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Review

Rheumatic Diseases in the Elderly

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Abstract

Musculoskeletal conditions represent one-third to more than one-half of all non-communicable disease multimorbidities in the elderly, worsening their disability because of pain and limited physical function, often concurring with their mental decline. Musculoskeletal conditions significantly contribute to frailty and global disability, second only to mental health conditions. Furthermore, premature mortality, generally due to an increased risk of developing cardiovascular disease, has been documented in several rheumatic diseases, including osteoarthritis, gout, vasculitis, etc., which largely affect older people. In the elderly, rheumatic diseases cover a spectrum of conditions affecting all age groups, especially those are seen more often in the aging population. This non-systematic review focuses on the elderly and may hopefully contribute to raising awareness of these issues beyond the rheumatology community. We believe that this constitutes a critical step

for prompt and proper diagnosis and referral of patients to ameliorate their overall long-term outcome.

Keywords
Geriatric rheumatic diseases; elderly rheumatic patients; musculoskeletal diseases; polymyalgia rheumatica; gout; septic arthritis

1. Introduction

According to the European League Against Rheumatism (EULAR) definition, "rheumatic diseases, also called musculoskeletal diseases, are characterized by pain and a consequent reduction in the range of motion and function in one or more areas of the musculoskeletal system; in some diseases, there are signs of inflammation: swelling, redness, and warmth in the affected areas. Rheumatic diseases can also affect internal organs" [1]. Most patients with chronic rheumatic diseases experience reduced workability and deteriorating quality of life because of pain and limited physical function, with a consequent adverse impact on their mental well-being [2].

Since the prevalence of many musculoskeletal conditions increases with age, these outcomes may even be more severe in older adults already weakened by limiting physical and mental capacities [2]. In 2001, the concept of physical frailty in the elderly was established, indicating the presence of five components: perceived exhaustion, weight loss, low levels of handgrip strength, gait speed, and physical activity [3]. This concept has subsequently been revisited. Therefore, physical frailty is now defined as a syndrome associated with aging that causes increased vulnerability to stressors due to deficiencies between various interrelated physiological systems, leading to a decline in homeostasis [4]. Furthermore, premature mortality, often due to an increased risk of developing cardiovascular disease, has been documented in several rheumatic diseases, including osteoarthritis (OA), gout, vasculitis, etc., that largely affect older people [5-7].

2. Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR) is a common inflammatory disease observed in individuals at the age of 50 years or older [8].

In Italy, its prevalence is between 0.37% and 0.62%, with an incidence of 2.3 cases/1000 population [9]. In a Japanese cohort, the prevalence of PMR was 0.22% in men and 0.36% in women [10]. The incidence in the Olmsted County (Minnesota) cohort was 69.8/100000 among women and 44.8/100000 among men [11].

An association between PMR and polymorphisms in the promoter region of the interleukin-6 (IL-6) gene has been reported [12], while HLA-DRB1*04 class II alleles were mainly found in PMR associated with giant cell arteritis (GCA) [13]. Acting on a genetic predisposition, many environmental factors including infectious agents, may have a role in the onset of the disease. A peak of incidence of PMR has been observed in correspondence of epidemics of M. pneumoniae, C. pneumoniae, Parvovirus B19, adenovirus (AdV), and respiratory syncytial virus. This observation, together with the occurrence of PMR a few months apart in non-consanguineous and

cohabiting subjects [14], suggests role of microbial agents. Another pathogenetic hypothesis derives from the observation that many patients rapidly respond to glucocorticoids (GCs), implying that disturbances of the hypothalamic-pituitary-gonadal axis may occur due to endocrinosenescence, an age-related decline of dehydroepiandrosterone (DHEA) or androstenedione (ASD) [15, 16].

The clinical presentation of PMR is characterized by sudden and severe pain and stiffness in the neck, shoulders, upper arms, and pelvic girdle, sometimes preceded by constitutional symptoms and elevation of inflammatory indexes [8]. Some clinical conditions associated with PMR may include GCA, subclinical vascular damage, and diverticular disease [17-19].

In 2012, a collaborative initiative of the EULAR and the American College of Rheumatology (ACR) prompted provisional criteria for the diagnosis of PMR [20]. These criteria, still needing further validation, apply to people aged 50 years or older with new-onset bilateral shoulder pain, abnormal C-reactive protein (CRP) levels and/or erythrocyte sedimentation rate (ESR). An algorithm then follows, where a score of at least 4 showed 65% sensitivity and 78% specificity for discriminating PMR from non-PMR patients. Ultrasonography (US) of shoulders and hips may be used to improve specificity. A score of 5 or greater should be achieved, with 66% sensitivity and 81% specificity for classification of PMR compared with other disorders [20].

A formula to assess disease activity (PMR activity score) is proposed below

PMR activity score = CRP (mg/dL) + VAS (visual analogue scale) patient's pain (0-10) + VAS physician assessment + morning stiffness (minutes) x 0,1 + EUL (elevation of the upper limbs)

Where EUL indicates the ability to elevate upper limbs, to which a score from 0 (ability to raise the upper limbs beyond the upper girdle) to 3 (incapacity to raise the upper limbs beyond the upper girdle) is given. A final score lower than 7 displays a low disease activity, from 7 to 17 a moderate activity, and greater than 17 a high activity [21].

The diagnosis of PMR is based on clinical features and laboratory work-up, but the US can be helpful, according to the provisional 2012 criteria. Magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) scans can also be used in situations where systemic vasculitis is suspected to be associated with PMR [22].

The treatment of PMR is based on GCs. In 2015, EULAR published the recommendations for the management of PMR, suggesting the use of the minimum effective GC dose, starting with 12.5-25 mg prednisone equivalent daily, with slow tapering to reach an oral dose of 10 mg/day prednisone equivalent within 4-8 weeks. If relapse occurs, the dose should be increased to the pre-relapse dose and then decreased within 4-8 weeks to the dose at which the relapse occurred. In cases of contraindications to GCs, or resistant PMR, methotrexate (MTX) can be considered. In the management of PMR, it is very important to evaluate comorbidities and to assess the potential side effects of GCs [23].

Cardiovascular risk seems to be increased in patients with PMR, as demonstrated in a cross-sectional study where the subclinical vascular damage was higher compared to patients with major cardiovascular risk factors [18]. Besides, the rate of vascular events was reported to be 36.1 per 1000 person-years in patients with PMR against 12.2 per 1000 person-years in patients without PMR [24].

3. Remitting Seronegative Symmetrical Synovitis with Pitting Edema

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) was first reported in 1985 by McCarty et al. [25]. A Japanese study recently reported a prevalence of 0.09% among patients of RS3PE in an outpatient clinic [10].

Infectious agents in a genetically predisposed host have been hypothesized as pathogenetic triggers [25].

