of pain relief and the risk of complications. Surgery of first CMC OA may be considered, with excision arthroplasty offering pain relief but frequently leaving the patient with a weakened thumb for those actions requiring power and thumb stability. Joint arthrodesis is associated with the consequence of restricted motion.

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Chapter 19
Polymyalgia Rheumatica

Tal Gazitt and Devy Zisman

19.1 Epidemiology and Immunopathogenesis

Polymyalgia rheumatica, a condition first reported as early as 1888 and later named by Barber in 1957 [1], is the most common inflammatory disorder affecting the elderly. It most commonly occurs in women of Northern European ancestry but can occur in any ethnic group, with increasing age and female sex being the two main risk factors. It almost never occurs in patients younger than 50 years of age with peak incidence occurring at age 70–75 years with 66–75% of patients being female with lifetime risk of 2.4% for women and 1.7% for men [2–4]. While the etiology of PMR remains unclear, its occurrence seems to stem from an interplay between genetic and environmental factors with a role for immunosenescence, the latter representing a series of changes that occur in the immune system of the elderly.

Unlike the overlapping condition giant cell arteritis (GCA), where HLA-DRB1∗04 genotype is a known risk factor for disease development, no clear HLA association has been shown in PMR [5]. However, even in PMR, genetic polymorphisms may play a role, such as polymorphisms of IL-6, as recent reports show relevance of this mediator in PMR immunopathogenesis (see below). Additional immunopathogenic factors involve the aging immune system, with a decrease in production of T-cells due to thymic involution. This, in turn, causes a reduction in the output of thymic regulatory T cells, leading to immune dysregulation and autoimmunity [6]. A consequence of immune dysregulation is an increase in pro-inflammatory cytokine production such as IL-6 in older adults [7, 8]. Indeed,

T. Gazitt
Rheumatology Unit, Carmel Medical Center, Haifa, Israel

D. Zisman (✉)
Rheumatology Unit, Carmel Medical Center, Haifa, Israel

The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel
e-mail: devyzi@clalit.org.il

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elevated IL-6 levels have been shown to correlate with PMR disease activity, [5] and IL-6 blocking agents are currently being trialed in PMR after having shown efficacy in GCA management [9].

Aside from genetic factors, environmental factors are also purported to play a role in PMR development. Indeed, cyclic fluctuations have been reported to correspond with incidence peaks of GCA during the winter months in the setting of mycoplasma, chlamydia pneumonia, and parvovirus B19 epidemics [10], and herpes zoster occurrence was recently found to be associated with an increased risk of GCA in two large GCA patient cohorts [11]. However, no infectious organism has been clearly associated with PMR occurrence to date [10].

19.2 Clinical and Laboratory Manifestations

Clinical signs and symptoms of PMR include abrupt onset (typically ranging between 2 weeks and up to 2 months, though a more subtle, progressive course can also occur) of pain and stiffness typically affecting the neck and one or both proximal girdles – the shoulder girdle, and less commonly, the pelvic girdle. Although symptoms may be unilateral on initial presentation, clinical manifestations are later bilateral [12]. Stiffness is particularly debilitating and is typically present for more than 30 minutes in the morning, making it difficult for patients to lift their arms to complete their activities of daily living (ADLs) including brushing their teeth, combing their hair, or in putting on a bra while getting dressed. Similarly, it may be difficult for patients affected by pelvic girdle stiffness to get out of bed or rise from a chair without assistance. Resting stiffness, in which stiffness worsens after periods of rest, may also occur. In some patients, the pain in the shoulder and pelvic regions may radiate to the elbows, hips, and even to the knees. Characteristic clinical signs of systemic inflammation, such as low-grade fever, anorexia and weight loss, and/or malaise and fatigue occur in approximately 40–50% of patients and are particularly common in patients over 70 years of age [4].

On clinical examination, the clinician may observe reduced active and passive ranges of motion, especially in shoulder elevation or hip flexion. It is noteworthy that while patients may experience a sensation of proximal muscle weakness, actual muscle weakness or findings supporting myopathy are lacking. Distal musculoskeletal manifestations may occur in 25–50% of patients, most frequently as transient, nonerosive asymmetrical arthritis primarily affecting the knee or wrist in up to 39% of patients [12–14]. Tenosynovitis, such as carpal tunnel syndrome, is also common [4, 14]. Pitting edema can affect the hands, wrists, ankles and feet, and occasionally is the presenting finding.

Among laboratory signs of inflammation, elevated erythrocyte sedimentation rate (ESR) typically over 40 mm/h, and elevated C-reactive protein (CRP) level are highly characteristic of PMR and are detected in more than 90% of patients [4]. Both tests should be ordered as they may be discordant when one test performs better than the other in certain individuals. Notably, both ESR and CRP may be normal

in a small percentage of patients [4]. Additional common laboratory markers of inflammation, including anemia of chronic disease, thrombocytosis, or elevated ferritin level can also be seen. Mild elevation of liver enzymes, especially alkaline phosphatase, may also occur [4].

19.3 Diagnosis

The diagnosis of PMR in the elderly can pose a significant challenge for treating clinicians because no universally accepted diagnostic criteria currently exist; and signs, symptoms and laboratory studies associated with PMR are all non-specific. Moreover, older adults may await seeking medical advice for several months due to attribution of musculoskeletal aches and pains to aging. PMR may also not be obvious in the elderly due to multiple co-morbidities [15]. For instance, dementia, which is more common in the elderly, may make history-taking and clinical examination more challenging. Older patients may also present with nonclassical features due to other co-existing disorders, further complicating the clinical picture. Especially notable in this regard is rotator cuff pathology or osteoarthritis (OA) of the shoulders and cervical or lumbar spine in older adults, which should normally be excluded when diagnosing PMR but which commonly co-exist with PMR in elderly patients [15]. Moreover, similar to other conditions in the elderly, PMR may present primarily as acute-onset functional impairment, which can be seen in a large variety of medical conditions as diverse as infection or stroke, thus making diagnosis more difficult. Last, other rheumatic inflammatory conditions which primarily affect older adults, such as elderly-onset rheumatoid arthritis (EORA) or Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE) may present initially like PMR [4, 15, 16].

Because of multiple mimics of PMR, the 2015 EULAR/ACR management guidelines recommend that, at a minimum, a basic workup to exclude alternative diagnoses of PMR and to establish a baseline for monitoring of therapy should include complete blood count, inflammatory markers, thyroid function tests, bone profile (vitamin D, calcium, alkaline phosphatase levels), kidney and liver function tests, creatine kinase level, rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA), urinalysis, and protein electrophoresis. Depending on clinical signs and symptoms and likelihood of alternative diagnoses, additional testing such as anti-nuclear antibodies (ANA), anti-cytoplasmic neutrophil antibodies (ANCA) or tuberculosis testing may be warranted [17]. Ultrasonography can be particularly useful in patients with typical proximal symptoms but normal inflammatory markers.

In 2012, the European League Against Rheumatism and the American College of Rheumatology jointly developed the Provisional Classification Criteria for Polymyalgia Rheumatica (Table 19.1) [18]. Ultrasonographic findings of shoulder or hip inflammation can be used to enhance specificity of these criteria (Fig. 19.1). These criteria, which were devised for clinical research and not for diagnostic

Table 19.1 2012 EULAR/ACR provisional classification criteria for PMR

Criteria	Score without US examination (0–6)	Score with US findings taken into account (0–8)
Morning stiffness duration >45 min	2	2
Hip pain or limited range of motion	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
≥1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (posterior or axillary) AND ≥1 hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	Not applicable	1

Required criteria: age ≥50 years, new onset of bilateral shoulder aching and abnormal CRP and/or ESR [18]

A score ≥4 without ultrasonography is categorized as PMR, and a score ≥5 with ultrasonographic demonstration of typical inflammatory changes in the shoulders and hips is categroized as PMR

ACPA anti-citrullinated protein antibody, *ACR* American College of Rheumatology, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *EULAR* European League Against Rheumatism, *PMR* polymyalgia rheumatica, *RF* rheumatoid factor, *US* ultrasound

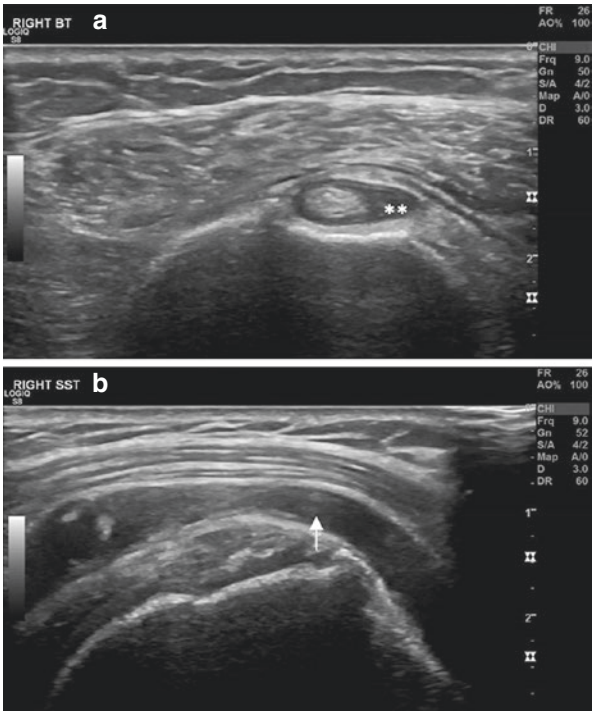

Fig. 19.1 (**a**) Biceps tenosynovitis (*represented by* asterisk) and (**b**) subacromial subdeltoid bursitis (*represented by Arrow*) as representative inflammatory findings on shoulder ultrasonography of PMR patients

purposes, include essential manifestations of PMR; when tested, they were found to have 66–68% sensitivity and 65–88% specificity, depending on the differentials being tested and whether ultrasonography was being used. Unfortunately, because these criteria are not of high sensitivity or specificity, they make it difficult to distinguish between PMR and other rheumatic conditions. For instance, they can distinguish PMR from other shoulder conditions with only 86% specificity, with even lower specificity of 65% when aiming to discriminate between PMR and RA [18].

19.4 Differential Diagnosis of PMR in the Elderly

Due to the nonspecific nature of its signs and symptoms and non-specific laboratory findings, PMR is considered a diagnosis of exclusion. Several categories of illnesses can present similarly to PMR (Table 19.2). Therefore, careful history taking and clinical examination must be conducted when considering PMR. Importantly, because of the overlap between PMR and GCA, this form of large vessel vasculitis must be considered in every patient presenting with PMR.

Several studies to date examine the reasons for initial misdiagnosis of PMR. In a retrospective case series by González-Gay et al., the most common finding present in cases initially misdiagnosed as PMR was lack of rapid response to GC treatment in most of these cases compounded with a lack of consideration of alternative diagnoses [21]. In another study, persistently elevated ESR despite GC treatment was a clue pointing to an alternative diagnosis [16]. Such studies highlight the significance of PMR being first and foremost a diagnosis of exclusion.

19.5 Conditions Commonly Co-occurring with PMR

Several conditions so frequently present with initial symptomology of PMR that an active effort to exclude these conditions is warranted.

19.5.1 Giant Cell Arteritis (GCA)

GCA, a form of large and medium vessel vasculitis, shares both epidemiological and immunological similarities with PMR. The clinical connections between PMR and GCA suggest that they may be different manifestations of the same disease process: both conditions have similar age and sex distributions and both present with increased levels of serum acute-phase reactants with swift response to GC [13]. Population based studies show that PMR is two to three times more common than GCA (PMR incidence 52.5/100,000 aged 50+ in Olmsted County, Minnesota where

Table 19.2 Differential diagnosis of PMR [2, 14, 15]

Differential diagnosis disease categories	Alternative diagnosis	Clinical clues
Malignancies	Hematologic malignancies (i.e. multiple myeloma) Vertebral metastases (i.e. prostate cancer)	Nocturnal pain, night sweats, anorexia and significant weight loss above 7 kg
Chronic infections	Common sources of infection found among the elderly (i.e. urinary and respiratory tracts) Deep seated infections (i.e. endocarditis, osteomyelitis, septic discitis/Brucella-induced sacroiliitis [19, 20]	While fevers can accompany PMR, they should be investigated for both common sources of infection and deep-seated infections particularly if other systemic symptoms are prominent
Systemic inflammatory Rheumatologic conditions	EORA Seronegative SpA Crystalline arthritis (i.e. CPPD) RS3PE Vasculitis, especially GCA	The presence of peripheral joint swelling and early morning or resting stiffness point toward an inflammatory arthritis A personal or family history of psoriasis, inflammatory bowel disease or eye inflammation, together with inflammatory hip, back or buttock symptoms suggests the presence of seronegative SpA The presence of peripheral hand or foot edema is suggestive of RS3PE The presence of headache, visual symptoms or jaw claudication and systemic symptoms should alert the clinician toward a possible diagnosis of GCA. Prominent symptoms of large vessel vasculitis should be specifically sought by the clinician, including arm or leg claudication, absence of peripheral pulses, difference in bilateral blood pressures or presence of arterial bruits
Neurologic conditions	Parkinson's disease	Neurologic exam can reveal parkinsonian features such as resting tremor, shuffling gait, and cogwheel rigidity (this is the only noninflammatory condition which produces true stiffness). In Parkinson's disease, unlike PMR, stiffness is greater than pain
Inflammatory/ metabolic myopathies		Painless muscle weakness is suggestive of an inflammatory or metabolic myopathy as true muscle weakness is not a sign of PMR

Table 19.2 (continued)

Endocrinopathies and metabolic bone disease	Thyroid, parathyroid disorders or osteomalacia	Bone pain, fatigue, and proximal muscle stiffness along with other specific signs and symptoms of specific endocrinopathy
Degenerative/ non-inflammatory arthritis	Bilateral adhesive capsulitis or shoulder/ hip osteoarthritis	Absence of systemic symptoms and limitation of symptoms to upper or lower limbs, especially if unilateral, suggests local joint pathology
Chronic pain syndromes	Fibromyalgia syndrome	Long chronicity of symptoms and lack of true inflammatory stiffness is not suggestive of PMR and is present in chronic pain syndromes. Fibromyalgia should be suspected when prominent depressive symptoms, profound fatigue and poor quality of sleep along with diffuse myofascial pain on exam are present

CPPD calcium pyrophosphate deposition disease, *EORA* adult-onset rheumatoid arthritis, *GCA* giant cell arteritis, *PMR* polymyalgia rheumatica, *RS3PE* remitting seronegative symmetrical synovitis with pitting edema, *SpA* spondyloarthropathy

GCA incidence is 20/100,000) [10]. Importantly, 16–21% of PMR patients present with clinical features of GCA; conversely, about 40% of patients with GCA have symptoms of PMR before, concomitantly, or following diagnosis of GCA [13]. Interestingly, both pathology and imaging studies reveal that subclinical vasculitis without clinical features of GCA may be detected in a subset of patients with PMR. For instance, a positive temporal artery biopsy was described in up to 9% of patients with PMR [22], and evidence of vasculitis was found in up to 31% of PMR patients undergoing 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) at diagnosis [23]. Signs of vasculitis were also found on ultrasound examination of the temporal arteries in 8% of patients with PMR [24]. Based on these findings, it has been suggested that PMR may represent GCA with incompletely developed vascular involvement [25]. Because patients with pure manifestations of PMR do not develop the characteristic clinical complications of GCA, no universal screening recommendations for subclinical vasculitis currently exist [22], but patients with PMR should be educated about signs and symptoms of GCA and asked about symptoms of GCA during followup.

19.5.2 Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE) and Elderly-Onset RA (EORA)

PMR, EORA, and RS3PE are a triad of clinically-overlapping inflammatory conditions affecting individuals over 60 years of age. Importantly, both PMR and EORA can initially present as RS3PE and both PMR and RS3PE can be initial presentations of EORA [4]. By definition, RS3PE is a symmetrical polyarthritis in which

pitting edema of the hands and/or feet is a prominent feature [26]. As in PMR, IL-6 has been implicated in the pathogenesis of RS3PE. RS3PE has been reported as an isolated syndrome, as a paraneoplastic syndrome in solid and hematologic malignancies, or in association with infectious agents or rheumatologic conditions [27]. In the case of EORA first presenting as PMR or RS3PE, it usually has sudden onset and is typically accompanied by elevated acute phase reactants and negative RF and ACPA [26]. Any one of these three conditions can be treated by GC doses varying between 10 and 20 mg/day with gradual taper. However, when difficulty arises in tapering down GC, the clinician should consider the onset of EORA [28].

19.6 Immune Checkpoint Inhibitors and Onset of PMR

Immune Checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are currently being successfully used to increase survival in many cancers. However, this treatment is associated with immune-related adverse events (IrAE). Recently, several case series reported PMR occurring following ICI treatment [29–32].

19.7 Management of PMR in the Elderly

In contrast to GCA, where GC therapy is started immediately because of possible risk of vision loss, patients with apparently isolated PMR should have a basic diagnostic work-up prior to starting therapy.

Goals of therapy in the majority of elderly patients with PMR are to treat and control chronic PMR symptoms and prevent disease relapse, to optimize and preserve activity level, and to optimize musculoskeletal function and improve quality of life with minimal adverse effects from medications. Long-term treatment goals include reduction in decline of mobility over time which may occur in older adults with PMR and reduction of cardiovascular complications [12, 15].

19.7.1 Non-pharmacologic Interventions

Physical therapy and range-of-motion exercises for the shoulder and hips are important for maintaining good physical function and mobility in PMR patients. Patient education on PMR and side effects of GC therapy is essential to good quality of patient care. Influenza and pneumococcal vaccinations are recommended for all patients receiving immunosuppressive medications, including PMR patients [33].

19.7.2 Pharmacologic Interventions

19.7.2.1 Glucocorticosteroids (GC)

GC therapy with slow taper is considered the mainstay of PMR treatment, with mean length of treatment of 1.8 years [14]. Response to GC is usually rapid, occurring within days of initiation of therapy. The British Society for Rheumatology Guidelines define a rapid response to GC as a patient-reported global improvement of ≥70% within a week of starting GC treatment with normalization of inflammatory markers within 4 weeks [34]. However, response may also be more gradual with studies showing that about one-third of patients have incomplete response at 4 weeks [4]. Because steroid-responsiveness is not a feature specific to PMR, an empirical GC 'test of treatment' is not recommended to aid in PMR diagnosis.

The 2015 EULAR/ACR recommendations for PMR management emphasize that there is no ideal GC regimen suitable for all patients, so that GC dosing and tapering schedule should be based on individual patient characteristics, including disease severity, comorbidities, other prescribed medications, risk of GC-related adverse events, and patient preference. Clinicians should aim at the minimum effective starting single-daily dose of GC within a range of 12.5–25 mg prednisone equivalent [17, 35]. Prednisone dose should be tapered to an oral dose of 10 mg/day prednisone equivalent within 4–8 weeks with progressive taper when response seems favorable. Relapse is common, occurring in about 50% of patients [4, 5], with female sex, ESR > 40 mm/h and peripheral arthritis indicating a higher risk for relapse [4, 17]. When relapse occurs, oral prednisone dose should be increased to the pre-relapse dose with gradual decrease within 4–8 weeks to the dose at which the relapse occurred. Once remission is achieved, prednisone should be tapered by 1 mg every 4 weeks (alternate day schedules can be used) until discontinuation when the patient is asymptomatic from their polymyalgic symptoms [17]. A more rapid tapering regimen is often associated with a high relapse rate and should thus be avoided [15, 35]. Elevated acute phase reactants in the absence of PMR symptoms is not an indication for continuation of steroid therapy; however, this finding should require further investigation [15]. The use of intramuscular (IM) methylprednisolone acetate has also been trialed but is not recommended due to its limited availability and due to limited studies with this agent [4, 36].

19.7.2.2 Conventional Disease-Modifying Antirheumatic Drugs (cDMARDs)

Because of need for long-term treatment of PMR with GC, GC-sparing agents have been trialed in PMR management. Of cDMARDs, methotrexate (MTX) is the only immunosuppressive agent that has been evaluated in randomized clinical

trials [4, 37, 38], with most studies showing benefit with regards to relapse rate, cumulative GC dose used and ability to discontinue GC treatment [4, 37, 38]. Accordingly, EULAR/ACR recommendations call for early use of MTX in individual patients at high risk of relapse (female patients, ESR > 40 mm/h, peripheral arthritis), in relapsing disease, or in patients with GC-related adverse events or comorbidities that might be exacerbated by GC use [17]. There are also reports of using azathioprine (AZA) [39] and leflunomide (LEF) [40, 41] in PMR patients.

19.7.2.3 Biologic Disease-Modifying Antirheumatic Drugs (bDMARDs)

Unlike GCA, the use of novel bDMARDs in PMR has been challenging due to the lack of proper animal models for PMR. In recent years, the interleukin-6 (IL-6) blocking agents have been successfully trialed in GCA [9], and given the overlap between PMR and GCA, they are currently being trialed in PMR [42, 43].

19.7.3 Monitoring PMR Disease Activity

Clinicians should closely monitor patients with PMR for clinical and laboratory signs of disease activity and evidence of GC-related toxicity. Monitoring is suggested every 4–8 weeks in the 2–4 months after treatment is started and then every 4–12 weeks during the first year of disease. In the second year, monitoring should be done every 8–12 weeks and as indicated in cases of relapse during tapering of GC or other immunosuppressive agents [4].

Currently, there is no generally accepted definition of remission or relapse in PMR, but the absence of PMR symptoms, particularly morning stiffness, in conjunction with normal ESR and CRP, has often been used to define remission in clinical studies [44]. Conversely, the reappearance of clinical signs of PMR, with or without ESR or CRP elevation, is considered to indicate relapse, as a PMR flare in the absence of an increase in markers of inflammation may be observed in up to 25% of patients even if these markers were abnormal at time of diagnosis [4, 44].

19.8 Prognosis

Epidemiological studies attest to PMR having a benign course without affecting patient survival, with median duration of the disease running up to 11 months (range, 2–54 months) [45]). The main morbidity related to PMR actually involves complications of GC therapy, as noted below.

19.8.1 Assessing for GC-Induced Damage

Patients being treated for PMR should be monitored regularly not only for disease activity, but also for GC-induced complications, which occur in up to 65% of patients [46]. Management of comorbidities including cardiovascular risks such as hypertension, diabetes, and hyperlipidemia as well as osteoporosis is necessary throughout the entire course of disease. Studies show that three variables independently increase the risk of adverse events among PMR patients: age at PMR diagnosis, a cumulative dose of prednisone ≥1800 mg, and female sex [46]. Indeed, population studies reveal that long-term GC treatment in PMR patients carries with it a 2–5 times greater risk of diabetes mellitus, osteoporotic fractures (vertebral fractures, femoral neck fractures, and hip fractures) compared with age- and sex-matched individuals [46]. Given this risk, osteoporosis prophylaxis should be initiated along with initiation of GC treatment. ACR 2017 recommendations [47] underline that calcium intake (1000–1200 mg/day) and vitamin D intake (600–800 IU/day) should be optimized in all patients starting on GC therapy along with lifestyle modifications and consideration of bisphosphonate therapy.

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Chapter 20
Giant Cell Arteritis

Abid Awisat and Raashid Luqmani

Giant cell arteritis (GCA), also termed temporal arteritis, is the most common form of systemic vasculitis occurring in adults, particularly the elderly, involving medium-size cranial arteries and occasionally the aorta and its extracranial branches.

20.1 Incidence and Epidemiology

GCA is almost exclusive to individuals above 50 years of age with higher prevalence in females and an age-dependent pattern peaking at the age of 70–80 [1–4].

The highest reported incidence of GCA occurs in Nordic countries and worldwide, it is higher in subjects of Scandinavian and north European ancestry with an estimated incidence of 29.1/100000 [5, 6] compared to relatively lower incidence of 19.8/100000,8.1/100000 and 1.4/100000 in the United States, Middle East and Asia, respectively [7–10].

A. Awisat (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel

R. Luqmani
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, Nuffield Orthopaedic Centre, University of Oxford, Oxford, UK
e-mail: raashid.luqmani@ndorms.ox.ac.uk

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20.2 Pathogenesis

GCA shares some pathogenetic and clinical manifestations with other vasculitides, particularly Takayasu arteritis (TAK); indeed, it has been suggested that both disorders represent distinct manifestations of the same disease spectrum of large vessel vasculitis affecting different age groups [11, 12].

GCA is a granulomatous vasculitis involving medium and large-size vessels and induced by an inflammatory process occurring in the arterial wall and involving activation of local T-cells (particularly Th-1 and Th-17 lymphocytes) and macrophages, leading to the production of pro-inflammatory cytokines including IL-6 and IFN-γ, and resulting in the formation of giant cells, granulomata and subsequently damage to the arterial wall.

IL-6 is a cytokine involved in numerous inflammatory processes with a well-established role in GCA as a promotor of differentiation cells of the Th17 lineage [13]. High concentrations of IL-6 have been demonstrated in both peripheral circulation and affected arterial walls, resulting in the generation of a local as well as a systemic inflammatory process [14].

Medium-size vessels, e.g., temporal or subclavian artery, respond to inflammation and damage by excessive proliferation of myofibroblasts, which leads to thickening of the intima and eventual narrowing or even occlusion of the vessel lumen with ischemia of the distal tissue or organ. Inflammation involving large-size arteries, e.g., aorta and major branches, can lead to the destruction of internal elastic laminae, manifesting as aneurysm formation, rupture or dissection [15, 16].

20.3 Clinical Presentation

GCA, both cranial and extracranial large vessel vasculitis (LVV), often presents indolently with constitutional symptoms including malaise, weight loss, night sweats, polymyalgia rheumatica (PMR) (Discussed elsewhere) and occasionally, fever.

New-onset, persistent or fluctuating headache (which patients often describe as pain in the head as distinct from a typical headache) is the hallmark symptom of GCA in almost all cases. It is frequently located over the temporal area, but frontal and occipital headaches have also been reported. Headache is occasionally accompanied by scalp tenderness and aggravated by applying local pressure upon the inflamed arteries, which may have diminished or even absent pulsation and can occasionally feel nodular on examination.

Jaw claudication is very important, though the relatively uncommon feature of GCA thought to be secondary to vasculitis of the blood vessels supplying masticatory muscles (masseter and pterygoid). Indeed, patients presenting with jaw claudication are more likely to develop visual loss or stroke as part of their presentation.

GCA has a predilection for the ophthalmic artery and its branches, which supply the choroid, retina, extraocular muscles and the optic nerve thus resulting in visual symptoms in 12–70% of affected patients [17]. These include diplopia, extraocular muscle weakness, and partial or complete visual loss, which can be the initial presentation on GCA. The clinical presentation of large vessel-GCA varies depending on the distribution of arterial involvement and may present as limb claudication, mesenteric angina, or much less commonly, abdominal or thoracic aneurysms. An audible bruit may be present in the affected artery on physical examination. Less frequent manifestations of GCA include cerebrovascular accidents, scalp necrosis and tongue ischemia.

GCA is associated with elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) at the time of diagnosis; however, 10–24% of patients with GCA lack this feature and present with normal ESR and CRP [18, 19]. Antinuclear antibody (ANA), rheumatoid factor (RF) are usually negative. Anemia, thrombocytosis, and leukocytosis are frequent and nonspecific laboratory findings (especially in the geriatric population), indicating an ongoing inflammatory process.

20.4 Diagnosis

20.4.1 Temporal Artery Biopsy

Since it was first introduced, in the 1930s [20], a temporal artery biopsy (TAB) has been regarded as the gold standard for diagnosis of GCA and was included in the 1990 American College of Rheumatology classification criteria for GCA [21]. GCA was previously thought to be confined to the cranial arteries; therefore, for many years, temporal artery biopsy (TAB) was considered to be the diagnostic "gold standard." Subsequently, these classification criteria have been updated; the new criteria give equal weight to histological or imaging findings (either in the temporal arteries or in other vascular beds with angiographic findings typical of GCA) in classifying patients as having GCA [22].

TAB should be performed by an experienced surgeon, and good-quality samples preferably to be obtained before or within seven days of commencing high dose glucocorticoid treatment, in order to enhance its sensitivity [23]. The optimal length of the biopsy specimen remains debatable, with segments of at least 0.7–1 cm post-formalin fixation considered acceptable in the majority of studies [24, 25]. In order to achieve this, biopsies should be around 1.5 cm in length to allow for an estimated 10% tissue shrinkage during fixation [26]. The biopsy should be obtained from the most symptomatic site; ultrasound guidance to direct the site for performing TAB has not improved the sensitivity for diagnosing GCA in one study [27]. Biopsy of the contralateral artery has been reported to only increase the diagnostic yield by 4–13% [24, 28–31] and is therefore not routinely recommended.

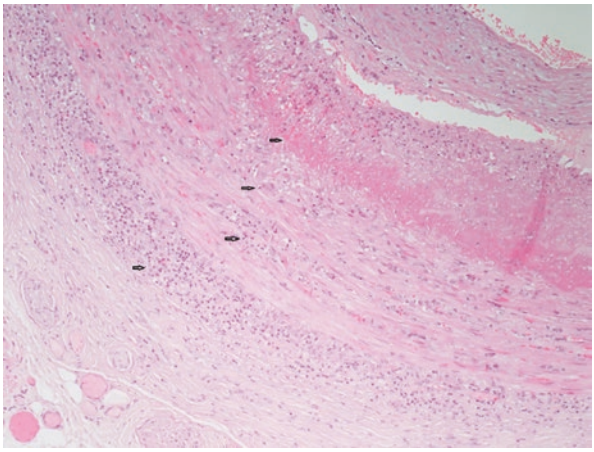

Fig. 20.1 Transmural inflammatory lymphohistiocytic infiltrate, involving intima, elastic internal membrane, media and adventitia (arrows). (Curtsey of Michael Lurie M.D)

The classic histological picture of GCA is a transmural inflammatory infiltrate associated with marked disruption of the internal elastic lamina and the presence of giant cells (Fig. 20.1). However, TAB may contain less obvious characteristics of the disease, such as isolated periadventitial/vasa vasorum inflammation [32] or just intimal hyperplasia, which make the histologic diagnosis less easy to interpret [33, 34]. An inter-rater analysis of the evaluation of biopsy findings was conducted in the multi-center TABUL (Temporal Artery Biopsy vs. Ultrasound in the diagnosis of Giant Cell Arteritis) study, revealing a significant amount of variability in agreement between experienced pathologists looking at the biopsies obtained from 30 patients. Forteen pathologists reviewed the samples and only in 11 cases did all pathologists agree on the results (consistent vs. not consistent with GCA), which corresponded to an intra-class correlation coefficient of 0.62 (95% CI 0.49–0.76). Thus, it is vital to interpret TAB results with caution and establish good communication between clinicians and pathologists.

