Chapter

Inflammatory Muscle Diseases

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Abstract

Inflammatory myopathies, also called idiopathic inflammatory myopathy or myositis, are rare conditions characterized by the involvement of various organs in addition to muscle tissue. These changes can lead to severe impairments and adversely impact the quality of life of affected individuals. The diagnosis and treatment of inflammatory myopathies involve the participation of an interdisciplinary team, due to the complexity of the disease and the high variety of possible signs and symptoms. In this chapter we will discuss the epidemiology and characteristics of the main subtypes of inflammatory myopathies, such as polymyositis, dermatomyositis, necrotizing myopathy, overlap myositis, and myositis of inclusion bodies. Next, we will discuss the existence of crosstalk between inflammatory processes in the oral cavity and their consequences on skeletal muscle. As oral inflammation can increase infiltration of macrophages in muscle tissue and this increase is related to the production of proinflammatory cytokines in this tissue, these cytokines can cause muscle weakness. It is important to consider the prevention of chronic inflammatory processes in order to maintain muscle integrity or even prevent the worsening of the clinical condition of patients with inflammatory muscle diseases.

Keywords: myositis, dermatomyositis, polymyositis, inclusion body myositis, inflammation

1. Introduction

Inflammatory myopathies, also called idiopathic inflammatory myopathy or myositis, are rare conditions characterized by the involvement of various organs in addition to muscle tissue. These changes can lead to severe impairments and adversely impact the quality of life of affected individuals [1, 2].

The diagnosis and treatment of inflammatory myopathies involve the participation of an interdisciplinary team, due to the complexity of the disease and the high variety of possible signs and symptoms. The integration of subspecialties, such as rheumatologist, neurologist, dermatologist, pulmonologist, cardiologist, and physiotherapist, among others, is necessary to achieve the ideal treatment plan. Diagnosis of inflammatory myopathies involves several steps and often requires autoantibody testing and histological evaluation of a muscle tissue biopsy in addition to several other tests, including muscle magnetic resonance imaging and electromyography. Typical symptoms of inflammatory myopathies include muscle weakness in the arms and legs, which may manifest in a few days or even several weeks. Muscular weakness is reflected in difficulties in performing daily activities such as walking, climbing stairs, or lifting an object above the head. In addition to muscle weakness, it is observed that pain is also a frequent detectable symptom in a

patient with inflammatory myopathies. Laboratory tests usually show a significant increase of creatine kinase and elevation in the concentration of liver enzymes that suggest the occurrence of damage to muscle cells [1, 3].

The adverse impact on quality of life highlights the importance of performing an accurate and reliable diagnosis from the combination of clinical and laboratory findings to establish the appropriate treatment for each individual [1, 2].

In this chapter we will discuss the epidemiology and subtypes of inflammatory myopathies. Next, we will discuss the existence of crosstalk between inflammatory processes in the oral cavity and their consequences on skeletal muscle.

2. Inflammatory myopathies

2.1 Epidemiology of inflammatory muscle diseases

All myositis subtypes can be considered rare diseases due to their relatively low prevalence. Studies indicate that overlap myositis represents the subtype of the disease that affects the largest number of people, comprising about half of the cases registered. Dermatomyositis accounts for more than a third of the cases of the disease and presents a prevalence of approximately 1–6 patients per 100,000 people in the United States [4–6].

It is important to emphasize that obtaining accurate epidemiological data is extremely difficult due to the different diagnostic criteria adopted in each study. Therefore, the information provided by the publications should be examined and evaluated with caution and attention [7].

A large study conducted from the analysis of 3067 patients from Belgium, China, Czech Republic, Hungary, Italy, Mexico, Norway, Sweden, Switzerland, the United Kingdom (UK), and Vietnam who were registered in the Euromyositis Registry demonstrated that the dermatomyositis was the most common disorder with 31% of the cases [7].

Data on the prevalence of necrotizing myopathy suggest that this subtype of the disease accounts for approximately one-fifth of the reported cases of inflammatory muscle diseases [4–6].

The information regarding the epidemiology of polymyositis varies and depends on the methodology and location of the study ranging from the largest fraction with prevalence of approximately 10 cases per 100,000 people in the United States [1–3], 27% in the Euromyositis Registry [7], to the rarest subtype that should be diagnosed only by exclusion [4–6].

