Pathophysiology of Temporomandibular Disorders

7

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Abstract

Temporomandibular disorder is the term used for the musculoskeletal disorders of the jaw system, which comprises the temporomandibular joints and its associated musculature. In the past decades, several concepts on the pathology, diagnosis, and management of temporomandibular disorders have been proposed, which have resulted in several classifications of these disorders. The most commonly used is the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) (Schiffman et al., J Oral Facial Pain Headache 28:6–27, 2014). In this classification, TMJ disorders are distinguished from masticatory muscle disorders, although these categories commonly coexist. Within the category of TMJ disorders, pain (arthralgia, arthritis) and disorders (internal derangements, including disc interferences, adhesions, ankylosis, hypermobility) usually represent manifestations of TMJ disease, which include arthritic diseases and growth disorders. This chapter focuses on the pathophysiologic processes occurring in the most common group of joint disorders, i.e., TMJ degenerative diseases (Stegenga, J Oral Rehabil 37:760–765, 2010).

7.1 Conceptual Approaches

The temporomandibular joint is classified as a complex synovial joint. It is termed "complex" due to the presence of an articular disc, which separates the intra-articular space into two compartments. Essentially it consists of several

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interdependent connective tissues, each with its specific adaptive capacity, which is the capacity to adapt to functional changes by remodeling. Pathologic changes may affect all joint tissues, including the articular cartilage, the disc, the subchondral bone, and the synovial membrane.

The appreciation of the importance of specific joint structures has considerable influence on the approach toward classification of TMJ disorders and consequently on their diagnosis and management. The presence of the disc has focused the attention on the joint's mechanical aspects. In this approach the primary focus is on a joint that is not working properly, in terms of impaired gliding and obstructions, especially by the disc in internal derangements. In this conceptual approach, degenerative changes are frequently regarded as the result of the mechanical derangement.

Based on the idea that the temporomandibular joint is affected by the same pathologic processes and diseases as the other synovial joints and supported by clinical observations in a large group of patients [1] and their long-term follow-up [2] and detailed observations of pathologic changes in articular cartilage [3] and the synovial membrane [4], we conceptually described TMJ osteoarthritis as a "whole joint" disease back in 1989 [5]. The focus was placed on pathological changes that begin whenever the connective tissues making up the joint have not successfully adapted to the demands imposed to them, eventually resulting in pain and function impairment. During the past 25 years, there has been a massive expansion of our understanding regarding the various pathologic events that take place in the development of synovial joint degenerative diseases, in general, and of TMJ degenerative diseases in particular. These findings support the adoption of the "joint is an organ" concept [6].

Osteoarthritis is the clinical and pathological outcome of a range of disorders and conditions that lead to pain, disability, and structural failure in synovial joints. Therefore, usually primary osteoarthritis (which may be localized or generalized when three or more joint sites are involved) is distinguished from secondary osteoarthritis, which follows a clearly defined predisposing disorder or disease. Throughout the years, besides the genetic background, mechanical and psychological stresses have been consistently connected to pain conditions and function impairment associated with the temporomandibular joints and masticatory muscles. An important notion that may unify the general thinking about synovial joint diseases is that there is a dynamic balance between the loads imposed on a tissue or system and its adaptive capacity, which results in ongoing structural changes aimed at enabling the tissue to optimally withstand the loads and functional demands [7].

7.2 Etiology and Risk Factors

The development of all types of TMJ degenerative diseases is associated with multiple etiological and risk factors. The primary etiological factor is usually unknown, but it is likely that one or more of the risk factors mentioned in Table 7.1 play a role in TMJ degenerative disease, supporting that this is a complex and probably multifactorial joint condition. Progress has been made in identifying mutations in

Table 7.1 Risk factors for TMJ degenerative disease

Trauma
Parafunctions
Functional overloading
Aging
Systemic disease
Hormonal factors

collagen genes that are associated with different types of bone and cartilage dysplasia where osteoarthritis is part of a more complex phenotype, but none of the single-gene mutations that code for structural matrix proteins appears to be important in determining the susceptibility to the common types of osteoarthritis [8].

Whatever primary factors may be involved, it is essential to note that they result in a disturbance of the balance between synthesis and breakdown. The adaptive capacity is insufficient to withstand the loads, which is expressed in a relative surplus of breakdown products. The balance may become disturbed due to excessive physical stress, such as a traumatic event, or due to reduction of the adaptive capacity of the tissues involved, for example, due to a systemic disease. This explains that a joint may become overloaded even when the amount of loading is normal [9, 10].