Despite the high specificity of TAB for diagnosing GCA (reported to be up to 100%), sensitivity can be as low as 39% [35, 36] mainly due to poor sampling (it is estimated that up to 7% of all TABs may not actually consist of arterial tissue [23]), reduced accessibility to the procedure, the segmented nature of the pathological findings, also described as "skip lesions" [37], and the presence of large vessel-GCA, which has less frequent temporal arterial involvement [38]. Antecedent high dose glucocorticoid treatment will rapidly resolve inflammation in the arterial wall giving a false negative result. Furthermore, the interpretation of any histological findings can be difficult in older patients due to atherosclerotic and structural age-related changes [39].

Although TAB is a generally safe procedure, it is still an invasive technique with a complication rate of approximately 0.5% [40]. The most severe complications include facial nerve injury [41–45], tongue and scalp necrosis [46], and stroke [47]. Therefore, less invasive options with higher sensitivity for diagnosis could improve patient care in GCA.

20.4.2 Imaging Modalities

Color doppler ultrasonography (CDUS) is a non-invasive feasible, readily available modality for visualization of the inflammation of the temporal arteries. Recent guidelines [48, 49] support its use as an alternative and more cost-effective diagnostic method, which often spares the need for more invasive procedures, e.g., TAB. In a growing number of centers across Europe, it is replacing TAB as the initial investigation for GCA in fast track clinics. CDUS allows an examination of the complete vascular tree of each temporal artery, hence overcoming the "skip lesion" obstacle, thus improving sensitivity. Other vessels are also readily examined using CDUS, including axillary, facial, occipital, and vertebral arteries. This provides for a more comprehensive evaluation of each patient, in comparison to TAB. The typical finding seen in CDUS suggestive of active vasculitis is the "halo" sign (Fig. 20.2), which represents edema of the vessel wall caused by inflammation [50].

In a large multi-center study (TABUL) comparing the diagnostic performance of CDUS and TAB in 281 patients with suspected new-onset GCA, we reported a better diagnostic yield of CDUS compared to TAB with the sensitivity of 54% vs. 39%, respectively [23]. However, it is important to ensure adequate training in the performance and interpretation of ultrasound findings [51].

Recent reports have highlighted the potential role of magnetic resonance angiography (MRA) in demonstrating inflammation in temporal arteries with good concordance to temporal artery biopsy findings and a high negative predictive value [52, 53].

In GCA, the aorta and its branches are involved in one half to two-thirds of patients depending on the diagnostic modality used. Consequently, patients with

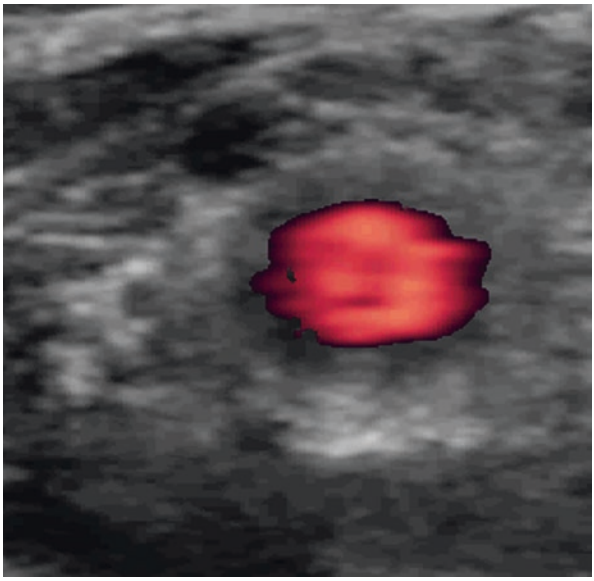

Fig. 20.2 "Halo sign" of the frontal branch of the right temporal artery in a 76 years old patient with GCA

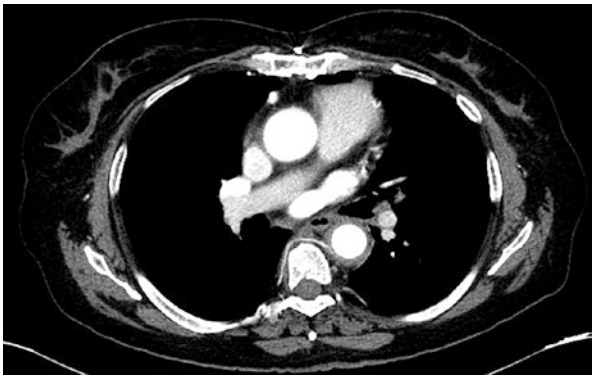

Fig. 20.3 Large vessel vasculitis in a patient with GCA, presenting as concentric wall thickening of the descending aorta

GCA are potentially at risk of aortic aneurysm and dissection. While some series report the risk to be up to 3.2 times compared to an age-adjusted control population [54], in a single large study [55], we found a lower risk of approximately two-fold amongst a cohort of almost 7000 patients compared to over 40,000 controls.

Hence, the role of imaging of the aorta and large vessels in the routine screening of patients with GCA remains unclear. For patients with established evidence of aortic involvement, it is usual practice to monitor for structural changes.

Computed tomographic angiography (CTA) and (MRA) are useful noninvasive modalities for screening of involvement of large vessels, presenting as luminal changes (stenosis, wall thickening, dilations and aneurysms) on CTA (Fig. 20.3), or edema and wall contrast enhancement on more sensitive and comparably specific MRA [56].

^{18}F-fluorodeoxyglucose-PET (FDG-PET) has been increasingly employed to detect and monitor LV involvement in TAK and GCA [57, 58]. Unfortunately, this tool still lacks accepted standardization for vascular inflammation, although several methods have been proposed. Moreover, false positive results are not uncommon, especially in elderly patients due to age-related vascular atherosclerotic changes, misdiagnosed as wall inflammation [59].

20.5 Treatment

Patients with suspected GCA should be referred to fast track GCA clinics [60, 61] for rapid evaluation and diagnosis to minimize the incidence of complications. If patients have been exposed to little or no glucocorticoid therapy, investigations such as imaging or biopsy have the highest diagnostic yield. Not only would this reduce the risk of sight loss from untreated disease, but it would also help to exclude GCA and prevent patients from being treated with high doses of glucocorticoid therapy unnecessarily.

Glucocorticoids (GC) remain the cornerstone treatment in GCA and ought to be started once a reasonable suspicion of disease arises, frequently before a definitive

diagnosis being made. The initial dose of glucocorticoid should be 40–60 mg per day until symptoms have resolved, and acute phase reactants are normalized. Current guidelines [49] recommend tapering GC dose by 10 mg every 2 weeks until 20 mg/day is reached, then reducing by 2.5 mg every 2–4 weeks to 10 mg and afterward by 1 mg every 1–2 months according to clinical response. The subgroup of patients with an ischemic presentation, whether ophthalmic or cerebrovascular, could be considered for additional intravenous pulse methylprednisolone, but the evidence base to support this practice is extremely limited.

Short- and long-term side effects of GC treatment are encountered in up to 80% of patients with GCA [62], which adds to the burden of the disease and negatively affects the well-being of these (usually) elderly patients. Side effects include osteoporosis, hypertension, increased risk of infection, cardiovascular events, and metabolic effects like diabetes mellitus and cataract. Prophylactic bone-protection (bisphosphonates, calcium, vitamin D) and proton pump inhibitors are recommended to offset some of these problems.

There is no evidence to support the routine use of anti-platelet therapy in patients with GCA.

Up to 50% of patients with GCA experience at least one relapse throughout their disease course, despite treatment with GC. Such relapses can manifest as recurrence of headache, constitutional complaints, or elevated inflammatory markers. However, the differential diagnosis is extensive and includes other conditions such as, for example, infection (which is more likely in immunosuppressed elderly patients); therefore, a careful clinical evaluation of these patients is important to determine the cause of their deterioration before attributing it to a relapse of their GCA. The treatment of a relapse is to increase the GC dose, usually to the last effective dosage with the subsequent resumption of GC reduction once the relapse has responded; in addition, it is possible to consider disease-modifying anti-rheumatic drug (DMARD) therapy. Patients should be constantly monitored for complications of their condition or its treatment.

DMARD therapy (biologic or non-biologic) should be used in cases of recurrent relapses or GC dependence/side effects.

Retrospective studies and a meta-analysis of randomized controlled trials suggest methotrexate (MTX) as a reasonable GC-sparing drug allowing the more rapid lowering of GC dose and less frequent relapses [63, 64].

Tumor necrosis factors blockage-based drugs were not proven beneficial in GCA and are not recommended for routine use [65–67].

In the past few years, the efficacy of the interleukin-6 (IL-6) blockade in GCA has been evaluated in several retrospective trials with promising results [68–70]. More recently, 2 randomized controlled trials [71, 72] demonstrated significant clinical responses and GC reduction following tocilizumab (an IL-6 receptor antagonist) administration for one year (either by intravenous or subcutaneous routes) in patients with GCA. Furthermore, recent Swiss study reported prolonged remission in about half of the GCA patients previously receiving tocilizumab during the subsequent follow up period, with significantly fewer relapses, as compared to placebo [73].

20.6 Summary and Prognosis

GCA is a disorder exclusively seen in the elderly. It requires long-term treatment and periodic assessment of disease activity and treatment side effects.

Rapid diagnosis, preferably through fast track GCA clinics, grants more effective treatment and minimizes the incidence of complications. Imaging, especially color Doppler ultrasound, is more sensitive, although less specific than biopsy in the diagnosis of GCA and is increasing in use as an established diagnostic test in GCA.

Apart from high dose glucocorticoid treatment, novel emerging biologic therapies targeting IL-6 have proven efficacy and should be considered.

Overall, GCA is not associated with increased mortality compared to the general population but is associated with an increase in morbidity, mainly cardiovascular and glucocorticoid-associated metabolic disorders (osteoporosis, hypertension, diabetes mellitus). Increasing use of effective glucocorticoid – sparing therapies that control disease and reduce risks of relapse should improve outcomes for patients in the future.

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Chapter 21
Psoriatic Arthropathy

Rema Bishara Garzuzi, Tal Gazitt, Muna Elias, and Devy Zisman

21.1 Epidemiology

Psoriasis affects approximately 2% of the population. The exact incidence and prevalence of PsA is unknown given variability in reported epidemiologic secular trends and the variations in the populations studied. A review of published data shows that the prevalence of PsA varies from 0.3 to 1% in the general population [1], while the reported incidence in recent publications ranges from 3.6 to 7.2 per 100,000 person years [2]. Of interest, a large population-based study conducted in Israel observed an increase in the reported prevalence of PsA in the general population over the past decade [3].

Aamong patients with psoriasis, the prevalence of PsA ranges from 6 to 41% [2] with an increase in incidence over time. Wilson et al. reported a cumulative incidence of 1.7%, 3.1%, and 5.1% at 5 years, 10 years, and 20 years following diagnosis of psoriasis, respectively [4]. It is estimated that 15% of patients with psoriasis have undiagnosed PsA [5].

While psoriasis usually precedes the development of arthritis by 10 years, in 10% of cases, psoriasis and arthritis occur simultaneously, whereas in 15% of cases, joint involvement precedes the onset of skin lesions (PsA sine psoriasis) [6]. PsA has equal gender susceptibility and can appear at any age. The peak incidence is reported to occur between ages 30–50, but PsA may appear in childhood or even in the geriatric population. Elderly onset PsA (EOPsA) has not been precisely defined [7], and

R. Bishara Garzuzi · T. Gazitt · M. Elias
Rheumatology Unit, Carmel Medical Center, Haifa, Israel
e-mail: munael@clalit.org.il

D. Zisman (✉)
Rheumatology Unit, Carmel Medical Center, Haifa, Israel

The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel
e-mail: devyzi@clalit.org.il

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few and insufficient data currently exist in the literature regarding the incidence and prevalence of EOPsA. Wilson et al. found that in 15.6% of patients, the disease occurred beyond 60 years of age [8]. In a Finnish epidemiological study, 26.1% of incident cases of PsA had disease onset after the age of 55 [9], while a Turkish epidemiological study showed 10.5% incidence of PsA over the age of 65 [10].

21.2 Etiology and Immunopathogenesis

PsA can be attributed to diverse genetic, immune, and environmental factors. These factors influence susceptibility to disease onset and disease phenotype.

Psoriasis and PsA are both highly polygenic diseases. Genome-wide association studies have shown that interleukin (IL)-23R, IL-12B, human leukocyte antigen (HLA)-C 06, proteins involved in nuclear factor κB (NF-κB) gene expression (i.e. tumor necrosis factor interacting protein 1, TNIP1) and signaling (i.e. tumor necrosis factor, alpha-induced protein 3, TNFAIP3) and tumor necrosis factor alpha (TNF-α) promoter polymorphisms are observed with greater frequency among patients with PsA. Additional associations have been found with HLA-B27, HLA-B08, HLA-B38, and HLA-B39. In particular, HLA C 06 is associated with early onset of skin disease and longer PsA latency without known associations as to sex predominance or any particular joint pattern. On the other hand, patients expressing the HLA-B27 antigen show earlier PsA disease onset, shorter PsA latency, male predominance, and symmetric sacroiliitis and enthesitis [7].

Of importance in the immunopathogenesis of PsA are activated dendritic cells as they secrete the pro-inflammatory mediators TNF-α, IL-23 and IL-12 in response to DNA released by stressed keratocytes [6]. IL-23 induces differentiation of naïve T cells into TH-17 cells, and activated TH-17 cells, in turn, overproduce the pro-inflammatory cytokines IL-17 and IL-12. TNF-α and IL-17 activate keratocytes, promote dermal hyperplasia, and recruit inflammatory cells such as neutrophils, TH-17 cells, osteoclast precursors, and dendritic cells into the joints. Increased levels of TNF-α, IL-17 and receptor activator of nuclear factor kappa-B ligand (RANKL) then drive differentiation of osteoclast precursors into osteoclasts with subsequent joint inflammation and bone resorption [11, 12].

Various environmental factors have also been found to be positively associated with the onset of 'psoriatic disease.' For instance, streptococcal infection is known to have strong association with the subsequent risk of guttate psoriasis [13]. Local skin trauma manifesting as the Koebner phenomenon also has well-recognized association with psoriasis. Namely, this phenomenon is characterized by the development of psoriasis along the site of skin trauma. It has also been proposed that trauma may play a role in triggering episodes of joint inflammation, and the term 'deep Koebner phenomenon' refers to the same principle, only involving deeper tissues including bones and joints. Along these lines, patients with history of psoriasis who are exposed to physical trauma have an increased risk of PsA with hazard ratio (HR) of 1.32 [14].

Other reported risk factors for PsA onset include family history of PsA, obesity, and involvement of the scalp, intergluteal, and perianal areas in psoriasis as well as nail involvement [2]. Studies examining the relationship between smoking and PsA have reported contradictory results [15].

21.3 Clinical Presentation

PsA is part of the 'psoriatic disease'- a term used to describe psoriatic skin disease and its various rheumatic features. It is characterized by rheumatic and non-rheumatic manifestations.

21.3.1 Rheumatic Manifestations

21.3.1.1 Arthritis

Moll and Wright describe five clinical subtypes of PsA [16]:

1. Asymmetric oligoarthritis
2. Symmetric polyarthritis
3. Predominant axial involvement
4. Predominant distal interphalangeal (DIP) joint involvement
5. Arthritis mutilans

Notably, PsA patients may present with more than one pattern of joint involvement and may experience a change in joint disease pattern over time. Figure 21.1 shows various joint involvement patterns and clinical findings specific to PsA.

Clinical characteristics of inflammatory arthritis include joint tenderness and swelling, slowly-developing low back pain with alternating buttock pain, prolonged morning stiffness alleviated by physical activity and worsened by immobility. In chronic disease, patients may experience a decrease in arthralgia with increasing joint deformity and a decrease in the range of motion of the affected joints and spine. A prospective study recently showed that erosive disease develops in up to 47% of PsA patients within 2 years of disease-onset [17]. Polyarticular subtype of arthritis, elderly-onset PsA (EOPsA), longer PsA disease duration, and elevated inflammatory markers are associated with increased joint damage and PsA disease progression [17–19].

PsA presents with an oligoarticular pattern in 60% of patients [20], with involvement of fewer than five joints distributed in a ray pattern. It is typical for joints in a single digit to be affected as opposed to the row-like symmetrical distribution of the same joints on both sides characteristic of rheumatoid arthritis (RA) [6]. Over time, or in late disease onset, patients may develop polyarticular (≥5 joint), symmetrical joint involvement resembling RA. Recently, a relative increase in the polyarticular

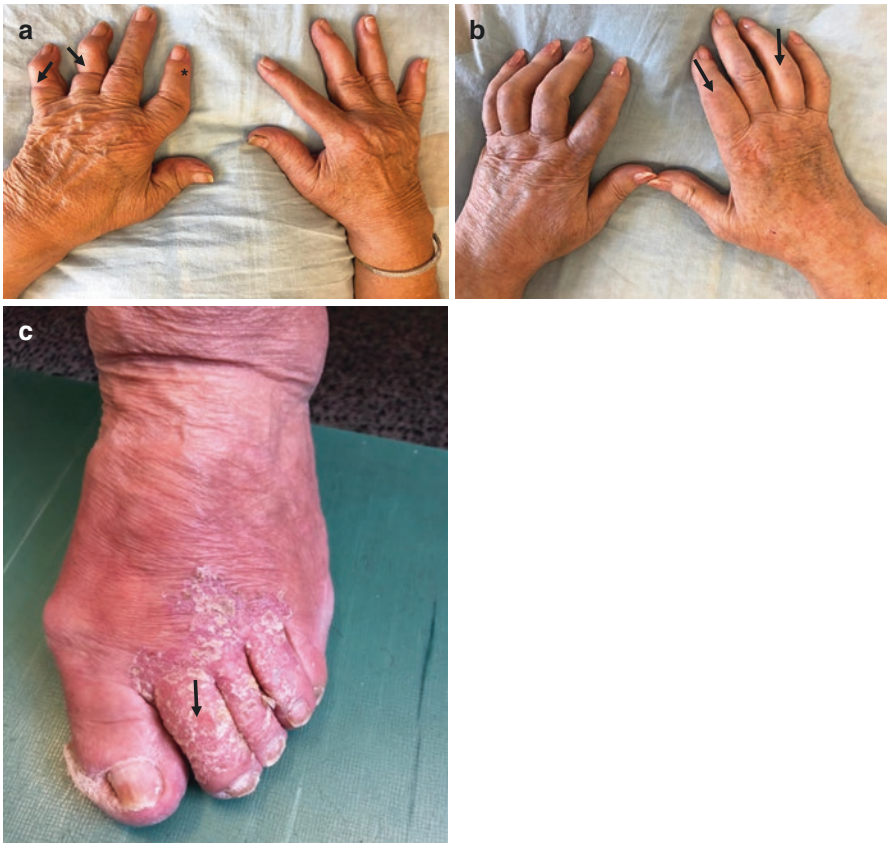

Fig. 21.1 Clinical subtypes and findings characteristic of PsA. (**a**) arthritis mutilans with telescoping of digits (designated by arrows), asymmetric joint involvement, and distal (DIP joint) involvement (designated by ∗) (**b**) polyarticular subtype of arthritis with dactylitis (designated by arrows). **C**) toe dactylitis (designated by arrow) and psoriatic skin involvement

subtype of PsA has been reported (49.7% of patients), correlating positively with age, female gender, and disease duration [21].

Axial disease may present with apophyseal spinal joint involvement as well as with asymmetrical sacroiliitis. This form of involvement usually occurs in conjunction with peripheral arthritis. Spinal involvement may be found in 40%–70% of PsA cases, but isolated axial disease is uncommon, occurring in approximately 5% of cases. Severe peripheral arthritis and HLA-B27 positivity are risk factors for axial involvement [22].

Distal joint involvement of DIP joints is considered a rather specific type of presentation for PsA. It is usually associated with other joint distribution patterns and with nail involvement. In 5% of patients, DIP joint involvement occurs alone [6].

Arthritis mutilans develops in 20% of patients. It is a severe destructive form of arthritis that may lead to irreversible joint deformity and loss of joint function. The most prevalent clinical features associated with arthritis mutilans are digital telescoping (34%), digital shortening (33%), and flail joints (22%) [23]. Patients with arthritis mutilans are diagnosed with PsA at an earlier age, possess more prevalent nail dystrophy and more radiographic axial disease involvement including sacroiliitis, and have overall poorer function than other PsA patients [24].

21.3.1.2 Elderly-Onset PsA (EOPsA)

EOPsA characteristically presents with more severe polyarticular joint involvement, more erosions, and more highly elevated inflammatory markers [25]. In a longitudinal cohort study, 566 patients were divided into two groups: late-onset psoriatic arthritis (LoPsA) - defined as disease onset ≥50 years, and young-onset PsA (YoPsA)- defined as disease onset <50 years. The LoPsA patients at presentation were characterized by female predominance, higher body mass index (BMI), more joint damage, and decreased prevalence of HLA-C 06 association. Following 5 years of follow-up, the LoPsA patients had worse prognosis manifested by a trend toward higher disease activity burden and significantly more joint damage [26].

21.3.1.3 Dactylitis

Dactylitis is a distinguishing feature of SpA occurring in 16–49% of PsA patients [27]. It is characterized by swelling and tenderness of the entire digit (fingers or toes) caused by inflammation of the joints, tendon sheaths, and soft tissue. It is often referred to as 'sausage digit.' It affects the feet more often than the hands and can affect multiple digits simultaneously. Dactylitis may be the only manifestation of PsA for months to years and is associated with a more erosive form of PsA [27].

21.3.1.4 Enthesitis

Enthesitis is an early manifestation of PsA, presenting in 35–50% of cases [28]. It is defined as inflammation at site of tendon or ligament insertion into the bone. Achilles tendon and plantar fascia insertions are the most common entheseal sites involved [20]. Other potential sites of involvement include the supraspinatus tendon insertion, the epicondyles, femoral condyles and the iliac crest. Enthesitis is thought to be integrally involved in the pathogenesis of PsA and is associated with worse prognosis [28].

21.3.2 Non-Rheumatic Manifestations

21.3.2.1 Skin and Nail Involvement

The assessment of skin and nails is a key factor in PsA diagnosis. Patients should be asked about and examined for hidden skin lesions. Psoriatic skin lesions tend to involve the scalp, ears, groins, umbilicus, and intergluteal cleft regions in particular, and these areas are most likely to be associated with the development of PsA. Currently, there is a weak association between the severity of skin lesions and PsA onset [29], although some studies suggest that severe psoriasis is a predictive risk factor for the development of PsA [2, 30].

Nail psoriasis is present in 80% of PsA patients. Characteristic lesions include nail pitting, onycholysis, nail bed hyperkeratosis, and splinter hemorrhages. Nail involvement is associated with DIP joint involvement and with increasing severity of joint disease [31].

21.3.2.2 Gastrointestinal (GI) Tract Involvement

Patients with PsA have a higher prevalence of both subclinical and clinical gut inflammation in the form of Crohn's disease or ulcerative colitis. Emerging evidence suggests that gut inflammation in patients with PsA is not a mere consequence of the systemic inflammatory process, but rather an important pathophysiological manifestation actively participating in the pathogenesis of the disease [32].

21.3.2.3 Eye Involvement

PsA may be associated with uveitis in 7–18% of patients. It has an insidious onset, is bilateral, and is more common in patients with extensive axial involvement (bilateral sacroiliitis and syndesmophytes) [33].

21.4 Laboratory Investigations

Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are usually normal in patients with PsA, but may be elevated in upto 50% of cases. When elevated, they signify poor prognosis [19, 34]. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) are typically normal, but low positive titers are reported in 5–10% of patients. Positive serology is associated with female gender, polyarticular involvement and more erosive disease [35–37]. Anti-nuclear antibody (ANA) > 1:80 titer is positive in 10–15% of patients. HLA-B27 is positive in up to 25% of PsA patients. Anemia of chronic disease may be

Table 21.1 CASPAR criteria [43]: In order to be diagnosed with PsA, a patient must have inflammatory articular disease (joint, spine, or entheseal inflammation) with at least 3 points from the following five categories:

Disease category	Typical findings	Score
1. Skin psoriasis	Current psoriasis, defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist	2 points
	Or a personal history of psoriasis, defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider	1 point
	Or a family history of psoriasis, defined as a history of psoriasis in a first- or second-degree relative according to patient report	1 point
2. Nail lesions	Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination	1 point
3. Dactylitis	Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist	1 point
4. Negative rheumatoid factor (RF)	Negative test by any method except latex but preferably by Enzyme-Linked Immunosorbent Assay (ELISA) or nephelometry, in accordance with the local laboratory reference range	1 point
5. Radiographic evidence of juxta-articular new bone formation	Appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hands or feet	1 point

present and hyperuricemia is present in 20% of patients, associated with increased BMI but not with the severity of the skin disease.

21.5 Radiographic Changes

Plain radiography remains the most common imaging modality in evaluation of PsA. Although it cannot detect early inflammatory changes, radiographic changes may be demonstrated with disease progression. Radiographic features of PsA can broadly be grouped into osteo-destructive and osteo-proliferative changes. This combination of radiographic features is typical for PsA, in contrast to RA, which is primarily an erosive disease. The proliferative changes found in PsA are seen as ill-defined ossifications around the joint contour, designated 'juxta-articular new bone formation.' This radiographic finding is considered pathognomonic for PsA and is an important component of the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria [38] (Table 21.1).

Radiographic features consistent with chronic articular damage are joint space narrowing, sclerosis, erosions, new bone formation, periostitis, bone ankylosis, and the presence of enthesophytes. In severe cases, bone lysis can occur leading to telescoping of digits and pencil-in-cup appearance of the joints [20]. Examples of such joint changes are seen in Fig. 21.2. A prospective study on early PsA recently showed that, at a median follow-up of 2 years, up to 47% of patients have erosions, 37% have joint space narrowing, and 29% have periostitis on X-ray imaging [17].

Spinal involvement in PsA is characterized by patchy and asymmetric bulky syndesmophytes throughout the axial spine. These bony outgrowths are paravertebral

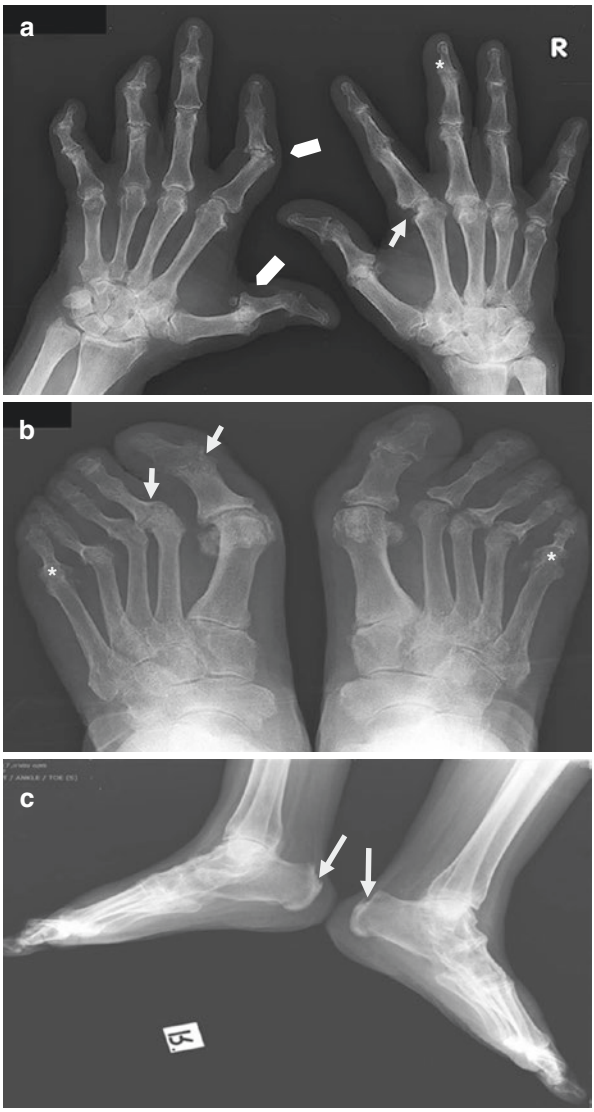

Fig. 21.2 Typical radiographic presentations of PsA (**a**) chronic PsA changes such as erosions (designated by arrow), joint subluxation (designated by arrowheads) and ankylosis (designated by asterisk). (**b**) ankylosis of metatarsophalangeal joints (designated by arrows) and pencil-in-cup deformities (designated by asterisk). (**c**) enthesophyte formation in the Achilles tendons (designated by arrows). (**d**) irregularity and sclerosis around the sacroiliac joints (designated by arrows). (**e**) MRI of the sacroiliac joints with bone marrow edema reflecting active disease (designated by asterisk)

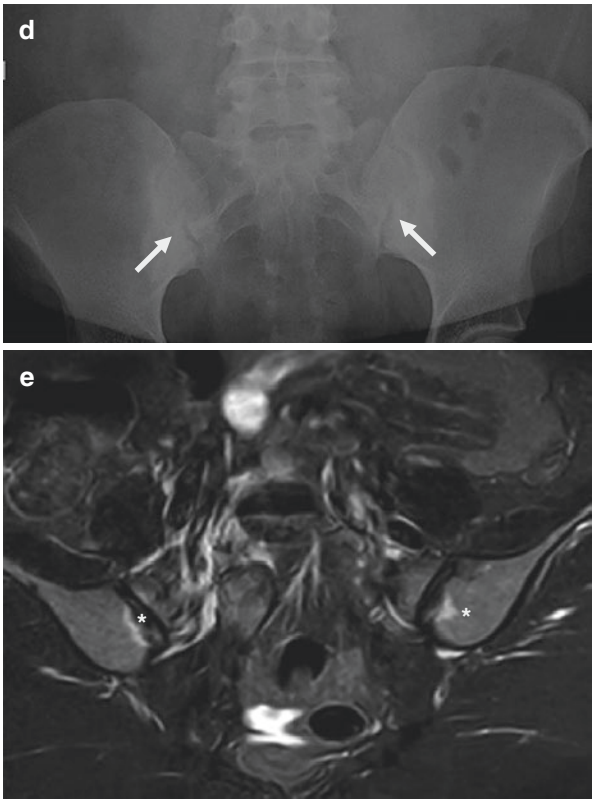

Fig. 21.2 (continued)

ossifications along the spine and are distinct from the classic 'marginal' syndesmophytes observed in ankylosing spondylitis. X-rays of the sacroiliac joints may reveal unilateral sacroiliitis with joint space narrowing, sclerosis, as well as ankylosis of the sacroiliac joints at later disease stages.