Currently there is some consensus that overlap myositis, necrotizing myopathy, and dermatomyositis represent about 90% of the cases of inflammatory muscle diseases [4–6]. It is estimated that the inclusion body myositis occurs with a prevalence of up to 14 per million people [8].

2.2 Dermatomyositis

Dermatomyositis is typically characterized by the development of proximal muscle weakness and cutaneous manifestations that may arise over a period of weeks to months. However, there are cases in which muscular impairment is not significant without signs and symptoms of muscle weakness, elevated muscle enzymes or changes in electromyography, magnetic resonance imaging (MRI), and muscle biopsy [9].

Skin signs frequently seen in dermatomyositis include an exacerbated periorbital rash with edematous features and erythematous lesions involving the extensor

surfaces of the joints. In some cases, myalgia and pruritus may also be observed as important symptoms of the disease. Muscle enzyme concentrations tend to be elevated, and electromyography commonly shows a myopathic pattern [10]. Intramuscular T2 hyperintensities resulting from inflammation or muscle necrosis can be observed on MRI. Dermatomyositis may present a characteristic less frequently observed in other types of inflammatory myopathies, which involves the presence of T2 hyperintensities around individual muscles due to fascial involvement [11].

Muscular biopsies in patients with dermatomyositis have perifascicular atrophy as a feature of high specificity [12]. Evidences show that the expression of perifascicular human myxovirus resistance protein 1 and retinoic acid-inducible gene 1 have higher diagnostic sensitivity than perifascicular atrophy with equivalent specificity [13]. Muscular biopsies of dermatomyositis patients usually present cellular infiltrates composed of plasmacytoid dendritic cells, B cells, CD4 T cells, and macrophages. These cells usually involve medium-sized blood vessels and invade the perimysium [14]. However, it is possible that dermatomyositis biopsy does not present this cellular infiltrate. Predominantly, necrotic pathologically indistinguishable from immune-mediated necrotizing myopathy may be observed. Some early features of dermatomyositis involve deposition of membrane attack complex and presence of microtubular inclusions on intramuscular capillaries [11]. In addition, like other inflammatory myopathies, class-1 major histocompatibility complex (MHC) is generally upregulated in the sarcolemma of muscle fibers. In patients with dermatomyositis, class-1 MHC upregulation and other pathological findings may be characteristically prominent in perifascicular regions [14].

Studies have shown that dermatomyositis autoantibody can be found in a considerable proportion of patients with dermatomyositis [15]. Typical features of dermatomyositis, including proximal muscle weakness and prominent cutaneous manifestations have been associated with the presence of autoantibodies recognizing the nuclear antigen Mi2 [16]. Patients with dermatomyositis and autoantibodies that recognize nuclear matrix protein (NXP) 2 are more predisposed to be affected by proximal and distal muscular weakness, subcutaneous edema, and dysphagia [17].

Patients with dermatomyositis who are positive for anti-NXP2 or anti-transcription intermediary factor (TIF)-1 autoantibodies are at increased risk for malignancy development; thus making comprehensive cancer screening 13–15 or positron emission tomography–computed tomography (PET-CT) scans is extremely important in these cases [18]. In cases of dermatomyositis patients who have autoantibodies recognizing the small ubiquitin-like modifier activating enzyme or melanoma differentiation-associated gene 5 (MDA5), it is observed that cutaneous tissue impairment is more prominent than in muscle. In addition to most commonly present cutaneous manifestations, these patients may develop ulcerous lesions on the flexor surface of the fingers and palm [19, 20].

Most patients with anti-MDA5 autoantibodies are hypomyopathic or amyopathic. In addition, it should be noted that unlike patients with other autoantibodies of dermatomyositis, those who are anti-MDA5 positive often develop an aggressive form of interstitial lung disease, reinforcing the importance of assessment through periodic lung function tests and high-resolution computed tomography [20–22].

Although the etiology of dermatomyositis is not fully elucidated, it is suggested that a combination of genetic risk factors and exposure to environmental factors may trigger the disease. In this sense, several immunogenetic risk factors, including certain class-2 human leukocyte antigen (HLA) alleles, have been implicated in dermatomyositis pathogenesis [23]. Studies suggest that exposure to ultraviolet light may also be considered an important risk factor for the development of dermatomyositis [24].