This condition typically affects elderly people and is characterized by acute symmetrical synovitis of the extremities associated with pitting edema of the dorsum of both hands and feet, with limitation of motion of wrists and fingers. Rheumatoid factor (RF) is not present, and elevation of inflammatory indexes is often detected. Radiological erosions are not reported [25]. In an Italian study, patients with distal extremity swelling (unilateral or lower extremity involvement or both) and pitting edema were investigated with hand and foot MRI scans, which demonstrated that the extensor tenosynovitis of the hands and feet is the predominant lesion, with concomitant joint synovitis in some cases. Patients responded rapidly to GCs, as previously reported in a study [26]. RS3PE may present as an idiopathic disease, but in some cases, it is associated with other conditions, including PMR [27], spondyloarthropathies [28, 29], RA [30], systemic lupus erythematosus (SLE) [31]. Moreover, paraneoplastic RS3PE syndrome has been reported [32, 33].

4. Giant Cell Arteritis

GCA is a non-necrotizing granulomatous vasculitis that affects large and middle-sized arteries and occurs in elderly people, more frequently in women (M: F ratio 1:2), although it has rarely been reported to occur before the age of 50 years. It is the most common type of primary vasculitis in Western countries, with a prevalence of 304 and 81 per 100000/population in women and men, respectively [34]. The incidence of the disease peaks in the 70-79-year age group [35, 36]. As mentioned above, patients with PMR can show manifestations of GCA, while 40% to 60% of GCA patients have manifestations of PMR [37, 38]. GCA and PMR also share an infectious pathogenetic hypothesis [39].

GCA symptoms include headache, jaw/tongue/limb claudication, scalp tenderness, and impaired vision. Ocular involvement (anterior optic ischemic neuropathy or retinal artery occlusion) is irreversible and can lead to permanent visual loss. Extra-ocular muscle palsies can also rarely occur [39]. The physical examination can reveal thickening and reduced pulsation of the temporal arteries [39]. The laboratory workup shows inflammatory anemia and increased levels of CRP and ESR, though both may be normal in less than 3% of the patients [39]. Critical for the diagnosis of GCA is the demonstration/examination by the US of the typical “halo sign”, a hypo-echoic ring around the vasal lumen reflecting edematous thickened artery wall, which is the opposite of the focal hyperechoic wall thickening seen in atherosclerosis [40]. MRI and PET scans can also be useful in assessing whether the vasculitic process has involved vessels other than the temporal arteries [41]. However, the gold standard for the diagnosis is the temporal artery biopsy (TAB). According to the EULAR recommendations, biopsies should be at least 1 cm in length, which corresponds to a postfixation length of at least 0.7 cm [6]. Histologic changes are recognizable up to two weeks after starting treatment with GCs [42]. However, several studies have shown that neither imaging nor TAB is 100% sensitive [43, 44].

According to the 2018 update of EULAR recommendations for the management of large vessel vasculitis, 40-60 mg/day prednisone-equivalent should be initiated immediately for induction of remission in active GCA. Once the disease is controlled, the GC dose should be tapered to 15-20 mg/day within 2-3 months and after one year to ≤5 mg/day. In patients with a refractory or relapsing GCA or those at an increased risk of GC-related adverse effects or complications, tocilizumab may be used. MTX is another option [45, 6].

A subset of patients with GCA is considered to have large-vessel involvement, with radiographic evidence of inflammation in the aorta or its major branches. These patients frequently present with constitutional symptoms, including fever of unknown origin, and may also complain of symptoms suggestive of limb claudication. Compared to patients with classical cranial GCA, those with large-vessel GCA are usually slightly younger, have a longer duration of symptoms, are more likely to experience concurrent PMR at diagnosis, and are less prone to develop vision loss [46]. GCA is profoundly intertwined with cardiovascular complications: atherosclerosis and hypertension. The presence of their risk factors in patients with a new diagnosis of GCA predisposes them to the development of severe ischemic complications [47].

5. Other Vasculitides

Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) affects small vessels and comprises granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA). Although people of all ages can be affected, AAV is more common in individuals aged older than 60 years, with a slight prevalence in men [48]. AAV is associated with the presence of ANCA to myeloperoxidase (MPO) or proteinase-3 (PR3).

GPA has an annual incidence rate of 2.1-14.4 per million in Europe, with a survival rate of 74-91% at five years [48]. The disease is characterized by inflammation of the upper and lower respiratory tract and kidneys, with the histological evidence of necrosis, granulomatous inflammation, and vasculitis [49]. The autoimmune process of GPA is mediated by ANCA, mainly those with a positive cytoplasmic staining pattern (c-ANCA), which usually targets PR3, while a perinuclear pattern (p-ANCA) is found in 20% of the patients and is generally caused by autoantibodies against MPO [49]. In 70-100% of cases, the initial clinical manifestation is reported in the ear-nose-throat system, especially with the involvement of the nasal cavity and the paranasal sinuses [49]. Though rare, cardiovascular complications, including cardiogenic shock, pericarditis, cardiomyopathy, and coronary artery involvement, have been reported [50].

EGPA has an annual incidence rate of 0.5-3.7 per million in Europe, with a 5-year survival rate of 60-97% [48]. The median age of onset is 49-59 years [51]. EGPA is characterized by an eosinophil-rich and necrotizing granulomatous inflammation that often involves the respiratory tract [51] and is associated with a personal history of bronchial asthma and eosinophilia. ANCA, observed in 30-47% of EGPA patients, are more frequent when glomerulonephritis occurs. Indeed, other than the respiratory tract, kidneys (20-25% of patients, necrotizing glomerulonephritis) and the peripheral nervous system (mono- and polyneuropathies) can be involved. CRP and creatinine are usually significantly elevated, compared to other forms of vasculitis [51].

MPA has an annual incidence rate of 2.4-10.1 per million in Europe, with a 5-year survival rate of 45-76% [48]. It is a necrotizing, non-granulomatous vasculitis, with few or no immune deposits.

Other clinical manifestations include necrotizing glomerulonephritis and pulmonary capillaritis [51], with alveolar hemorrhage [52].

Current treatment strategies for severe AAV, supported by randomized control trials, aim to achieve remission with high-dose GCs and either rituximab (an anti-CD20 chimeric monoclonal antibody) or cyclophosphamide, followed by relapse prevention with sustained low-dose treatment. This approach has dramatically improved outcomes in AAV; however, a significant proportion of patients experience serious treatment-related side effects or suffer relapse [53].

Another vasculitis potentially affecting the elderly is polyarteritis nodosa, which involves medium vessels. Like other vasculitides, it is a very heterogeneous disease characterized by cutaneous, vascular, and neurological involvement. An association with the hepatitis B virus is notably reported [54].

One of the overarching principles of the 2018 EULAR recommendations for the management of large vessel vasculitis underlines the necessity of screening for cardiovascular comorbidities [6]. The pivotal importance of lifestyle advice to prevent and reduce cardiovascular risk in such patients is also stressed [6, 53].