Recent advances in imaging modalities including musculoskeletal ultrasound (MSK-US) and magnetic resonance imaging (MRI) allow early and accurate evaluation of the extent of inflammation and damage in the peripheral joints, spine, and the entheses [39].

MSK-US is an accessible, non-invasive and relatively inexpensive modality. It demonstrates good accuracy, reliability, and sensitivity in the assessment of various peripheral lesions such as synovitis, tenosynovitis, bursitis, entheseal thickening, enthesophyte formation, increased vascularity and bony erosions [40, 41]. Typical imaging findings of PsA ultrasonography are demonstrated in chapter 12 on MSK-US use in the diagnosis of rheumatic disease in the elderly.

MRI is a very sensitive modality which can visualize all structures involved in inflammatory arthritis, but is expensive, time-consuming, and not readily available. In assessment of peripheral joint involvement, MRI can detect bone marrow edema, synovitis, tenosynovitis, periarticular inflammation, erosions, and bony proliferations. MRI has a crucial role detecting inflammation of the sacroiliac joints and spine at an earlier stage than plain x-rays [42].

21.6 Diagnosis

Early diagnosis of PsA is important for better disease control and prevention of permanent joint damage and long-term functional disability. The diagnosis relies on clinical features, musculoskeletal and dermatologic evaluation, blood tests, and imaging of the peripheral joints and the spine.

Several classification criteria have been proposed, but the most widely used are the CASPAR criteria (see Table 21.1 above), published in 2006, with sensitivity of 91.4% and specificity of 98.7% [43]. Their accuracy as diagnostic criteria was demonstrated as well.

21.7 Differential Diagnosis

Different patterns of involvement of PsA can resemble other inflammatory arthropathies; therefore, it is crucial to differentiate between these conditions in order to provide the most appropriate immunosuppressive treatment before irreversible joint destruction occurs.

Major conditions that should be considered in the differential diagnosis of PsA include:

1. Rheumatoid arthritis (RA):
   Differentiation between PsA and RA can be challenging particularly in the clinical setting of polyarticular PsA. Typical features that are consistent with the diagnosis of PsA include presence of psoriasis, nail involvement, DIP joint involvement, dactylitis, enthesitis, axial involvement, periosteal new bone formation and negative RF and anti-CCP. Unlike PsA, RA is characterized by proximal symmetric involvement of the joints with sparing of the DIP joints and involvement particularly only of the cervical spine [44].
2. Other forms of spondyloarthritis:
   Unlike PsA, ankylosing spondylitis (AS) and reactive arthritis (ReA) are notable for younger age at disease onset and male predominance. PsA is more often associated with the presence of asymmetric sacroiliitis, non-marginal syndesmophytes, and more frequent involvement of the cervical spine than patients with AS. Palmoplantar pustular rash (keratoderma blennorrhagicum), a feature of ReA, may be clinically and histologically indistinguishable from pustular psoriasis, but the presence of genitourinary/gastrointestinal symptoms as well as conjunctivitis can help to differentiate between these two conditions [45].
3. Crystal-associated arthropathies:
   Psoriatic monoarthritis, particularly involving the toes, may be misdiagnosed as gout or calcium pyrophosphate deposition disease (CPPD, also termed ‘pseudogout’). Serum uric acid levels are not reliable in distinguishing between PsA and gout, however, as these levels may also be elevated in patients with PsA due to the high prevalence of the metabolic syndrome among PsA patients. Synovial

fluid analysis for crystals and MSK-US can be helpful in determining the correct diagnosis, though it should be noted that PsA and gout may coexist in the same patient.

4. Osteoarthritis (OA):
   Distal joint involvement can be observed in PsA and osteoarthritis, and can exhibit some inflammation even in OA. Involvement of the first carpometacarpal joint, the presence of Heberden and Bouchard's nodes on clinical examination, and the presence of radiographic joint space narrowing, subchondral sclerosis, and osteophytosis can help to differentiate between these two conditions.
5. Fibromyalgia:
   The presence of somatic symptoms such as profound fatigue and poor quality of sleep along with diffuse tenderness in myofascial soft tissue areas is helpful in differentiating fibromyalgia from PsA [45]. The differential diagnosis is complicated since patients with PsA may suffer from coexisting fibromyalgia [46, 47].

21.8 Comorbidities in Psoriatic Arthritis

PsA is associated with a wide spectrum of comorbidities such as obesity, type-2 diabetes mellitus, insulin resistance, hypertension, dyslipidemia and fatty liver disease.

The metabolic syndrome (MetS) is a systemic proinflammatory state which includes abdominal obesity, dyslipidemia, hypertension, and insulin resistance. The prevalence of MetS and its components is higher in PsA patients as compared to other rheumatic diseases such as RA or ankylosing spondylitis (38%, 20%, and 11%, respectively) [48, 49]. A significant association was also noted between the MetS and the severity of underlying PsA (OR 4.47, $P < 0.001$) [50].

Several studies demonstrate that patients with PsA have a significantly increased risk of major adverse cardiovascular events (MACE) such as myocardial infarction, stroke, and cardiovascular death [51, 52]. Indeed, all-cause mortality is increased in PsA patients, with standardized mortality ratio of 1.22, and with CVD as the major cause of mortality among these patients [53]. Death is associated with combined axial and peripheral disease involvement and an increase in PsA disease activity index, indicating an association between CVD-related mortality and more aggressive disease phenotypes [53]. Irrespective of the classical CVD risk factors, systemic inflammation, premature atherosclerosis, increasing arterial stiffness, impaired endothelium-dependent vasodilation and platelet hyperreactivity play an important role in increasing the risk of MACE in PsA patients [54]. Given the association between CVD risk and inflammatory arthritis, the European League Against Rheumatism (EULAR) published evidence-based guidelines for CVD risk management in patients with inflammatory arthritis [55]. Targeted lifestyle interventions, healthy diet, regular exercise, and smoking cessation should be recommended to all patients with inflammatory arthritis. Effective long-term anti-inflammatory, disease-modifying therapy aimed at controlling disease activity may aid in CVD risk reduction [55, 56].

21.9 Monitoring and Assessing of Disease Activity

Given that PsA is a heterogeneous disease with involvement of multiple disease domains, various clinical and patient- derived assessment tools have been developed to measure the overall disease burden. These composite measures of psoriatic disease address different domains such as peripheral arthritis, enthesitis, dactylitis, axial involvement, skin/nail disease, pain level, physical function, health-related quality of life, and fatigue.

Peripheral arthritis is predominantly assessed by the tender and swollen joint counts but these are often combined with patient reported outcomes (PROs). Several dactylitis and enthesitis scoring measures have also been developed and are currently used in clinical practice [57, 58]. Psoriasis can be measured by the Psoriasis Area and Severity Index (PASI) and body surface area (BSA) [59], while the Nail Psoriasis Severity Index (NAPSI) is the most comprehensive assessment tool for nail disease [60].

Common composite measures used are the Composite Psoriatic Disease Activity Index (CPDAI) [61], the Disease Activity Index for Psoriatic Arthritis (DAPSA) [62] and the PsA Disease Activity Score (PASDAS) [63]. The Minimal Disease Activity (MDA) is a composite outcome measure of disease state developed specifically to be a target of therapy [64, 65].

21.10 Treatment

The treatment of late-onset PsA and PsA in older age groups poses many challenges. In the elderly, alterations characterized by immunosenescence occur in both innate and adaptive immunity, leading to increased susceptibility to autoimmunity and cancer, impaired response to vaccinations, and impaired protection against infections. There is limited data in the literature regarding treatment of PsA in this population [66]. The treatment in elderly PsA patients resembles that of younger patients, though consideration should be given to age-related metabolic changes in drug pharmacokinetics and pharmacodynamics, interactions with other medications, and the presence of comorbidities which may affect medication choices and adherence [67]. Patients should be treated according to EULAR and the Group for Research Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations updated in 2015 [68]. Treatment strategy should address all aspects of PsA including peripheral arthritis, dactylitis, enthesitis, axial involvement, the magnitude of skin and nail involvement, as well as the presence of comorbidities. Early treatment contributes to better long-term outcomes [69].

Monoarticular disease involvement, mild oligoarticular disease, dactylitis, enthesitis, and axial involvement can be treated initially with nonsteroidal anti-inflammatory drugs (NSAIDs). Intra-articular steroid injections may also be used for treatment of mono- or pauciarticular disease, enthesitis, and dactylitis. Systemic

glucocorticosteroids (GC) may be used at the lowest effective dose as needed, but may induce a flare of psoriasis [68].

In more severe oligoarticular disease, polyarticular disease, or in the presence of poor prognostic factors, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) such as methotrexate, sulfasalazine or leflunomide should be considered early. Of these, methotrexate is considered by clinicians as a first-line agent in PsA. It is effective in managing arthritis and psoriasis; alternatively, sulfasalazine and leflunomide can be administrated for peripheral arthritis but not for skin involvement.

In cases refractory to csDMARDs, treatment with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is recommended. These treatments target major pathogenic cytokines involved in PsA immunopathogenesis such as TNFα, IL-23 and IL-17. Anti-TNF agents are usually recommended as the first-line bDMARD. This class of agents includes infliximab, adalimumab, golimumab, etanercept and certolizumab pegol. These therapies target joint inflammation, axial disease, dactylitis, enthesitis and help prevent radiographic damage [70]. Secukinumab and ixekizumab are therapies that target the IL-17 pathway. They are also effective in managing axial disease, peripheral arthritis, enthesitis and have great efficacy in managing psoriasis [71]. Ustekinumab is an antibody directed against the shared P40 subunit of IL-12 and IL-23. It is effective in managing psoriasis, enthesitis, and peripheral arthritis although treatment results in the skin are more impressive than in the joints [72, 73]. Abatacept is a selective T cell costimulation modulator. It is a potential treatment option for a select group of patients with PsA, particularly those with active peripheral arthritis. While it can improve radiographic progression, enthesitis and dactylitis, abatacept had minimal effects on psoriasis. There is insufficient data regarding the effect of abatacept on nail and axial disease [74, 75].

In patients with predominantly axial disease who fail therapy with NSAIDs, bDMARDs should be considered, including anti-TNF, anti-IL-17 and anti-IL23 agents. Notably, GRAPPA recommendations do not suggest a particular order with which to use any of the bDMARDs when disease is refractory to csDMARDs, thus offering great flexibility in selecting the appropriate treatment for each patient.

Apremilast is a tsDMARD acting as a phosphodiesterase-4 inhibitor. Clinical trials demonstrate moderate effect on joints, skin, and enthesis [76]. It is recommended for patients with oligoarthritis, enthesitis, and/or dactylitis who fail csDMARD therapy. It has a good safety profile, and unlike csDMARDs, treatment with this agent does not require regular blood monitoring. Tofacitinib is another tsDMARD which is a Janus Kinase (JAK) inhibitor. It is recommended for arthritis and psoriasis [77].

Both tsDMARDs and bDMARDs are considered safe; side effects include injection site reactions, increased risk of bacterial infections, candida infections (particularly with secukinumab and ixekizumab), weight loss and diarrhea (particularly with apremilast) [20]. Anti-TNF agents are not recommended in patients with New York Heart Association (NYHA) class III/IV heart failure due to their potential risk to aggravate heart failure. The EULAR/GRAPPA recommendations address

regular disease monitoring and appropriate therapy adjustments to reach the target of remission or minimal/low disease activity [68]. In patients who fail to respond to one bDMARD, switching to another bDMARD should be considered including switching between TNF-α inhibitors. Studies demonstrate that tight control of PsA disease activity through a treat-to-target approach significantly improves joint outcomes for newly diagnosed patients, with no unexpected serious adverse events reported [69]. Addressing comorbidities such as the MetS by lifestyle modifications, smoking cessation, weight reduction, and physical activity are also very important to reach optimal disease outcomes.

Patients with PsA treated with immunosuppressive therapies are at increased risk of infections and associated morbidity and mortality. Therefore, as in other rheumatic diseases, vaccination administration is of high importance with a recent update in EULAR recommendations for vaccinations in patients with inflammatory rheumatic diseases [78].

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Chapter 22
Septic Arthritis in the Elderly

Mohammad Adawi, Nicola Luigi Bragazzi, and Abdulla Watad

22.1 Epidemiology and Etiopathogenesis

Septic arthritis, also known as joint infection or infectious arthritis, is the invasion of a joint by an infectious agent that, if not treated, can result in severe joint damage. Symptoms typically include redness, heat, and pain in a single joint associated with a decreased ability to move the joint. Etiopathogenetic mechanisms include: (a) hematogenous seeding and spreading, (b) direct inoculation (previous orthopedic interventions, joint surgery, and therapeutic intra-articular injections of corticosteroids), and (c) continuous extension from a contiguous infectious focus affecting adjacent structures, such as bones or skin [1].

M. Adawi (✉)
Azrieli Faculty of Medicine, Padeh and Ziv Medical Centers, Bar-Ilan University, Zefat, Israel

N. L. Bragazzi
Laboratory for Industrial and Applied Mathematics (LIAM), Department of Mathematics and Statistics, York University, Toronto, ON, Canada

Department of Health Sciences (DISSAL), Postgraduate School of Public Health, University of Genoa, Genoa, Italy

A. Watad
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Department of Medicine B, Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

Section of Musculoskeletal Disease, NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Institute of Molecular Medicine, Chapel Allerton Hospital, University of Leeds, Leeds, UK

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Older adults are at a higher risk of developing septic arthritis, because of (a) frailty and significantly reduced physiological reserve, (b) co-morbidities (diabetes mellitus, metabolic impairments, immunological dysfunctions, HIV, or malignancies), and (c) degenerative musculo-skeletal disorders (including osteoarthritis, chondrocalcinosis, and rheumatoid arthritis) [2, 3] or rheumatic diseases (such as gout and systemic lupus erythematosus). Whereas the incidence of septic arthritis is 2–5 cases *per* 100,000 person-years in the general population, it can increase up to 70 cases *per* 100,000 person-years among patients suffering from rheumatic disorders [4].

With respect to the previous reports [5], the incidence of septic arthritis among the elderly is on the rise, by approximately 0.61 cases *per* 100,000 person-years [6], probably due to increasing aging rate among the population, immunosenescence [7], higher drug consumption (especially of immunosuppressive therapeutics) [8], and more invasive interventions, among others.

22.2 Clinical Presentation

Generally, the patient with septic arthritis displays red, swollen, painful warm joints with the decreased range of motion of the affected joint, with or without fever. The clinical presentation of septic arthritis among the elderly is particularly challenging because it may be atypical, above all in patients with cognitive impairment, dementia, or atherosclerosis. Other issues are given by false positive serologies, and by the underlying co-morbidities that may confound or make more difficult the diagnosis of septic arthritis, even among experts [9].

Culture-negative septic arthritis should be considered as presumptive, while at least 14–15% of these patients develop systemic rheumatic disease during the follow up [10].

Septic arthritis is generally mono-articular, mainly affecting the knee, followed by the hip, the shoulder, the ankle, the wrists, and, exceptionally, the elbow, the inter-phalangeal, the sterno-clavicular, and the sacro-iliac joints. Septic arthritis can be polyarticular as well, especially in patients with underlying joint disorders [11].

22.3 Microbiology

Generally, the most common infectious agent is *Staphylococcus aureus*, even though the precise microbiological pattern can vary depending on the age of the patient, as summarized in Table 22.1. Among the elderly, mixed bacterial infections (especially by Gram negative pathogens) can be frequent as well. Other

Table 22.1 Main features of septic arthritis broken down according to the age of the patient

Septic arthritis	Neonates	Infants	Children	Adolescents	Adults	Older adults
Causative infectious agent	Group B *streptococci*, *staphylococci*, gram negative organisms (*Kingella kingae*, *Haemophilus influenzae*), *Candida*	*Haemophilus influenzae*, *Staphylocccus aureus, Pneumococcus*	*Staphylococcus aureus*, *Salmonella* and group A *streptococci*	*Staphylococcus aureus*, *Neisseria gonorrheae*	*Staphylococcus aureus*, *streptococci* and gram negative organisms	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*
Route	Haematogenous spreading and seeding	Haematogenous spreading and seeding	Haematogenous spreading and seeding	Haematogenous spreading and seeding	Haematogenous spreading and seeding, continuous extension	Haematogenous spreading and seeding; direct contact
Affected site	Hip	Hip	Hip	Knee	Large joints	Knee
Clinical manifestation	Mono-articular	Mono-articular	Mono-articular	Poly-articular	Mono-articular and poly-articular	Mono-articular and poly-articular

common microbes are *Staphylococcus epidermidis*, others coagulase-negative *staphylococci*, *Propionibacterium acnes*, *Escherichia coli,* and *Pseudomonas aeruginosa*.

22.4 Differential Diagnosis

Septic arthritis should be differentiated from osteoarthritis, which is the most common cause of joint pain among the elderly, and inflammatory joint diseases [12]. No clinical symptom (chills, gradual onset, local redness, entry site for infection, a history of crystal-induced arthritis), laboratory parameter (purulent synovial fluid appearance, elevated synovial white blood cells or WBC count, erythrocyte sedimentation rate or ESR, C-reactive protein or CRP levels), or radiological signs alone can be conclusive for the diagnosis of septic arthritis. Clinical suspicion and experience guide towards the correct diagnosis [13].

22.5 Prognosis

Septic arthritis among the elderly has grave prognosis. Wu and coworkers [14] performed a retrospective analysis, utilizing the "Taiwan National Health Insurance Research Database" (NHIRD). A sample of 1667 geriatric individuals suffering from septic arthritis was matched with 16,670 geriatric subjects without septic arthritis. Authors found that geriatric participants with septic arthritis had a significantly increased mortality than those without septic arthritis, with a computed adjusted hazard ratio (AHR) of 1.49 [95% confidence interval (CI) 1.34–1.66], especially the older elderly (aged equal to or greater than 85 years, with an AHR of 2.12 [95%CI 1.58–2.84]. The increased mortality risk was highest in the first month with an AHR of 3.93 [95%CI 2.94–5.25] and remained increased even after following up for 2–4 years with an AHR of 1.30 [95%CI 1.03–1.65].

Molloy and coworkers [15] conducted an epidemiological analysis of spontaneous community-acquired cases of septic arthritis among the elderly and enrolled seven patients aged from 65 to 82 years. The hips and the knees were affected in 2 and 5 cases, respectively. Complications of treatment included acute renal failure, cardio-respiratory failure, disseminated infection (bacteremia and septicemia), and, ultimately, death.

Ferrand and collaborators [16] enrolled a sample of 109 patients aged 60.1 ± 20.1 years. Most patients displayed co-morbidities, especially cardiovascular and rheumatic disorders. Septic arthritis affected most frequently the small joints (31.2%) and the knee (22.9%). Direct septic arthritis-related mortality rate was 5.6%, with most deaths occurring promptly after the onset of septic arthritis, from 1 to 42 days (median 24 days). A poor functional outcome was reported for 31.8% of the patients.

22.6 Preventative Strategies

Preventative strategies include: (a) physical activity, in order to achieve weight loss, since a high BMI is a risk factor for developing septic arthritis, and (b) a thorough monitoring of catheters, devices and/or prostheses, to avoid the insurgence of skin infectious diseases, urosepsis or bloodstream infections.

22.7 Surgical Management

The initial management of patients with septic arthritis consists of removing the infected fluid, which can be done performing an arthrocentesis or a series of needle aspirations.

In case of persistent effusion, surgical drainage is indicated (arthroscopically or carrying out an arthrotomy). However, few articles have specifically addressed surgical management of septic arthritis among the elderly. A notable exception is given by the retrospective, database-based study by Chen and coworkers [17]. Authors enrolled 72 patients aged 67.7 years: 7 underwent arthrodesis, 22 underwent total knee arthroplasty, 19 were indicated for total knee arthroplasty but did not undergo surgery, and 30 did not receive any surgical procedure. Delayed treatment, performing multiple debridement surgeries, more antibiotics administered, longer duration of antibiotic treatment, and more pathogenic agents present were significantly correlated with a poor prognosis.

22.8 Pharmacological Management

Concerning the empirical treatment, amoxicillin/clavulanate or cefuroxime can be considered as adequate pharmacological options for empirical coverage of large-joint septic arthritis. A broad-spectrum antibiotic could be, instead, a better solution for small-joint infections in people with diabetes. Generally, systematic coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) is not justified but can be considered for known carriers [18]. On the other hand, the prevalence of multi-drug resistant strains is increasing throughout time, and empirical therapy can depend on the local guidelines [19].

Prolonged suppressive antibiotic therapy (PSAT) can be a valid therapeutic option in older adults with joint prostheses in order to prevent the insurgence of acute sepsis.

According to a recent national, multicentre, cross-sectional, cohort study [20], recruiting a total sample of 136 patients with a median age of 83 years and with Staphylococcus aureus being the predominant infectious agent involved, a single antimicrobial drug was prescribed in 96 cases (70.6%). 25 (18.0%) patients

developed an adverse drug event, leading to definitive discontinuation or switch of the PSAT, whereas in 8 (5.9%) patients sepsis progressed and 13 (9.6%) patients died. The overall survival rate without an event at 2 years was 61% [95%CI 51–74]. At the multivariate Cox analysis, patients with higher World Health Organization (WHO) score had an increased risk of an event (hazard ratio or HR of 1.5, p = 0.014), whereas patients treated with beta-lactams developed less events (HR of 0.5, p = 0.048).

Another investigation, a single-center, prospective cohort trial carried out by the "Lyon Bone and Joint Infection Study Group" [21] confirmed the safety profile of the PSAT and its feasibility as "salvage therapy" when oral pharmacological treatment and/or surgical management are not possible. The study enrolled 10 patients with a median age of 79 years, with a poly-microbial (n = 5) or multi-drug resistant (MDR) bacterial (n = 4) prosthetic joint infection (affecting the knee or the hip in four and three cases, respectively) or chronic osteomyelitis (n = 3). After initial intensive therapy, seven patients received ertapenem, while three patients received ceftriaxone and one patient ceftazidime by sub-cutaneous injection. Only in one patient with recurring infection the PSAT failed, whereas in three patients, the PSAT had to be discontinued due to the insurgence of side effects. Median duration of the treatment was 433 days, leading to a favorable outcome in six other patients.

In another study [22], 38 patients of 80 to 95 years old with hip (n = 24), knee (n = 13) and shoulder (n = 1) infections, caused by *Staphylococcus aureus* (39%) and *Streptococcus agalactiae* (16%) received PSAT, which included penicillins. After 24 months, 60% of the patients were event-free. Overall, 15 events (namely, 6 failures and 9 unrelated deaths) were observed, with hypoalbuminaemia, the presence of a sinus tract, and a staphylococcal PJI being statistically significant predictors of treatment failure.

22.9 Conclusion

Septic arthritis should be considered an emergency among the elderly, leading to reduced functioning, morbidity and, ultimately, mortality [23]. As such, patients should be promptly diagnosed and treated. Removal of infected efusion, early administration of antibiotics, timely surgery and supportive care are the best evidence-based domains for the proper management of older adults with septic arthritis.

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Chapter 23
Autoinflammatory Diseases in the Geriatric Population

Michal Brodavka and Merav Lidar

23.1 Introduction

Autoinflammatory disorders are inherited diseases of innate immunity leading to uncontrolled activation of the interleukin-1 pathway. The disorders are characterized by unprovoked recurrent inflammation affecting primarily the skin, as well as the serosal and synovial membranes. As innate immunity is the culprit, there are no autoantibodies or autoreactive T-cells to aid in the diagnosis and reactive amyloidosis is a potential severe long-term complication [1, 2].

Autoinflammatory diseases can be classified into monogenic disorders or multifactorial polygenic disorders. Whereas the monogenic diseases typically manifest during the first years of life, a minority may be diagnosed only during adulthood, usually due to delayed diagnosis on account of a milder clinical phenotype. Albeit, recently somatic mutations have been described in late onset disease and may serve to explain atypical autoinflammatory syndromes encountered in the older population.

23.2 Familial Mediterranean Fever (FMF)

FMF is the most common monogenic autoinflammatory disease characterized by recurrent attacks of fever, serositis and arthritis, resulting in pain in the abdomen, chest and joints. Attacks last 1–4 days on average and abate spontaneously with

M. Brodavka
Rheumatology Unit, Autoimmune Disease Center, Sheba Medical Center, Ramat Gan, Israel

M. Lidar (✉)
Rheumatology Unit, Autoimmune Disease Center, Sheba Medical Center, Ramat Gan, Israel

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
e-mail: Merav.Lidar@sheba.health.gov.il

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Table 23.1 Tel-Hashomer diagnosis criteria

Major criteria	Minor criteria
Recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis)	Recurrent febrile episodes
Amyloidosis of AA type without a predisposing disease	Erysipelas-like erythema
Favorable response to regular colchicine treatment	FMF in a first-degree relative

complete convalescence between attacks [3]. The inter-attack interval is diverse and differs from patient to patient as well as in the same patient between times of stress to times of tranquilty.

The diagnosis of FMF is based on Tel-Hashomer criteria [4] and requires two or more major symptoms or one major plus two minor symptoms (Table 23.1).

FMF is caused by mutations in the MEFV gene [5], which encodes the pyrin protein. Pyrin protein is associated with the interleukin (IL)-1-related inflammatory cascade which regulates apoptosis and inflammation. Although over 80 mutations in the MEFV gene have been reported, the majority of clinical cases are associated with five mutations.

The disease is classically transmitted in an autosomal recessive pattern although only a single mutated allele is found in a substantial minority of cases. Somatic mosaicism in late onset disease shall be discussed later in this chapter.

FMF primarily affects ethnic groups originating in the Mediterranean basin including Jews (mainly non-Ashkenazi), Armenians, Turks, Arabs, and less commonly Greeks and Italians. In these geographic areas, most of the patients are diagnosed before the age of 20. However, in recent years, more and more cases have been reported in countries outside of this area, such as the United States and Japan [6]. Disease onset in Japanese patients is later in life compared to the Middle Eastern population, yet in only 6% of reported patients were first disease manifestations reported after 50 years of age. Late onset disease in the far-Eastern population may be attributed to different mutations in the FMF gene which are associated with a milder clinical phenotype. The MEFV gene, is located on chromosome 16p13.3 [5]. (A). Mutations have been found in exons 1, 2, 3, 5, 9 and 10 of the MEFV gene.

Five founder mutations, V726A, M694V, M694I, M680I, and E148Q, account for approximately 75 percent of FMF chromosomes from typical cases in Armenians, Arabs, Jews, and Turks [7].

The most frequent mutation is M694V prevalent in 20–65% of patients. In 10–20% of patients who meet the FMF diagnostic criteria no *MEFV* mutations are found [8].

It has been reported that a subgroup of patients who carry only one *MEFV* mutation, express the phenotypic clinical picture [5].

M694V and M680I, clustered in exon 10, are the mutations associated with the most severe forms of disease. Genetic variants found in exons 2 (e.g., E148Q) and 3 (P369S) are usually associated with less severe clinical presentation.

Most mutations in Japanese patients are located in exons 2, 3, and 4, and their presentation in usually mild and easily controlled with colchicine [9]. Homozygous

M694V genotype, compared to FMF patients with other genotypes, have a more severe disease, a higher rate of chronic FMF associated morbidity and comorbidity and consume higher doses of colchicine to which they respond less favorably [10].

It is unclear if the E148Q mutation is a benign polymorphism rather than a mutation causing disease [11].

There are few reports about onset of disease in the geriatric population, with the oldest patient diagnosed at 86 years of age [1].

As in the far-East, elderly onset FMF is mainly associated with low penetrance genetic mutations causing phenotypically similar disease of reduced severity.

Tamir et al. [12] reported absence of M694V homozygosity in late-onset FMF compared to the regular FMF population. They concluded that the onset of FMF in a late age defines a milder form of disease with typical clinical, demographic and molecular genetic characteristics. Absence of mutation in 39% of the studied chromosomes indicates that a large number of mutations have not been identified yet. It is possible that in late-onset FMF, these unidentified mutations will pre-dispose to a milder disease or else, that the disease results from acquisition of de novo mutations as in somatic mosaicism.

Tamir et al. reported that in patients with disease onset after 40 years of age, the prevalence of arthritis and erysipelas-like erythema was 10 and 15%, respectively, in contrast to patients with earlier onset disease in which the respective prevalence of these manifestations was 78% and 20%, respectively [12].

Sayarlioglu et al. [13] confirmed that arthritis and erysipelas-like erythema were significantly less frequent in patients with adult-onset FMF compared to patients with disease onset before 20 years of age.

Aside from these differences in attack sites, attack severity tends to decrease with age in most FMF patients [14].