Regardless of the origin of dermatomyositis, it is not known which mechanisms are involved in the development of muscle damage and weakness. Studies suggest

that muscle damage may result from hypoperfusion due to endothelial destruction [14]. In addition, the presence of plasmacytoid dendritic cells, along with the increase in expression of type-1 interferon-inducible proteins in the perifascicular area, suggests that interferon may mediate perifascicular atrophy [12, 25].

Overlap myositis is being recognized as an individual form of myositis. This myositis manifests itself without a rash typical of dermatomyositis, with prominent pathologic changes in the perifascicular, interfascicular, and perimysial regions, and is frequently associated with anti-synthetase antibodies [2].

Laboratory evaluation shows a significant elevation of muscle enzymes including creatine kinase (CK), which is generally present [3]. Approximately 30% of patients with myositis were positive for Jo-1O antibody (most common of the eight anti-synthetase antibodies) [26].

2.3 Polymyositis

Polymyositis is a rare disease, which belongs to the various idiopathic inflammatory myopathies. It is estimated that the incidence of polymyositis is 5% of all cases of myositis [2, 5, 27]. Polymyositis consists of muscle weakness, elevated creatine phosphokinase concentrations, and myopathic electromyography features [2]. However, rash or other signs of skin inflammation do not occur in polymyositis. Therefore, its diagnosis is by exclusion [3].

Histopathological hallmarks of polymyositis include invasion of endomysial cytotoxic CD8 T cells and widespread upregulation of class I MHC in muscle fibers [2, 24]. Polymyositis is a chronic, degenerative disease that has no cure. The treatment consists in the relief of the symptoms with the use of corticosteroids, such as prednisone, intravenous glucocorticoids (when weakness at onset is severe or rapidly worsening), azathioprine, methotrexate, mycophenolate, cyclosporine, and intravenous immune globulin [3].

2.4 Inclusion body myositis

Inclusion body myositis is a very common disease among inflammatory myopathies affecting mainly men from the age of 50. The disease begins insidiously and develops over a period of years, sometimes asymmetrically; it may begin with unilateral affection of a leg or arm, progress steadily, and lead to deep muscular atrophy [2]. Laboratory evaluation shows that an elevated CK is much blander. Skin changes are not present [3].

There is a higher mortality rate in patients with inclusion body myositis, since muscle weakness (long flexors of the fingers, quadriceps, anterior tibial, and, to a lesser extent, all other muscles of the arms and legs) usually leads to harmful falls and dysphagia can cause aspiration pneumonia [3].

The antibody, identified a few years ago, that is present in inclusion body myositis is cN1A (5NT1A/5NTC1A) [3]. The frequency of this antibody is about 30%; other forms of myositis such as dermatomyositis and other conditions such as Sjögren's syndrome and systemic lupus erythematosus (SLE) were also positive even in the absence of any muscle symptoms [3, 28, 29]. Study suggested that the presence of cN1A is associated with a more severe course of disease, dysphagia [3, 30], and increased mortality [3, 31]. However, in another study in German patients, the presence of cN1A did not correlate with the severity of dysphagia or muscle impairment [3, 32].

In the histopathological hallmarks, the distribution and the immunophenotypic profile of the inflammatory cells are similar to those seen in polymyositis macrophages and CD8+ T cells which invade nonnecrotic muscle fibers that express MHC

class I antigen on the sarcolemma [33], signs of protein accumulation by detection of amyloid (Congo red, thioflavin S, immunohistochemistry for p62 or TDP-43), detection of tubulofilaments on EM, vacuoles and signs of mitochondrial damage as evidenced by histochemical proof of COX-deficient muscle fibers, and paracrystalline inclusions [3, 34, 35].

2.5 Immune-mediated necrotizing myopathy

Immune-mediated necrotizing myopathy is an acute or subacute proximal weakness of the arms and legs, most prominent in the lower limbs [3]. It often affects adults, but it can also occur in children [3]. The progression of the disease is constantly more rapid and severe compared to other myopathies (dermatomyositis and polymyositis) [3]. Laboratory evaluation shows very high muscle enzymes, with an elevated CK of 20–50 times [3]. Neck muscle weakness and dysphagia are common [3].