Although many etiologic factors may be important in the etiopathogenesis of the disease, mechanical stress appears to play a critical role in the events that lead to the initiation and progression of osteoarthritic diseases. There are at least two mechanisms through which mechanical loads can trigger molecular events that may lead to degenerative disease in susceptible individuals. The first is the production of reactive free radicals [11, 12]; the second is the stimulation of sensory neurons resulting in release of neuropeptides [13, 14].

7.3 Biochemical Responses

Compressive loading not only may lead to direct damage of the loaded tissues but also may disturb synovial capillary perfusion. This induces a relative hypoxia, which on reperfusion is followed by the generation of highly reactive free radicals (oxidative stress). Normally, scavengers neutralize these radicals to prevent damage to occur. When the free radicals exceed the concentration of scavengers, chondrocyte apoptosis may be the result, and damage to the articular tissues and to the molecules in the synovial fluid may occur [15]. Further research is needed to support (or reject) that this hypoxia-reperfusion injury actually occurs in TMJ osteoarthritis [16]. The other mechanism concerns mechanically stimulated sensory nerves releasing neuropeptides, such as substance P and calcitonin gene-related peptide, which produce several cytokines, nitric oxide, and other molecules that contribute to an inflammatory response. In a recent study, it was suggested that hyaluronic acid may inhibit substance P and CGRP expression in the TMJ [17].

Since pain is one of the cardinal symptoms of TMJ degenerative disease, the importance of inflammation in the progression of the disease has received considerable attention. In painful joints, prostaglandin E_2 and COX-2, which are important

for the production of prostaglandins, appear to be detectable [18]. However, concentrations of prostaglandin E_2 and several other markers were not significantly increased in the synovial fluid of patients with TMJ osteoarthritis compared with healthy controls [16]. It has been suggested that celecoxib (which is a selective COX-2 inhibitor) has protective effects on condylar chondrocytes [19].

A growing number of inflammatory cytokines (e.g., interleukin (IL)-1-beta, IL-6, IL-12, and tumor necrosis factor-alpha) that are produced by macrophages and synovial cells have been identified in the synovial fluid of patients with TMJ degenerative diseases [20, 21]. Synovial fluid levels of IL-1-beta and IL-6 appear to correlate with the degree of pain and synovitis. IL-1 and TNF-alpha play an important role in the upregulation and activation of matrix-degrading enzymes [22–24].

The most important matrix-degrading enzymes found in osteoarthritic joints include aggrecanases and collagenases, which are members of the matrix metalloproteinase (MMP) family. The enzyme activity is not only controlled by various cytokines but also by steroid hormones and by specific inhibitory molecules (the so-called tissue inhibitors of metalloproteinases). Excessive mechanical stress has been shown to activate the plasminogen activator system, which may lead to proteolysis of extracellular matrix components [25]. Type I collagen is the primary component of TMJ articular cartilage, which can be degraded by several types of MMPs and by cathepsin K. Aggrecan is a proteoglycan which is critical in imbibing water into the matrix, thereby giving the joint surface the ability to withstand compressive forces. Degradation of aggrecan (by several MMPs and aggrecanases, such as ADAM-TS-4 and ADAM-TS-5) has been shown to occur early in the osteoarthritic process [26]. With the degradation of cartilage matrix proteins, fragments are produced that can stimulate the production of inflammatory cytokines and MMPs and further matrix destruction (Fig. 7.1).

Several authors have shown an increase in vascular endothelial growth factor (VEGF) expression in diseased TMJs following mechanical overloading and hypoxia [27, 28]. It is known that angiogenesis is stimulated by metabolic stress (e.g., due to hypoxia), mechanical stress, inflammation, and alteration in hormonal levels, and these are all factors that play a role in the susceptibility for or in the etiopathogenesis of osteoarthritis.

An increasing number of studies have focused on the significance of subchondral bone in the pathogenesis of TMJ degenerative disease. The chondrocytes of degraded cartilage influence osteoclastogenesis by affecting the ratio of receptor activator of nuclear factor kappaB ligand (RANKL) and osteoprotegerin (OPG), resulting in subchondral bone loss and turnover [29, 30]. Transforming growth factor (TGF) beta-1 has been suggested to play an initiating role in decreasing bone mineral density and increasing subchondral bone turnover [31], which is frequently observed in early stages of in TMJ degenerative disease.

The female preponderance and the occurrence of TMJ degenerative diseases mainly during the reproductive years [32] suggest a possible role of female hormones in the pathogenesis. In a rat model, Wang et al. [33] showed that estrogen aggravates the degradation of cartilage and destruction of subchondral bone, which could be inhibited by an estrogen receptor antagonist. Studies on the role of estrogen and effects of other female hormones should be further evaluated.