These findings were corroborated in a recent study of late onset (>40 years of age) FMF from Armenia [15]. Here, 354 of 10,370 patients, or 3.4% had late onset disease which was characterized by a milder disease phenotype with less frequent fever, skin manifestation, and chest pain compared to individuals with a disease onset before 40 years of age. The late-onset variant was associated with the following genotypes: M680I/E148Q ($P = 0.004$), M694V/E148Q ($P < 0.001$), and V726A/V726A ($P < 0.001$). Of note, 12/354 (3.40%) patients were found to be homozygous for the M694V mutation.

Colchicine is the mainstay of treatment of FMF which aims at preventing acute attacks and minimizing subclinical inflammation in between attacks as well as preventing the progression to amyloidosis.

Colchicine [16] should be started in all patients as soon as a clinical diagnosis is established and continued indefinitely.

Wason et al. [17] compared the relative bioavailability of colchicine after a single 0.6 mg dose in young (18–30 years of age) and elderly (≥60 years of age) healthy subjects to determine whether dosing adjustments are required in elderly patients. The results showed no statistically significant differences in mean colchicine

pharmacokinetic parameters between young and elderly subjects and hence dose modification may be unnecessary in healthy elderly patients.

Interestingly, Leibovitz et al. [18], who evaluated the cognitive status of elderly FMF patients on long-term colchicine treatment concluded that long-term colchicine treatment may confer protection from cognitive decline in patients with FMF. Approximately 5–10% of FMF patients are colchicine non-responders, and 2–5% do not tolerate the drug mainly due to gastrointestinal side effects [19]. These patients are more prone to develop amyloidosis which is the most dreaded complication of FMF. Amyloidosis mainly affects the kidneys, resulting in nephrotic syndrome and renal insufficiency progressing to end stage renal disease [20]. The incidence of amyloidosis increases with age and it is most prevalent in the subgroup of FMF patients who suffer from chronic inflammation with persistently elevated inflammatory markers. Amyloidosis typically manifests in the fourth decade of life in patients with early onset disease, delayed diagnosis, non-compliance with colchicine therapy, M694V homozygosity and comorbid inflammatory diseases such as spondyloarthropathy and inflammatory bowel disease [21]. Patients usually succumb to this complication and hence it is uncommonly found after the seventh decade of life.

Interleukin (IL)-1 inhibition is the preferred second-line therapy in colchicine non-responders however its ability to prevent amyloidosis is yet to be proven.

Shinar et al. [22] reported a unique case of acquired FMF in a 59 years old Ashkenazi Jewish female, diagnosed with Polycythemia Vera (PV) at 52 years.

Four years after PV diagnosis the patient's spleen enlarged dramatically and a bone marrow biopsy confirmed transformation into myelofibrosis. At that time, the patient developed fever bouts, initially reaching 38 °C and lasting 24 h, at 2 months intervals with occasional abdominal pain and muscle aches. Following a negative workup for fever of unknown origin, a diagnosis of FMF was considered and an NM_000243.2:c.1955G > A mutation (rs28940581), in the MEFV gene was found in exon 10 predicting a p.Arg652His substitution in the PRYSPRY domain of pyrin. Daily treatment with 1 mg colchicine abated the fever. The first peripheral blood DNA sample identified a negligible levels of the mutation compared to affected 46% of the MEFV alleles in DNA samples obtained 4 years later. The mutation was in a mosaic pattern, restricted to JAK2-positive, polymorphonuclear cells and CD3-depleted mononunuclear cells - the disease effector cells. Kestner et al. [23] described somatic genetic mosaicism causing autoinflammatory disease.

As opposed to germline mutations, where all cells in the body contain the mutation, in mosaicism a mutation is present only in a certain population of cells.

Mosaicism can be germ-line or somatic, depending if it happened early during embryogenesis or during life, respectively.

Somatic mosaic mutations may occur over time, explaining the possibility of late-onset disease.

23.3 Tumor Necrosis Factor (TNF)-α Receptor-Associated Periodic Syndrome (TRAPS)

TRAPS is an autosomal dominant autoinflammatory condition which is characterized by recurrent febrile attacks typically lasting from 1 to 3 weeks. In addition to fever, its most common clinical manifestations include periorbital edema, conjunctivitis, a migratory erythematous rash simulating erysipelas with underlying myalgia [24]. Serosal membrane inflammation is also prevalent. Abdominal pain may occur due to inflammation of the peritoneal cavity and abdominal wall muscles. Arthralgias are common, and in rare cases, non-erosive arthritis may be present, mainly affecting single large joints.

Febrile attacks recur at varying intervals either spontaneously or after minor triggers, such as local injury, infection, stress, exercise and hormonal changes.

TRAPS is caused by mutations in the gene TNFRSF1A, located on chromosome 12p13, encoding the 55-kD receptor for TNF-α (TNFRSF1A) [25].

To date, more than 70 TNFRSF1A mutations have been associated with TRAPS, the majority of which are localized in the first two N-terminal cysteine-rich domains CRD1 and CRD2.

TNF-α is a type II transmembrane protein produced mainly by monocytes and macrophages but also by other cell types including lymphocytes, natural killer cells (NK) cells, polymorphonuclear leukocytes, keratinocytes and astrocytes. TNF is a major cytokine involved in systemic inflammation known to arbitrate a variety of biological processes including apoptosis, cell proliferation, immune modulation, inflammation, arthritis, autoimmune diseases and other pathological conditions [26].

About 25% of TRAPS patients carrying mutations involving cysteine residues may, over time, develop kidney amyloidosis (versus 2% among low-penetrance mutations carriers), usually manifesting with proteinuria [27].

The average age at disease onset is around 3 years of age but diagnosis in adolescence or adulthood is not uncommon [24]. Indeed, Adult-onset TRAPS is reported in about 22% of a well characterized 158-case cohort from the Eurofever/EUROTRAPS international registry [28]. Similar symptoms are reported in all age groups except for cervical lymphadenopathy and periorbital edema that are more prevalent in children and chest pain that is more often seen in adults [29].

Adult-onset TRAPS patients may present a phenotype that mimics other autoinflammatory disorders such as FMF, even in terms of the duration of inflammatory attacks, which can be short, frequently leading to misdiagnosis and improper management.

Low-penetrance TNFRSF1A variants may contribute to the development of the disease during adulthood [30]. A study which compared age of onset of TRAPS according to mutation status found that patients with a structural mutation had a significantly earlier disease onset and a longer disease duration than patients with recurrent inflammatory attacks carrying a low-penetrance variant and genetically negative individuals, respectively (14.0 years vs. 26.6 and 30.6, respectively, $p = 0.01$) [31].

Low-penetrance TNFRSF1A variants may also cause oligosymptomatic TRAPS and atypical inflammatory responses, including cardiac diseases such as myocarditis and pericarditis as the only clinical manifestation [24]. Overall, symptoms in adult onset disease are generally milder, the episodes are shorter in duration and the risk of amyloidosis is lower [32].

As for previously described for FMF, somatic mosaicism may also explain late onset TRAPS. Just recently a 60 year old male who suffered from daily fever for 3 weeks at time with rash, peritonitis, and lymphadenopathy, was found to carry hematopoietic mosaicism involving different white blood cell populations. A de novo mosaic missense variant, c.265 T > C (p.Phe89Leu), in the *TNFRSF1A* gene was found in the patient's buccal swab, B cells, neutrophils, and NK cells but not in monocytes, T cells, and hair roots [33]. This case highlights the role of somatic mosaicism in adult-onset or atypical phenotypes of autoinflammatory conditions.

TRAPS patients may gain some symptomatic relief from high-dose non-steroidal anti-inflammatory drugs, whilst colchicine or immunomodulators such as methotrexate, cyclosporine and thalidomide produce little benefit. Inflammatory attacks usually respond to corticosteroid administration, but often require increasing doses, especially in patients with frequent relapses or continuous symptoms [34].

Anti-TNF therapy in TRAPS has been based on etanercept, a recombinant human TNFR (p75)-Fc fusion protein comprising two receptors linked by an IgG1 Fc fragment. In contrast, the administration of other anti-TNF agents, such as infliximab, a mouse-human chimeric monoclonal IgG1 antibody to TNF, or adalimumab, a fully humanized anti-TNF monoclonal antibody, may lead to enhanced anti-apoptotic activity, over-secretion of pro-inflammatory cytokines (IL-1, IL-1R, IL-6, IL-8, and IL-12) and paradoxical exacerbation of the TRAPS clinical picture [35, 36].

More recently interleukin 1 (IL-1) inhibition either with anakinra or with canakinumab has shown to induce a prompt and stable disease remission [37]. The experience with IL-6 inhibition is limited to a several patients resistant to etanercept and successfully administered with the humanized anti-IL-6 receptor antibody tocilizumab [38].

From the understanding that the so-called monogenic periodic fevers are the prototype of pure autoinflammatory disorders, our knowledge has now expanded to encompass multifactorial and polygenic diseases among autoinflammatory disorders. Several syndromes belong to a group of acquired autoinflammatory disorders on a potential multifactorial or polygenic basis. Only a minority has been described in the elderly population; Behçet disease, recurrent idiopathic pericarditis, and adult-onset Still's disease.

23.4 Behçet's Disease

Behçet's disease (BD) is a multisystem vasculitis, characterized by recurrent oral and genital ulcers, ocular and skin lesions and positive pathergy test. In addition, arthritis and variable vessel vasculitis, predominately affecting the central system and gastrointestinal tract, may be seen [39, 40].

Most patients initially manifest with recurrent painful oral ulcerations which may range up to 2 cm in size.

The most specific lesion is genital ulceration which afflicts more than three quarters of patients. They are similar in appearance to the oral aphthae and are usually painful [41].

A myriad of cutaneous lesions also occur in over 75% of patients with Behçet's syndrome including pseudofolliculitis, erythema nodosum, superficial thrombophlebitis, pyoderma gangrenosum and more.

Ocular disease is present in 25–75% of patients with Behçet's syndrome with most untreated cases progressing to blindness.

The incidence of panuveitis decreases as age increases, while the incidence of anterior uveitis increases. Ocular involvement is usually bilateral, and there is no correlation between gender and uveitis type. In older ages ocular involvement is mild [42].

Neurologic disease occurs in less than 10% of patients and may be classified as parenchymal or non-parenchymal.

Focal parenchymal lesions and complications of vascular thrombosis are the most common abnormalities.

Symptoms of intestinal Behçet's syndrome include abdominal pain, diarrhea, and bleeding. The association of gastrointestinal BD and myelodysplastic syndrome in the elderly population shall be discussed later on [43].

The pathergy test is quite a specific test for Behçet's syndrome, but its sensitivity has been gradually declining over the past decades from 64.2 to 35.8% [44].

Most clinical manifestations of Behçet's syndrome are believed to be due to vasculitis which is remarkable for involvement of arterial and venous vessels of all sizes. Behçet's disease has high prevalence in countries lying along the ancient Silk Road, a route of travel and commerce, extending from the eastern Mediterranean to East Asia coinciding with the high distribution of *HLA-B5* and *HLA-B∗51* along its route [45]. Turkey demonstrates the highest prevalence of Behçet's disease in the world, with up to 421 per 100,000 persons affected. Iran, Israel, northern China, and Korea follow with the next highest prevalence [46].

The typical onset of the disease is between 20 and 40 years [47] [4], varying from early in life to the age of 70 years [48], but Behçet's disease is still exceptional after the age of 60 years. The severity is generally greater in men.

The pathogenesis of Behçet's disease in not fully understood. Studies indicate that environmental factors may trigger it, in patients with a genetic susceptibility [49]). Other studies have shown the association between *HLA-B∗51* with more than 60% of patients are positive for *HLA-B∗51* [50].

Most cases of Behçet's syndrome are sporadic however families with multiple affected members, have been reported, and having a first-degree relative with Behçet's syndrome does increase risk for the disease [51, 52].

Myelodysplastic syndrome (MDS) is a blood disorder characterized by impaired generation and maturation of hematopoietic cells in the bone marrow, leading to peripheral blood cytopenia. It may also transform into acute leukemia. BD and MDS may be inter-related in that MDS patients have a propensity to develop autoimmune diseases as well as numerous case reports which have shown an association

between trisomy 8 and intestinal BD with MDS. Indeed, trisomy 8 in MDS associated BD has been reported in 87% of the patients compared with 7–9% of patients with primary MDS, but without BD. Trisomy 8 with BD but without MDS has also been reported [53].

Behçet's disease like symptoms can occur concurrently as well as before or after MDS diagnosis and symptoms frequently does not meet the diagnostic criteria.

In a retrospective study of patients with BD and MDS from the Shanghai Behçet's disease database BD was found in 2% (16/805) of patients with MDS. These patients with BD and MDS were more likely to be female and older; display fever and intestinal lesions; have more severe cytopenias and show higher inflammatory markers than patients with BD without MDS (all $P < 0.05$). Trisomy 8 was common (81.3%) in patients with BD-MDS. Ulcers in the ileocecal region were more frequently seen in intestinal patients with BD-MDS than in BD without MDS (90.0% versus 48.9%; $P = 0.032$). The authors concluded that cytogenetic aberrations, especially trisomy 8, may play a role in the pathogenesis of intestinal involvement in patients with BD-MDS [53].

In addition to GI involvement which seems to be an inherent feature of BD associated with MDS, the presence of trisomy 8 seems to modify the disease expression with an increased frequency of fever.

Hanako Koguchi-Yoshioka et al. [54] demonstrated the frequency of symptoms among 31 cases; recurrent oral aphthae and recurrent genital aphthae were found in more than 70% of the cases while ocular lesions were only rarely detected. About 50% exhibited skin lesions, the majority were erythema nodosum or papulopustular lesions. Pathergy test was positive in about 50%. Other clinical manifestations frequently seen in these patients were high fever and gastrointestinal ulcers.

The intestinal involvement can result in perforation. Ileocecal lesions are most common. Histologic findings often indicate chronic active inflammation with or without vasculitis.

First-line treatment for MDS-associated inflammatory and autoimmune diseases is steroids, and response rates as high as 83% have previously been reported [55].

23.5 Adult-Onset Still's Disease

Adult onset Still's disease (AOSD) is an inflammatory disorder characterized by daily attacks of fever, arthritis, and an evanescent rash.

The etiology of AOSD still remains unclear, and viral infections, genetic factors, and immune dysregulation, including cytokine mediated inflammation and dysregulated apoptosis, have all been implicated in the development of this disease [56–60].

Kötter et al. [61] demonstrated high IL-1 and IL-18 in active disease as well as moderately elevated levels of TNF- α and IL-6, which fell significantly following treatment with the IL-1 receptor (IL-1R) inhibitor.

The prevalence of AOSD is estimated to be 0.16 cases per 100,000 people, with an equal distribution between the sexes [62]. There is a bimodal age distribution, with one peak between the second-third decade of life and another peak between the 4th–fifth decades. There are several case reports describing elderly onset.

The usual clinical manifestations include spiking fevers, polyarthritis or arthralgias, evanescent rash, and sore throat or pharyngitis [63].

Other features include generalized lymphadenopathy, myalgia, hepatosplenomegaly and cardiopulmonary involvement.

Laboratory findings include leukocytosis, neutrophilia and elevated inflammatory markers in association with negative antinuclear antibody (ANA) and rheumatoid factor (RF) [64]. Liver dysfunction has been found to be more common in AOSD than in other inflammatory diseases [65].

The clinical course can be divided into three main types, each carrying a different prognosis: (1) self-limited or monophasic; (2) intermittent or polycyclic systemic; and (3) chronic articular.

Self-limiting or monophasic type is characterized by a single episode of systemic symptoms such as fever, rash, serositis and organomegaly. Complete remission is achieved within 2–4 weeks in 19–44% of cases. The intermittent or polycyclic systemic type seen in 10–41% of cases and is marked by recurrent disease flares with or without articular symptomatology interspersed with complete remissions. These flares are separated by periods of remission lasting from 2 weeks to 2 years. Chronic articular type seen in 35–67% of cases and is characterized by persistent active disease, frequently mimicking other, more common, chronic inflammatory arthritides such as rheumatoid arthritis with a polyarticular symmetric pattern. These patients can also present with an oligoarticular pattern which has a more favorable prognosis [66].

Severe and even life-threatening complications, such as macrophage activation syndrome with a reported mortality rate ranging between 10 and 22% has been described. .

Steroids form the first-line treatment in AOSD, especially during the acute phase in order to ameliorate the systemic manifestations.

Case reports and case series have described a rapid disease response after initiation of IL-1 inhibition with anakinra, an IL-1 receptor antagonist, with resolution of fever and rash as well as normalization of the hematologic and biochemical parameters. Successful treatment of AOSD with canakinumab, a monoclonal antibody against IL-1β has been reported even in patients refractory to anakinra.

Tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, has proven successful in ameliorating signs of inflammatory arthritis in patients with AOSD.

Several case reports of elderly onset Still's disease have been published; Overall, onset in older people is very rare and has been described only occasionally in Japan, Europe and the United States [67–70]. Patients of Asian origin tend to be older for reasons that are not clear, and more than half of the reported cases in individuals older than 70 years of age are Japanese.

A diagnosis of AOSD should be suspected in the elderly population when presenting with fever of unknown origin in association with a rash.

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Chapter 24
Rheumatic Syndromes Related to Malignant Diseases

David Joshua Ozeri and Merav Lidar

24.1 Introduction

The burden of rheumatic diseases and malignancy has increased in parallel to the aging of the world population over the past century, as both conditions are more prevalent in the elderly. The increased co-occurrence of the two conditions is not only a matter of chance as patients with rheumatic diseases have an increased risk of malignancy independent of age. There are many shared features of rheumatic diseases and malignancies suggesting shared pathophysiology. For example, in inflammatory arthritis synovitis is propagated through increased angiogenesis promoted by increased expression of VEGF. The serum VEGF concentration is correlated with the ESR, serum CRP concentration, serum rheumatoid factor, number of tender and swollen joints, Modified Health Assessment Questionnaire, and patient and physician global assessments of disease activity in RA patients [1]. In colorectal cancer angiogenesis again plays an important role in disease severity and spread. In one study VEGF expression significantly correlated with advanced stage, unfavorable survival, and an increase in the rate of invasion and distant metastases [2]. Furthermore, malignancies may manifest with rheumatic symptomatology such as constitutional symptoms and arthritis. Therefore, recognizing these masquerading patterns is vital for the timely diagnosis of cancer. When a malignancy initially presents with rheumatic symptoms it is termed a rheumatic disease mimic (RDM).

D. J. Ozeri
Department of Medicine A, Sheba Medical Center, Ramat Gan, Israel

Rheumatology Unit, Autoimmune Disease Center, Sheba Medical Center, Ramat Gan, Israel

M. Lidar (✉)
Rheumatology Unit, Autoimmune Disease Center, Sheba Medical Center, Ramat Gan, Israel

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
e-mail: Merav.Lidar@sheba.health.gov.il

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Examples of this are solid tumor metastases and presentations of lymphoproliferative and myeloproliferative diseases. In addition, there are rheumatic paraneoplastic diseases that are associated with occult malignancies, again suggesting a shared pathophysiology. The twenty-first century has provided cancer patients with revolutionary treatment options, the newest of which are the immune checkpoint inhibitors. While these treatments have improved longevity and quality of life in many patients with malignancy, rheumatic side effects of treatments are frequently recognized. Finally, certain autoimmune diseases and treatments are associated with an increased risk of malignancy such as Sjogren's syndrome and lymphoma.

24.2 Rheumatic Disease Mimics

Both solid tumors and hematologic malignancies may mimic rheumatic diseases. Solid tumors: Primary musculoskeletal tumors present with pain, stiffness and an effusion in area of lesion. The most common primary musculoskeletal tumor is osteosarcoma. It is associated with Paget's disease and radiation therapy. It most commonly affects the femur, humerus, skull and pelvis.

Solid tumor metastases: Metastatic cancer usually spares muscle, joints and adjacent connective tissue and most commonly infiltrates bone. The bones that are most susceptible to metastasis are the spine and the pelvis. The primary tumors that are generally associated with bone metastases are cancers of the prostate, lung, breast, kidney and thyroid [3]. Most skeletal metastases are asymptomatic. However, when pain is present it is typically constant and increases in intensity at night. Metastases distal to the elbow and knee are very rare. Metastases can sometimes infiltrate a joint in which case they are usually mono-articular and typically involve the knee. Bone and joint metastases can be confused with several rheumatic diseases. For example metastases to spine can be confused with lumbago or sacroiliitis. When metastases infiltrate joints they can be confused crystal arthropathy or tenosynovitis.

Hematologic diseases can mimic rheumatic syndromes as well. These diseases are often life-threatening and vigilance should be taken to avoid confusing these diagnoses with a primary rheumatic syndrome.

1. **Multiple Myeloma:** multiple myeloma can be associated with musculoskeletal complaints. Patients may present with low back pain, carpal tunnel syndrome, destructive arthritis, and a scleroderma-like rash, all with an elevated ESR. Therefore, a high index of suspicion should be retained in patients with an elevated ESR and non-specific rheumatic manifestations.
2. **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes** (POEMS) is a syndrome associated with monoclonal gammopathy. In addition to neuropathy, there is radiologic evidence of osteosclerosis. The combination of neuropathy and skin changes can sometimes be confused with an autoimmune rheumatic syndrome. However, this condition is associated with

Castleman's syndrome, an inflammatory lymphoproliferative disease that leads to lymphoma [4].

3. **Hairy Cell Leukemia:** A chronic B-Cell lymphoproliferative disease affecting adults which manifests with arthritis, splenomegaly and pancytopenia. The identification of hairy cells in the synovial fluid confirms the diagnosis [5].
4. **Angioimmunoblastic T-Cell Lymphoma:** A lymphoproliferative disease presenting with constitutional symptoms, lymphadenopathy, splenomegaly and a maculopapular rash. Occasionally symptoms include seronegative peripheral symmetric inflammatory arthritis that mimics rheumatoid arthritis [6].

24.3 Rheumatic Paraneoplastic Disease

Rheumatic diseases are deemed paraneoplastic when associated with a malignancy, of which they can well be the initial manifestation. In general, rheumatic paraneoplastic disease (RPD) improves after treating the underlying malignancy. An atypical presentation of a rheumatic disease and failure to respond to glucocorticoids should urge ruling out an underlying malignancy. The entity of a rheumatic paraneoplastic disease implies an overlapping pathophysiology of the rheumatic disease and the malignancy. Several growth factors have been implicated in both neoplastic disease and connective tissue diseases such as fibroblast growth factor-23, connective tissue growth factor, and vascular endothelial growth factor. The importance of recognizing RPD is critical to facilitating a timely diagnosis and potential cure of a malignant disease.

Carcinomatous Polyarthritis is an inflammatory arthritis that develops with malignancy. It usually occurs in older patients and tends to progress rapidly. It can mimic RA or a migratory polyarthritis. While it is most closely associated with breast and ovarian cancer, it has been reported with virtually all types of cancers. Carcinomatous Polyarthritis improves with treatment of the underlying malignancy [7].

Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE) is a rare condition. It generally affects elderly patients and is strongly associated with an underlying malignancy. It is characterized by synovitis of hands and is associated with adenocarcinomas, lymphomas and myelodysplastic syndrome [8].

Erythromelalgia is a condition affecting the distal extremities (feet and hands). It is characterized by episodic intense burning pain, erythema, and local warmth. It is associated with several myeloproliferative disorders such as essential thrombocytosis and polycythemia vera [9].

Palmar Fasciitis and Inflammatory Arthritis is characterized by bilateral contractures of the fingers, with fibrosis of the palmar fascia, and polyarthritis of the hands. Palmar erythema has a strong association to underlying malignancy, most often breast, ovarian pancreatic and gastric tumors [10].

Raynaud's Phenomenon is the development of transient acrocyanosis. While raynaud's phenomenon is most strongly associated with autoimmune inflammatory

syndromes, it has an association with underlying malignancy as well. Specifically when acrocyanosis starts at an older age and is associated with digital necrosis – an underlying malignancy should be suspected [11].

Multicentric Reticulohistiocytosis is a rare disease characterized by red to purple fleshy skin papules and nodules. It is also associated with severe inflammatory arthritis that leads to deformity and arthritis mutilans. In 25% of cases an underlying malignancy is discovered [12].

Hypertrophic Osteoarthropathy *(HOA)* is a condition characterized by proliferation of skin and bone in the distal extremities. This leads to arthritis, periostitis and clubbing of fingers and toes. HOA is strongly associated with lung cancer [13].

Panniculitis is characterized by inflammation of subcutaneous adipose tissue. While rare, it is more common in females and is associated with hematologic malignancies and pancreatic cancer. It is difficult to differentiate paraneoplastic panniculitis from erythema nodosum, however, paraneoplastic panniculitis is associated with poor response to conventional therapy [14].

Atypical Polymyalgia Rheumatica is a form of polymyalgia rheumatica (PMR) that is associated with malignancy [15]. PMR is characterized by stiffness and pain in the shoulder and hip girdles in the elderly. It is usually accompanied by an elevated ESR and responds to prednisone. However, atypical features such as young age of onset, asymmetry, lack of ESR elevation and lack of response to prednisone suggest a paraneoplastic phenomenon.

Cryoglobulinemia is the presence in the serum of immunoglobulins that precipitate at reduced temperatures. They are categorized into three types; type I, II, and III. Type I cryoglobulinemia is associated with a monoclonal protein (IgM and IgG) and is usually associated with myeloma, Waldenstrom's macroglobulinemia, and other lymphoproliferative diseases. Patients with cryoglobulinemic vasculitis present with fatigue, purpura, neuropathy and renal failure. Treating the underlying malignancy is essential to controlling the cryoglobulinemia [16].

Vasculitis can be triggered by an underlying malignancy. It is most commonly associated with lymphoproliferative disease.

Giant cell arteritis and polymyalgia rheumatica represent large vessel vasculitides in the elderly. Classically manifesting with constitutional symptoms, headache, shoulder and hip girdle pain, jaw claudication and occasionally vision symptoms such as amaurosis fugax. However, there are times when constitutional symptoms such as fever, weight loss, night sweats and fatigue predominate, and the symptoms are difficult to differentiate from typical B symptoms associated with hematologic malignancies. There is conflicting evidence however regarding the association of giant cell arteritis and underlying malignancy [2].

Leukocytoclastic vasculitis (LCV) is nonspecific small vessel vasculitis characterized by palpable purpura. This condition has been associated with infection, autoimmune disease and underlying malignancy. In patients with a history of neoplastic disease the development of LCV can signify recurrence of the malignancy [17].

Inflammatory Myopathy is a rare disease characterized by proximal muscle weakness and elevated muscle enzymes. Dermatomyositis and polymyositis

specifically are strongly linked to an underlying malignancy. Some studies suggest that up to 30% of patients diagnosed with dermatomyositis will have a malignancy discovered within 1 year of myositis diagnosis. The most common malignancies associated with DM are ovarian, lung, pancreatic, bladder, gastric, colorectal tumors and non-Hodgkin's lymphoma. Studies suggest that myositis specific antibodies such as anti-JO1 decrease risk of underlying malignancy. However, there have been several recent antibodies described that are correlated with myositis and underlying malignancies. Anti-NXP2, and anti-p155/140 are serologies that are strongly linked to underlying malignancy in myositis and are becoming more readily available [18, 19].

Clinically amyopathic dermatomyositis (CADM) describes a condition with the cutaneous manifestations of dermatomyositis (photosensitivity, raynauds, gottron's papules, and heliotrope rash) without myositis. However, many patients with amyopathic dermatomyositis suffer from a fierce form of interstitial lung disease that is many times fatal. CADM patients have antibodies for anti-melanoma differentiation-associated protein 5 (anti-MDA-5). CADM in addition to the aforementioned inflammatory myopathies has been linked to occult malignancy.

There is still no consensus on screening for malignancy in patients with newly diagnosed inflammatory myopathy. Currently age and gender appropriate malignancy screening should be performed. In addition, a careful history and physical examination should be completed. Other tests such as tumor markers and FDG PET/CT are controversial but may play a role in the diagnosis of inflammatory myopathy. FDG PET/CT remains an attractive modality due to its ability to provide information regarding the diagnosis of inflammatory myopathy, interstitial lung disease, and occult malignancies [20].

24.4 Treatment Associated Rheumatic Syndromes

Post-Chemotherapy Rheumatism is a noninflammatory, migratory, self-limited arthropathy. It usually has a temporal relationship to chemotherapy and is associated with pain and morning stiffness. Usually arthralgia affect hands, knees and ankles and resolves within 1 year of cessation of treatment. The treatments that have been more commonly implicated in this entity include cyclophosphamide, 5-fluorouracil, and cisplatin.

Hormone directed therapies such as aromatase inhibitors and anti-androgen therapies are frequently used as adjuvant therapies for breast and prostate cancers. Joint pain and morning stiffness is reported in 50% of aromatase inhibitor recipients, though the majority of patients only have mild symptoms [21]. Furthermore, patients receiving aromatase inhibitors and anti-androgen adjuvant treatment have a decrease in bone mineral density and increased risk of osteoporosis and subsequent fracture risk.

Bacillus Calmette-Guerin (BCG) is an intravesical injection used to treat localized bladder cancer. Aseptic arthritis develops in up to 5% of patients receiving

BCG. Some patients develop reactive arthritis with sacroiliitis, dactylitis and ocular inflammation. Symptoms typically remit with cessation of BCG injections [22].

Immune Checkpoint Inhibitors (ICI) are novel agents used to treat a growing number of cancers. ICIs block negative co-stimulation of T-lymphocytes leading to enhanced anti-tumor response. The general targets of ICIs are programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte associated protein-4 (CTLA-4). Nivolumab, atezolizumab, and pembrolizumab target PD-1 while ipilimumab targets CTLA-4. In metastatic melanoma the combination of the ICIs nivolumab and ipilimumab improved efficacy and survival. However, stimulating T-cells especially in combination can cause an undesired immune response with serious consequences.