Approximately 10–20% of patients with immune-mediated necrotizing myopathy have anti-signal recognition particle (SRP); however its detection varies from 0 to 54% [36]. This antibody may be associated with cardiomyopathy and a severe disease with muscle atrophy, interstitial lung disease, and dysphagia [37, 38]. Another antibody that has been identified is reductase (HMGCR) antibody; its detection in certain cohorts was 60% [39].

Histopathological hallmarks in necrotizing myopathy show dispersed necrotic myofibers of varying degrees; moderate and predominantly MHC class I focal regulation, particularly in areas with necrotic fibers; and complement binding to the sarcolemma [2, 3, 40–42]. Some inflammatory T cells and other immune cells may be present around these focal points, but there are no primary inflammatory lesions. Necrotic fibers typically exhibit a secondary invasion by macrophages to clean the cell debris [3].

2.6 Crosstalk between oral cavity and skeletal muscle

In addition to these inflammatory muscular diseases mentioned above, a localized inflammation at a distance from the skeletal muscle may promote change in this tissue. Recent study proposed the existence of crosstalk between oral cavity and skeletal muscle [43]. The researchers induced oral inflammation in rats and observed that the skeletal muscle was affected by increased infiltration of macrophages, which was suggested by the authors as an explanation for the glucose intolerance shown in animals with oral inflammation [43].

Research conducted over the last 15 years has investigated possible mechanisms that cause changes in macrophages polarization and the effects of these changes on insulin signaling in metabolic organs [44]. These cells exhibit a high degree of functional plasticity, so that the nature of an inflammatory trigger, as well as the cytokines present, can determine their polarization and their functional status [44]. In analogy to the nomenclature T-helper cells (Th), Th1 Th2, macrophages can be classified into two distinct phenotypes: type 1 (M1) classically activated and type 2 (M2) alternatively activated [45].

In vitro, these subsets can be induced by stimulation with interferon gamma (IFN-γ) and lipopolysaccharides (LPS) for M1 or interleukin-4 (IL-4) for M2 [46]. The M1/M2 dichotomy is often used to classify macrophages into pro-inflammatory (M1) or anti-inflammatory (M2) [44]. Among the functions performed by the M1 macrophages, tumor necrosis factor-alpha (TNF-α) production is outstanding [47]. Saghizadeh [48] and collaborators observed that diabetic or insulin-resistant patients have increased expression of TNF-α in skeletal muscle when compared to normoglycemic individuals, suggesting that cytokine plays an important role in the