6. Crystal-induced Arthritis

Crystal-induced arthritis is characterized by the deposition of crystals in and around the joints and can affect older adults. Different types of crystals can be found in synovial fluid (SF). The crystals capable of inducing arthritis are constituted of monosodium urate (MSU), which is typical of gout, calcium pyrophosphate dihydrate (CPPD), associated with a variety of clinical presentations, including acute pseudogout, and basic calcium phosphate (BCP; hydroxyapatite, octacalcium phosphate, and tricalcium phosphate), which can be observed in as much as 60% of samples from osteoarthritic joints [55].

6.1 Gout

Gout is a chronic, systemic disease resulting from the deposition of MSU crystals in and around the joints as a consequence of persistent hyperuricemia [56]. It affects almost 4% of adults in the USA [57], 0.9% in France and Italy, 2.5% in the UK, 1.4% in Germany, and 3.2% to 6.1% in New Zealand, where 3.2% refers to those with European ancestry and 6.1% to Maori ancestry, suggesting a genetic background [57, 58]. The incidence of the disease has increased over the last few years, progressing from 0.30 per 1000 person-years in the 1970s to 2.68 per 1000 person-years in the 2000s in the UK and USA [57]. While it seems to be more frequent in men (2- to 6-fold) [59], the peak age is 70 years for both genders [57]. However, it may also affect young people, especially when associated with genetic mutations [57].

The disease can be classified into renal overload (ROL) gout and renal underexcretion (RUE) gout [60]. A genetic predisposition to gout has been highlighted by genome-wide associated studies (GWAS) [60].

Among non-genetic risk factors, the role of some drugs (diuretics, angiotensin-converting enzyme inhibitors, β blockers, non-losartan angiotensin II receptor blockers, cyclosporine, tacrolimus, ritonavir, pyrazinamide) and foods (red meat, alcohol, seafood, sugar-sweetened, and fructose-rich beverages) [57, 61] is well known. Increased urate formation may also derive from an

exaggerated cellular turnover, as it may occur in psoriasis and malignancies [57], which have an increased prevalence in elderly people.

Asymptomatic hyperuricemia and MSU crystal deposition precede the onset of clinically overt acute gout [57]. Hyperuricemia becomes pathological above MSU levels of 6.8 mg/dL ; beyond this threshold, MSU starts to form and deposit in many tissues [57]. The solubility of uric acid and capacity to form MSU crystals are influenced by many factors, such as SF pH, water concentration, electrolyte levels, the integrity of intraarticular proteoglycans, and collagen [59]. MSU crystals interact with resident macrophages, prompting the activation of the NLRP3 inflammasome that leads to the production of IL-1, via caspase 1 activation [57]. Following the asymptomatic deposition of crystals inside the joints, an acute flare of gout may occur [57]. This is often monoarticular, accompanied by a violent pain associated with all other typical signs of inflammation. It peaks within 24 h, usually appearing at night, when lower temperatures facilitate the precipitation of crystals [57, 59]. In most cases, it affects the first metatarsophalangeal joint, but also knees, ankles, wrists, and metacarpophalangeal (MCP) joints [59]. Bursitis and tendonitis, fever, headache, and malaise may be present [59]. The acute gouty attack may self-resolve in 1-2 weeks [57], but further attacks may suddenly develop and also become more frequent and severe if proper treatment for hyperuricemia is not started. The asymptomatic period between acute phases is called the intercritical period [59]. Chronic gout is characterized by synovitis in multiple joints, cartilage damage, bone erosions, and tophi, which are formed by accumulated crystals mixed-up with collagen and other debris from previous inflammation [57, 59].

Apart from joints, tophi may be found in the viscera, spine, and subcutaneous tissues [57-59], where they may ulcerate, leading to the excretion of white, chalky material and possible infection.

In 2015 ACR/EULAR investigators elaborated criteria for the classification of gout [58].

The gold standard for gout diagnosis is the presence of MSU crystals in the SF [57-59], with 100% specificity [62]. MSU crystals are identified by compensated polarized light (CPL) microscopy [57, 59]. They appear needle shaped under simple light microscopy, strongly birefringent under a polarized microscope, and show a negative birefringence or elongation in CPL microscopy [57, 59]. Culture and cell count analysis of the SF shows predominance of polymorphonucleates that may exceed 50000 cells/μL. No bacteria are found, but culture must always be performed to formulate a differential diagnosis with septic arthritis (SA), especially when the onset of gout is monoarticular [59]. Hyperuricemia is not a proper marker for gout during a gouty attack, because its levels may be normal [62]. Other nonspecific findings commonly found in gout are elevated acute phase reactants and neutrophils count [57]. US shows several features, including a hyperechoic enhancement on the surface of the articular cartilage, known as the double contour sign, some hyperechoic foci floating in the joint space (snowstorm appearance), and tophi, as hyperechoic aggregates in the joint or along with tendons [62], which are surrounded by an anechoic rim [57]. Erosions in advanced gout can also be found and confirmed in two perpendicular planes with the US and conventional radiography (CR) [57, 59]. Dual-energy CT (DECT) evaluates the difference in attenuation of a material exposed to two distinct X rays spectrums, creating a colored map of the urate deposits, with 87% sensitivity and 84% specificity [57].

The 2016 EULAR recommendations and 2020 ACR guidelines provide an update on the treatment of the disease. In compliance with EULAR recommendations, flares should be neutralized by using colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intra-

articular GCs, or even using a combination of these drugs. In patients with frequent flares and contraindications to the above-mentioned drugs, an IL-1 inhibitor should be considered. Once the flare is controlled, urate-lowering therapy (ULT) is crucial to maintain serum uric acid levels at <6 mg/dL or <5 mg/dL in severe gout. Allopurinol is recommended as the first-line ULT; as an alternative, febuxostat or the combination of a xanthine oxidase inhibitor with a uricosuric should be considered. For patients with refractory gout, pegloticase is recommended. Besides, EULAR recommendations focus on the education of the patients and the assessment of comorbidities [63]. Hypertension, hyperlipidemia, diabetes mellitus, and cardiovascular events are all associated with gout. It is reported that this disease carries about 50-70% increased risk of cardiovascular disease compared with the general population [64]. Moreover, high levels of uric acid were shown to be important predictors of frailty in older adults [65].

6.2 Calcium Pyrophosphate Deposition Disease (CPPD)

CPPD is one of the most common rheumatic diseases occurring in people over 60 years of age [66]. The prevalence of CPPD ranges from 4% to 7% of the adult population in Europe and the USA and increases with advancing age [67, 68]. As outlines in EULAR guidelines, CPPD is the umbrella term for all forms of CPPD, which may occur as chondrocalcinosis, an asymptomatic condition associated with OA, acute arthritis (also known as pseudogout), or chronic arthritis [69].