ICIs have been associated with a wide range of rheumatic syndromes. When ICIs cause a rheumatic syndrome it is termed an immune-related adverse events (irAEs). Arthralgia is the most common form of irAE reported in up to 43% of patients receiving an ICI. Myalgia is also quite common reported in up to 21% of patients receiving ICI. Other more rare irAEs are inflammatory arthritis, PMR-like syndrome, and sicca symptoms. Generally, symptoms are controlled with steroids and disease modifying anti-rheumatic drugs and ICI therapy in continued. Sometimes however, irAEs are more severe and can lead to life threatening organ damage. ICIs rarely can manifest as severe colitis, autoimmune hepatitis, inflammatory myopathy, glomerulonephritis and systemic vasculitis. When symptoms are more severe ICI treatment is discontinued and higher doses of steroids with a combination of tumor necrosis factor inhibitors or mycophenolate mofetil, are frequently administered. In general symptoms subside with the cessation of immunotherapy [23]. Early recognition of organ damage due to irAE is crucial to avoiding serious adverse events associated with therapy.

24.5 Risk of Malignancy in Rheumatic Disease

Epidemiologic studies suggest that malignancies are more common in patients with autoimmune diseases. The increase in malignancies is believed to be partially due to chronic immune hyperactivity leading to malignant transformation. In addition, many of the medications used to treat autoimmune diseases have oncogenic properties. The increased risk of developing malignancies in patients with chronic autoimmune diseases requires vigilance, age appropriate cancer screening, and reduction of carcinogenic behaviours such as smoking.

Systemic Lupus Erythematosus (SLE) is a prototypic heterogenous autoimmune disease with a predilection for women. Large multicentered registries have demonstrated an increased risk of malignancies in patients with (SLE), particularly, non-Hodgkin's lymphoma, cervical cancer and lung cancer [24]. Data suggests that patients with SLE are less likely to receive recommended cancer screening despite increased risk. This is possibly due to the complex nature of SLE and the difficulty of screening patients with other chronic illnesses for malignancy.

Scleroderma is a systemic condition characterized by skin fibrosis, and raynaud phenomenon that can be complicated by end-organ involvement such as interstitial lung disease and pulmonary hypertension. Scleroderma patients have an increased risk of being diagnosed with neoplastic disease [25]. One study found that 13% of deaths in scleroderma were caused by cancer. The organs that develop cancer are usually the same organs affected by scleroderma; skin, lung, breast, and esophagus.

Rheumatoid Arthritis is strongly associated with increased risk of the development of a lymphoproliferative disorder [26]. Some studies suggest that the risk of lymphoproliferative disease is correlated with the degree of inflammation [27]. The most common lymphoproliferative disorder associated with RA is diffuse large B cell lymphoma. Large granular lymphocyte (LGL) syndrome is considered a rare complication of rheumatoid arthritis characterized by bone marrow infiltration, splenomegaly, neutropenia and anemia.

Sjogren's syndrome is an autoimmune exocrinopathy leading to sicca syndrome. One study showed a 44-fold increase in the development of non-Hodgkin's lymphoma in patients with sjogren's syndrome [28]. The development of lymphoma is considered a late manifestation of sjogren's syndrome with most cases occurring more than 5 years after the diagnosis of Sjogren's syndrome. The most common lymphoproliferative disorders associated with sjogren's are diffuse large B cell, mucosa-associated lymphoid tissue lymphoma, and other marginal zone lymphomas.

24.6 Immunosuppression and Malignancy

The immune system plays a role in tumor surveillance, with an increasing body of evidence suggesting that the immune system can eliminate pre-clinical cancers. Furthermore, the immune system can be artificially stimulated with immune checkpoint inhibitors to fight cancers. It stands to reason that treating patients with immunosuppressive therapies will increase the risk of cancer. However, studies aimed to show the link between specific immunosuppressive therapies and cancer have been unsuccessful for several reasons. Firstly, chronic inflammatory diseases inherently increase the risk of malignancy. Secondly, patients with malignancies were excluded from clinical trials. Finally, malignancy is a relatively rare outcome making most studies too small to prove increased risk of malignancy.

Disease modifying anti-rheumatic drugs (DMARDs) are medications often used to manage autoimmune diseases. They include methotrexate, azathioprine and leflunomide. They have a variety of mechanisms that usually result in immunosuppression. Several studies based on rheumatoid arthritis registries have demonstrated that DMARD therapy in patients suffering from RA did not increase the incidence or prevalence of cancer.

Tumor Necrosis Factor inhibitors (TNFi) are biologic therapies used to treat several chronic autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease. The research available regarding malignancy risk after TNFi exposure is mainly derived from rheumatoid arthritis registries. There are early studies

that suggested an increased risk of lymphoma and skin cancer, however, the majority of observational studies did not confirm these findings. Most evidence suggests that there is no increased risk of malignancy with TNFi use aside from non-melanoma skin cancer. A meta analysis published in 2011 pooled patients with RA that were DMARD naive and received TNFi. The study included over 3400 patients and showed no increased risk of malignancy [29]. Patients with prior malignancy were excluded from all of the TNFi randomized trial. Therefore, TNFi should be used cautiously in patients with prior malignancy.

Biologics other than TNFi have less data regarding risk of developing malignancy. A meta-analysis published in 2012 that included over 29,000 patients that had been treated with TNFi, rituximab, abatacept, tocilizumab and anakinra did not show an increased risk of malignancy. Albeit, patients with prior malignancy were excluded from randomized control studies. Therefore, most biologics should be avoided in patients with prior malignancy. With the exception of using rituximab in a patient with a history of lymphoma.

Given the lack of data regarding immunosuppression and cancer risk, treatment should be individualized to the patient. It is necessary to have close communication between the rheumatologist, oncologist, and patient in order to find the best treatment option. Patients should be informed comprehensively regarding the risk benefit of receiving immunosuppression and be willing to accept residual uncertainty in order to receive effective treatment.

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Part III
Approach to a Geriatric Patient with Rheumatic Disease

Chapter 25
Approach to a Geriatric Patient with Monoarthritis

Shiri Keret and Gleb Slobodin

Monoarthritis can be a symptom of many rheumatic and infectious diseases involving a single joint or be the initial presentation of polyarticular disease. Crystal-related and septic arthritis are the most frequent etiologies in the extensive list of possible causes of monoarticular arthritis, some of which are particularly prevalent in the elderly population (Table 25.1) [1]. Since the delay in diagnosis and treatment of a patient with monoarthritis can sometimes result in grave consequences, such as permanent joint damage, disability or sepsis, the timely diagnosis and treatment are of utmost importance [2]. Still, in a substantial proportion of patients with monoarthritis, the exact diagnosis can remain obscure even after extensive investigation [1].

Table 25.1 Causes of monoarticular disease in elderly

The most prevalent	Occasionally seen	Rare
Crystal induced arthritis	Psoriatic arthritis and other spondyloarthropathies	Bone and synovial malignancies
Septic arthritis	Rheumatoid arthritis	Pigmented villonodular synovitis
Osteoarthritis	Infectious non-septic arthritis	Amyloidosis
Trauma and mechanical derangement	Pseudoseptic arthritis	Vasculitidies
	Hemarthrosis	Foreign-body synovitis
	Avascular necrosis	

S. Keret
Internal Medicine, Rambam Health Care Campus, Haifa, Israel

G. Slobodin (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel
e-mail: gleb.slobodin@b-zion.org.il

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25.1 Initial Evaluation

The thorough history-taking and physical examination are still the first and indispensable tools for the timely diagnosis of monoarthritis. The most important first questions to be answered are the rapidity of onset of the current monoarticular disease and the presence of the previous similar episodes, preceding or concomitant complaints, and the patient's background. Sudden onset of the monoarticular disease is more typical for crystal related arthritis, septic joint, avascular necrosis, hemarthrosis, or trauma-related condition. Psoriatic or rheumatoid monoarthritis, as well as reactive arthritis usually develop within days or weeks, while osteoarthritis, pigmented villonodular synovitis, amyloidosis typically have a more indolent course. Previous episodes of monoarthritis in the same or different joints are emblematic for crystal related arthritis. Patients with prior septic arthritis, avascular necrosis, or hemarthrosis may be at higher risk for recurrent disease. Concomitant fever will robustly support the possibility of septic arthritis, while chronic anticoagulation treatment can be a clue to a straightforward diagnosis of hemarthrosis. Immunosuppression or recent travel to the endemic areas should raise suspicion for the infectious, mycobacterial, or fungal disease. The monoarthritis of the prosthetic joint is always suspicious for septic arthritis, but flares of crystal-induced arthritis after total joint replacement have been reported as well [3, 4]. In general, comprehensive history is beneficial in the narrowing the differential diagnosis in the majority of patients with monoarticular disease, but the exclusion of a specific cause of monoarthritis, based only on the absence of emblematic anamnestic data, such as fever in septic arthritis, can be unwise particularly in aged persons, as some rheumatic conditions have diverse and atypical presentations in this specific cohort and, on the other hand, elderly people may have memory disorders, preventing physician from getting access to full anamnestic data.

Proper physical examination is mandatory before further workup. Sometimes, the finding of clinical signs of polyarticular or systemic disease will completely change the differential diagnosis, and the whole approach to a patient as, for example, the presence of unmentioned by a patient typical rash or dactylitis can lead directly to the diagnosis of psoriatic arthropathy. Secondly, the joint disease should be differentiated from bursitis, tendonitis, ganglion, referred pain or another non-articular disorder. Finally, arthritis or inflammatory joint disease should be separated from non-inflammatory articular conditions, such as avascular necrosis or mechanical joint derangement. In this regard, clinical signs of synovitis, including warmth, erythema, and joint swelling and effusion should not be missed.

Bedside ultrasonography (US) of the affected joint is very useful in the diagnosis of synovitis with or without effusion and can readily differentiate articular from soft tissue rheumatic conditions and, thus, should be a regular part of an initial probe of a patient with the monoarticular disease. Moreover, the US can accurately diagnose gout or calcium pyrophosphate deposition disease by revealing crystals within the articular cartilage [5]. However, the US can not exclude septic arthritis, which happens as well in patients with the crystal-induced disease, and thus can not replace aspiration of joint fluid when the latter indicated.

Conventional radiography can demonstrate a suspected fracture, chondrocalcinosis, changes typical of osteoarthritis or rheumatoid arthritis or tumor. However,

joint damage secondary to arthritis can take weeks or recurrent arthritis episodes to appear on X-ray, e.g., bone erosions. Hence, radiography cannot be used for the exclusion of the diagnosis. Magnetic resonance imaging (MRI) is a method of choice for the diagnosis of avascular necrosis, mechanical intraarticular derangement, pigmented villonodular synovitis, and malignancies [6]. On the other hand, the yield of MRI in the etiological diagnosis of an inflammatory articular disease is low. Therefore, the relevant imaging modality should be carefully chosen for confirmation of clinically suspected diagnosis and not performed without a specific question because of differential sensitivity and specificity of each particular imaging tool for different conditions and also because of frequently seen in geriatric population incidental and unrelated to current problem findings [7].

Laboratory tests that can promote the evaluation process include first of all markers of inflammation. Blood white cell (WBC) count can be mildly elevated in the frame of any acute arthritis, but the significant elevation is more typical for septic arthritis. C-reactive protein and erythrocyte sedimentation rate feature acute inflammation as well but may still be normal or near-normal in the first hours of even significant inflammatory process. Uric acid, typically high in a patient with gout, can decline and yet be within the normal range during the acute gouty attack. Abnormal levels of calcium, phosphorus, magnesium can be seen in patients with calcium pyrophosphate deposition disease (CPPD). Coagulation tests and the platelet count can show abnormalities in patients with hemarthrosis. Serologies for infectious diseases, such as Lyme disease, brucellosis, Q-fever should be examined when appropriate. Immunologic tests such as antinuclear antibodies (ANA) and rheumatoid factor (RF) should be performed only to confirm clinical suspicion since they are not specific.

25.2 Joint Aspiration

Arthrocentesis is essential in the majority of patients with the monoarticular disease when there are signs of synovitis and effusion [8]. The primary goal of diagnostic joint aspiration in this setting is to exclude septic arthritis, and it should be carried out promptly to prevent permanent joint damage or septic state. The absence of high fever or typical for septic joint extreme tenderness on the motion should not avert the decision to tap the joint, particularly in the elderly population, where many disease features can be obscure. It should be remembered that a patient with known gout, for example, can have septic arthritis as well, and patients with established systemic rheumatic disease, such as RA have even increased rates of septic arthritis. Hence, a patient with otherwise controlled RA but a sudden monoarthritis with effusion should be assessed for the presence of septic arthritis, particularly if immunocompromised secondary to the anti-rheumatic treatment. In general, the decision not to perform diagnostic arthrocentesis is one of the most common pitfalls in the management of a patient with monoarthritis and effusion. Bedside US can be used for confirmation of effusion and arthrocentesis navigation in unclear and difficult cases [9]. Anti-platelet and anticoagulation treatments are not generally considered contra-indication nor cause to postpone the arthrocentesis if septic arthritis is suspected [10].

The role of synovial fluid aspiration is not limited just for exclusion or confirmation of septic arthritis but also is crucial for the diagnosis of crystal-induced articular disease, hemarthrosis or differentiation of inflammatory joint effusion from the non-inflammatory fluid. Arthrocentesis is used as well for therapeutic purposes, such as drainage of accumulating fluid from the inflamed joint or pharmacological intraarticular injections.

After arthrocentesis, the synovial fluid should always be assessed macroscopically and sent to the relevant studies. The gross appearance is essential. The non-inflammatory synovial fluid is transparent and viscose, usually contains less than 2000 WBC/mm^3 (e.g., osteoarthritis, meniscal tear). Inflammatory effusion is opaque or cloudy, it loses its viscosity, and its WBC count is usually over 2000/mm^3, being typically up to 15,000 in RA or SpA, 20,000–50,000 in gout and over 50,000 in septic arthritis. However, these numbers are approximate only, and exclusions are frequently seen. As such, septic arthritis can have a WBC count of less the 25,000/mm^3, particularly in the early stage and, on the other hand, pseudoseptic arthritis in the course of RA or acute gouty arthritis can be featured by more than 50,000 WBC/mm^3. Hemorrhagic effusion correlates with trauma, coagulopathy, or anticoagulant treatment, pigmented villonodular synovitis, and can be seen in patients with CPPD as well.

The examination of synovial fluid for crystals has its peculiarities. Classically, monosodium urate crystals of gout have needle-like shape and strong negative birefringence, while CPPD crystals are small, polymorphic, and weakly positive under birefringent microscopy. Of importance, the fluid should be examined for crystals as soon as possible after the aspiration. Leaving the synovial fluid for hours can lead to the dissolution of crystals and result in a pseudo-negative study. Secondly, the intra- or extracellular location of the crystals should always be noted. An acute attack of gout, for example, is featured by the presence of intracellular crystals of monosodium urate, while extracellular crystals can be found in the synovial fluid also beyond the acute attack and can as well be seen in a patient with septic arthritis and background of gout. Thirdly, staining with alizarin red should be performed, if possible, for better recognition of basic calcium crystals, which are usually missed during the standard examination [11].

In summary, the aspirated joint fluid should be evaluated for WBC count and differential, gram stain, cultures, and presence of crystals. Additional studies, such as panbacterial, mycobacterial, fungal PCR can be considered in relevant cases.

25.3 Monoarthritis of Unknown Origin and Pitfalls in the Diagnosis

The composite of careful history, physical examination, relevant imaging, and laboratory diagnostics will generally result in the precise diagnosis of the monoarticular disease (Table 25.2). However, the etiology of monoarthritis can remain obscure even after the extensive evaluation and arthrocentesis [12]. The management of such

Table 25.2 Typical diagnostic features of some disorders, presenting as a monoarticular disease in elderly

Disease	Anamnesis	Physical examination	Imaging	Articular fluid
Gout	Recurrent acute episodes of arthritis, peaking within 24 h. Family history. Hyperuricemia	Predilection for the first metatarsophalangeal joints, ankles, midfoot and knees. Redness over the affected joint, sometimes extensive swelling of soft tissues and extreme tenderness on palpation and movement. Tophi (subcutaneous nodules) deposition in soft tissues.	US – double contour sign overlying the articular cartilage. Radiography - erosions with sclerotic margins in long-standing disease.	Cloudy fluid with WBC count up to 50,000/mm^3, monosodium urate needle-shaped intracellular crystals.
Pseudogout (CPPD)	Recurrent acute episodes of arthritis. Possible history of renal stones or disorders of calcium metabolism.	Predilection for the knees, wrists.	US – intraarticular deposition of calcium crystals. Radiography – chondrocalcinosis.	Cloudy, sometimes hemorrhagic fluid with WBC count of 5000-50,000/mm^3, calcium pyrophosphate rhomboidal intracellular crystals.
Septic arthritis	Acute onset with fever. History of chronic articular disease, *i.e.*, rheumatoid arthritis, joint surgery, prosthetic joint. Immunosuppression	Any joint can be involved, predilection for large joints. Extreme pain, redness, erythema, and swelling over a joint. Joint effusion.	Not diagnostic nor exclusive	Cloudy, turbid or hemorrhagic fluid, WBC count over 50,000/mm^3. Positive gram stain, culture, PCR.
Osteoarthritis	Progressive pain exacerbating with physical activity and relieved by rest. Possible short morning stiffness.	Predilection for the knees, hips, first carpometacarpal, and proximal and distal interphalangeal joints. Possible swelling and deformity. With or without joint effusion.	Radiography - joint space narrowing, subchondral sclerosis, marginal osteophytes. US – thinned cartilage, possible effusion.	Transparent, WBC count less than 2000/mm^3.

(continued)

Table 25.2 (continued)

Disease	Anamnesis	Physical examination	Imaging	Articular fluid
Hemarthrosis	Sudden appearance of articular pain, stiffness. History of anticoagulation therapy, coagulation disorder, trauma.	Tenderness, reduced range of motion, swelling, and warmth of the affected joint.	US- joint effusion with or without internal echoes. Radiography – tense effusion with the displacement of normal structures	Hemorrhagic, red, pink or brown non-clotting fluid, with high RBC count.
Psoriatic arthritis	Usually, the subacute onset of joint pain and swelling. Personal or family history of psoriasis.	Any joint can be involved. Swelling and redness over the joint and articular effusion are usual. Enthesitis, tenosynovitis, and dactylitis are typical findings. Psoriatic skin plaques and nail changes.	Radiography can show only soft tissue swelling in the early disease stage. US - synovitis, enthesitis.	Inflammatory WBC count with more than 2000 cells/mm^3
Avascular necrosis	Acute onset of intractable articular pain, exacerbating on movement. History of glucocorticoid excess, alcohol abuse, chronic renal failure, diabetes mellitus, systemic lupus erythematosus.	Predilection for large joints. No joint swelling or significant effusion.	Radiography is usually normal in the early disease stage. MRI is the diagnostic imaging of choice. Bone scintigraphy can be utilized if MRI is unavailable.	Is not diagnostic

cases should be based on an individual approach and usually requires additional imaging studies, recurrent diagnostic arthrocentesis, or synovial biopsy. Nevertheless, the most common cause of failure to diagnose monoarthritis accurately is an erroneous decision to avoid diagnostic arthrocentesis in various situations, such as in a patient with possible septic arthritis due to the absence of high fever or extreme pain or because of anticoagulation treatment, in a patient with established RA or well-controlled gout or CPPD and additive septic arthritis, or in a patient with the suspected first attack of gout due to typical localization of arthritis or presence of hyperuricemia, while none of those is a direct proof of articular gout [13]. The flawed physical examination and wrong choice of diagnostic imaging are two other significant factors leading to the delay in the diagnosis of monoarticular disease in daily practice.

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Chapter 26
Approach to a Geriatric Patient with Pauciarticular and Polyarticular Rheumatic Disease

Gleb Slobodin

The process of diagnosis in a geriatric patient with pauciarticular or poly-articular rheumatic disease is frequently both a challenge and an act of artistic creation for a rheumatologist who, in the absence of a single decisive test for the majority of rheumatic conditions, collects a puzzle of final diagnosis using multiple details, obtained from patient's history, physical examination and critical analysis of laboratory data and imaging. Rheumatic disorders in the elderly can be classified by the disease prevalence, etiology, pattern of joint involvement, inflammatory versus degenerative nature, or systemic involvement. However, not uncommonly an older person presents with clinical, laboratory, and imaging features typical of two or even more unrelated articular diseases simultaneously (Fig. 26.1). The diagnostic process can also be complicated by a fact that some conditions, such as RA or septic arthritis can have atypical presentations in this specific cohort or, sometimes, two distinct disorders, as osteoarthritis (OA) and psoriatic arthritis (PsA) for example, can have substantially similar clinical appearance and imaging features in particular joints [1]. This diversity of possible combinations and presentations of rheumatic disorders in the elderly leads oftentimes to the diagnostic conundrum, where the success to diagnose the disease timely depends on both the critical analysis of clinical features, such as disease chronology or patterns of joint involvement, as well as the deliberated interpretation of the laboratory and imaging data. It should be particularly emphasized that physical examination coupled with discriminative thinking is still the method of choice for the diagnosing of peripheral arthritis with imaging studies mostly used for confirmation or further characterization of clinical findings [2]. This chapter discusses the diagnostic significance of various disease manifestations in a spectrum of situations, characterized by pauciarticular or polyarticular presentations in the elderly, commonly seen in rheumatology practice (Table 26.1).

G. Slobodin (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel
e-mail: gleb.slobodin@b-zion.org.il

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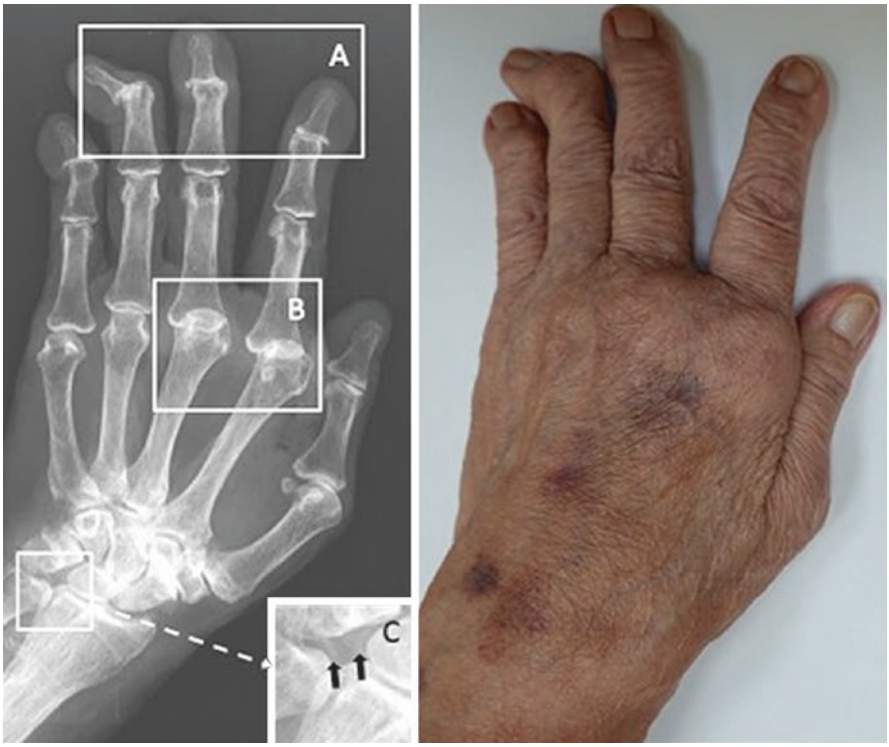

Fig. 26.1 A radiogram and a picture of a hand of an 86-year-old patient with long-standing seropositive rheumatoid arthritis. (**a**) Joint space narrowing, osteophytes and deformities typical for osteoarthritis in the distal interphalangeal joints; (**b**) joint space narrowing with subluxation of second and third metacarpophalangeal joints, emblematic for rheumatoid arthritis; (**c**) calcifications within the triangular cartilage complex and between triquetrum and lunate bones (arrows), pathognomonic of calcium pyrophosphate dihydrate deposition disease

Table 26.1 Rheumatic diseases with polyarticular involvement in elderly

Common	Less common and rare
Osteoarthritis	Septic arthritis
Rheumatoid arthritis	Paraneoplastic arthritis
Crystal-related arthritis	Vasculitis with arthritis
Psoriatic arthritis	Autoinflammatory diseases
Polymyalgia rheumatica	
Reactive or postinfectious arthritis	

26.1 Disease Chronology

Acute versus insidious disease onset. Acute onset of arthritis in the elderly is not uncommon. Typically, episodes of gout or pseudogout begin all of a sudden and may involve more than one joint. Polymyalgia rheumatica (PMR) starts at once in the majority of the patients, and RA frequently begins as an acute illness in the elderly as well. Acute onset of joint disease, particularly if accompanied by any fever or unexplained leukocytosis should lead to the suspicion for infectious or septic arthritis. The latter can occasionally present with only low-grade fever or even with normal body temperature while involving more than one joint. Also, arthritis in the frame of infective endocarditis can be acute, wandering, and transient. Some paraneoplastic rheumatic syndromes, particularly remitting symmetric seronegative synovitis with peripheral edema (RS3PE) can develop within a frame of several days. Even OA, which is widely counted as a chronic and insidious disease, can sometimes flare-up in an acute fashion. On the other hand, a classic variant of RA, PsA and other spondyloarthropathies usually have more gradual development. Both gout and pseudogout can present as a chronic indolent articular disorder in the elderly as well and should not be excluded only based on the lack of acute attacks.

Intermittent versus uninterrupted disease course. The intermittent course is typical, but not pathognomonic for crystal-related arthropathies. The bouts of gout usually last from hours to 5–7 days but can have a more slow resolution, while attacks of pseudogout (CPPD) can trouble for weeks. RA can present at first as recurrent episodes of short-living arthritis with joint swelling, tenderness, and redness, called palindromic rheumatism. Infective endocarditis can manifest with short episodes of arthritis, usually reactive to non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticosteroids. The autoinflammatory syndromes, while rare in the elderly, are characterized by sporadic disease attacks. The vast majority of other rheumatic diseases in the elderly have an uninterrupted course.

Preceding events. Preceding and causally related to the development of arthritis events can be sometimes revealed during history taking and include episodes of infectious or other illness and administration of new medicines or vaccinations in some patients. For example, recent administration of allopurinol can at first boost gouty attacks if a patient did not receive colchicine or other anti-inflammatory medication simultaneously. Many modern anti-tumor agents can propagate a variety of rheumatic syndromes as well. Vaccinations can occasionally cause PMR-like syndrome with severe joint and muscle pain, morning stiffness, and elevated inflammatory markers. Infections, both viral and microbial, can be associated with concomitant or subsequent arthritis. Post-viral arthritis, for example, can mimic PMR or RA and sometimes lasts up to several weeks or even months. An implication of an infectious agent in the development of rheumatic syndrome in this setting has the utmost importance as it can prevent unnecessary chronic anti-rheumatic treatment.

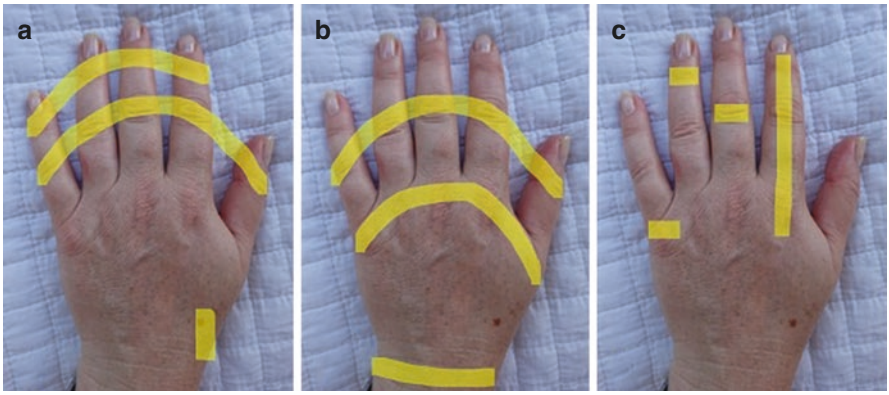

Fig. 26.2 Patterns of involvement of hand joints in major rheumatic disorders. (**a**). Osteoarthritis: distal interphalangeal, proximal interphalangeal and first carpometacarpal joints are typically involved in symmetric or asymmetric fashion, while metacarpophalangeal joints and wrists are usually spared; (**b**). Rheumatoid arthritis: proximal interphalangeal, metacarpophalangeal joints and wrists can be affected, usually symmetrically, but distal interphalangeal and first carpometacarpal joints are spared; (**c**). Psoriatic arthropathy: any joint of hand and wrist can be involved, frequently in asymmetrical pattern; tendency to ray-like involvement of finger joints

26.2 Patterns of Joint Involvement

26.2.1 Hands

Hand involvement is very common in the course of major rheumatic diseases of the elderly. Daily functioning can be critically impaired in patients with swollen, painful, or distorted hand joints, and early diagnosis can be of utmost importance to keep an elderly patient active and independent. Fortunately, the patterns of hand joint involvement are distinct and well described for the major arthropathies (Fig. 26.2). Thus, simple, but a thorough physical examination of hands can lead straight to the diagnosis in some patients.

The first goal of the examination is to determine whether hand pain or disability are consequences of the articular disease. Some prevalent non-articular conditions, like carpal tunnel syndrome (CTS), de Quervain's tendonitis or trigger finger, can often mimic arthropathies.

Patients with CTS can complain of chronic unilateral or bilateral hand pain, with or without numbness, sometimes with slight morning stiffness. Distribution of CTS-related pain may not follow the classic scheme with the involvement of 1–3 fingers and engage all five fingers in some individuals. Physical examination, showing the absence of synovitis, is pivotal. The history of long-standing diabetes mellitus or clinical signs of uncontrolled thyroid disease, as well as positive Tinel or Phalen signs, should raise the suspicion for CTS and a patient should be referred to the diagnostic ultrasound or nerve conduction study.

De Quervain tendonitis, inflammation of the tendons of extensor pollicis brevis and abductor pollicis longus muscles, causes pain, located proximal to first

carpometacarpal (CMC) joint. However, the whole area of the thumb base can become tender with thumb movement limited by sharp pain.

Trigger finger usually manifests with transient locking of the finger in the bent position due to disease of the flexor tendon. However, some patients can complain of pain in the proximal interphalangeal (PIP) joint of the affected fingers and be evaluated for arthritis. Again, the absence of synovitis on physical examination is critical in this setting for the exclusion of inflammatory rheumatic disease.