pathogenesis of insulin resistance. TNF-α impairs the insulin signal by decreasing the phosphorylation of insulin receptor substrate 1 (IRS-1) in tyrosine residues [49]. In addition, TNF-α can stimulate some serine kinases including IκB kinase (IKK) and c-Jun amino-terminal kinase (JNK), which promote IRS-1 phosphorylation in serine residues, resulting in insulin signal attenuation [50]. On the other hand, M2 macrophages are associated with tissue repair, angiogenesis, reduction of inflammation, and the improvement of insulin signaling in adipose tissue [45, 51]. In addition to the studies that relate obesity to insulin resistance, there are studies in the literature that demonstrate a correlation between this hormonal resistance and inflammatory processes, such as rheumatoid arthritis and oral inflammations [52–54]. In this context, the apical periodontitis (AP), an oral inflammation, stands out. AP occurs as a consequence of various aggressions to the dental pulp, including physical, iatrogenic, infectious, and endodontic traumas. This inflammatory picture can cause a wide variety of immunological responses, in order to protect the dental pulp and periapical regions. The regulation of periapical inflammation is extremely complex, as it involves host mediators, including immunological components such as antibodies, cytokines, arachidonic acid metabolites, and neuropeptides [55]. The characteristic inflammatory process of AP presents different types of gram-negative anaerobic bacteria [56] with LPS in the cell wall [57]. Studies have reported that bacteria which are present in the oral cavity can release LPS into the systemic circulation [58]. This substance has the ability to activate toll-like receptors (TLRs), a cell surface receptor that activates innate immunity and induces inflammatory responses. LPS is a specific ligand for TLR2 and TLR4 but has a higher specificity for TLR4 [59, 60]. When released by gram-negative bacteria, LPS binds to a soluble plasma protein called LPS binding protein. LPS or LPS binding protein [61, 62] binds to the CD14 co-receptor via lipopolysaccharide binding protein (LPB), forming the LPS-CD14 complex. This complex, in turn, is recognized by the TLR4-MD-2 complex, present on the cell surface, which is capable of promoting intracellular recruitment of adapter molecules with N-terminal TIR domain, such as myeloid differentiation primary response 88 (MYD88). This molecule can activate the serine kinases JNK and IKKα/β, which promote activation of the activating proteins-1 (AP-1) and factor nuclear kappa B (NF-κB) transcription factors, respectively [63, 64]. NF-κB regulates the expression of several genes involved in different cellular processes such as inflammatory and immune responses and cell growth and development. In the absence of an NF-κB-activating stimulus, this protein is present in the cytoplasm inactive with an inhibitory protein, IκB [65]. Activation of NF-κB can occur not only by exposure of the cells to LPS but also by the action of inflammatory cytokines (TNF-α and IL-1), activation of T and B lymphocytes, UV radiation, and expression of products [66]. After stimulation, the IKK is phosphorylated and activated. The IKK complex consists of two catalytic subunits, IKK-α and IKK-β, in addition to the NF-kappa-B essential modulator (NEMO) or IKK-γ [67]. After activation, IKK recruits and phosphorylates the IκB that is recognized by the ubiquitin ligase machinery, which leads to its polyubiquitination and consequent degradation. In this way, the NF-κB dimers translocate to the nucleus, binding at specific sites of the deoxyribonucleic acid (DNA) and promoting the transcription of a large number of genes [65, 67].

In addition to activating the IKKα/β/NF-κB pathway, TLRs are capable of activating the JNK pathway [68]. The serine/threonine kinase group called JNK (JNK-1, JNK-2, and JNK-3) belongs to the family of mitogen-activated protein kinase (MAPKs), responsible for the regulation of various cellular functions. This regulation occurs largely because of its ability to control the transcription of specific genes by AP-1 [69]. AP-1 is a transcription factor that, when activated, promotes the expression of genes related to innate immunity [70]. In addition to LPS, the signaling pathway of TLRs can be activated by heat shock proteins [71]. Heat shock proteins

(HSP) are proteins characterized as chaperones because they have an important function in adaptation to stress and cellular protection, acting mainly in the synthesis and protein degradation, besides regulating fundamental cellular processes [72]. The family of HSPs is divided into subfamilies, classified according to the molecular mass, being small HSPs (8–27 kDa) and large HSPs (100–110 kDa), among which stand out HSP90, HSP70, and HSP60 [73]. In addition to its essential functions as a chaperone [74], HSP70 has an anti-inflammatory effect by inhibiting the activation of NF-KB when present in the intracellular environment [75]. However, stimuli such as cell necrosis and bacterial products such as LPS can cause the passage of HSP70 through the membrane into the extracellular environment [76, 77]. Studies have suggested that elevated serum levels of HSP70 may be correlated with cardiovascular disorder, pulmonary fibrosis, renal damage, oxidative stress, and inflammation [78]. The development of these conditions may occur due to the ability of HSP70 to bind to TLR2 and TLR4, promoting the activation of the NF-κB pathway which, as mentioned above, induces the expression of inflammatory mediators related to insulin resistance [79]. Studies suggest that insulin sensitivity may undergo regulatory action by the adaptive immune system [80, 81]. This system is composed of different types of cells, among which the B and T lymphocytes [82] stand out. T lymphocytes are classified into two main classes: helper T lymphocytes, also known as T helper (Th), and cytotoxic T lymphocytes. The "naïve" Th1 lymphocytes, when interacting with antigen presenting cells, undergo activation and can differentiate into different subtypes [83]. The Th1 subtype expresses proinflammatory cytokines, such as TNF-α and IFN-γ; Th2 expresses mainly anti-inflammatory cytokines, such as interleukin-4 (IL-4) and interleukin-13 (IL-13), and regulatory T cells secrete predominantly anti-inflammatory cytokine and transforming growth factor-β (TGF-β) [84]. Th1 cells play a central role in the recruitment of macrophages and induction of insulin resistance in obesity-induced diabetes models. These effects are counterbalanced by the function of Th2 and Treg cells that maintain an anti-inflammatory state and increase insulin sensitivity [85]. Appropriate regulation of Th cells is of extreme importance for the control and prevention of various diseases [86]. An increase or decrease in the Th1 or Th2 subtypes, as well as the cytokines produced by these cells, indicates an imbalance that may be one of the factors responsible for the development of insulin resistance [87]. It is known that insulin resistance is one of the main characteristics of diabetes mellitus [88]. This disease is also closely related to muscle weakness due to altered insulin action [89], standing out that insulin is an important anabolic hormone for protein metabolism [90].