Apart from age, many other risk factors including OA, hemochromatosis, concurrent gout, previous trauma, meniscectomy, conditions involved in the inorganic pyrophosphate (iPP) metabolism (hypophosphatasia, hypomagnesemia, hyperparathyroidism), intraarticular preparations of hyaluronic acid, and systemic medications (pamidronate, loop diuretics and granulocyte-macrophage colony-stimulating factor) play a role in the development of CPPD [68].

CPPD pathogenesis is based on the formation of CPP crystals from extracellular iPP in pericellular matrix of cartilage [68]. iPP derives from extracellular adenosine triphosphate (ATP) efflux, which is regulated by the membrane protein human homolog of the protein product of the murine progressive ankylosis homolog gene (ANKH), found in articular cartilage, in the meniscus and synovium [70]. ATP extruded from the cell by the ANK transporter is metabolized by ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1) to iPP [66, 68]. Interestingly, ENPP1 activity increases with age and in patients with OA [66]. Some pyrophosphatases and alkaline phosphatase, instead, degrade iPP. CPP crystals are formed from the binding of extracellular iPP and calcium. Crystals can then activate the NLRP3 inflammasome and start inflammation, similarly to gout, by production of the destructive matrix metalloproteinases (MMPs) and prostaglandins which alter the integrity of cartilage [68].

Pseudogout, the acute CPP crystal arthritis, is characterized by the acute onset of mono- or oligo-articular arthritis, commonly involving knees or wrists that may last for weeks [68]. The main differential diagnosis is gout and SA, which must be excluded in the diagnostic process. Chronic CPPD can affect shoulders, wrists, and MCP joints, or even simulate RA [68]. Crowned dens syndrome is caused by the deposition of CPP crystals around the C2 vertebra and is characterized by acute severe neck pain, fever, and elevated levels of inflammatory markers [71]. The diagnosis of CPPD requires SF analysis, CR, and US. SF analysis should be performed with CPL microscopy, which reveals the presence of rhomboidal crystals with a positive elongation and wide range (from none to quite brilliant) of birefringence, though about 80% of CPP crystals do not show any

birefringence [68]. CR can identify chondrocalcinosis, by detecting calcifications within the joint space of the affected sites [68]. US is also useful in identification of hyperechoic calcifications in the fibrocartilage (menisci, triangular fibrocartilage of the wrist), hyaline cartilage (knees and MCF), tendons, and SF (hyperechoic spots) [67].

EULAR experts delivered recommendations for the management of CPPD, and indicated both non-pharmacological and pharmacological intentions. For acute CPPD, cool packs, temporary rest, and joint aspiration combined with GC injection should be applied. For prophylaxis or chronic disease, oral NSAIDs with gastroprotective treatment and/or low-dose colchicines (0.5-1.0 mg daily) may be used. Parenteral or oral GCs for acute CPPD in patients who are unresponsive or unsuitable for other measures, and low-dose GCs, MTX, or hydroxychloroquine for chronic CPPD is advised , while for asymptomatic CPPD, no treatment is suggested [72].

6.3 Basic Calcium Phosphate Crystal Deposition Disease

BCP deposition (BCPD) disease has a peak age of incidence that spans from the fourth decade till death (beyond the sixth decade of life) [73]. A Swedish study unearthed low prevalence of BCPD in a southern region of Sweden (0.23%) and evidenced higher occurrence in people above 80 years of age [74].

The disease pathogenesis is not well understood. Mild trauma or overuse of the joints with autoimmune, and metabolic conditions are associated with spontaneous onset in most cases [75].

Calcific deposits can be found in all peri-articular soft tissues, including in the tissues of arteries, skin, breast, etc. [76]. These deposits may be asymptomatic or express several clinical syndromes. Among these, acute calcific periarthritis of the shoulder, characterized by a rapid onset of severe pain, swelling, and restriction of motion, is the most frequent [77]. Calcific tendinitis of the hip causes monoarticular pain and restriction of joint movement similar to acute hip arthritis, although acute calcific periarthritis tends to resolve within 2-3 weeks [77]. Regarding the genesis of calcific periarthritis, it is believed that the rupture of pre-existing calcific deposits causes their transport into adjacent soft tissue spaces, with subsequent acute inflammatory reaction [78].

A peculiar and very severe condition associated with BCP crystal deposition is the Milwaukee shoulder syndrome (MSS), which can occur in patients between 60 and 90 years of age, due to intra-articular deposition of BCP crystals that release lysosomal enzymes leading to the destruction of articular and peri-articular structures, including the rotator cuff [79]. Apart from shoulders, other joints, including the knees, hips, and/or elbows, might be involved [80]. Patients with MSS typically have large, synovial effusions with abundant aggregates of BCP crystals [76]. However, individual BCP crystals are non-birefringent and are too small to be detected by conventional or polarized light microscopy [81]. Furthermore, despite their tendency to clump, especially when present in large amounts, BCP crystals remain undetectable in the SF [66], which is usually noninflammatory with a low leukocyte count [79]. US, CR, CT, MRI, and DECT can all be helpful for the diagnosis [82].

Treatment of CPB crystal deposition disease is based on NSAIDs, colchicine, GC injections, rest, physiotherapy, and even surgery in advanced arthropathies [79, 83].

7. Osteoarthritis (OA)

OA is a disease of aging more frequently observed in women than men after the age of 50 years [84]. Among the many definitions provided, one from the American Academy of Orthopedic Surgeons appears mentionworthy and extensive: "OA is the result of both mechanical and biological events that destabilize normal coupling of degradation and synthesis of articular cartilage and subchondral bone. Although it may be initiated by multiple factors, including genetic, developmental, metabolic, and traumatic, OA involves all of the tissues of the diarthrodial joint. Ultimately, OA is manifested by morphologic, biochemical, molecular, and biomechanical changes of both cells and matrix, which lead to softening, fibrillation, ulceration, and loss of articular cartilage, sclerosis, and eburnation of subchondral bone, osteophytes, and subchondral cysts. When clinically evident, OA is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation" [85].

OA shows a high prevalence across the world. Globally, the World Health Organization (WHO) estimated that 10% to 15% of all adults, aged over 60 years, have some degree of OA, with 9.6% of men and 18% of women aged over 60 years having the a symptomatic disease (https://www.who.int/chp/topics/rheumatic/en/). The prevalence of OA, however, varies greatly depending on the definition used, age and gender of the patient, and geographical area studied [86]. Incidence depends on the committed joint and is estimated to be 240/100,000 person-years for knee OA; 100/100,000 person-years for hand OA; and 88/100,000 person-years for hip OA in the USA [87].

