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Nutrition and Polymyositis and Dermatomyositis

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Summary

- Chronic muscle inflammation in polymyositis or dermatomyositis causes muscle weakness and fatigue.
- The chronic inflammation could lead to a catabolic state and additional loss of muscle mass.
- The chronic muscle inflammation could induce a metabolic myopathy.
- Body weight may not be reliable to measure muscle loss, rather measurement of body composition is recommended.
- For patients with polymyositis or dermatomyositis it is important to provide the body with the right amount of macronutrients and trace elements for maintenance and improvement of body functions.
- One recommendation is supplementation with calcium and vitamin D.
- Another recommendation is regular physical exercise that during limited periods can be combined with supplements such as creatine, if done under the care of a physician.

Key Words: Creatine supplement; dermatomyositis; exercise; glutamine; inflammatory myopathies; polymyositis; vitamin D

1. INTRODUCTION

Polymyositis and dermatomyositis are chronic, rheumatic muscle disorders that are characterized by slowly progressive, symmetrical muscle weakness and fatigue in the arms, legs and neck, and by inflammation in muscle tissue. Other organs are frequently involved, such as the skin in dermatomyositis. In both polymyositis and dermatomyositis the inflammation may also affect the lungs, the heart, and joints. The gastrointestinal (GI) tract is frequently involved and may cause problems that affect nutritional status. Chronic inflammation may also lead to general symptoms such as weight loss, fatigue, and fever, all of which could potentially affect nutritional status. In most cases, these chronic conditions require life-long immunosuppressive treatment and side effects are common.

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1.1. Epidemiology

Polymyositis and dermatomyositis are relatively rare diseases with a yearly onset of approximately 1 case per 100,000 people per year. Women are two to three times more often affected than men. The peak of incidence is in the 60s although polymyositis or dermatomyositis may start at any age, even in children. These forms of myositis are worldwide disorders, but there is a latitude gradient of polymyositis and dermatomyositis. The latter form occurs more frequently closer to the equator and polymyositis is more frequent in northern countries (1,2).

1.2. Etiology

Both polymyositis and dermatomyositis are autoimmune diseases, where the immune system that normally protects us from foreign agents is directed against our own tissues, causing inflammation and damage. Further support for polymyositis and dermatomyositis being autoimmune diseases is the presence of autoantibodies in serum, which can be seen in two-thirds of the patients. Some of these autoantibodies are specific for myositis and are not present in other diseases. One of these myositis-specific autoantibodies is anti-Jo-1 autoantibody, directed against histidyl-tRNA-synthetase. This autoantibody is present in approx 20% of patients with myositis and is often associated with the presence of arthritis in finger joints, lung disease, Raynaud's phenomenon, and skin problems of the hands (mechanic's hands) (3).

The mechanisms that cause autoimmune reactions are not known, but both genetic and environmental factors are likely to be involved. The role of genes as a risk factor for polymyositis or dermatomyositis is supported by familial association with other rheumatic or autoimmune diseases. Moreover, genetic traits have been found to be associated with polymyositis and dermatomyositis but the traits vary between populations (4,5). Furthermore, the same genetic traits are also associated with other autoimmune diseases, such as Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE), suggesting that other genetic as well as environmental factors are important for the development of myositis.

One such environmental factor is exposure to ultraviolet (UV) light. This is based on the observation of the aforementioned regional differences in the ratio between polymyositis and dermatomyositis, which is correlated to latitude. The higher frequency of dermatomyositis is directly correlated with high UV light irradiation (2). This observation suggests that UV light may be an environmental risk factor for the development of dermatomyositis.

Another environmental risk factor that has been suggested is viral infections. One viral infection associated with polymyositis is HIV (6,7). Myositis could also develop together with some parasite infections such as trypanosome cruzi. In most patients with polymyositis or dermatomyositis no infections have been detected.