The study performed by Boon et al. [91] with healthy lean individuals observed that only 5 days of hyperlipidic diet promoted increased messenger ribonucleic acid (mRNA) expression of macrophage markers in skeletal muscle and reduced expression of the glucose transporter type 4 (GLUT-4) glucose transporter protein in this tissue. Similarly, Patsouris et al. [92] demonstrated increased macrophage content in skeletal muscle in diabetic patients independently of body mass index (BMI). An increased macrophage content (assessed by F4/80 protein detection) was observed in muscle tissue of rats with AP in the absence of obesity, highlighting the key role of these cells in the etiology of insulin resistance. It should be noted that only F4/80 detection is not able to provide details on M1-type and M2-type macrophage polarization although evidence demonstrates that under obesity conditions, macrophages infiltrated into muscle tissue exhibit phenotype characteristic of M1 polarization [92–95]. The reprogramming of the M1 polarization toward the M2 polarization may represent a promising strategy for the treatment of glycemic homeostasis in patients with diabetes and insulin resistance [44].

As previously reported, inflammation causes insulin resistance. According to Pereira et al., rats with AP had increased IKKα/β and JNK phosphorylation status

in gastrocnemius muscle. These results are in agreement with the study of Yaspelkis et al. [96], who observed a higher IKKα/β phosphorylation status in the skeletal muscle of rats treated with a hyperlipidic diet for 12 weeks, and also the study by Todd et al. [97] that identified an increase in JNK activity in the skeletal muscle of rats subjected to 3 weeks of hyperlipidic diet. Kaneto et al. [98] reported that treatment of diabetic rats with JNK inhibitors improved the insulin sensitivity of the animals. Similarly, studies by Yuan et al. [99] and Hundal et al. [100] have reported that inhibition of IKK-β by the administration of salicylates improves insulin action in obese and diabetic human and rats. Furthermore, it has been demonstrated that genetically modified mice, which do not express IKK-β or JNK, are protected from obesity-induced insulin resistance [99, 101–103].

In addition to stimulating inhibitory effects on insulin signal transduction, TNF-α may interact with tumor necrosis factor receptor 1 (TNFR1) in skeletal muscle [104] and thereby stimulate the NF-κB and/or MAPK pathway [105, 106], which are related to the phosphorylation of IKK and JNK and, in their turn, may impair insulin action. Pereira et al. [43] evaluated the plasma concentrations of LPS and HSP70 in AP models. Rats with AP showed a significant increase in both LPS and HSP70 when compared to the control group. Research on diabetes suggests that chronic elevation of LPS levels may play a key role in the development of insulin resistance [107, 108].