Rheumatoid arthritis of hands involves PIP and metacarpophalangeal (MCP) joints, most often second and third MCPs, as well as wrists in a typical symmetric fashion. However, some patients demonstrate arthritis solely of the wrists or MCP joints, and others can have asymmetrical distribution. The affected joints are tender, swollen, limited in their motion, but rarely red on inspection. Notably, distal interphalangeal (DIP) and first CMC joints are usually spared by RA, and the involvement of these joints should lead to the alternative diagnosis or be a manifestation of a combination of several rheumatic diseases (Fig. 26.3).

OA affects DIP and PIP joints, causing characteristic posterolateral firm swellings, called Heberden and Bouchard nodes. Joint deformities can be prominent. Sharp pain, usually worsened by joint engagement, sometimes redness over the affected joint and even morning stiffness can feature progressive disease or its flare, but in other patients, OA does not cause much pain and presents mostly as an aesthetic problem. Besides, the involvement of the first CMC joints with their squaring and, sometimes, severe pain and dysfunction is typical for OA and can be a sole manifestation of the disease (Fig. 26.4). Other hand joints, including MCPs and wrists, are usually spared by primary OA. In general, functional impairment in hand OA may be as bad as in RA [3].

Gout can superimpose on the of DIP joints, affected by OA, and contributes to the flares of acute arthritis. Tophi can be recognized as whitish subcutaneous nodules, often located close to the DIP joints (Fig. 26.5).

CPPD can masquerade as RA or OA and can involve any joint of the hand, but the disease of second and third MCP joints and wrists, similarly to RA, is the most

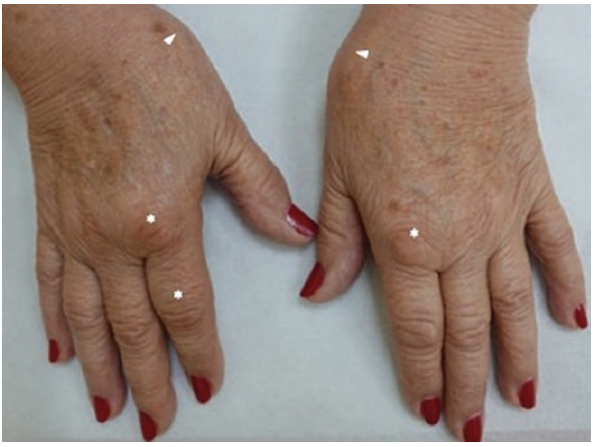

Fig. 26.3 Hands of a 75-year-old patient with seropositive rheumatoid arthritis manifesting with synovitis of both second metacarpophalangeal and right second proximal interphalangeal joints (asterixis). Bilateral squaring of the first carpometacarpal joints relates to concomitant osteoarthritis (arrowheads)

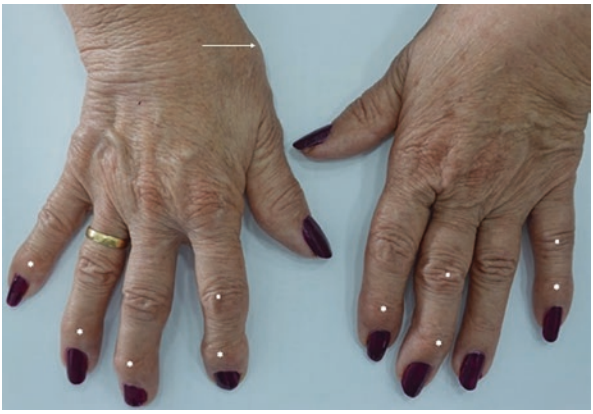

Fig. 26.4 Hand of a patient with osteoarthritis. Symmetric or asymmetric bony enlargement of the distal interphalangeal joints (asterixises) and proximal interphalangeal joints (dots), as well as squaring of the first carpometacarpal joints (arrow) are typical for osteoarthritis. Metacarpophalangeal joints are spared

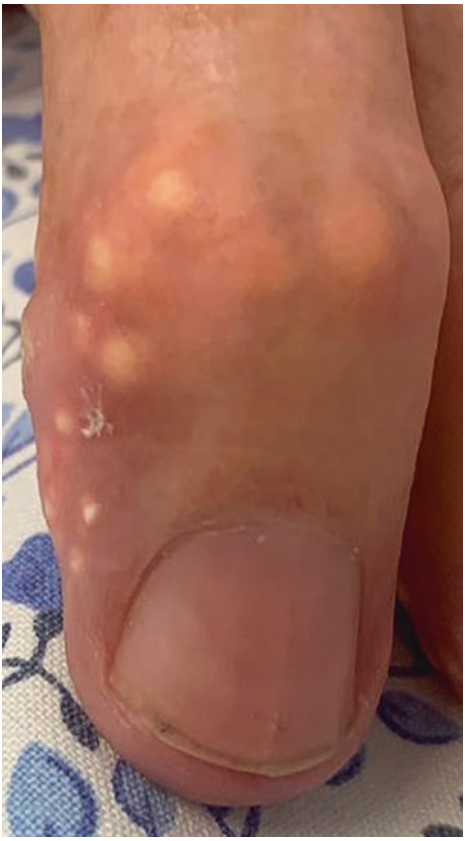

Fig. 26.5 Tophi over the distal interphalangeal joint

frequent, and the diseases can be undistinguishable solely on clinical grounds. Conventional X-rays of the hands, showing typical calcifications are characteristic for CPPD in this setting and represent a single most useful diagnostic investigation. Nevertheless, CPPD and RA can coexist in the same patient (Fig. 26.1).

PsA can also manifest in any joint of the hand, and the presence of skin psoriasis should always raise the suspicion for PsA. However, PsA can develop in the absence of skin disease as well. DIP joints are frequently involved in PsA, obligating the differentiation with OA. Psoriatic nail involvement, presence of dactylitis, the involvement of atypical for OA joints, such as MCPs, can lead to the diagnosis already during the first encounter with the patient. Different from RA, PsA is commonly asymmetric; the skin over the involved joints can be red or purple, and entheses are involved more often.

In general, the finding of joint swelling and/or deformity is a sine qua non for the diagnosis of arthritis. However, arthralgia can precede the appearance of clinical arthritis in the course of many rheumatic diseases, including RA and, in patients with joint pain but without clinical synovitis or other compelling explanation, further relevant investigation, including appropriate laboratory and imaging studies should be considered. In this respect, recent onset of arthralgia, accompanied with morning stiffness and involving MCP joints with difficulty making a fist and positive squeeze test for MCP joints on examination, particularly in patients with a first-degree relative with RA was defined as arthralgia at risk for RA by EULAR [4].

26.2.2 Shoulders

Isolated shoulder disease, while frequently a manifestation of a rheumatic disorder, is commonly at first treated by orthopedic surgeons. In many of these cases, nevertheless, timely assessment by a rheumatologist can lead to the earlier diagnosis, administration of a specific treatment, prevention of unnecessary overtreatment by NSAIDs or recurrent glucocorticosteroid injections and a better outcome. Four primary rheumatic conditions with predominant or sometimes solely shoulder engagement include CPPD and calcific tendonitis of the rotator cuff, Milwaukee shoulder disease, PMR and late-onset RA. Osteoarthritis of the acromioclavicular joint should not be missed as well. Finally, referred pain, originating from the cervical spine, can mimic shoulder disorder. However, the clinical details of these diseases overlap and, on the other hand, the same person can have more than a single cause for shoulder pain. Thus, the diagnosis of shoulder pain should not be based on a single disease sign, but instead built from a bulk of data acquired during history taking, physical examination, and additional necessary investigations. A patient with PMR, misdiagnosed as having acute bilateral calcific tendonitis based on calcifications seen on radiographic examination of the shoulders, is a relatively common example of confusion, caused by the unbalanced analysis of clinical data.

The exact location of shoulder pain is of importance and can lead to the easy diagnosis of the disease of acromioclavicular joint or, for example, point to the primary problem of the cervical spine (Fig. 26.6). Physical examination can help to further diagnose involvement of the glenohumeral or acromioclavicular joints by revealing swelling or local tenderness, enthesitis and tendonitis - by analysing the spectrum of affected movements or using the known provocation tests, while

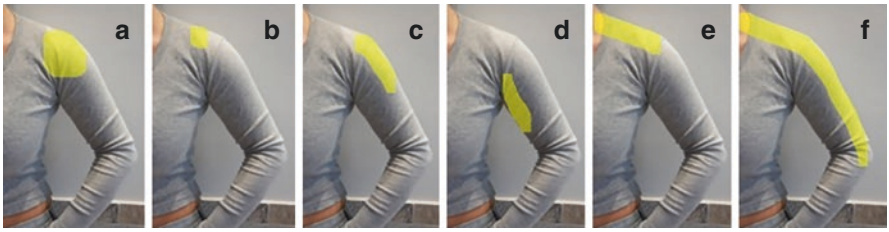

Fig. 26.6 Distribution of pain in the shoulder area in different musculoskeletal conditions. (**a**) pain originating from the glenohumeral joint; (**b**): acromioclavicular joint pain; (**c**): pain of subacromial/deltoid bursitis, rotator cuff disease; (**d**): pain of bicipital tendonitis; E and F: pain referred from the cervical spine

cervical spine disease will usually manifest with painful and limited rotation or bending of the neck spine and tender adjacent muscles [2–4]. However, many elderly persons have symptoms of cervical spine disease, pain over the acromioclavicular joint or calcifications of the rotator cuff without complaining about the significant shoulder pain or limitation. Thus, at least some findings, revealed in the course of medical investigation of shoulder pain, can have a role of an innocent bystander and should be given proper weight in the contest of the patient's current disease.

The understanding of the dynamics of the rheumatic shoulder disease is of primary importance. An acute illness with bilateral shoulder pain, myalgia, and profound morning stiffness in an elderly patient is a typical presentation of PMR. Significantly elevated levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and the rapid and full response of symptoms to the administration of 10–20 mg of daily prednisone will undoubtedly support the diagnosis of PMR. Will the finding of the wrist synovitis or the presence of shoulder calcifications on radiograms question the PMR diagnosis in this patient? The late-onset PMR-like RA will certainly be a possibility in this case. It can start acutely and respond adequately to the applied dosage of glucocorticosteroids, and synovitis of peripheral joints, particularly wrists or MCPs, maybe its sole distinguishing feature. Specific testing for rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA), ultrasonography and, sometimes, magnetic resonance imaging of shoulders for detailed localization of the inflammatory process will be indicated in this patient, and concomitant treatment with methotrexate should be strongly considered [5]. On the other hand, the role of shoulder calcifications, seen on x-rays, is less distinct in this setting. Acute calcific tendonitis or attack of CPPD is typically unilateral; its pain is commonly worse during shoulder motion and requires larger dosages of glucocorticosteroids to be recovered. Thus, the clinical significance of shoulder calcifications in this particular situation is limited. However, if patient's pain starts in one shoulder, and the second shoulder begins to hurt 3 weeks later, his CRP and ESR levels are mildly elevated or even normal, the likelihood of PMR becomes to be very low, while both RA and CPPD or calcific tendonitis will stay the preferred diagnoses to be considered.

On the contrary, *chronic* unilateral or bilateral shoulder pain is a very common manifestation of undiagnosed CPPD or chronic calcific tendinopathy, which can be easily diagnosed by conventional radiography or US. Significant shoulder swelling with large effusions is typical for Milwaukee shoulder disease, a destructive crystal-related arthropathy. Capsulitis or 'frozen shoulder', which manifests with limitation of both active and passive movements of the shoulder in all directions should be differentiated from the arthritis of glenohumeral joint.

26.2.3 Knees

Knee involvement by polyarticular rheumatic disease is common in the elderly. RA causes chronic knee pain, swelling and, sometimes, massive effusion in a predominantly symmetric fashion, while PsA commonly causes a single knee disease as well. Knees are frequently involved in the course of crystal-related arthropathies, being frequently the first joints affected by CPPD. Of importance, both acute or fulminant attacks of arthritis and chronic indolent inflammation can feature CPPD disease. Gout, on the other hand, typically starts in the articulations of feet and ankles and affects knees commonly in the later disease stage. Crystal-related knee arthritis, particularly CPPD, can coexist with and even mimic RA. However, the combination of CPPD with knee OA is much more common. In these cases, CPPD is believed to be a catalysator of OA development and related disability [6, 7]. OA, which can be primary or secondary to other diseases or events, is by itself the most prevalent rheumatic disorder affecting the knees and is a leading cause for knee-related disability and knee surgery in the elderly [8]. Thus, the differentiation between different rheumatic processes affecting the knees is essential for both therapy planning and determining the prognosis. In this regard, conventional radiography, US, and fluid examination in patients with knee effusion help establish the etiology of knee involvement in the majority of the patients. X-rays can reveal clinically silent chondrocalcinosis and characterize the severity and distention of the structural damage of the knee joint. The US is a sensitive tool for the characterization of the pattern of synovial involvement and the activity of the inflammation; it can reveal crystals within the articular cartilage and detect concomitant entheseal involvement. The synovial fluid examination can differentiate active inflammatory effusion from low-grade indolent inflammation or fluid accumulated as a result of degenerative disease by the white blood cell (WBC) count and its differential, as well as reveal pathogenic crystals of monosodium urate, calcium pyrophosphate and basic calcium phosphate [9].

Many mechanical non-inflammatory conditions of the knees can cause chronic knee pain and disability as well, and those should not be missed or confused with rheumatic disease. Some of them, such as patellofemoral syndrome, can be diagnosed clinically, while others should be confirmed by the appropriate imaging. Thus, patients with knee pain and ambiguous clinical picture or mismatching clinical, laboratory or imaging data should be referred for further investigations.

26.3 Arthritis with Fever

Arthritis with concomitant fever can be a manifestation of the infectious disease, vasculitis or be a paraneoplastic phenomenon with septic arthritis being always the first disease to be excluded in this setting. Polyarticular presentation of septic arthritis can be seen in about 10% of patients and is more frequent in those with preexisting RA or prosthetic joints [10, 11]. Notably, the diagnosis of polyarticular septic arthritis in the elderly can be more easily missed comparing to the younger patients because of the relatively common absence of high fever and, frequently, lower WBC count in the joint fluid. The time to diagnosis of septic arthritis in persons of 80 years and older was more than 20 days in one study [11]. Thus, a sample of fluid, aspirated from the involved joint should always be sent for direct staining and culture in all patients. Infective endocarditis can manifest with septic or reactive migratory arthritis and should be excluded by blood cultures and echocardiography in patients without a precise diagnosis. Brucellosis, Lyme disease, Q-fever, chikungunya, and other viral and bacterial diseases can manifest with arthritis and fever as well and should be considered in relevant settings. Finally, giant cell arteritis and paraneoplastic syndromes can manifest with arthritis and fever as well [12–14].

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Chapter 27
Approach to a Geriatric Patient with Back Pain

Arsen Shpigelman and Gleb Slobodin

Back pain is one of the most frequent complaints of all ages. However, older patients with spinal problems commonly experience the pain of greater severity, tend to develop chronic misery rather than temporary episodes of pain, and frequently advance to disability [1, 2]. It has been reported that back pain is the most prevalent medical cause of retirement in older age, as well as a common cause of reduced activities of daily life, and a risk factor for falls in the elderly patients [1–3]. On the other hand, the number of medical studies dedicated to the pathogenesis, diagnostics, and management of backache in the elderly is limited, which translates to the undertreatment of this particular cohort of patients in practice [1]. Delayed or limited pain management, due to the hope that an acute episode of back pain will eventually resolve, or because of existing co-morbidities of elderly, commonly leads to the development of chronic or constant spinal suffering and eventually result in disability in these individuals. Also, the spectrum and the differential diagnosis of the medical conditions, manifesting with spinal pain in the elderly is different from the younger people. The extensive gamut of spinal disorders, as well as the possibility of cardiovascular and other co-morbidities occasionally presenting with back pain, necessitate a systematic approach to every adult patient, and especially to the older one, presenting with back pain. Meticulous history and relevant physical examination are the cornerstones of the rational diagnostic approach to these patients, while the choice of the confirmatory imaging depends on the suggested clinical diagnosis. It should be remembered that multiple abnormalities are almost always revealed on the imaging of the elderly spine; however, only one is usually responsible for the current patient's complaints (Fig. 27.1).

A. Shpigelman
Department of Orthopedic Surgery, Nazareth Hospital EMMS, Nazareth, Israel

G. Slobodin (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel
e-mail: gleb.slobodin@b-zion.org.il

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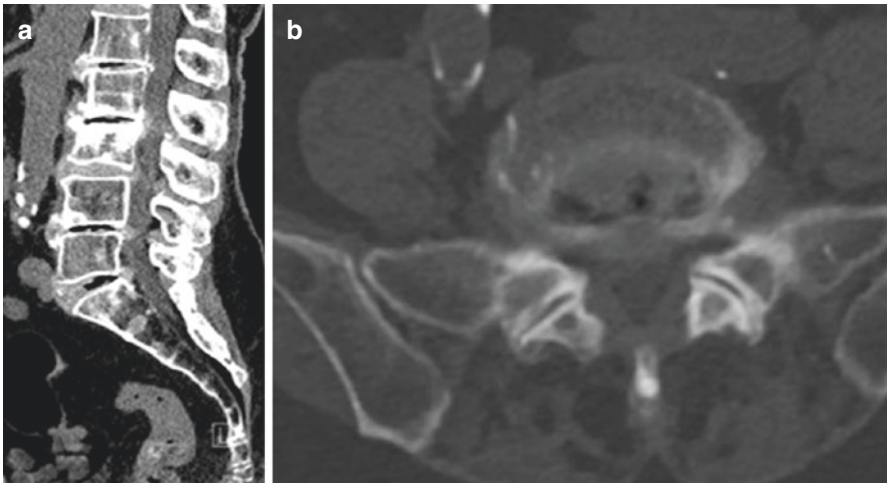

Fig. 27.1 Computed tomography of the spine of a 76-year old female presenting with excruciating lower back pain during the last 2 months. Fractured L3 vertebra and multiple calcified intervertebral disks, protruding into the spinal canal are evident (**a**). Facet joints with osteoarthritic hypertrophic changes are shown at axial section (**b**). All reported imaging findings can serve as potential pain sources. The clinical diagnosis was most compatible with facet joint pain, originating in the right L5-S1 facet joint, and it was confirmed by an immediate and almost full disappearance of pain after local injection of betamethasone/esracain

27.1 An Elderly Patient with New Spinal Pain

Any NEW back pain in an elderly patient should be assessed for the probability of emergent or urgent conditions, including spinal infections or tumors, vascular compromise, fractured vertebrae, and spinal cord compression [1]. It is important to remember that the herniation of the intervertebral disk as a cause of acute back pain is rare in elderly patients, and the approach to older people with new back pain differs from that in younger individuals. Accordingly, spine imaging of older adults with new back pain should not be delayed for weeks, but rather oppositely, performed promptly in those with the suspicious or poorly understood condition. However, the skillful history-taking and physical examination remain indispensable diagnostic tools. The patient should be asked to describe character (C) of the pain, location (L), exacerbation (E), dependence on activity (A), a pattern of radiation (R), weakness (W), incontinence (I), numbness (N). The mnemonic CLEAR WIN is a convenient memory device for a patient's evaluation. Traditionally used for the straightforward diagnosis of spinal emergencies, 'red flags' have been repeatedly shown as tools of relatively low sensitivity. A recent study, which reviewed 9940 cases of low back pain, concluded that the absence of 'red flag' features did not decrease the likelihood a 'red flag' diagnosis, demonstrating, for example, that almost 2/3 patients with spinal tumors did not have associated 'red flags' [4]. Thus, the absence of the 'red flags'

does not necessarily exclude spinal emergencies, and probably even less in the elderly population.

Spinal infections, including infectious discitis, vertebral osteomyelitis, epidural abscess or septic facet joint arthritis are usually suspected in the presence of back pain with local tenderness, fever and abnormal laboratory parameters of inflammation, including elevated white blood count (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). However, almost half of elderly patients with spinal infections can present without fever or leukocytosis [5]. The reported diagnostic delay in these older individuals with spinal infections can be catastrophically long, irrespectively of the affected structure, and leads to very high mortality rates [5]. The history of previous infections, immunosuppression, diabetes mellitus should always raise suspicion for possible spinal infection in an elderly individual with significant acute or new back pain, and elevated levels of CRP, which seem to be the most sensitive sigh of current infection should never be neglected in this setting.

Spinal malignancies most often represent a metastatic disease, and the prior history of cancer in any individual with new back pain is a single most sensitive predictive feature of bone metastases [6]. Weight loss and anemia should surely raise suspicion for the current malignant disease in an older individual, while the constant character of the back pain and nightly exacerbations have as well been suggested as clinical signs typical for spinal tumors [7]. However, these well-known 'red flag' features can be seen in a minority of these patients only [4]. The most common primary tumors, sending metastases to the spine, include breast, prostate, lung, and kidney cancers. The prevalence of spinal malignancies as the cause of new back pain is very low in children and younger adults but has been reported extremely high, up to 7%, in patients of ≥50 years old [7]. Thus, relevant imaging should be promptly considered in older individuals with new back pain of unclear origin and a history of cancer or clinical features, suspicious for malignant disease (Fig. 27.2).

Compression vertebral fracture, while frequently asymptomatic, can present clinically with sharp back pain, exaggerated by movement, cough, or percussion over the affected vertebra. It is most often a manifestation of osteoporosis, and more frequently occurs in older females, patients with known osteoporosis, particularly those with previous osteoporotic fracture, or on chronic glucocorticosteroid treatment (Fig. 27.3) [8]. However, malignant disease, primary or metastatic, can manifest with fractured vertebrae as well; thus the diagnosis of osteoporotic fracture should not be granted automatically after seeing the compressed vertebra on the radiogram, but rather relevant diagnostic clinical, laboratory investigation and, in some patients, advanced imaging studies should be performed [9].

Cauda Equina Syndrome (CES) has been described in patients with mechanical compression of cauda equine itself or several of its roots. Characteristic new bilateral radicular syndrome with neurological deficits in the legs should always raise suspicion for CES, but the clinical presentation is not classic in many patients, and back or perianal pain can dominate. Concomitant urgency and difficulties in micturition or any change in bladder function, or saddle dysesthesia are signs of early potentially reversible disease, and these patients should be immediately imaged

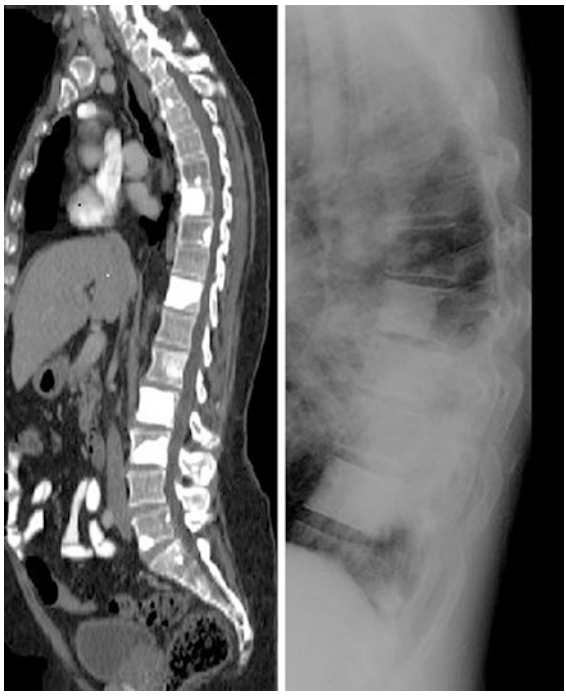

Fig. 27.2 A radiogram and computed tomography of the spine of a 67-year old patient with recent constant thoracic back pain, who was consequently diagnosed with metastatic cancer of prostate (curtesy of Doron Rimar, MD, with permission)

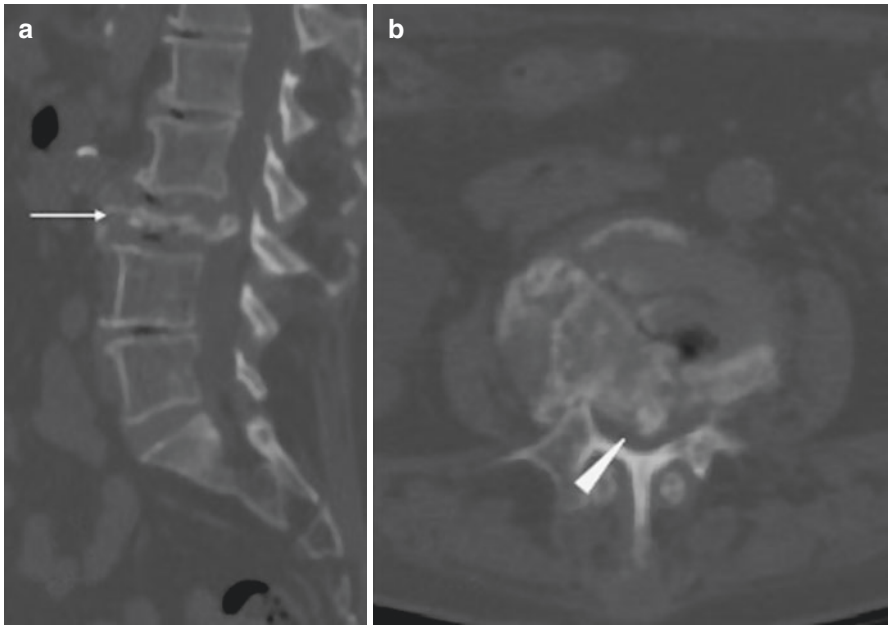

Fig. 27.3 Computed tomography of the lumbar spine of an 82-year old female, admitted to the spine clinic with mild back pain and leg weakness. She reported a fall with no major trauma a week ago. Saggital (**a**) and axial (**b**) views show severe osteoporotic fracture of L3 vertebra (arrow) with critical compression of the spinal canal by bone fragments (arrowhead)

by MRI and referred to the neurosurgeon for possible surgical intervention. Painless urinary incontinence, perianal numbness, loss of the anal reflex with diminished rectal tone characterize an advanced cauda equine syndrome with worse prognosis [10].

Diseases of the aorta can manifest with back pain. Aortic dissection, growing or ruptured aortic aneurysm, penetrating aortic ulcer can manifest with severe, intractable back pain, and the examination of leg pulses and palpation of abdomen for a pulsatile mass is a must in any elderly individual with new poorly understood back pain [11]. Long-lasting aortic conditions, including aortitis, can present with chronic back pain, sometimes of inflammatory character.

Crowned dens syndrome (CDS) is caused by acute inflammation in the peri-odontoid area, most often mediated by the soft tissue calcifications within the transverse and alar ligaments. Initially described in patients with calcium pyrophosphate deposition disease, CDS has been recently reported in patients with other rheumatic diseases, as well as in previously healthy individuals (Fig. 27.4) [12, 13]. Sharp upper neck pain, exaggerating on motion and accompanied by sudden stiffness, is the most characteristic clinical presentation of CDS. The pain frequently radiates to the occiput area. A low-grade fever is possible. CRP and ESR are typically elevated. Computed tomography of the odontoid area is diagnostic. Treatment consists of glucocorticosteroids in the daily dosage of 30–40 mg of prednisone, or non-steroidal anti-inflammatory drugs and colchicine [13].

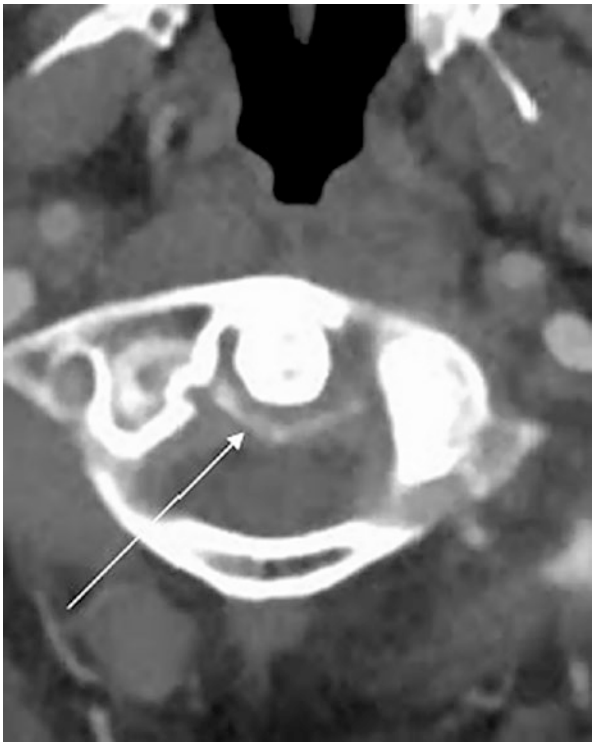

Fig. 27.4 Computed tomography of the cervical spine of a 67-year old female, presenting to the emergency room with acute head and neck pain, accompanied with severe neck stiffness. Calcification of the transverse ligament, an imaging hallmark of the crowned dens syndrome, is seen (arrow)

27.2 An Elderly Patient with Long-Lasting or Chronic Back Pain

27.2.1 Cervical Spine

Cervical spondylosis or degenerative cervical spine encompasses age-related changes in all anatomical elements of the cervical spine, including intervertebral disks, facet joints, and spinal ligaments. Of importance, only a minority of the older patients with radiologically diagnosed cervical spondylosis are symptomatic and complain most frequently of neck pain and limitation on movement. Some of these patients develop narrowing of the spinal canal or intervertebral foramina and can suffer from significant protracted pain and disability [14]. MRI is usually the preferred method of the diagnosis in this setting.

Cervical radiculopathy is caused by mechanical pressure on the nerve root by herniated disc or bone spur. Often, and different from younger individuals, elderly patients, having extensive degenerative changes in their cervical spine, present with signs and symptoms of more than one root involvement. Radiculopathy of the upper cervical spine can manifest with headache, located predominantly in the occipital area. Arm pain with, sometimes, tactile disturbance and, later, muscle weakness can result from cervical radiculopathy as well. In these cases, Spurling's test with head rotation and lateral bending toward the affected side exacerbates the arm pain. Many patients describe grinding or crepitation during the cervical motion. Typically, activities that involve the cervical spine exacerbate symptoms of radiculopathy.