OA negatively affects patients' quality of life, with a burden similar to that of RA accounting for 2.4% of all years lived with disability (YLD) [88]. Between 1990 and 2013, a 75% increase was seen in OA-related YLDs worldwide, making the disease the third most rapidly rising condition associated with a disability after diabetes and dementia [7]. As a consequence, OA consumes a high rate of healthcare resources, both directly (hospitalization, emergency room visits, physician visits, outpatient visits, and medications) and indirectly (absenteeism, presenteeism, disability, and worker's compensation) [89]. It has been estimated that OA accounts for 1% to 2.5% of the gross national product of some countries, such as France, Canada, the UK, and the USA [89].

The pathogenesis of OA is complex and in completely understood. Genetic factors are involved, as demonstrated by epidemiological studies, linkage studies, candidate gene approaches, and genome-wide association studies [90]. It was recently hypothesized that the disease is the consequence of the balance of two types of inflammation, i.e., mechanoflammation, due to mechanical stress, and metaflammation, caused by metabolic stress. Mechanoflammation leads to local inflammation driven by regional trauma with subsequent activation of proteolytic enzymes, such as MMPs. On the other hand, metaflammation is a chronic, systemic low-grade inflammation led by adipokines discharged from adipose tissue. In obese people, these two types of inflammation work together and reinforce each other [91, 92]. The sentence should be like this: Typically, the response to injury branches off across repairing mechanism, largely driven by transforming growth factor β (TGF β) and fibroblast growth factor 2, and a destructive mechanism. The latter is mediated by TGF β -activated kinase 1 (TAK1), which lies upstream of the inflammatory mitogen-activated protein kinases, bringing to the release of nerve growth factor, a mediator of pain [93] and other pro-inflammatory molecules, such as tumor necrosis factor (TNF),

IL-1 and IL-7 [94]. These stimulate the production of MMPs, with a dominant role taken by MMP-1 and MMP-13 [95], which is responsible for the degradation of type II collagen [96].

OA affects the axial skeleton as well as peripheral joints, mainly hands, knees, and hips that can be radiologically and clinically classified according to ACR criteria [84]. The natural history of OA can vary greatly. OA generally develops progressively, although symptoms may remain relatively stable for prolonged periods. Still, flares can occur during the disease [97]; in such cases, inflammatory arthritis, infection, and crystal-induced arthropathies should be excluded. Furthermore, the correlation between clinical outcomes and the radiographic course is rather poor, and not all radiologically affected joints are symptomatic [98].

The main symptom of OA is pain, typically exacerbated by joint use and relieved by rest. However, with disease progression, pain occurs even at rest and finally, during sleep. Because cartilage has no nerve supply, pain is likely to arise from other articular and peri-articular tissues, but central pain processing is also altered in patients with OA [99]. Stiffness in the morning or after periods of inactivity is another feature of the disease, which tends to resolve within 15 min. Limitations of function develop as the disease progresses, and patients report significant deterioration in the quality of life and experience limitations in performing day-to-day activities, such as walking, fulfilling household duties, kneeling, and climbing the stairs. The physical examination reveals bony swelling, joint tenderness, crepitus on passive or active movement of a joint, and finally joint deformities. The blood tests are not routinely indicated to confirm the diagnosis since they are usually within the normal range [84]. A EULAR task force developed evidence-based recommendations on the use of imaging in patients with symptomatic and peripheral joint OA [100]. According to these recommendations, imaging should only be performed in atypical presentations to confirm the diagnosis or in cases of unexpected rapid progression of symptoms or change in clinical characteristics to ascertain disease severity or the presence of an additional diagnosis. If imaging is neede7d, CR should be preferred, while US or MRI are indicated to make additional diagnoses for soft tissues and CT or MRI for bone [100].

Treatment of OA is aimed at reducing pain and stiffness while maintaining functional capacities. To this purpose, non-pharmacological (education and information access, support for self-management, exercise, weight loss, biomechanical aids, and appliances), pharmacological (paracetamol, oral or topical NSAIDs, opioids, intra-articular GCs or hyaluronan, nutraceuticals, duloxetine), and surgical options, even in combination, may be applied according to individual needs and risk factors. Their use is tuned by the recommendations from experts of international organizations, including EULAR, the Osteoarthritis Research Society International, and the National Institute for Health and Care Excellence (NICE) [101-106]. Notably, no drug is currently recommended for modification of OA due to limited evidence. Treatment of depression, which is frequent comorbidity, is important and may be targeted by using low-dose amitriptyline at night in patients with non-restorative sleep because of pain. Symptomatic OA is strongly associated with frailty in the elderly, with a three-fold increase in risk compared to the non-symptomatic OA population. The prevalence of frailty in OA patients aged 65-85 years old is estimated to be around 10.4% in Europe [107].

8. Osteoporosis

Osteoporosis (OP) is a systemic skeletal disorder defined by WHO in 1994 as "a generalized bone disease characterized by a decreased bone mass and a deterioration of bone microarchitecture resulting in an increased fracture risk" [108]. In 2001, the US National Institute of Health (NIH) defined OP as "a disease of compromised bone strength, resulting in an increased risk of fracture" [109]. Both definitions highlight the uniqueness of a clinical condition being at the same time disease and a risk factor. For epidemiological purposes, WHO allows a diagnosis of OP to be made when the bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is lower than −2.5 standard deviation below the mean peak BMD in young healthy adults of the same gender, which is also known as T score [110]. Primary OP may occur after menopause (postmenopausal OP) or with advancing age (senile OP). The prevalence of OP ranges from 22.2% to 33.2%, depending on the bone evaluated, but most women with OP are asymptomatic, which makes epidemiological research difficult [111]. Osteoporotic fractures have important social and economic effects since the fragility fractures are associated with increased mortality and morbidity. Death is directly related to hip fracture in 24% of cases, and 28% of deaths in patients hospitalized for vertebral fractures are thought to be secondary to the fracture itself [112]. Fractures of the hip, vertebrae, and wrist are considered as the typical osteoporotic fractures, although prospective studies have shown an increased risk of almost all types of fractures in case of low BMD [113]. Moreover, adults experiencing a fracture are at greater risk of having a subsequent fracture [113, 114]. Between 55 and 75 years of age, the risk of vertebral fractures in postmenopausal women is higher than by any other type of fracture, but at the age of >75 years, the risk of hip fracture and other non vertebral fractures also increases [115]. Apart from a reduction in BMD, aging and previous fragility fractures, risk factors for OP and related fractures include female gender, current cigarette smoking, family history of hip/vertebral fractures, alcohol intake, vitamin D deficiency, early menopause (before the age of 45 years), low physical activity, several chronic diseases and drugs (GCs, aromatase inhibitors, gonadotropin-releasing hormone agonists, selective serotonin recapture inhibitors, antiepileptic drugs, proton pump inhibitors) [116]. Special attention should be given to interventions that reduce the risk of falls in the elderly by improving home safety [117]. It is well known that OP derives from the altered balance between reabsorption and new deposition of bone. The most important role is played by osteoblasts and osteoclasts. Osteoblasts derive from mesenchymal stem cells, and their role is to favor bone regeneration. Their activity is enhanced by TGFβ, IL-4, IL-10, IL-13, and IL-18. These molecules stimulate osteoblasts activity, favor their proliferation, block apoptosis, and induce elevation of osteoprotegerin. On the other hand, bone reabsorption is run by osteoclasts. Activated macrophages and cytokines such as TNF, IL-1β, IL-6, and M-CSF promote osteoclast differentiation, proliferation, and activity, but the most important stimulus is given by the receptor activator of nuclear factor κB ligand (RANKL), which stimulates osteoclasts into mature multinucleated osteoclasts [118]. Even hormones can influence the balance between bone promotion and bone reabsorption. In particular, parathyroid hormone (PTH) triggers both resorption and formation, ultimately leading to promote bone mass. Vitamin D has a protective role as well. Other hormones can favor or induce OP, such as GCs, or protect the bone (estrogens) [119].