Among the possible mechanisms involved in this alteration, we highlight the ability of LPS to bind to the TLR4 receptor, which may trigger the activation of inflammatory signaling pathways related to inhibition of the insulin signal [108]. Another mediator that plays an active role in the modulation of inflammation is the heat shock proteins. The study by Goodman et al. [109] reported higher expression of 44 HSP genes in periapical granulomas compared to healthy periodontal tissues. Elevation of HSP70 plasma concentrations observed in rats with AP may indicate that increased local HSP expression is associated with higher concentrations of this protein in serum [43]. Interestingly, studies have shown that serum concentrations of HSP70 are higher in diabetic patients [110, 111]. Asea et al. [79] reported that HSP70 can bind to the TLR4 receptor, suggesting a possible involvement of this protein in the development of insulin resistance. With regard to the adaptive immunity markers, animals from the AP groups showed an increase in the Th1 response represented by increased T-bet expression in the spleen and elevated plasma concentrations of INF-γ [43]. A study carried out with knockout animals for the T-bet gene treated with hypercaloric diet showed that even with weight gain and increased adiposity, the animals were protected from insulin resistance [112]. The authors attributed the lack of insulin resistance to reduced production of INF-γ. These results are consistent with studies that reported that IFN-γ deficiency may improve glycemic homeostasis under obesity conditions [113–115]. In addition, treatment of adipocytes (3 T3-L1) with interferon gamma (INF-γ) reduces insulin signal and glucose uptake [116]. The functions of Th1 cells are antagonized by the Th2 subpopulation presenting the transcription factor GATA3 and IL-4 as specific markers. The AP in rats promotes a reduction of IL-4 [43]. Chang et al. [117] reported that IL-4 treatment promotes improved insulin sensitivity and glucose tolerance and simultaneously reduces body weight in obese rats. These findings suggest that IL-4 plays beneficial effects on glycemic homeostasis. The role of Th2 cells in insulin sensitivity was demonstrated in the study by Gonzales et al. [118]. In this study, a model of inactivation of Th2 response was developed through the inhibition of the activator of transcription 6 (STAT6) protein, in which it was observed that animals with Th2 response deficiency were more prone to insulin resistance. Thus, the reduction of the Th2 response observed in rats with AP may contribute to the understanding of the mechanisms involved in insulin resistance observed in animals with AP [43, 54].

Studies suggest that TNF-α contributes to age-related muscle loss and that resistance exercise may attenuate this process by suppressing TNF-α expression in skeletal muscle [119]. Other findings demonstrate that decreased muscle strength in diabetic individuals is associated with elevated plasma concentrations of TNF-α and interleukin-6 (IL-6) [120]. Therefore, considering that oral inflammation, such as AP, may increase infiltration of macrophages in muscle tissue and this increase is related to the production of proinflammatory cytokines, it is possible to suggest that prevention of chronic inflammatory oral diseases contributes to the maintenance of muscle integrity.

3. Conclusions

The main subtypes of inflammatory muscular diseases are polymyositis, dermatomyositis, necrotizing myopathy, overlap myositis, and myositis of inclusion bodies. The origin of these diseases is idiopathic, making it difficult to prevent them. As oral inflammation can increase infiltration of macrophages in muscle tissue and this increase is related to the production of proinflammatory cytokines in this tissue, these cytokines can cause muscle weakness. It is important to consider the prevention of chronic inflammatory processes in order to maintain muscle integrity or even prevent the worsening of the clinical condition of patients with inflammatory muscle diseases.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Appendices and nomenclature

AP	apical periodontitis
AP-1	activating proteins-1
BMI	body mass index
CD14	cluster of differentiation 14
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CK	creatine kinase
COX	cyclooxygenase
DNA	deoxyribonucleic acid
GLUT4	glucose transporter type 4
HLA	human leukocyte antigen
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
HSP	heat shock proteins
IFN-γ	interferon gamma
IKK	IkB kinase
IL-13	interleukin-13
IL-4	interleukin-4
IL-6	interleukin-6

IR	insulin resistance
IRS-1	insulin receptor substrate 1
JNK	c-jun amino-terminal kinase
LPB	lipopolysaccharide binding protein
LPS	lipopolysaccharides
M1	M1-type macrophage polarization
M2	M2-type macrophage polarization
MAPKs	mitogen-activated protein kinase
MDA5	melanoma differentiation-associated gene 5
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MyD88	myeloid differentiation primary response 88
NEMO	NF-kappa-B essential modulator
NF-κB	factor nuclear kappa B
NXP	nuclear matrix protein
PET-CT	positron emission tomography–computed tomography
SLE	systemic lupus erythematosus
SRP	signal recognition particle
STAT6	activator of transcription 6
TDP-43	transactive DNA-binding protein 43
TGF-β	transforming growth factor-β
Th	T-helper
TIF	transcription intermediary factor
TLR	toll-like receptors
TNFR1	tumor necrosis factor receptor 1
TNF-α	tumor necrosis factor-alpha
UK	United Kingdom
USA	United States of America

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