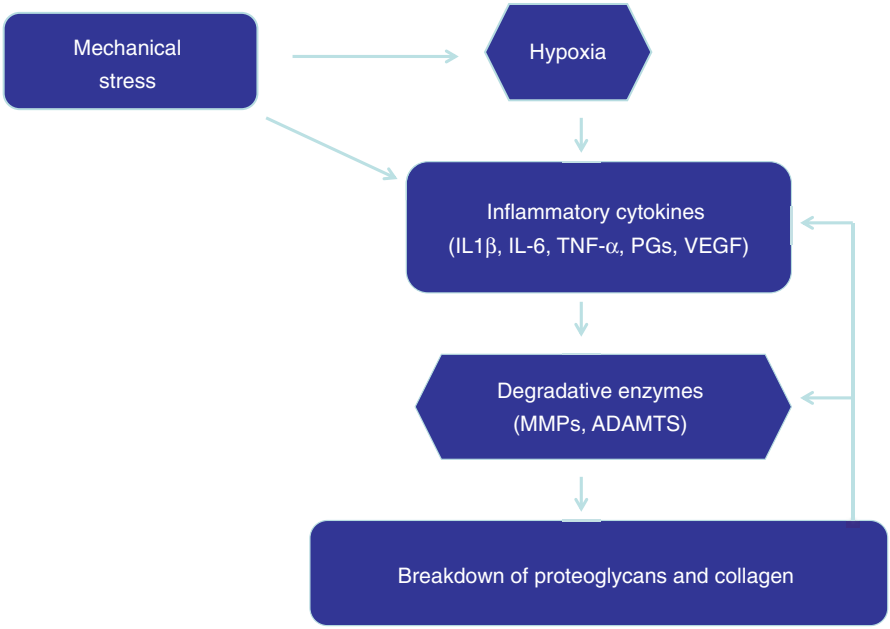

Fig. 7.1 Biochemical responses involved in TMJ osteoarthritis disease. *IL* interleukin, *TNF* tumor necrosis factor, *PG* prostaglandin, *VEGF* vascular endothelial growth factor, *MMP* matrix metalloproteinases, *ADAMTS* a disintegrin and metalloproteinase with thrombospondin motifs. To summarize, several key cytokines and degradative enzymes have been identified, setting up a biochemical cascade that represents the complex processes that occur in a pathologic joint, and sets up a vicious cycle that is potentially destructive for the joint. Despite the identification of these events, the number of properly controlled studies is still limited. Nevertheless, we seem to be on the threshold of the identification of TMJ degeneration biomarkers that can be easily detected in saliva, blood and urine. Theoretically, the explosion of knowledge is also interesting from a therapeutic perspective, although trials involving anticytokine therapy have produced disappointing results in osteoarthritis so far. I will come back to this issue later

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The relative increase of breakdown products within the joint leads to natural attempts at repair, which have to compete with ongoing damaging events. Initially chondrocyte activation and proliferation of clusters of chondrocytes are associated with anabolic responses with increased synthesis and turnover of matrix collagens and proteoglycans. Anabolic mediators include growth factors (e.g., insulin-like growth factor, fibroblast growth factor, transforming growth factor β) and bone morphogenetic proteins (BMPs): the anti-inflammatory cytokine interleukin-4 and proteinase inhibitors such as TIMPs and plasminogen activator inhibitor. In many cases

these processes reach a state of nonprogressive equilibrium. However, catabolism of cartilage matrix proteins may outstrip the capacity for cartilage repair, leading to decreased cartilage thickness and chondrocyte apoptosis. Catabolic mediators include nitric oxide, prostaglandins, and the pro-inflammatory cytokines IL-1β, tumor necrosis factor α, IL-6, and IL-7, as well as metalloproteinases and aggrecanases (ADAM-TS-4 and ADAM-TS-5). When damaging events are allowed to go on and repair and adaptive attempts are insufficiently successful, the disease gradually progresses from local damage to an interactive combination of degenerative changes and inflammatory responses and, eventually, to adhesion formation and radiographically visible degenerative changes. So, the vicious cycle of breakdown has to be interrupted to promote healing and to prevent further damage to occur.