Cervical spondylotic myelopathy (CSM) is a common type of cord dysfunction in elderly patients, diagnosis of which is commonly delayed. In this disorder, myelopathy of the cord develops due to extrinsic compression by the degenerated spine or alteration in cord blood supply. The condition is frequently multi-segmental in patients older than the age of 65 and, due to multilevel distribution, does not have pathognomonic symptoms or signs. CSM can present with a broad spectrum of findings, including muscle weakness in upper more than lower extremities, ataxic wide-based shuffling gait, sensory changes, and spasticity. Hyperreflexia, Hoffmann's sign, which is a quick flexion of both the thumb and index fingers when the middle fingernail is snapped, clonus, or Babinski's sign, may be present [15].

27.2.2 Thoracic Spine

The thoracic spine is more stable, comparing to the cervical or lumbar parts, and pain in the thoracic area is less common. Still, some elderly patients suffer from symptomatic degeneration of the thoracic spine and can develop thoracic cord compression as well. Usually, these patients report pain during repetitive movements or prolonged periods in a certain position. Sensory dysfunction, if present, manifests

at the level below the compression and can be unilateral or bilateral, depending on the localization of the cord compression. Clinical signs of thoracic cord compression usually progress slowly and should not be missed.

27.2.3 Lumbar Spine

A systematic approach to an elderly patient with low back pain starts with the carefully taken history and appropriate physical examination. Older patients presenting with back pain rarely suffer from a symptomatic herniated disk. On the other hand, they commonly complain of irradiation of the pain to one or both lower extremities. The first task in this setting is to distinguish among referred pain, radicular pain, neurogenic claudication, and myofascial pain. Referred pain is usually felt over the posterior aspect of the legs, but not distally to the knee and is variable in severity. Root pain is commonly dermatomal by distribution. Differently, patients with neurogenic claudication have vague, diffuse pain in the low back, pelvis, and upper legs, sometimes described as heaviness. Myofascial pain describes a wide spectrum of non-specific musculoskeletal symptoms by both quality and localization. It should be remembered that low back pain can be a sign of hip disease or abdominal, retroperitoneal, and pelvic conditions.

Lumbar spinal stenosis due to mechanical compromise of the spinal canal is a common pathology in older people with the prevalence of related symptoms in almost up to 50% of individuals at the age of 60 or older (Fig. 27.5) [16]. Vague upper leg pain or 'heaviness', frequently with dysesthesias and paresthesias over the

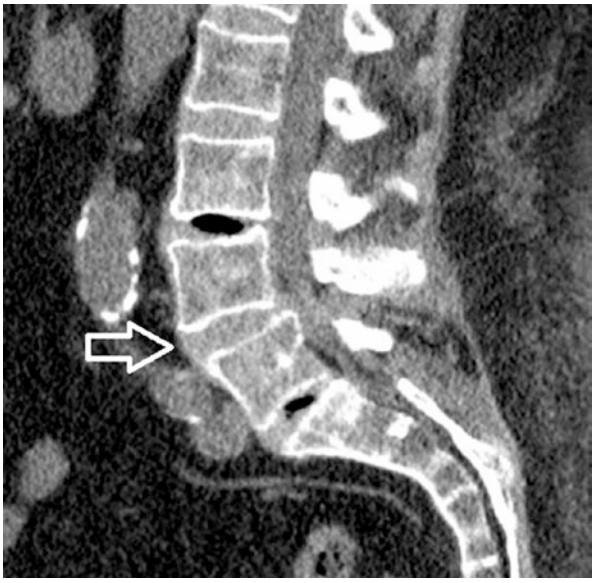

Fig. 27.5 Computed tomography of the lumbar spine of a 79-year old female with low back pain and neurogenic claudication. Commonly seen at this age degenerative disc disease with vacuum phenomena at L3-L4 and L5-S1 level is evident. However, patient's clinical symptoms are better explained by the L4-L5 spondylolisthesis with secondary stenosis of the spinal canal (arrow)

thighs, exacerbating on walking and disappearing in sitting position are the most common clinical symptoms, called intermittent neurogenic claudication. The signs of intermittent neurogenic claudication are usually preceded by years of central low back pain and progress very gradually [17]. The gait of patients with symptomatic spinal stenosis is usually wide-based. The physical examination can support the anamnestic diagnosis by provoking typical thigh pain by lumbar hyperextension. The correlation between clinical symptoms and severity of the narrowing of the spinal canal on imaging is poor, and while imaging of the spine should be performed in the symptomatic persons, mild spinal changes do not negate the clinical diagnosis of intermittent neurogenic claudication [17].

Facet joint arthropathy is another prevalent condition, affecting usually the cervical or lumbar spine. Facet joints are true synovial joints, which form a common motion unit with intervertebral disks. Thus, facet joint arthropathy often develops and is related to the disease of the intervertebral disk at the same level. However, facet joints can be involved in the pathologic processes independently, as in the cases of calcium pyrophosphate deposition disease, spondyloarthritis or, more often, osteoarthritis with degenerative and proliferative features, including joint space narrowing, the formation of osteophytes and, possibly, engagement of adjacent ligamentum flavum. Pain originating in the facet joints is usually localized, can be unilateral or bilateral, respectively, can be propagated by palpation of the affected joint and worsens with lumbar hyperextension and extension with rotation. Referred pain component is usually felt in the buttocks or posterior thighs [18]. While the correlation of the severity of imaging findings with the clinical appearance of the facet joint pain is disappointing, the vanishing of pain after anesthetic injection in the diseased facet joint is diagnostic.

De-novo scoliosis, which develops in the elderly, most commonly affects the lumbar spine. It is a progressive disorder, which starts as a degenerative process in the intervertebral disks and corresponding facet joints. The resulting instability of this weight-bearing unit is amplified by age-weakened spinal muscles and ligaments, and the condition gradually evolves, frequently causing constant back pain, with or without radiculopathy or spinal stenosis [19].

27.2.4 Systemic and General Conditions

Diffuse Idiopathic Skeletal Hyperostosis (DISH), also known as Forestier's disease, is common in elderly patients. It is asymptomatic in the majority but can as well cause limitation of spinal range of motion and back pain. DISH is a radiographic diagnosis, based on the imaging of the ossification of anterior and lateral spinal ligaments of at least four vertebral bodies in the thoracic spine. However, DISH can affect any part of the spine, as well as sacroiliac joints and large joints [20].

Paget disease of the bone frequently affects vertebrae, mostly of the lumbar spine, and can cause back pain and neurological deficits. However, in other patients, Paget's disease of the vertebra is an accidental finding. The affected vertebra looks more condensed and enlarged in both anteroposterior and lateral dimensions and

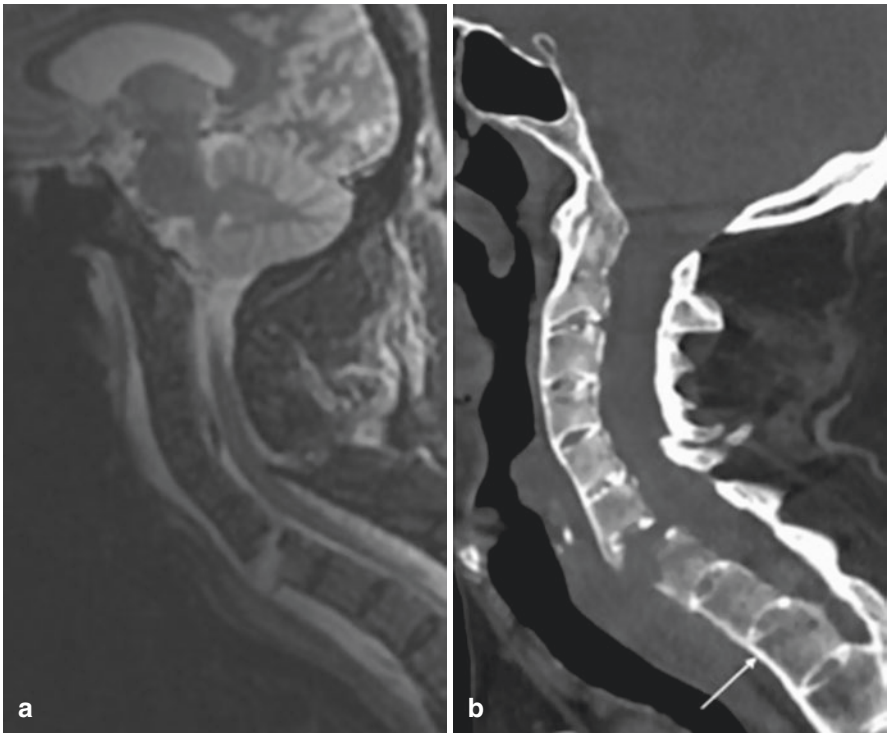

Fig. 27.6 Magnetic resonance imaging (**a**) and computed tomography (**b**) of the fractured cervical spine of a 68-year old male with long-standing ankylosing spondylitis and Whiplash injury. A continuous line of intervertebral syndesmophytes (arrow) is representative of 'bamboo' spine

can lead to the narrowing of the spinal canal and nerve compression [21]. Alkaline phosphatase, elevated in cases of extensive Paget disease of the bone, is often normal when a single vertebra is involved.

Ankylosing spondylitis rarely starts in the elderly. However, the disease can be unidentified and untreated for decades. Typical back pain of ankylosing spondylitis is of an inflammatory character, with exacerbations at night and during rest, and improves during exercise. Any segment of the spine can hurt, but low back pain is the most common. Spinal syndesmophytes grow gradually and lead to the characteristic 'bamboo' appearance. The immobile spine of patients with long-standing ankylosing spondylitis is usually extremely osteoporotic and prone to fractures (Fig. 27.6).

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Chapter 28
Approach to a Geriatric Patient with Suspected Vasculitis

Abid Awisat

28.1 Clinical Manifestations

When assessing a patient with suspected vasculitis, clinician ought to be aware to the heterogeneity of this disorder ranging from limited single organ injury, e.g., cutaneous vasculitis, to fulminant multi-organ involvement.

Vasculitides can be categorized as primary or secondary, infectious or non-infectious, and small, medium, or large vessel vasculitis as summarized in Table 28.1.

Over the years, numerous classification criteria have been suggested. However, perhaps the most influential event in the past decades was the detection of anti-neutrophil cytoplasmic antibody (ANCA) [1, 2], which led to the more precise classification of small vessel vasculitides to ANCA-associated vasculitis (AAV) and non-AAV (mainly polyarteritis nodosa and Henoch-Schonlein purpura) in the American college of rheumatology 1990 criteria for the classification of vasculitis [3], and redefined and updated in 1994 and 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides [4, 5].

Diagnosis can be challenging, particularly in the geriatric population, as symptoms can be either insidious or abrupt. Neurologic, respiratory, renal, cardiac and cutaneous involvement is well established in vasculitis among other less frequent manifestations (Table 28.2).

A thorough physical checkup should always be performed starting with skin inspection in search of purpura or painful nodules, which, if present, should be sampled. Temporal arteries should be inspected for tenderness or stiffness, while subclavian arteries and peripheral limb arteries auscultated for bruits. Deliberate assessment for respiratory, ophthalmic, para-nasal and neurological abnormalities is mandatory.

A. Awisat (✉)
Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel

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Table 28.1 Vasculitis syndromes in geriatric population

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis:
Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis (GPA)
Eosinophilic granulomatosis with polyangiitis (EGPA)
Cryoglobulinemic vasculitis
Hypocomplementemic urticarial vasculitis
Cogan syndrome
Giant cell arteritis (GCA)
Polyarteritis nodosa (PAN)
Primary angiitis of the central nervous system (PACNS)
Cutaneous leukocytoclastic vasculitis
Anti-glomerular basement membrane (anti-GBM) antibody disease
Vasculitis secondary to systemic disorder or infection:
Rheumatoid vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Malignancy associated vasculitis

Table 28.2 Clinical manifestations and organ involvement in vasculitides

Constitutional complaints and arthralgia
Dermal: Purpura, nodules, livedo reticularis, ischemic changes of digits
Neurologic: Headache, cerebrovascular accidents, seizures, peripheral neuropathy, mononeuritis multiplex
Respiratory and paranasal: Dyspnea, alveolar hemorrhage, pulmonary infiltrates, subglottic stenosis, sinusitis, oral and nasal ulcers, septal perforation and saddle nose
Renal: Hematuria, renal failure, glomerulonephritis
Gastrointestinal: Abdominal pain/angina, mesenteric ischemia, rectal bleeding
Cardiac and cardiovascular: Coronary vasculitis, pericarditis, myocarditis, limb claudication, aneurysm and dissection
Ocular: Diplopia, uveitis, scleritis, visual loss

28.2 Laboratory Investigation

Laboratory workout should include inflammatory markers, mainly erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are routinely used in both diagnosis and follow up. Fluctuations in CRP and ESR levels may represent the response to treatment or, on the contrary, predict relapses.

The additional advisory test includes complete blood count and eosinophils level, protein electrophoresis with quantitative immunoglobulin levels, cryoglobulins, serology for hepatitis C and B antibodies, which are essential to rule out secondary causes of polyarteritis nodosa (PAN), complement levels, anti–glomerular basement membrane (anti-GBM) antibody and urinalysis for red blood cells and proteinuria.

ANCA test substantially facilitates vasculitis workup. Combining Enzyme-Linked Immunosorbent Assay (ELIZA) and immunofluorescence (IF) ANCA directed against proteinase 3 (C-ANCA) yields a sensitivity of 96% and a specificity of 98.5% for the diagnosis of granulomatosis with polyangiitis (GPA) [6]. In contrast, ANCA directed myeloperoxidase (P-ANCA) is found in 30–40% of patients with eosinophilic granulomatosis with polyangiitis (EGPA) [7, 8], and in 60% of patients with microscopic polyangiitis (MPA) [9].

Rheumatoid factor (RF) is found positive in up to 30–50% of patients with AAV [10], but on the other hand, positive RF may be mistaken as a sign of rheumatoid arthritis-related vasculitis. In this instance, anti-cyclic citrullinated peptide antibodies (ACPA) may come in handy as it is a highly sensitive marker of rheumatoid arthritis [11].

Histology is a gold standard for diagnosis of systemic vasculitis and should be obtained whenever possible according to the clinical context. Typical findings in temporal artery biopsy in suspected GCA are diagnostic (discussed in the GCA chapter). Moreover, lung specimens with active vasculitis and granuloma or kidney biopsy with necrotizing pauci-immune glomerulonephritis are diagnostic for AAV in the appropriate clinical context.

28.3 Imaging Studies

Imaging studies are of great importance in staging and diagnosis of vasculitis, particularly in those subtypes with no specific biomarkers or auto-antibodies e.g., LLV, PAN, and primary angiitis of the central nervous system (PACNS).

Recommended imaging modalities for GCA are discussed in GCA chapter in detail. They should include the screening for cranial involvement, preferably using temporal artery color doppler ultrasound, while computered tomography angiography (CTA), magnetic resonance angiography (MRA) or positron emission tomography-computed tomography (PET-CT) are used for the imaging of large vessel involvement by vasculitis.

Angiography or CTA should be implemented when investigating PAN. The typical imaging findings are micro-aneurysms or stenotic lesions of visceral arteries (renal, hepatic, mesenteric and splenic arteries) or less commonly, cranial arteritis.

Imaging is advisory when AAV is suspected, mainly for assessing the extent of the disease e.g., CT of lungs and sinuses.

Echocardiography should be performed in patients with suspected vasculitis in order to rule out disorders that may be misdiagnosed as primary vasculitides, such as endocarditis and atrial myxoma.

28.4 Summary

Vasculitides is a heterogenous group of disorders with diverse clinical presentation and prognosis.

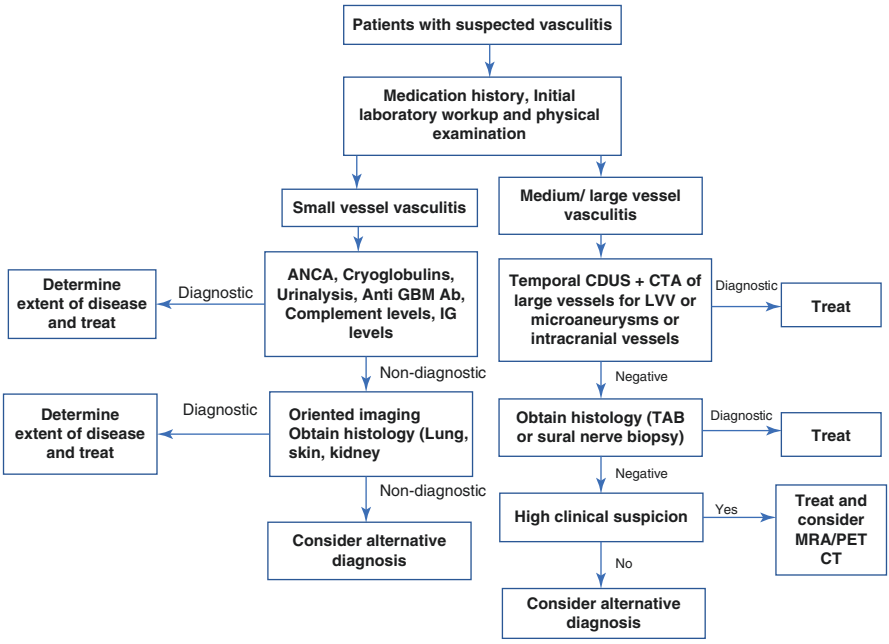

Fig. 28.1 Diagnostic algorithm in suspected vasculitis. ANCA Antineutrophil cytoplasmic antibody; GBM Glomerular basement membrane; IG immunoglobulins; CDUS Color doppler ultrasound; CTA Computered tomography angiography; LVV Large vessel vasculitis; TAB Temporal artery biopsy

Rapid diagnosis and treatment are crucial for preventing damage, minimizing organ injury and complications.

Diagnostic workup should integrate clinical, laboratory and imaging studies (Fig. 28.1).

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Chapter 29
Approach to a Geriatric Patient in Pain Clinic

Simon Vulfsons and Yael Orion

29.1 On Pain in General

The working definition of pain, as described by the International Association for the Study of Pain (IASP), is thus: *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*.

In qualifying this definition the IASP Terminology taskforce then explain that Pain is a purely subjective experience, not necessarily tied to tissue damage [1].

A more novel definition suggested recently suggests that *"Pain is an unpleasant feeling that is felt somewhere in the body and urges us to protect that body part"* [2].

Thus from both these slightly different definitions we can learn that nociception, the physiological process of somatosensory propagation, is neither sufficient nor necessary for pain. Further, pain is an output and not an input, thus even in the lack of any external stimulus we may experience severe pain.

Acute pain is considered a warning signal of actual or impending damage. Thus, trauma, infection, contusion etc. can and should all manifest with pain, signaling to the patient that he or she needs to attend to the painful stimulus. There is generally a good correlation to the inciting incident and the painful experience. On occasion, the degree of the painful experience seems to be well outside the degree of the stimulus- and we can assume that the patient's appraisal of the danger involved is exaggerated, possibly by previous life experiences. Well researched in this perspective is the phenomenon of pain catastrophizing [3–5].

S. Vulfsons (✉)
Rappaport Faculty of Medicine, Technion, Israel Institute for Technology, Haifa, Israel
e-mail: s_vulfsons@rambam.health.gov.il

Y. Orion
Geriatric Internal Medicine A, Tel Aviv Souraski Medical Center, Tel Aviv University, Tel Aviv, Israel
e-mail: yaelor@tlvmc.gov.il

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Chronic pain is less well-understood and in fact far more complex, for usually or often, there is no nociceptive process ongoing. We must then question ourselves about the seat of the pain. Is it in fact all produced by the brain as an output? Are there signals from the periphery that are decoded by the brain to infer tissue damage? In chronic pain, the correlation between the inciting incident and the painful experience is poor. How do we reconcile a patient with chronic back pain of many years with no clear tissue damage (but possibly evidence of degenerative changes that are nonspecific)? And such patients can often report worsening of their pain during periods of stress and while contemplating increased physical activity [6, 7].

Neuropathic pain is defined as *"Pain caused by a lesion or disease of the somatosensory nervous system"* [1]. In this case the input may be peripheral such as occurs in peripheral neuropathy or central such as may occur after central nervous system damage. Although the painful experience is often described differently in these cases than in nociceptive pain (burning, stabbing, shock like, tingling etc.), there is no pathognomonic descriptor for neuropathic pain.

29.2 The Anamnestic Approach to Pain in the Geriatric Patient

Taking a medical history of pain follows the same general course in all ages, thus we attempt to elicit details of the following (Table 29.1):

Onset: How and when did the pain began? Was it sudden or gradual? Was it due to trauma or disease? Elderly patients have a tendency not to report falls and minor traumatic events, thus occult fractures may be underdiagnosed [8].

Provoke: What makes the pain worse? Sitting, bending, getting up, turning in bed etc.? Is it worse during the day or night? Is it worse or better from cold, warmth, specific activities?

Palliate: What helps the pain? Lying down, moving around, activity, keeping occupied or medications?

Table 29.1 OPQRST Heuristic for history taking in pain and musculoskeletal medicine

O	Onset	Describe the **Onset** of the pain- when and how did it begin (sudden, gradual etc.)?
P	Palliate provoke	What eases the pain (rest, positioning, medication, etc.)? What makes the pain worse (movement, cold, agitation, etc.)?
Q	Quality	How would you describe the **quality** of your pain (deep, superficial, stabbing, itching, etc.)?
R	Radiation	Does your pain **radiate**? If so, how and where (down the leg, along the arm, etc.)?
S	Severity	How would you rate your pain **severity** (visual analogue scale, numerical pain scale, etc.)?
T	Timing	When does the pain occur (at night, on ambulation, while attempting to straighten up after sitting, etc)?

Quality: How is the pain described?- burning, tingling deep, superficial, fleeting, stabbing etc.? (the McGill Pain questionnaire has many descriptors of pain quality [9]). Special attention should be given to the elderly patient who might not use the word "pain", but may refer to their problem as "hurting," "aching," or other descriptors. It is important to identify pain in the patient's own words and use them for subsequent follow-up evaluations [8].

Radiation: From where to where does the pain radiate? Is this constant or changing?

Severity: Various scales can be used such as Visual Analogue Scale and Numerical Pain Scale.

Temporal: When does the pain occurs?

General history in the elderly: History of the elderly patient should include the effect of pain on function, mood, behavior and nutrition. Complaints of chronic pain may be a possible marker for elderly mistreatment or abuse. A rare entity may be physical assault, but more people who suffer abuse tend to report pain and other medical complaints than the abuse. Special attention should be made in these cases in order to rule this out as a call for help.

29.3 Anamnestic Clues for Patients with Dementia

Dementia has a slow deteriorating course. Patient suffering of early dementia can often give medical history. Sometimes dementia can be missed in an educated patient who may confabulate and give erroneous details. Interviewing a patient with dementia is important but positive affirmation of the history from a caregiver/relative is crucial.

In patients suffering from moderate and severe dementia an effort should be made to communicate with the patient as much as possible using yes/no questions and nonverbal communication. Caregivers (family and professional workers) may be able to identify changes in the patient's behavior, distinguishing pain behavior from agitation or delirium.

Intensity of pain in patient suffering of severe dementia without verbal communication can be assessed using the PAINAD scale – an observational tool that includes breathing pattern, vocalization, facial expression, body language and consolability [10]**.**

29.4 The Physical Examination

While we can expect the elderly patient to be far less supple than younger patients a full physical examination, focused on the pain complaint should never be missed (Table 29.2). The following components are important:

Table 29.2 ARTNS Heuristic for physical examination in pain and musculoskeletal medicine

A	Appearance	Observation of asymmetries, also including signs of color differences, swelling and edema, limb or joint inequalities
R	Range of motion	Passive, active and resisted range of motion
T	Tissue texture	Tenderness, temperature differences, edema – Pitting, Trophedema
N	Neurological	Motor, sensory and reflex functions, allodynia and dysesthesias
S	Special tests	Neurological and musculoskeletal tests such as straight leg raise, femoral stretch and Spurling test

Appearance: Evidence of swelling, discoloration or distortion and especially left to right comparisons are important. Often elderly patients will have deformed spines and joints- Do these seem associated with the pain complaint?

Range of Motion: It is very important to compare sides, as decreased range of motion might be general.

Tissue texture and tenderness: Looking for areas of tenderness, localized heat or cold, induration, pitting edema are all important signs of tissue damage. In addition, signs of neuropathic pain such as allodynia, hyperalgesia and dysesthesia are important.

Neurological examination: an essential part of the physical examination and should include sensory, motor, autonomic and reflex examinations. In the head and neck cranial nerve, function should be examined.

An assessment of the patient's walking is an essential part of the neurological examination. The "get up and go" test is one tool to assess the patient's balance, speed and gait as well as to predict the risk of falls [11].

29.5 Ancillary Tests for the Elderly

A search for the cause of pain, especially tissue damage should be supplemented with ancillary testing where the index of suspicion is high and the expected clinical yield worthwhile. Thus, for example, an elderly patient who is complaining of back pain after a fall should have imaging studies performed to rule out fracture. Sudden onset of pain should raise the index of suspicion concerning a new pathological condition and can warrant further testing. The concepts of red flags, although recently challenged, has been used as a tool to help clinicians decide whether to utilize further tests, especially imaging [12–14].

Spinal pathology has been the most extensively discussed when attempting to predict those patients who have serious disease, but the principles can be extrapolated thus:

1. Is there suspicion of tissue damage?
   (a) Suspicion of fracture? Infection? Infiltration (metastases)?
   (b) Suspicion of generalized condition (rheumatic disorder? hematological disorder?)

2. Is there suspicion of a referred pain?
   (a) A dermatomal pattern suggesting radicular pain?
   (b) A peripheral nerve pattern?
   (c) A somatic referral pattern?

29.6 Types of Pain

Many classification systems exist for describing types of pain. We find that the following classification, based on the mechanism of pain has the most clinical pertinence.

(a) Tissue damage pain such as trauma, infection contusion etc.
    This pain, the most common, is usually acute, seems to have a clear pathophysiological explanation and is mediated by mechanical, thermal or chemical stimuli. It is often accompanied by signs and symptoms of inflammation (dolor, rubor, calor, tumor and functio laesa) [15].
(b) Referred pain of neural origin is often a cause of painful experience such as in cases of neural insult due to herniated intervertebral discs or inflammatory and infiltrative pathologies of plexii or nerves (see Case Vignette #1). Central nervous system insult may also manifest as referred pain. The hallmark of this type of pain is usually the quality of the pain (burning, tingling, stabbing etc.) and the distribution (dermatomal, peripheral nerve).
(c) Referred pain of somatic origin is probably the most common type of referred pain seen in primary care and is usually myofascial pain [16]. Well described in the back by Bogduk, This pain may be referred from muscle, tendon ligament joint and bone and usually has well defined referral patterns [17–19] (see Case Vignette #2).
(d) Dysfunctional Pain as such that does not well fit into the above categories mainly because there is no evidence of tissue damage and no clear referral pattern. Thus, patients suffering from fibromyalgia, irritable bowel syndrome, irritable bladder syndrome etc. seem to experience pain that is not associated with tissue damage and seems to be associated with pain threshold perception.
    Other classifications exist and can be used together with the above classification such as acute/chronic pain, cancer pain, neuropathic pain (central, peripheral or visceral) and rheumatological pain.

Case Vignette #1: Herniated Lumber Disc with Radicular Pain
An 82-year-old male presented to the pain clinic suffering from severe pain for 3 weeks in the anterior distal thigh and knee on the left. The pain had started quite suddenly while touring overseas, but there was no history of trauma or any inciting incident. The patient returned home, and underwent a workup including venous ultrasound Doppler study of the left lower leg, radiology of the left knee and blood workup for signs of infection, inflammation or clotting disorders. All the studies were normal. Orthopedic examination of the left lower limb including the knee was normal.

On examination in the pain clinic, marked allodynia was noted over the left knee area with dysesthesia over the anterior left thigh, there was no weakness of the quadriceps muscles and deep tendon reflexes of the patella were absent bilaterally. The allodynia suggested a neuropathic origin, probably a prolapsed disc. An MRI study of the lumbar spine performed, demonstrating a prolapsed disc in the far lateral recess between L3 to L4 on the left. A selective nerve root injection with steroid deposition was performed with excellent result. The pain decreased markedly and the patient was able to resume normal functioning.

Case Vignette #2: Somatic Referred Pain
An 80-year-old male was referred to the pain clinic suffering from pain in his right shoulder. He had fallen 2 years previously and fractured his right proximal humerus at the surgical neck. An attempt to fuse the fracture failed and he was now suffering from pain associated with a functioning non-union of the fracture. He stated that the use of his forehand, wrist and hand were quite well preserved, but all attempts to mobilize his upper arm met with pain, and limitation of movement. The pain was aggravated if he turned on his right side during sleep. The pain responded well to Paracetamol. On examination, the musculature around the upper arm and shoulder displayed many trigger spots, taut bands, tenderness, and muscle weakness. The fracture was noted by crepitation while gently mobilizing the upper arm- and was generally not tender.

Gentle myofascial release techniques were employed as well as dry needling of the trigger points with marked decrease in pain although the upper arm remained limited in movement. The patient was seen on a regular basis approximately once every 2 months for similar treatment and remained virtually pain free until he passed away 3 years later.

29.7 Special Considerations in the Geriatric Population

29.7.1 Physiology of Pain in the Elderly

The effect of aging on pain perception has been intensively studied. Age related changes in the nervous system occur in various levels:

Pain receptors- Aging is associated with a decreased number of some pain receptors.

Nerve fibers- Aging is associated with a decreased number of some of the nerve fibers, slow conduction velocity, changes in myelin and in some of the neurotransmitters.

Central nervous system- Aging is associated with a loss of neurons in cortex, midbrain, brain stem, thalamus and spinal cord and altered levels of various neurotransmitters.