The treatment of OP combines the need to remove preventable risk factors together with non-pharmacological interventions (physical activity, correction of poor protein intake) and the use of drugs with proven anti-fracture efficacy. Most of these drugs decrease osteoclastic activity (bisphosphonates, selective estrogen-receptor modulators, denosumab), while teriparatide is the only bone anabolic agent available. Bisphosphonates are the first-line therapies for most patients with OP. Selective estrogen-receptor modulators (SERMs) are non-steroidal agents that bind to the estrogen receptor and act as estrogen agonists or antagonists, depending on the target tissue [120, 121]. Denosumab is a humanized monoclonal antibody that binds selectively and with high-affinity RANKL expressed by osteoblasts, hindering the engagement of RANK on osteoclasts [122]. Teriparatide is a form of PTH given as daily subcutaneous injections. Interestingly, this intermittent administration of PTH increases the number and activity of osteoblasts, leading to an increase in bone mass and an improvement in skeletal architecture [123]. Adequate calcium and vitamin D intake is essential in all pharmacological approaches to limit the risk of hypocalcemia [124]. OP, with its high burden of disability, is strongly connected to frailty due to low levels of BMD. On the other hand, frailty is strongly associated with a significant risk of recurrent falls and, subsequently, of death [125, 126].

9. Septic Arthritis

SA is caused by the presence of a bacterial agent within a joint. The infection can reach the joint from the blood flow, from infected contiguous foci, from neighboring soft-tissue sepsis, or by direct inoculation due to trauma or an iatrogenic event. SA should be promptly recognized and treated due to its potential to cause rapid joint destruction [127]. The overall estimated incidence of SA in the general population is about 2-10 cases per 100,000 person-years in industrialized countries, but an increase has been observed over the last years [128, 129]. SA shows two peaks, one below five years of age and the other over 64 years, without significant gender differences [130]. According to some studies, around 60% of cases are diagnosed in 60-year-old persons or older [131]. This may be explained by several factors, such as increased orthopedic procedure-related infections, aging population, and more frequent use of immunosuppressive therapies [129, 132, 133]. The main risk factors for SA include age >80 years, cardiovascular diseases, such as coronary artery disease, congestive heart failure, and chronic pulmonary obstructive disease, the presence of prosthetic joint, recent joint surgery, skin infection, prior intra-articular therapeutic injections; immunosuppression due to diabetes, renal and liver diseases, drugs, human immunodeficiency virus infection, alcohol abuse, cancer, and RA [128, 134-138]. Interestingly, patients with RA have an approximately 10-fold-higher incidence of SA than the general population [127]. A significant increase in the mortality rate in elderly adults both at six months and at 1-2 years after the infection has been observed [134]. SA typically presents as an acute, very painful monoarthritis with fever. Irreversible loss of joint function develops in 25-50% of patients, generally because of delayed diagnosis and treatment. If SA is suspected, arthrocentesis of the joint is mandatory; the SF is analyzed for Gram stain, white blood cell count, and cultured for bacteria. Gram-negative organisms are more common in older patients and immunocompromised patients. However, the sensitivity of Gram staining to detect the infection is limited, being positive in 71% of Gram-positive SA and 40-50% of cases of Gram-negative SA [139]. Laboratory markers of systemic inflammation have only a limited diagnostic value due to low

sensitivity [140]. Imaging may be of help in supporting the diagnosis. In later stages, CR may reveal juxta-articular OP, diffuse joint space narrowing due to cartilage destruction and erosions, and finally destruction of the joint [127]. Musculoskeletal US may show non-echo-free effusions, characteristic of the disease, while MRI aids in early diagnosis of SA because of high resolution for soft-tissue abnormalities [141].

Prompt treatment with parenteral antibiotics without waiting for the results of bacterial cultures should be initiated. The choice of antibiotic is empirical, based on the likelihood of the organism involved. When the culture results are available, antibiotics can then be chosen according to the sensitivity pattern, starting with intravenous treatment for 10-14 days, often followed by oral antibiotics for minimum six weeks. Needle aspiration is recommended to support antibiotic therapy. More invasive procedures, such as arthroscopy and drainage, can be adopted if the infection is resistant to medical treatment to preserve joint function and limiting joint destruction [142]. Arthrotomy should be performed when urgent decompression of the joint is needed or, in particular circumstances, to make the etiologic pathogen more attackable by the action of antibiotics [143]. While the surgical approach in the case of prosthetic joint infection is generally accepted to obtain better absorption of antimicrobial agents [133], indications are less fruitful for native joints [142]. Moreover, NSAIDs or analgesics, unloading of the affected joint, and physiotherapy to prevent muscular atrophy and contractures should all be considered.

10. Elderly-Onset Rheumatoid Arthritis

RA is a chronic, autoimmune, inflammatory joint disease responsible for persistent synovitis with cartilage and bone destruction and consequent development of disability. Despite the prevalent joint involvement, RA should be considered a syndrome characterized by extra-articular manifestations, including rheumatoid nodules, pulmonary involvement or vasculitis, and systemic comorbidities [144]. Disease onset usually occurs between the 4th and the 5th decade of life. Term elderly-onset RA (EORA) describes the disease with an onset at age over 60 [145]. The proportion of elderly patients with RA is continuously growing as a result of the increasing aging population. The incidence of EORA in Spain was reported to be 14.5-15.3 for females and 9.1-15.8 for males per 100.000 population [146]. Prevalence in the USA has been estimated to be around 2% in persons with at least 60 years of age [147].