7.4 Pathological Changes

Pathological changes may become obvious within all the tissues making up the joint. Microscopic breakdown of the articular cartilage in the early stages of osteoarthritis starts with clustering of chondrocytes. As the disease progresses, further matrix depletion occurs, affecting the proteoglycans and altering the collagen fiber architecture. This results in softening of the cartilage, which loses its normal resilience and capability of absorbing loading. The articular surface subsequently undergoes vertical and horizontal splitting, fibrillation, and thinning. Figure 7.2a shows a microscopic picture of a TMJ with the disc in a normal position. The enlarged view (Fig. 7.2b) shows signs of cartilage splitting, as well as early degenerative changes within the subchondral bone, i.e., fibrosis in the bone marrow spaces. Thus, early changes occur not only within the cartilage (especially in the deeper layers) but also within the subchondral bone. This can be explained by the changes occurring at the cartilage-subchondral bone interface. Chondrocytes become hypertrophic and produce more growth factors, such as vascular endothelial growth factor, and less sulfated glycosaminoglycans. The thickness of the cartilage reduces as a result and is increasingly depleted from proteoglycans. Cytokines produced by osteoblasts may

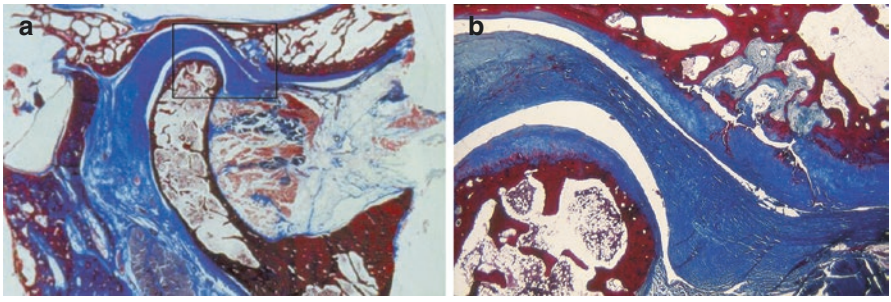

Fig. 7.2 (**a**) Histologic sagittal coupe of a right temporomandibular joint. (**b**) Enlargement of the area depicted in (**a**), showing signs of osteoarthritis in cartilage (vertical and horizontal splitting of cartilage) and subchondral bone (fibrosis of bone marrow)

diffuse to the cartilage region, while osteoclast activity and vascular ingrowth are increased due to growth factors that are produced by chondrocytes and diffuse to the bone marrow region [34].

The biomechanical properties of the cortical and subchondral bone play an important role in protecting articular cartilage following impact loading. The pathogenesis of osteoarthritis may in some cases be initiated by an increase in the density and stiffness of the subchondral bone following the healing of microfractures caused by unprotected loading of joints [35]. The consequent loss of bone viscoelasticity results in steep stiffness gradients in the bone. This in turn results in stretching and fibrillation of the overlying articular cartilage as well as focal osteonecrosis and the formation of bone cysts.

In inflamed joints, the compressive and tensile moduli of the TMJ disc significantly decrease, indicating that the disc becomes relatively softer [36]. This results in greater strain under the same stress, contributing to overloading and subsequent tissue breakdown. These changes are opposite to age-related biomechanical changes of TMJ discs, which imply stiffening of discs [37]. Thickening and increased stiffness of the disc with a loss of the characteristic biconcave shape may represent a defense mechanism to maintain the smoothness of the joint by compensating for the degeneration of the cartilage surface [38]. The integrity of the disc maintains the homeostasis of the joint; degenerative changes in the disc, including perforation, lead to disruption of the joint [39]. There appears to be interdependency between the integrity of the cartilage and the integrity of the disc, and that changes in either structure will have an effect on the health of the joint [38].

Important changes also occur within the synovial membrane and synovial fluid. First of all, recruited T-cells and B-cells contribute to local synovitis and neovascularization, signs of which may be observed during arthroscopy. Hyaluronic acid and lubricin have been shown to be deficient in osteoarthritic joints [40, 41]. Synovial fluid lubricates the joint and protects the articular cartilage surfaces from erosion and protein deposition. Damage of important synovial fluid molecules lowers the fluid's viscosity, which not only has consequences for the fluid as a lubricant but also disturbs the important function of the synovial fluid in nutrition as well as protection of the articular cartilage. In a study by Asakawa and co-workers [42], it was demonstrated that a compromised lubrication in the TMJ is associated with altered frictional properties, and Koolstra [43] showed that surface wear mainly occurred at the bone-supported cartilage surfaces but hardly in the articular disc.