2. HISTORICAL PERSPECTIVES

Dermatomyositis and polymyositis were first described as disease entities in the 19th century, characterized by symmetrical edema, stiffness, pain, and limited motion of muscles. Lung and skin involvement were described in the first reports. No specific treatment was available until the introduction of adrenocorticotrophic hormone and

glucocorticoids as therapeutic possibilities in the early 1950s. Before this, different therapies were used, such as amino acids, vitamin E, and anabolic steroids, without any consistent beneficial effect. During this time, the mortality rate in these disorders was high. The major cause of death was pulmonary infection resulting from involvement of respiratory muscles and inflammation of the lungs.

Treatment with glucocorticoids made a remarkable difference in the survival of patients with myositis. Although treatment with glucocorticoids improved the survival rate, the frequent and profound side effects soon became evident. Features reminiscent of Cushing's syndrome became apparent; glucose intolerance requiring dietary control or a small dose of insulin was also quite common. To prevent toxicity of glucocorticoids, supplements such as potassium and antacids were given frequently. Later on, anabolic steroids were used in addition to glucocorticoid treatment in an attempt to preserve body protein but the value of this therapy was never determined.

From 1950 to 1965, supportive therapy for patients with myositis included dietary management. Patients experiencing difficulties with swallowing, for instance, were fed with a high-calorie liquid diet. Some patients experienced constipation owing to weakness of abdominal musculature or lack of physical activity; this was treated with a gentle enema. The improved muscle function with glucocorticoid treatment was not seen in all patients; some only had a limited beneficial effect and others did not improve at all.

During the 1980s, therapies started to include additional immunosuppressants, such as azathioprine and methotrexate, to achieve both a steroid-sparing effect and additional benefits when glucocorticoid treatment was not sufficient. Treatment was based on high doses of glucocorticoids with the supplementation of antacids and potassium. During the last two decades, several new immunosuppressive agents have been tested in patients with myositis with inconsistent results, as is discussed further, and improved therapy is still required (8–12).

3. CLINICAL AND LABORATORY FEATURES

3.1. *Clinical Features*

The predominant clinical features of myositis are muscle weakness, muscle fatigue, and sometimes muscle pain, mainly affecting thigh, shoulder, arm, and neck muscles. The onset of symptoms is often slow over weeks to months. Although muscle symptoms predominate, other organ systems are frequently affected. As the name implies, the skin is involved in dermatomyositis. The type of skin rash varies and could affect all parts of the body, although the most characteristic rash is localized to the eyelids, characterized by a red or purple rash with edema, called heliotropic exanthema. Another typical skin rash for dermatomyositis is seen on the dorsal side of the finger joints or hand and is characterized by small red to purple slightly elevated papules (Gottron's papules).

Other organ systems that are frequently involved are lungs, joints, heart and the GI tract. Lung involvement could be caused by different mechanisms. Chronic noninfectious inflammation causing symptoms like cough or breathlessness is common and could vary from mild to severe. Involvement of the respiratory muscles of the chest may also cause breathlessness and impairment of physical activities. The muscle inflammation may also affect muscles in the GI tract, most frequently in the throat

and esophagus resulting in problems with swallowing and regurgitation, and ultimately leading to nutritional problems. The arthritis may affect one or several joints. It is often mild and does not cause deformities. Although the heart is a muscle, clinical manifestations of heart involvement are less common, but may occur and give rise to symptoms such as arrhythmia or congestive heart failure.

3.2. Muscle Tissue Features

A typical finding in polymyositis and dermatomyositis is inflammation in muscles and muscle fiber damage. The inflammation is characterized by the presence of inflammatory cells such as lymphocytes and macrophages. This can be seen in muscle biopsies, which are helpful both for diagnosis and to exclude other muscle disorders. In the muscle tissue of patients with myositis, several inflammatory and immune-mediated molecules are produced. These are likely to be important for the clinical symptoms and for the muscle fiber damage and loss of muscle strength. These molecules are of interest as targets for new therapies that are more specific than glucocorticoids and other immunosuppressants that are used today. Such new therapies can be developed by modern molecular biology technology, as has successfully been the case, for example, in rheumatoid arthritis (RA) and Crohn's disease. A better understanding of the key molecules that cause the disease could lead to the development of new and better therapies for patients with polymyositis or dermatomyositis.