Clinical examples of reduced pain sensation in elderly people are well known, such as silent myocardial infarction and asymptomatic bone fracture. Even though the real clinical significance of all the age related physiological changes is still uncertain [8].

A recent review and meta-analysis concluded that aging decreases sensitivity for pain of low intensity, especially for heat pain and for pain applied to the head and that aging does not have a strong effect on pain tolerance [20].

29.7.2 Epidemiology

Several studies have demonstrated that the frequency of chronic pain increases with age. Other studies have shown a similar pattern of increase in chronic pain prevalence until approximately the age of seventy, at which point pain prevalence plateaus or even declines slightly.

Specific pain conditions associated with aging includes osteoarthritis (30% of the people over 80), low back pain, neuropathic pain and visceral pain [21].

29.7.3 Consequences of Chronic Pain in the Geriatric Patient

Chronic pain in the geriatric patient has a significant influence on physical, emotional and cognitive function. Limitation of activity may represent particular problems in older adults.

1. BADL (basic activities of daily living): Chronic pain is associated with reduced mobility and can adversely affect basic activities such as walking, bathing, eating, dressing, and going to the toilet.
2. IADL (instrumental activities of daily living): Activities such as shopping, cooking and driving as well as leisure activities are negatively influenced by chronic pain.
3. Mood and behavior: Chronic pain can cause sleeping disorders, depression and anxiety in elderly patients as in young patients. In the elderly, as well as in the general population chronic pain increases the risk for depression. On the other hand the presence of depression can lower pain threshold [22]. Pain in dementia patients can cause other behavioral disorders such as agitation, aggression and wandering. These patients can suffer mistreatment with neuroleptic or sedative medications instead of pain treatment.
4. Nutritional status: The complex connection between pain, depression, frailty, decreased performance status and malnutrition is a well-known geriatric issue. Chronic pain is an associated factor for malnutrition in clinical studies [23].
5. Frailty: Frailty is an important predictor of serious adverse outcomes, such as disability, health care utilization, and death. The phenotype of frailty includes the five following characteristics: unintentional weight loss, weakness, slow gait, exhaustion, and low activity. In addition there is a complex relationship between frailty and cognitive functioning. Frailty represents various characteristics including reduced physiologic reserves and reduced capacity to maintain internal homeostasis. As a result the patient suffers from decreased resistance to

stressors and increased vulnerability. Clinically the patient suffers from multi-system dysregulation, failure to thrive, impaired mobility, functional decline, cognitive impairment and depression [8].

6. Falls: Activity limitation, malnutrition and frailty increase the hazard for falls.
7. Cognitive Impairment: Impaired cognitive function is known to be associated with chronic pain in all ages. Poor cognitive reserves in the elderly population as well as co-existing depression and frailty can cause a cognitive decline (see Case Vignette #3). Recognizing and treating this reversible cause of cognitive decline is crucial.
8. Quality of life: Chronic pain has various effects on the elderly persons- sleep disorders, anxiety, depression and fatigue.

Case Vignette #3: Pain in the Patient Suffering from Advanced Dementia
An 86 years old widow and mother of three, was admitted to the Advanced Nursing Department due to pressure sores.

She is known to suffer from advanced dementia. In the last year she was in a nursing home, sitting in a wheelchair. She needed help in all ADL (activities of daily living). She spoke a few words and identified relatives inconsistently.

For the last 3 months she started to suffer of stage IV decubitus ulcers in the left heel and both greater trochanters. She refused to eat and drink. On admission to the Advanced Nursing Department her son and legal guardian stipulated to receive palliative care only.

The treatment was based on excellent nursing including good oral care and alternate pressure mattress. The ulcers were treated with advanced dressings. She received oral comfort feeding and subcutaneous hydration. Pain was measured by using the PAINAD scale. Pain treatment started on Paracetamol 1 gr 3 times a day and Oxycodone syrup 2 mg as premedication for the ulcer dressing replacement. Due to persistent pain Oxycodone treatment was gradually escalated to four times a day in increased doses and then converted to Fentanyl patch. On treatment with Paracetamol, Fentanyl patch of 12 mcg/hour and Oxycodone syrup before the ulcer dressing replacement she seemed pain free and alert. The patient started to eat and drink and 3 months later, as the pressure ulcers gradually healed, Fentanyl treatment was stopped.

29.7.4 An Approach to the Geriatric Patient Suffering from Pain

The geriatric patient suffering of chronic pain should be approached by a multidisciplinary team using a multidirectional approach.

Goals of treatment should be discussed repeatedly. In many cases the treatment cannot eliminate the pain but can reduce it and avoid undesirable influences on the patient's life.

Although the pharmacological treatment is the most common strategy employed**,** the concurrent use of non-pharmacological treatment is essential first to reduce dosage and duration of medication use and mainly to prevent and treat the dangerous consequences of chronic pain in the elderly patient [5].

A multidisciplinary team should be comprised of physicians (family physician, geriatric consultant and pain consultant as needed), nurse, physiotherapist, social worker, dietitian and other team participants such as psychologists, complementary medicine therapists etc.

The roles of the physician are primarily to make a correct diagnosis and design multidirectional treatment including the pharmacological and interventional treatment. Often the input of other members of the team is essential in refining the diagnosis and emphasizing other aspects associated with the pain such as psycho-social issues and daily function (see Case Vignette #4). Follow up must include the medical response to treatment and monitoring side effects in addition to preventing the influence of pain on physical and cognitive function, mood and nutrition. Repeated re-evaluation of the pharmacological therapy is important and recommended.

Case Vignette #4: Psychosocial Aspects of Chronic Pain
An 82 year old women suffering from chronic upper and lower back pain is referred to a multidisciplinary pain clinic. She is found to have spinal stenosis and degenerative changes on spinal radiology and she is depressed. A biomedical diagnosis would direct the clinician to analgesic pharmacotherapy combined with antidepressant pharmacotherapy. Prior to this referral she underwent 8 epidural steroid injections, radiofrequency ablation for facet joint arthropathy and received antidepressants. Undergoing a biopsychosocial evaluation it was clear that she was also suffering from chronic post-traumatic stress disorder as a holocaust survivor, anxiety and loneliness. A combined approach of psychotherapy, group support and gradual physical reconditioning brought about a marked improvement in her situation.

29.8 Non-pharmacological Treatment for Pain in the Elderly

Treatment of the painful elderly should always include one or more modalities of non-pharmacological treatment. The non-pharmacological treatment can contribute to pain relief itself and simultaneously help to prevent some of the "vicious cycle" of frailty and deconditioning case by the pain [21].

Reasons for using non-pharmacological modalities include patient and physician concerns about the potential for drug-related adverse events and physician concerns about polypharmacy [24].

Non- pharmacological approaches help to maintain muscle strength and function, prevent falls, treat mood and sleep disorders and prevent functional deterioration. These therapies are safe, can reduce pain, and in many cases improve functioning.

Non- pharmacological pain treatment includes modalities such as:

1. Local interventions- massage, acupuncture, shiatsu.
2. Physiotherapy for local treatment, muscle strengthening and adjustments of walking accessories.
3. Complementary medicine physical activities such as Tai Chi or Chi-gong.
4. Psychosocial and cognitive interventions such as Cognitive Behavioral Therapy [24].

29.9 Pharmacological Treatment for Pain in the Elderly

Prescribing for older patients offers special challenges. A few considerations have to be made before prescribing pharmacological treatment for pain to an elderly patient:

1. Pharmacokinetics: Alternation in pharmacokinetics makes the elderly patient more susceptible for side effects. Change in pharmacokinetics can prolong the time to clinical effect.
2. Concurrent illnesses: Most elderly patients suffer from medical conditions that may interact with pain medications such as renal failure, heart failure and dementia.
3. Polypharmacy: Older people take about three times as many prescription medications as do younger people. Taking several drugs together substantially increases the risk of drug interactions and adverse events [5] (Case Vignette #5).

Case Vignette #5: Delirium in the Geriatric Patient
An 85-year old woman was hospitalized in the geriatrics department due to delirium and hyponatremia. She had started treatment with a Transdermal Buprenorphine patch 10 days previously due to back pain of 6 months duration. Her medical history included hypertension and asymptomatic gallstones. Until recently, she had lived alone, was independent in ADL (activities of daily living) and had no cognitive impairment.

The patient had received analgesic treatment at the hospital pain clinic, including lidocaine injections and radiofrequency ablation without clinical improvement.

After admission, the Buprenorphine was stopped with spontaneous resolution of her delirium and hyponatremia. During the hospitalization, she received counseling with a spinal neurosurgeon and pain specialist. Physical examination revealed muscle weakness and unstable gait and she was advised to use a walker. She was discharged under a medical regimen of Pregabaline (25 mg once daily), Dipyrone 1 g three times daily, and Paracetamol (1 g three times daily). Depression was diagnosed during hospitalization, and she was recommended to begin treatment with Venlafaxine (37.5 mg once daily). She was recommended to receive help in bathing and dressing, use a walker and start physiotherapy and hydrotherapy.

Upon visiting the geriatric clinic 3 weeks later, the patient reported a decrease in pain. She moved temporarily to live with her daughter and received government-sponsored assistance for 7 h per week. She underwent physical therapy in order to improve her muscle strength and was being weaned off her walker. She also began hydrotherapy. She reported slight improvement in her mood and was planning to return to her house.

Medications and combinations inappropriate for use in elderly patients are extensively discussed in the American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults [25].

Common geriatric practice concerning drug treatment is based on the motto “Start low and go slow …. And sometimes say “No“ …. “.

The pharmacological treatment for the elderly patient suffering from chronic pain should be based on “around the clock” treatment with the least harmful medication such as Paracetamol (or Dipyrone, in countries where it is licensed). Patients should be repeatedly advised to take the treatment regularly and not “as needed”.

In cases of neuropathic pain adjuvant drugs in low dose maybe added.

Non Steroid Anti-inflammatory Drugs (NSAID's) have a limited role in the treatment of chronic pain in elderly patients due to potentially hazardous side effects such as gastrointestinal bleeding, renal failure and thrombotic events. Patients aged over 75 years have increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups. Beers criteria advise to avoid chronic use, unless other alternatives are not effective and the patient can take a gastro protective agent (proton-pump inhibitor or misoprostol). All NSAID's (including COX 2 selective drugs) should be avoided in patients suffering of renal failure or heart failure. Indomethacin is not recommended for use in the elderly population [25].

Failure of treatment with paracetamol, adjuvant drugs and non-pharmacological treatment or intractable pain raises the possibility of treatment with opioids. The option of opioid therapy should be discussed with the patient and the caregivers. The ability of the patient and caregivers to cope with opioid therapy should be assessed. The patient should receive an explanation about the side effects of the drugs including "geriatric" side effects such as the risk for falls and cognitive impairment. Opioid treatment should be started with short acting medications in low doses (half of the normal starting dose). Fentanyl patch should not be started in an opioid-naïve patient.

Table of common analgesic medications in the elderly (see Table 29.3).

This table should not be taken as a recommendation for any medication in any specific patient. The use of medications is entirely the responsibility of every practicing physician.

29.10 Invasive Treatment for Pain in the Elderly

There are a multitude of invasive treatment options for patients suffering from pain including such therapies as epidural steroid injections, nerve blocks, intra and peri-articular injections (with or without steroids), and more recently fascial plane blocks. Although a thorough discussion of all these options is beyond the scope of this chapter, a few important caveats can be described including special considerations in the elderly population.

1. The physical examination in the elderly can often be challenging and often it is impossible to make a clear single diagnosis of the seat of the pain. It is not uncommon to perform therapeutic trials with local anesthetics such as lidocaine 1% injected towards or near the suspected pain generator such as a joint or tendon.
2. Elderly patients usually have many degenerative features on imaging studies such as CT or MRI radiology studies. These are often incidental and not the cause of pain.
3. The inherent risk of invasive therapy in the elderly is higher than in younger populations due to co-morbidities such as diabetes mellitus and hypertension as well as the risk of polypharmacy and anti-coagulant therapy.

Table 29.3 Common drugs for pain in the elderly

Drug	Dose recommendation for the elderly		Common side effects	Special comments for elderly patients
Acetaminophen (Paracetamol)	Max daily dose 3000–4000 mg No special reduction for geriatric population		Liver failure	Prolonged half-life in elderly patients; no specific dosage adjustment is necessary based on current kinetic data.
Dipyrone	Max daily dose 4000 mg/day No special reduction for geriatric population		Not approved in USA and other countries due to serious adverse effects including agranulocytosis, aplastic anemia, thrombocytopenic purpura, and hemolytic anemia	
NSAIDS	Aspirin	Up to 4 g orally per day in divided doses	Increased risk of gastrointestinal bleeding or peptic ulcer disease. Can increase blood pressure and induce kidney injury	**Use with caution or avoid use as potentially inappropriate in older adults (beers criteria). Begin at the lower end of the dosing range. Use for minimal duration as possible.** Before initiating treatment with NSAIDs weigh the potential benefits and risks of NSAIDs. To reduce the risk of serious adverse effects, use the lowest effective dose for the shortest possible duration. Avoid chronic use, unless other alternatives are not effective and patient can take gastro protective agent (proton-pump inhibitor or misoprostol) avoid indomethacin.
Non-selective	Ibuprofen	200–400 mg orally every 4–6 h as needed, MAX 1200 mg/day		
	Diclofenac	18 or 35 mg orally 3 times daily		
	Naproxen	Initial, 500 mg orally followed by 250 mg every 6–8 h as required; titration, adjust dose and frequency to individual patient requirements; MAX 1250 mg/day		
	Etodolac	Immediate release, 200–400 mg orally every 6–8 h as needed; max 1200 mg/day		

NSAIDS cox 2 selective	Celecoxib	Initial, 400 mg orally once, plus one additional 200-mg dose if needed on the first day	Can increase blood pressure, increase risk for myocardial infarction and induce kidney injury.	**Use with caution or avoid use as potentially inappropriate in older adults (beers criteria). Begin at the lower end of the dosing range. Use minimal duration as possible.** Before initiating treatment with NSAIDs weigh the potential benefits and risks of NSAIDs. To reduce the risk of serious adverse effects, use the lowest effective dose for the shortest possible duration.
		Maintenance, 200 mg orally twice a day as needed		
	Etoricoxib	30–90 mg once daily (120 mg for gout)		
Weak opioids	Codeine	Initial, 15–60 mg orally every 4 h as needed; individually titrate to a dose that provides adequate analgesia while minimizing adverse reactions; MAX 360 mg/24 h	Constipation, dizziness, somnolence, drug dependence	**See FDA black box warning. Use with caution or avoid use as potentially inappropriate in older adults (beers criteria).**
		Geriatrics- start at the low end of the dosing range and titrate slowly		
	Tramadol	Maintenance, 50–100 mg orally every 4–6 h as needed following initial titration; MAX 400 mg/day		
		Geriatric patients: Immediate release: Reduce dose, extended release: Avoid		
	Buprenorphine	Transdermal patch- initial, 5 µg/hour transdermally; titrate based on analgesic requirement and tolerance at a minimum interval of every 72 h; replace patch every 7 days; MAX 20 mcg/hour		

Table 29.3 (continued)

Drug	Dose recommendation for the elderly			Common side effects	Special comments for elderly patients
Strong opioids		Morphine	Opioid-naïve patients-immediate-release tablet-initial, 7.5 mg orally every 4 h as needed.	Pruritus, constipation, nausea, somnolence, urinary retention, coma, respiratory depression, drug dependence	**See FDA black box warning. Use with caution or avoid use as potentially inappropriate in older adults (beers criteria). Start at lower end of dosing range and titrate slowly.**
		Oxycodone	Opioid-naive patients: Initial, 2–5 mg orally every 4–6 h as needed.		
		Fentanyl	Fentanyl transdermal system patch is only for use in opioid-tolerant patients.		
			See literature for converting short action opioids to fentanyl patch.		
Adjuvants	Anti-depressants	Amitriptyline	10–25 mg at bedtime	Constipation, xerostomia, dizziness, headache, somnolence, cardiac dysrhythmia, myocardial infarction.	**Use caution or avoid use as potentially inappropriate in older adults (Beer's criteria).**
		Duloxetine	Initial, 30 mg orally once daily for 1 week; maintenance, 60 mg orally once daily; MAX 60 mg/day	Gastrointestinal manifestations, asthenia, dizziness, sedation, somnolence	**Avoid use in GFR less than 30 mL/min.**
	Anti-epileptics	Gabapentin	Initial 300 mg orally increasing to 900 mg daily. Then may be increased to 2400 mg by titration.	Dizziness, somnolence	
		Pregabaline	Start 25 mg at bedtime. Monitor side effects and titrate slowly to the minimal effective dose.	Constipation, nausea, xerostomia, asthenia, ataxia, dizziness, incoordination, somnolence.	**Use caution or avoid use as potentially inappropriate in older adults (Beer's criteria).**

4. Musculoskeletal injections include mainly intra and periarticular injections. Many of these conditions are chronic and a strict risk benefit ratio should clearly demonstrate the advantage of invasive therapy over inherent risks of the procedure indicated.
5. Having stated the above, old age is by no means a contra-indication for invasive palliative pain therapy.

29.11 The Role of the Pain Clinic

There are a few definite advantages for referring patients to the pain clinic. These will include a deeper understanding and familiarity with pharmacological therapy, knowledge in utilizing invasive procedures and, where practiced, a multidisciplinary approach to the elderly patient suffering from chronic pain.

Pharmacotherapy and invasive therapy have been discussed above. We should consider the multidisciplinary biopsychosocial approach to patients suffering from chronic pain [26, 27]. According to this model, first described by Engels in 1980, clinicians must attend simultaneously to the biological, psychological, and social dimensions of illness. This is in sharp contrast to the biomedical model so prevalent today [28]. A good example is outlined in Case Vignette #4.

Thus a timely referral to a multidisciplinary pain clinic would be appropriate for the following indications:

Uncontrolled pain:

(a) In a patient who has undergone a full work-up and initial treatment and is still suffering considerably.
(b) In a patient referred for possible invasive therapy such as nerve block, fascial plane block, epidural or facet joint injection etc.

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Chapter 30
Principles and Protocols of Rehabilitation of Geriatric Patients with Rheumatic Disorders

Emanuel Marcovici

30.1 Principles of Rehabilitation of Geriatric Patients with Rheumatic Disorders

The general purpose of rehabilitation is to restore the patient's physical and mental capacities lost as a result of disease, injury, or illness and to obtain the highest possible level of function, independence, and quality of life.

Older adults with multiple co-morbid conditions are particularly prone to develop a disability in short periods. The goals of rehabilitation for older adults usually focus on the recovery of self-care ability and mobility. The recovery of older adults requires a more extended period to achieve, and functional outcomes are usually worse when compared with younger patients [1, 8, 17].

Rehabilitation manages disease consequences, the most significant being pain, fatigue, joint stiffness, deformities. The target is, besides the control of the rheumatic disease, to restore the physical, medical, cognitive, emotional, and socioeconomic status at a minimum 70–80% of the before disease period.

The pre-rehabilitation evaluation should always include the identification of co-morbidities that may directly or indirectly affect rehabilitation outcomes. Another goal of the evaluation is to determine the best site for rehabilitation. Several settings are available, including an inpatient rehabilitation department, a nursing home for patients with sub-acute conditions, or home-based protocols.

Assessment for rehabilitation potential should be performed when the acute medical illness has passed, i.e., after a flare of arthritis or another rheumatic condition. The factors to foresee the rehabilitation usefulness include motivation,

E. Marcovici (✉)
Head of the Geriatric Rehabilitation Department,
Flieman Governmental Rehabilitation Hospital, Haifa, Israel
e-mail: emanuel-olivia@bezeqint.net

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cognition, and prior functional status. As already mentioned, co-morbid illnesses may have a significant effect on the rehabilitation process and frequently dictate the framework and the intensity of rehabilitation therapy [7, 21].

Inpatient rehabilitation for the most severely affected patients takes place in rehabilitation centers and skilled nursing facilities. Patients must be managed by an interdisciplinary team of experienced nurses and therapists, be seen daily by a physician, and require 24-h rehabilitation nursing care. Elderly patients are required to actively participate in the rehabilitation process and focus on physical and psychological therapies for a minimum of 3 h a day. Around clock availability of a physician for urgent consults is a must. There are no thresholds for the intensity or duration of therapy sessions. In general, the inpatient rehabilitation settings provide a slower rehabilitation pace together with 24-h nursing care, necessary for some older patients with multiple co-morbid diseases.

Home-bound rehabilitation, including part-time nursing and ambulatory therapy services, is another possibility for patients with moderate functional impairment or wheelchair-confined patients that cannot reach a community rehabilitation center [1, 7, 10].

The interdisciplinary approach is a cornerstone for the success of rehabilitation and necessitates the participation of several professionals (Table 30.1).

Of importance, assessment of both cognitive state and neuropsychological deficits should precede any rehabilitation therapy in geriatric patients to provide proper expectations and rational therapy plan. While some degree of age-related cognitive decline is reasonable even in healthy elderly adults, patients with various rheumatic conditions, particularly with systemic lupus erythematosus, rheumatoid arthritis, fibromyalgia, and chronic fatigue syndrome, can have an accelerated cognitive deterioration, which should not be missed. (15,16).

Table 30.1 Example of an interdisciplinary rehabilitation team [2–6, 9]

Specialty	Field of care
Physical therapist	Fitness, balance, gait, exercises for strength and endurance, physical treatments, fitting of an orthosis.
Occupational therapist	ADL∗ evaluation, home, family ambiance evaluation, training self-care and use of devices adapted to patient's impairment.
Nurse	Education and training of self-care skills, link with community and family
Social worker	Evaluation and solutions of problems related to the integration in family and community
Orthosist	Making and adaptation of braces, orthosis, splints, shoes and insoles, special canes, crutches and walkers.
Dietician	Proper nutrition for different conditions, maintain body weight within normal limits.
Recreational therapist	Using leisure for improving physical and psychological impairments: Crafts, music, dance, sports.

ADL activities of daily living

30.2 Examples of Physical Treatment in the Course of Rehabilitation in Rheumatic Diseases

1. Muscle training for prevention of sarcopenia and osteoporosis

   In isometric or static exercises, muscle contractions are achieved without joint movement and lengthening or shortening of muscle fibers; they can be generated with the help of a fixed object like the hand of the therapist, a belt, small ball or elastic band. Isometric exercises increase strength and resistance and are easy and safe to perform by patients with inflammatory arthritis. Isotonic or dynamic exercises involve changes in the muscle fiber length through their elongation or shortening; nearby joints move through the full range of motion. Aerobic conditioning and strengthening exercises including walking, running, cycling, swimming, and stair climbing in moderate-intensity with an increase in heart rate up to 70%–80% of maximal (maximal heart rate is equal 220 minus patient's age) are efficacious as well [11, 12].
2. Improving elasticity of tendons, ligaments, capsules, and prevention of contractures

   Range of motion and flexibility exercises help preserve joint movements and are passive when performed by the physiotherapist or active when implemented by the patient. Training devices like bicycles, stepper, Continuous Passive Movement machines can be utilized for this goal as well [13, 20].
3. Heat

   Heat is used for pain relief, reduction of tissue stiffness and inflammation, relief of muscle spasms, and increase of local blood flow. Superficial heating can be achieved with hot packs, heating pads, paraffin, whirlpool, or therapeutic pool. Ultrasound, microwaves, and short waves are used for deep heating [18, 20].
4. Cold

   Cold packs, cold water immersion, ice massage, and vapor-coolant sprays can be used for the reduction of edema and pain, decrease of spasticity, and for the alleviation of symptoms of inflammation or bleeding locally [8, 14].
5. Electrotherapy

   Transcutaneous electrical nerve stimulation (TENS), neuromuscular stimulation, and functional electrical stimulation can be prescribed for pain and spasm relief or neuro-muscular stimulation [8, 14].
6. Phototherapy and laser therapy

   Phototherapy and laser therapies are in use for chronic articular pain and stiffness, as well as for skin ulcers and chronic wound treatment [17, 22].
7. Shock wave therapy

   Shock wave therapy is usually used for pain reduction in joints, tendons, fascia, and ligaments. Additional effects of shock wave therapy include the promotion of neovascularization in ischemic tissues and fragmentation and resorption of calcifications [22].

8. Mobility aids

   Mobility aids include canes, axillary and forearm crutches, walkers, including four-point walker, two-wheeled walker, and four-wheeled walker, as well as manual wheelchairs, power chairs, and scooters [8].
9. Bathroom and Self-Care aids

   Grab bars, raised toilet seats, shower chairs, dressing, shoes and socks aids, adapted handles for cooking and eating are commonly used tools [8, 22].
10. Electronic devices

    Electronic devices include communication boards, voice amplifiers, telephone adaptations, and environmental control units, using a joystick, mouth stick, or voice command units [17].
11. Orthoses

    The main target of orthoses is to restrict or assist motion in the limbs and spine. Shoe inserts, metatarsal pads, ankle-foot orthoses, lumbar and thoracic spine braces, hand and wrist splints, and others are commonly used in patients with musculoskeletal limitations [9].

30.3 Example of Protocols of Rehabilitation Exercise for a Patient with Rheumatic Disease

1. Cardiopulmonary fitness exercises

   Walking for at least 30 min/5 days per week, or high-intensity exercises, for example, walking in the fastest possible pace or swimming for 20 min/3 days a week. Monitoring of blood pressure, pulse, O2 saturation before and after exercise is recommended. Exercise stress tests and spirometry should be performed yearly [21].
2. Exercises for increasing muscle strength

   Eight to ten individually adjusted exercises to increase muscle strength with ten repetitions each should be performed at least two times per week. Exercises should be focused on affected joints, muscles, tendons, and should be preceded by a 5–10 min warm-up with Range of Motion (ROM) exercises [20–22].
3. Flexibility and balance exercises

   Flexibility exercises aim to preserve ROM within physiologic limits. They involve the most used joints and are particularly useful when local inflammation is present or for contracture prevention. The exercises are generally recommended for daily use. Besides, balance exercises can be added to reduce falling risk [17, 22].

30.4 A Differential Approach to Rehabilitation According to the Disease State

There are certain differences in planning rehabilitation, particularly physical therapies during the acute, subacute, and chronic phases of various rheumatologic conditions (Table 30.2) [10, 19, 20].

Table 30.2 Recommended rehabilitation programs in different phases of rheumatic disease

Disease phase	Treatment
Acute phase	Total body rest, splints and self-management. Active and passive ROM∗ exercises Isometric exercises Cold therapy Orthotics
Subacute phase	Increased repetitions of ROM∗ exercises Progression from isometric to isotonic dynamic exercises Heat therapy and massage before stretching, to prevent muscle spasm and improve flexibility Ergonomic changes Orthosis and splinting Aquatic therapy
Chronic phase	Integrate dynamic strengthening exercises with exercise against resistance. Dynamic exercises for muscle strength, aerobic capacity. Aerobic exercises should be started. Low-impact exercise, such as walking, dancing, aquatic training, cycling and dynamic-resistance exercises would be added at the later stage

ROM range of motion

30.5 Recommended Rehabilitation Modalities in Various Rheumatic Conditions

1. Osteoarthritis [9, 10, 14, 21]

Modalities	5. Manual therapy	10. Walking aids	15. Adaptive devices
1. Aerobic exercise	6. Joint taping	11. Tai chi	16. Phonophoresis
2. Mobilization exercises	7. Medial-lateral wedged insoles for lateral-medial compartment knee OA	12. Acupuncture	17. Iontophoresis
3. Aquatic therapy	8. Joint protection, bracing	13. Tens	
4. Weight loss, if needed	9. Thermal modalities	14. Psychosocial interventions	

2. Rheumatoid arthritis and other inflammatory arthritidies [8, 9, 10, 14]

Modalities	3. Thermal modalities	6. Joint protection, orthoses	9. Tai Chi
1. Isometric exercises	4. Iontophoresis	7. Adaptive devices	10. Psychosocial intervention
2. Water and land-based aerobic exercises	5. Phonophoresis	8. Walking aids	

3. Myopathies and connective tissues diseases [10, 17]

Modalities	3. Resistance training in chronic phase	6. Respiratory exercises	9. Acupuncture
1. Bed rest, passive ROM exercises in acute phase	4. Aerobic exercise	7. Dietician consult for esophageal problems	10. Shock wave therapy in enthesopathies, soft tissue calcifications, fibrosis
2. Active ROM exercises after stabilization	5. Aquatic exercise	8. Tai chi	

4. Fibromyalgia and Myofascial Pain Syndromes [7, 14, 20]

Modalities	4. Water and land-based aerobic training	8. Acupuncture and acupressure	12. Regular meals and sleep hours
1. Interdisciplinary approach	5. Massage	9. Strenth training	
2. Prevetion of repetitive movements (i.e., computer operations)	6. Superficial and deep heat	10. Meditation and cognitive behavioral therapy	
3. Correct posture and positions during sitting, standing, walking, sleeping, driving.	7. Treatment of trigger points by spraying ethyl chloride and stretching the muscles under the sprayed area, insertion of dry needles in motor points, phonophoresis and iontophoresis	11. Repetitive transcranial magnetic stimulation	

5. Tendinitis and bursitis [8, 17, 21]

Modalities	3. Cold packs	6. Soft tissue massage and stretching
1. Rest and immobilization of the related joints	4. Elevation of the affected limbs	7. Phonophoresis
2. Taping around the inflamed area	5. Isometric exercise to preserve the related muscles	8. Iontophoresis

6. Spinal stenosis, Spondylosis, Sacroiliitis [13, 21]

Modalities	4. Avoidance of bed rest to prevent deconditioning	8. Superficial and deep heat	12. Iontophoresis
1. Stretching the tight paravertebral muscles	5. Maintain cardio-respiratory fitness by ergometric bike and 4 limbs activation instead of treadmill	9. Hydrotherapy	

2. Isometric abdominal strengthening exercises	6. Spinal manipulation and traction	10. Tens	
3. Lumbar sacral soft corsets only for acute phase	7. Correction of legs' length difference	11. Phonophoresis	

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