Especially lubricin has been shown to protect against glycosaminoglycan depletion, collagen degradation, and loss of cells in the cartilage superficial zone [38, 44]. Lubricin is a large proteoglycan encoded by the gene proteoglycan 4 (Prg4) and is essential in the boundary lubrication to maintain joint integrity. It has been shown to prevent adhesion and regulate synoviocyte cell proliferation in the knee joint [45], and recently this has been shown to occur in the TMJ as well [38]. Hyaluronic acid does not have these specific protective effects, but the therapeutic benefit from lubricin appears to be enhanced by the addition of exogenous hyaluronic acid [46, 47].

7.5 Clinical Symptoms

Obviously, these pathologic changes eventually may become clinically manifest. Pain is the presenting symptom in the majority of patients, usually insidious in onset and intermittent at first, typically aching in character. Initially it is provoked by loading or movement of the joint and relieved by rest, but as the disease progresses, the pain may be more prolonged and experienced at rest and may become severe enough to wake the patient at night. A few minutes of early morning stiffness and transient stiffness (gelling) after rest are common. Pain may result from low-grade synovitis, inflammatory effusions, capsular distension, increased pressure or microfractures in the subchondral bone, hyperemia in subchondral bone (nocturnal aching), and tendinitis, myalgia, or muscle spasm.

As the disease progresses and the ligaments and the disc become involved, mechanical changes may occur, resulting in derangements within the joint that may interfere with or even interrupt smooth joint motion. Patients may develop painful or painless functional impairment due to restricted movements. Common physical signs include clicking, restriction of range of movement of the joint (due to obstruction of movement by a displaced disc, capsular fibrosis, or blocking by osteophytes), joint crepitus, periarticular tenderness, deformity, and muscle weakness and wasting. In the late stages, gross bony changes may eventually result in the loss of height of the mandibular ramus, which become manifest as asymmetry, tilting of the occlusal plane, and radiographically visible changes.

Kalladka et al. [48] summarized the etiopathogenesis of TMJ degenerative disease and the corresponding clinical features in different slow-progressive phases (Fig. 7.3). The early phase, in which there is evolution of the disease, may take 2.5–4 years on average and is clinically associated with clicking joints and intermittent locking. The intermediate phase, associated with TMJ destruction resulting in joint pain and functional limitations, lasts 0.5–1 year on average. The late (burned out) phase is the stage at which the joint tends to stabilize to a steady state.

7.6 Diagnosis

The most commonly occurring pathologic changes fit the diagnosis osteoarthritis or degenerative joint disease, which is a whole-organ disease involving biological mechanisms giving rise to pathological tissue changes and subsequent clinical manifestations. The diagram shown in Fig. 7.4 from a recent review, beautifully, summarizes the major biological mechanisms [49]:

- Cytokines such as IL-1β, TNF, and IL-6 are produced by chondrocytes and macrophages.
- Pro-MMPs, released by synoviocytes and macrophages, are cleaved into MMPs and further contribute to tissue damage.