3.3. Molecules Present in Muscle Tissue in Inflammatory Conditions

Cytokines are important signaling molecules in inflammatory responses and immune regulation. These molecules have also become successful targets of therapy in several other autoimmune diseases such as RA, pelvispondylitis, psoriasis, and Crohn's disease. The most frequently observed cytokines in the muscle tissue of patients with inflammatory myopathies are cytokines with proinflammatory properties, namely, interleukin (IL)-1 α , IL-1 β , high-mobility group box1, and tumor necrosis factor (TNF)- α (13–18). These cytokines are secreted by cells in the immune system and by endothelial cells in the lining of blood vessels. Endothelial cells control the passage of compounds and white blood cells into and out of the bloodstream (19).

Cytokines stimulate several inflammatory responses, such as the production of other families of molecules: chemokines, which regulate adhesion of white blood cells to muscle tissue, and adhesion molecules that allow trafficking of circulatory inflammatory cells to endothelial cells, thus letting inflammation pass from the blood into the tissue. One possible mechanism leading to an increased local expression of proinflammatory cytokines might be found in an enhanced activation of the signal substance regulator of DNA transcription, nuclear factor (NF)- κ B. This transcription factor regulates the expression of proinflammatory cytokines, for example, TNF- α and IL-1 β (20). NF- κ B occurs in chronic muscle diseases and is believed to be involved in the reduced maturation and regeneration of skeletal muscle by activating cytokine production (20).

IL-1 β and TNF- α also induce the production of prostaglandin E₂ (PGE₂), a molecule that mediates pain, fever and inflammation. PGE₂ is the most common PG and is produced in various cells, such as fibroblasts and macrophages (21–23). There are several enzymes involved in the PG-production pathway converting different fatty acids

to biologically active metabolites, including PGs and thromboxanes. In muscle tissue, PGE₂ in concert with these other mediators, controls blood flow in the microvessels, and thereby the nutrient supply, to the muscle tissue. PGE₂ also has a role in muscle regeneration upon injury and in the early inflammatory response in order to remove damaged tissue and to induce tissue formation (24,25).

Similar inflammatory responses with IL-1 and TNF expression in muscle tissue could also be induced by hypoxia and, interestingly, hypoxia could be a consequence of chronic inflammation in affected tissues (26). This is well established in the membrane of joints in chronic arthritis (27). Hypoxia could also be a consequence of loss of microvessels, capillaries, in muscle tissue that is a typical finding in dermatomyositis. Interestingly, a loss of capillaries seems to be an early event in dermatomyositis. More recently, we have also observed a reduced number of capillaries in muscle tissue in patients with polymyositis (unpublished data). As oxygen supply is crucial for aerobic muscle metabolism, hypoxia can have several negative consequences that affect the working capacity of muscles and could also affect the nutritional status of patients with chronic muscle inflammation.

3.4. Pharmacological Treatment

As presented earlier, glucocorticoids have become the cornerstone of treatment since 1950 when they were first introduced. Although treatment with glucocorticoids made a dramatic improvement in patient survival, it soon became apparent that some patients with myositis do not respond at all and very few patients recover their former muscle performance. Furthermore, as also discussed previously, a disadvantage of high-dose glucocorticoid treatment is the substantial risk of side effects. For these reasons, combination therapies with other immunosuppressive agents have been developed. Today, glucocorticoids are still recommended as baseline treatment (starting doses of 0.75–1 mg/kg body weight per day), although most authors recommend combination with another immunosuppressant from the start as a glucocorticoid-saving drug and to improve the efficacy of treatment. The most often used immunosuppressants are azathioprine and methotrexate. Other therapies that are used in severe cases are cyclophosphamide, cyclosporine A, mycophenylate mofetil, tacrolimus or infusions with high doses of intravenous immunoglobulin. Only a few of these drugs have been tested in controlled trials of adequate size and duration to show beneficial effects. They are mostly used based on observed beneficial effects in occasional individuals or reported case series. Glucocorticoids can have profound negative effects on metabolism, making the immunosuppressive treatment of myositis an important issue with regard to nutritional status in patients with polymyositis and dermatomyositis. These topics are discussed further.