The hypothesis of different pathogenesis for EORA is supported by the evidence of a diverse clinical picture, including higher recognition of overlapping manifestations with PMR and RS3PE [145, 148]. Due to the high prevalence of patients with inflammatory involvement of shoulders, the differential diagnosis between EORA and PMR is quite challenging, and in these cases, the presence of anti-citrullinated protein/peptide antibodies (ACPA) is highly suggestive of RA [149]. Nonetheless, in patients with EORA, there is a lower prevalence of autoantibodies compared to young-onset rheumatoid arthritis (YORA) [148, 150]. Although the presence of autoantibodies in RA is generally associated with a worse disease outcome, a higher frequency of acute disease onset especially in patients with EORA and negative RF has been observed [151]. A diverse genetic background between EORA and YORA has been found. As known, the human leukocyte antigen (HLA)-DRB1 named “shared epitope” is an important genetic risk factor for RA development, and its presence is associated with a specific disease phenotype [152, 153]. Both the shared-epitope-coding alleles and the HLA-DQ*04 were less frequently found in EORA patients compared to YORA

[154]. Additionally, in a study conducted on RA Colombian patients, HLA-DRB1*0403 and *1402 were more frequent in the elderly than in young patients [150]. A different distribution of the DRB1 genotypes between YORA and EORA patients has also been demonstrated in a Japanese population [155].

The diverse pathogenic background between EORA and YORA is further supported by a different serological profile. In patients with EORA, higher IL-6 and lower TNF serum levels have been documented. Interestingly, extremely high serum levels of IL-6 were mostly detectable in elderly patients with PMR-like symptoms [156]. These findings need to be considered when choosing among the spectrum of the currently available therapeutic strategies for RA. In the past decades, different studies underlined the existence of clinical and serological differences between patients with EORA and those with YORA [145, 148, 151]. In contrast with YORA, which mainly occurs in women, in EORA, a balanced gender distribution has been reported, with evidence of a clinical course characterized by important systemic features, higher disease activity, and more pronounced inflammatory parameters [145, 148, 151]. Also, compared to YORA, EORA shows more common involvement of large joints 145, 148, 151], and a higher frequency of distal-proximal involvement seems characteristic [150]. Additionally, a fast-radiographic progression with advanced destructive changes is quite frequent and seems more evident in patients with positive autoantibodies [145]. Interestingly, cardiovascular risks, as well as disability, have been demonstrated to depend on disease duration and not on the age , at which the patient develops AR. On the other hand, EORA has a significant association with cardiovascular comorbidities [157].

The treatment of EORA pursues the same objectives as in younger patients, including the achievement of remission or at least a low disease activity and the prevention of structural damage [158]. However, the presence of comorbidities in elderly RA patients is not a negligible aspect, and the occurrence of drug-related adverse events is quite frequent [159]. The prescription of GCs is a remarkable approach in clinical practice, and its use in EORA is more common than MTX and biologic drugs [148]. However, the role of GCs is still controversial, as their short-term symptomatic relief and potential medium-term effects on structural damage are counter-balanced by their side effects. In the elderly, MTX is effective and, despite possible limitations due to renal impairment, it does not seem to be less tolerated than in younger patients [160]. Finally, biological agents are largely and successfully administered, although in the elderly, the use of anti-TNF agents seems slightly less effective, and the frequency of adverse effects is a bit higher. Nonetheless, similar findings were shown from conventional disease-modifying treatments in another study [160]. RA patients tend to develop frailty at a younger age and with a severe prognosis. The prevalence of frailty in patients with RA over 60 years of age is approximately 36.4% greater than that of the general population which is around 14-16% for the same age span. The main factors associated with frailty in this cohort of patients were age, disease activity, and comorbidity burden [161].

11. Sjögren's Syndrome

Sjögren's syndrome (SS) is a systemic autoimmune condition characterized by chronic inflammation of exocrine glands. The presence of sicca symptoms, including xerophthalmia and xerostomia, is the hallmark of the disease and mostly represents the first clinical sign at disease onset [162]. SS mainly affects middle-aged people and a late-onset is considered as a disease

appearing after age 65 [163]. However, the age cut-off used to identify patients with a late disease onset is not univocal being also reported in 50-, 60, or even 70- year- old individuals [163]. Although SS is highly prevalent among middle-aged individuals, elderly patients account for up to 20% of SS cases [163, 164]. A systematic review of all the epidemiological studies on primary SS published up to October 2013 found a global prevalence rate of 60.82 (95% CI 43.69 to 77.94) cases per 100 000 inhabitants with a female/male ratio of 10.72 (95% CI 7.35 to 15.62). [165].

In the elderly population, SS is one of the most under-diagnosed conditions, as sicca symptoms are frequently attributed to medications and/or aging. When considering SS diagnosis in the elderly, it is important to obtain a thorough drug history as the use of tricyclic antidepressants and antipsychotic drugs can frequently cause dryness. In a population-based study of elderly individuals, approximately 27% of the participants reported dry eyes or dry mouth, and among them, about 62% were related to the use of concomitant medications [166]. It is also important to remind that exocrine glands naturally undergo histological changes with time, including acinar atrophy, fibrosis, and ductal dilatation, which are all responsible for a reduction in secretory function [167]. Hence, standardized histological diagnostic criteria have been developed to identify lip biopsy displaying histological features indicative of SS [168]. These include the presence of lymphocytic infiltrates measured by the focus score calculation [169] as well as the identification of germinal center-like structures [170].

The incidence of Xerostomia in the elderly population is estimated to be 17% [171], and, in a previous study, SS was suggested as an underlying cause in approximately 40% of patients [164]. To the same extent, dry eye symptoms are fairly frequent in older people, as demonstrated in 62 healthy elderly individuals, where 22% were found to have an abnormal Schirmer's test [172].

As stated by the American-European classification criteria [173], the detection of anti-Ro/SSA and anti-La/SSB antibodies is important for SS diagnosis. However, compared to young SS patients, in the elderly, a lower prevalence of serological manifestations was found [174, 175]. For instance, in 17 patients with SS with a median disease onset of 71 years, RF and anti-Ro/SSA antibodies were significantly less common compared to 68 young patients; in the same study, despite the lack of statistical significance, the elderly onset group also presented milder clinical symptoms [174]. Accordingly, SS patients with early disease onset (<35 years old) presented a higher prevalence of lymphadenopathy, rheumatoid factor, anti-Ro/SSA antibodies, and monoclonal immunoglobulins as compared to patients with the late- onset disease [176]. However, in a previous study on 31 patients with late-onset SS (>70 years old), the prevalence of immunological features, as well as glandular and extra-glandular manifestations, was similar compared to the young-onset group [175]. The lack of agreement arising from these studies is possibly related to different age cut-offs used to distinguish the elderly from young patients.

As reported in the most recent recommendations, management of SS involves both treatment of dry eyes and dry mouth with local replacement and/or stimulation therapies and, in case of serious systemic involvement, the use of immunosuppressive therapies [177]. In the elderly, medications may have limited use because of potential comorbid conditions and multiple concurrent medications. Additionally, in these patients, an increased rate of adverse events related to therapeutic agents has been described with consequent need of a careful follow-up in most of them [178]. For instance, the use of stimulation therapies, such as pilocarpine, is limited by adverse effects, including sweating, flushing, abdominal pain, headache, and increased urination and is contraindicated in patients with ischemic heart disease [178]. Additionally, the use

of immune-suppressive agents in the elderly may be burdened by increased infectious risk [178]. However, the treatment of SS in the elderly does not differ from that in younger patients and aims to control glandular and extraglandular manifestations, to prevent damage to organ systems, and to decrease morbidity and mortality [179]. In SS, subclinical atherosclerosis has been reported in half of the patients; thus, enhancing the importance of prompt screening [180-181].