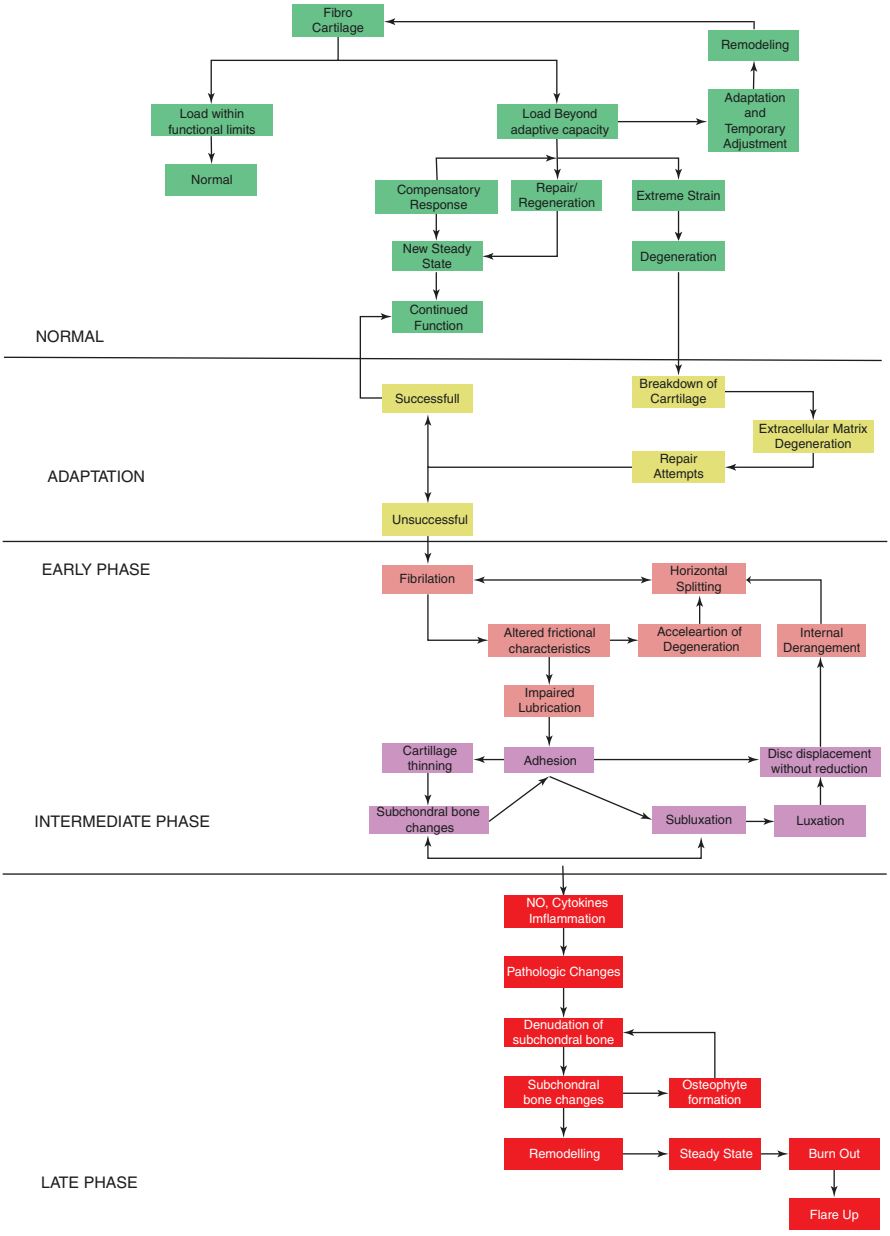

Fig. 7.3 Flowchart showing the etiopathogenesis of osteoarthritis in different phases (modified from [48])

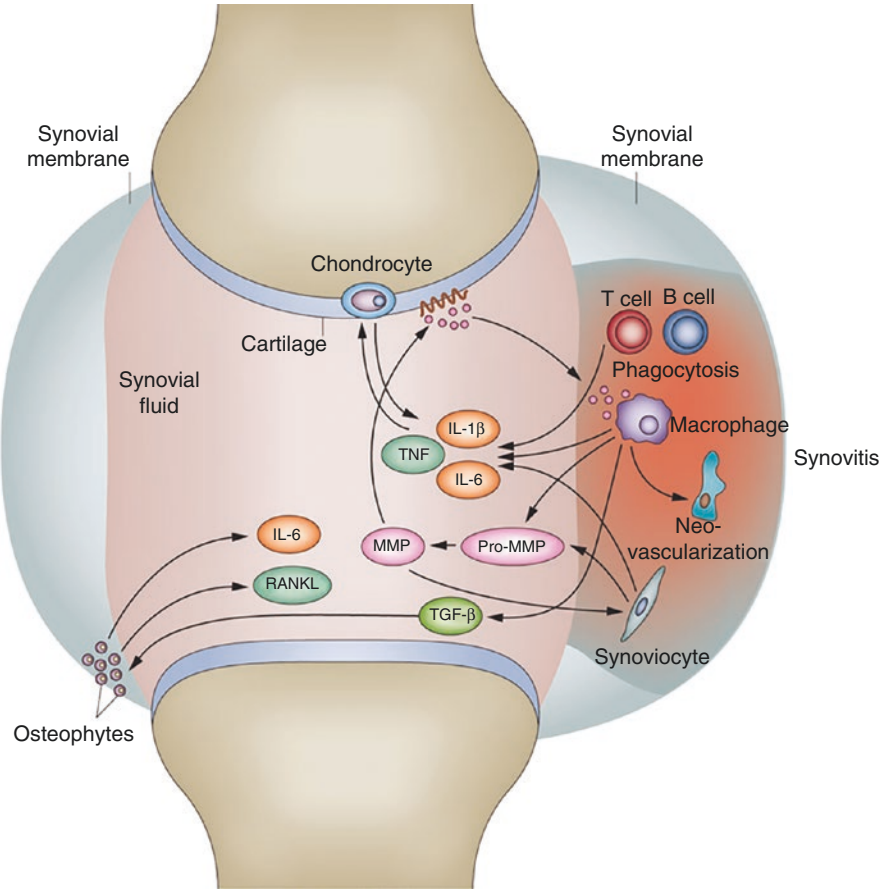

Fig. 7.4 Osteoarthritis as a whole-organ disease involving cytokine production by the cartilage, synovial membrane, and bone. Cytokines such as TNF, IL-1β, and IL-6 are produced by chondrocytes, macrophages, T-cells, and osteophytes in response to tissue damage. Pro-MMPs, released by synoviocytes and macrophages, are cleaved into MMPs and further contribute to tissue damage. T-cells and B-cells are recruited by the cytokine milieu in the synovial fluid and contribute to local synovitis. Bone cells release several cytokines, most notably IL-6 and RANKL. *MMP* matrix metalloproteinase, *RANKL* receptor activator of nuclear factor κB ligand (also known as tumor necrosis factor ligand superfamily member 11), *TGF-β* transforming growth factor β (ref. [49])

– T-cells and B-cells are recruited by the cytokine milieu in the synovial fluid and contribute to local synovitis.
– Bone cells release IL-6, and receptor activator of nuclear factor κB ligand (also known as tumor necrosis factor ligand, or RANKL) stimulates osteoclastogenesis, while growth factors stimulate osteophyte formation.

Commonly, the pathological changes include degeneration of cartilage and bone, as well as inflammatory changes. These changes lead to clinical signs and

symptoms, such as pain, interferences with smooth movement, and gross deformities. The impact on the patient may vary and depends on the extent of damage and inflammation, his or her coping skills, cognitions, emotional stability, social environment, and support. The net result is reflected by the extent of physical and psychosocial function impairment and impairment of the quality of life.

The primary conceptual focus inevitably has implications for diagnosis of temporomandibular joint diseases. When the mechanical changes are the primary focus, the position of the disc is a major concern. Most of the classification systems that have been proposed in the past emphasize the importance of disc position and are primarily designed to differentiate between anterior disc displacement with and without reduction, mechanical bone changes, accompanying joint sounds, and restriction of motion due to obstruction of the condyle by the displaced disc. During the past decades, there has been much discussion with regard to the course of internal derangements in several consecutive stages, reflecting a progression from disc displacement with reduction to a joint in which reduction does not take place anymore. This course was mainly based on retrospective and cross-sectional studies. In prospective controlled studies, it appeared that reducing disc displacement may remain unchanged throughout many years and also that a permanent disc displacement can occur without a preceding stage of disc displacement with reduction [50, 51]. In addition, it has been repeatedly established that the disc is in an anterior position in about 1/3 of asymptomatic persons, while in patients with clicking joints or with restricted movement, the disc is in a normal (i.e., nondisplaced) position [52, 53]. Moreover, clinically successful nonsurgical and minimally invasive treatment modalities do not influence the position of the disc [54, 55]. Therefore, there is a growing doubt with regard to the significance of disc position in TMJ afflictions, which makes it noteworthy that the emphasis in diagnosis is so often put on the position of the disc.

Focusing on the pathological events described in this chapter implies that the diagnostic workup is directed to changes in the articular cartilage, bone, and synovial fluid. Although cartilage degradation products (hyaluronan, keratin sulfate, cartilage oligomeric protein) and cartilage synthesis markers (collagen c-pro-peptide) have been shown to be increased in the plasma, synovial fluid, or urine of patients with osteoarthritis, there are currently no biochemical markers that have clinical utility for diagnosis, monitoring the progress of structural changes or assessing the prognosis of osteoarthritis in clinical practice. Biologic agents may have dramatic effects in rheumatic inflammatory diseases, and they were hoped to have similar effects in the treatment of degenerative joint diseases. Chevalier et al. [49] reviewed the results of several types of cytokine blockers, targeting IL-1β, TNF, and nitrogen oxide production mainly in osteoarthritic knee and hand joints. These results have been repeatedly negative in clinical trials. The same was the case for growth factor therapy, which not only showed very limited beneficial effects but also local effects (in the form of excessive formation of osteophytes) and systemic adverse effects [56, 57].

To date, synovial fluid analysis in osteoarthritis is indicated only to exclude bacterial joint infection or gout. Research efforts are ongoing to investigate the significance of potential risk factors and markers in the synovial fluid or other easily accessible body fluids.

7.7 Implications for Management

Management should not be focused on restoring the position of the disc but should primarily be aimed at restoring the balance between synthesis and breakdown, i.e., by load reduction and controlling other stress factors and by removing damaging products in an attempt to increase the tissue's adaptive capacity and provide for a favorable environment to allow tissue healing to occur. In the TMJ, arthrocentesis has been shown to be an effective therapeutic modality in terms of clinical improvement, aimed at reducing inflammation by removing damaging molecules and inflammatory mediators from the joint [58–61]. In many clinics, it is common to flush the joint with anti-inflammatory medications, or leaving hyaluronic acid as viscosupplementation.