12. Late-onset Systemic Lupus Erythematosus

Late-onset SLE (LSLE) presents some peculiarities in clinical features, autoimmunity profile and disease course compared to younger patients, even though data from various studies are not always consistent [182, 183]. LSLE refers to patients who receive a diagnosis of SLE after the age of 50 years. It is reported to occur in 3-18% of SLE patients, with a lower male-to-female ratio (1:2.6) than in the adult-onset group (1:13) [184, 185]. LSLE is characterized by serositis, pulmonary involvement, and secondary SS, all of which appear more frequently than in adult-onset SLE. Moreover, the first manifestations are usually weakness, fatigue, weight loss, while arthritis, cutaneous manifestations (such as photosensitivity and malar rash), Raynaud's phenomenon, lymphadenopathy, renal involvement show a lower incidence [184, 186, 187]. LSLE patients present a lower incidence of hypocomplementemia, lower rates of anti-dsDNA and anti-Sm antibody positivity, and no differences in anti-SSA and anti-SSB antibody positivity rate compared to adult-onset SLE [184]. In an age-stratified Caucasian population, no significant differences were found among groups, except a more frequent peripheral nervous system involvement and the more frequent finding of anti-dsDNA antibody and RF positivity in patients ≥65 years [183]. LSLE is believed to have a mild course with a low number of flares and low disease activity, but the accumulation of organ damage does not differ from adult-onset SLE. As a consequence, LSLE does not have a lower mortality rate, probably due to the burden of comorbidities [188, 189, 190], mainly hypertension and diabetes mellitus [187, 188], while infectious diseases are reported to be the first cause of death [191]. In a Colombian study, a higher incidence of HLA-DR17 (DR3) in patients with LSLE was observed compared to patients without autoimmune diseases [192], in accordance with the finding that DR3 haplotype is linked to a strong risk of SLE susceptibility [193]. Lower use of GCs is reported in LSLE patients, while adequately validated data are lacking on the use of immunosuppressants [182, 185, 186, 194]. SLE patients seem to be more prone to develop frailty at a younger age than the general population. The prevalence of frailty was estimated at around 20%, much higher than in the general population, implying a higher risk of death and disability [195].

13. Discussion

More than half of older people experience multimorbidity [196], with musculoskeletal conditions representing one-third to more than one-half of all non-communicable disease multimorbidity [197]. The current study has relevant socioeconomic implications since several rheumatic conditions are among the most disabling diseases, concurring to global frailty and posing major threats to healthy aging by limiting physical and mental capacities and functional ability. Indeed, musculoskeletal conditions significantly contribute to global disability, second only to mental health conditions [7]. This perspective prompted the current useful review, aimed at providing an abridgment of the popular rheumatic conditions typically observed in the elderly. The

knowledge of these diseases and related issues beyond the rheumatology community constitutes a critical step for prompt and proper referral of patients to ameliorate their overall long-term outcome.

14. Conclusion

In the current review, a broad spectrum of more than 50 rheumatic diseases is covered. More than 150 rheumatic diseases affect during various stages in life, especially from the 4th decade of our life. If no timely interventions are taken, lifestyle modifications are not done, these conditions can debilitate very severely and may lead to permanent disability also.

To conclude, the current review will prove an eye-opener for the professionals and researchers to broaden their research and enlighten the ever-expanding but much-shrouded field of rheumatic diseases. The importance of this paper can be underscored for therapeutic interventions as well.

15. Abbreviations Used

AAV: ANCA-associated vasculitis; ACPA: Anti-citrullinated protein/peptide antibodies; ACR: American College of Rheumatology; ANCA: Anti-neutrophil cytoplasmic autoantibody; ANKH: Progressive ankylosis homolog; ATP: Adenosine triphosphate; BCP: Basic calcium phosphate; BMD: Bone mineral density; c-ANCA: Cytoplasmic- ANCA; CPPD: Calcium pyrophosphate dihydrate; CR: Conventional radiography; CRP: C-reactive protein; CT: Computed tomography; DECT: Dual-energy CT; DXA: Dual-energy X-ray absorptiometry; EGPA: Eosinophilic granulomatosis with polyangiitis; ENPP1: Ectonucleotide pyrophosphatase phosphodiesterase 1; EORA: Elderly-onset rheumatoid arthritis; ESR: Erythrocyte sedimentation rate; EUL: Elevation of the upper limbs; EULAR: European League Against Rheumatism; GCs: Glucocorticoids; GCA: Giant cell arteritis; GPA: Granulomatosis with polyangiitis; HLA: Human leukocyte antigen; IL: Interleukin; iPP: Inorganic pyrophosphate; MCP: Metacarpophalangeal; MMPs: Matrix metalloproteinases; MPA: Microscopic polyangiitis; MPO: Myeloperoxidase; MRI: Magnetic resonance imaging; MSS: Milwaukee shoulder syndrome; MSU: Monosodium urate; MTX: Methotrexate; NICE: National Institute for Health and Care Excellence; NIH: National Institute of Health; NSAIDs: Non-steroidal anti-inflammatory drugs; OA: Osteoarthritis; OP: Osteoporosis; p-ANCA: Perinuclear ANCA; PET: Positron emission tomography; PMR: Polymyalgia rheumatica; PR3: Proteinase-3; PTH: Parathyroid hormone; RA: Rheumatoid arthritis; RANKL: Receptor activator of nuclear factor κB ligand; RF: Rheumatoid factor; ROL: Renal overload; RS3PE: Remitting seronegative symmetrical synovitis with pitting edema; RUE: Renal underexcretion; SA: Septic arthritis; SERMs: Selective estrogen-receptor modulators; SF: Synovial fluid; SLE: Systemic lupus erythematosus; SS: Sjögren's syndrome; TAB: Temporal artery biopsy; TAK1: TGFβ-activated kinase 1; TGFβ: Transforming growth factor β; TNF: Tumor necrosis factor; ULT: Urate-lowering therapy; US: Ultrasonography; UUE: Urinary urate excretion; VAS: Visual analog scale; WHO: World Health Organization; YLD: Years lived with disability; YORA: Young-onset rheumatoid arthritis.

Author Contributions

C. Castellani, E. Molteni, S. Colafrancesco collected the references and wrote the paper. F. Conti and R. Priori critically revised the paper. R. Scrivo analyzed the references and critically revised the paper.

Competing Interests

The authors have declared that no competing interests exist.

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