Currently, it is widely advised to start the management of patients with temporomandibular joint disorders with conservative treatment modalities and to consider invasive treatment only in cases where noninvasive treatments have failed. A serious limitation of this strategy is the time it takes to try conservative treatment modalities first, without being able to predict their success. The degenerative process is allowed to persist, which might result in less favorable circumstances for subsequent invasive treatment measures.

In a controlled study from our group, we clinically and economically compared arthrocentesis as *initial* treatment to the usual conservative approach that is advised in current textbooks [61]. This study not only confirmed that arthrocentesis is an effective treatment modality for painful osteoarthritis but also suggests that early timing of this procedure appears to be more cost-effective than the usual approach. Early arthrocentesis might interrupt the degenerative process and prevent the disease from getting worse, leaving better conditions for additional conservative treatments.

We all recognize that patients with the same disorder, when given the same treatment, do not tend to respond in the same way. This implies that besides the pathologic process and the resulting clinical manifestations, the disorder's impact on the patient's physical and psychosocial well-being should be incorporated in both the diagnostic workup and management approach. In fact, the axis II diagnosis appears to be very important indeed, as was shown once more in a recent study by Manfredini's group [62]. Moreover, there is increasing evidence from the psychological literature [63, 64] that supports the importance of the calming care system in emotion regulation. We tend to enter the *danger* mode as soon as external and internal threats elicit mechanisms of self-protection, while we enter the *competitive* mode when we hunt for achievements in life. In both systems, the level of stress is relatively high as sympathetic activity is dominating, ensuring a necessary state of readiness (Fig. 7.5). These systems are opposed to the "care system," giving rise to a mode of compassion, which brings the body in a state of tranquility and relaxation. Here the parasympathetic system dominates, supporting an environment allowing for growth, repair, and healing. So, we not only have a responsibility to accurately assess the extent of physical pathology and its clinical manifestations in order to determine possible

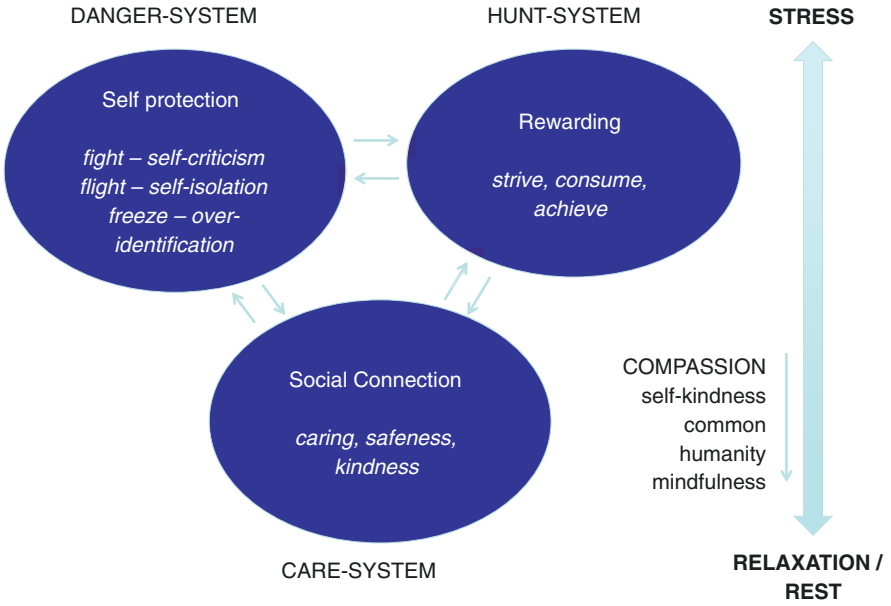

Fig. 7.5 Care system as opposed to the danger and hunt systems. Moreover, there is increasing evidence from the psychological literature that supports the importance of the calming care system in emotion regulation. We tend to enter the *danger mode* as soon as external and internal threats elicit mechanisms of self-protection, while we enter the *competitive mode* when we hunt for achievements in life. In both systems, the level of stress is relatively high as sympathetic activity is dominating, ensuring a necessary state of readiness. These systems are opposed to the care system, giving rise to a mode of compassion, which brings the body in a state of tranquility and relaxation. Here the parasympathetic system dominates, supporting an environment allowing for growth, repair, and healing

treatment options, but we must also incorporate the impact of the disease in order to establish the management option that fits the individual patient best as well as a third axis addressing compassionate care which is crucial for healing to occur. Each of the three axes is necessary, but not sufficient on its own, to enable optimal care for our patients.

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