3.5. Prognosis

Currently, there is only limited information available on the survival rate of patients with polymyositis and dermatomyositis. The few studies are mainly based on cohorts from one hospital; they are not population based and they include only a small number of patients. With this limitation in mind, the 5-year survival was estimated to be 95% and 10-year survival to be 85 or 89% in two recent papers (28,29).

4. NUTRITIONAL STATUS

As with other chronic inflammatory diseases, many patients with polymyositis and dermatomyositis experience general symptoms such as muscle fatigue and weight loss. This may be a catabolic effect caused by the systemic chronic inflammation, or it may be a side effect of long-term glucocorticoid treatment, which is a well-known muscle catabolic agent.

In patients with myositis, muscle wasting may also be caused by muscle atrophy and damage as a consequence of muscle inflammation, or to nutritional deficits depending on difficulties with swallowing. Inactivity, lack of physical activity, and at worst, bed rest, together with inappropriate nutrition, may further play a part in the metabolic alterations as seen in critically ill patients. Because of the inflammatory process and to glucocorticoid treatment, muscle mass may be replaced by fat and muscle wasting may not always be signaled by weight loss. A more appropriate way to follow nutritional status is by assessment of body composition. This can be done by a dual energy X-ray absorptiometry scan, typically used for bone densitometry.

Little detailed information on nutritional status is available in the literature that is specific for polymyositis and dermatomyositis. Here, we summarize available information that we find relevant for patients with myositis after a literature survey.

4.1. Muscle Metabolism

The use of muscles for all kinds of movement requires energy. The major source of energy for muscles is adenosine triphosphate (ATP) and creatine phosphate (CP). Every muscle contraction demands an enormous amount of ATP that cannot be stored in the body and therefore needs to be generated continuously. The body only contains small amounts of energy stores, ATP, and CP, and these stores only last for about 1 minute during muscle work. After the first minute of work, the skeletal muscle is dependent on oxygen-generated ATP. The oxygen is provided to muscle by blood vessels including the small capillaries. By using the macronutrients—carbohydrates (glycogen), proteins (amino acids) and fat (fatty acids and glycerol)—energy is produced in the mitochondria in muscle cells, and the muscle will be able to contract (30).

4.2. Glucocorticoids

A special problem in patients with myositis that may affect nutritional status is their need for long-term (often over months to years), high-dose, glucocorticoids. Glucocorticoids are used to suppress muscle inflammation by acting on most cell types.

The effects on T lymphocytes and macrophages are both direct and indirect, by influencing the mediators released by these cells (31,32). The anti-inflammatory and immunosuppressive effects of glucocorticoids in myositis are mediated by inhibiting the expression of IL-1 β , TNF- α , IL-6 and interferon- γ . One way to achieve this inhibition is to interfere with the inflammatory pathway directed by NF- κ B through promoting the production of the specific NF- κ B inhibitory factor, or by binding directly to NF- κ B itself, to restrain the inflammatory action (33). Via this mechanism, blocked gene expression of proinflammatory cytokines will occur and therefore the amount of these inflammatory molecules will decrease.

Glucocorticoids can also inhibit inflammatory cells to migrate over the endothelium, from the bloodstream into the muscle tissue and further into sites of inflammation. Glucocorticoids also suppress cyclooxygenase (COX)-2, one of the enzymes involved in the regulation of PGE₂ synthesis, as well as other lipid mediators synthesized from the same fatty acid precursor (34). As mentioned previously, it was noticed early that treatment with glucocorticoids had negative effects on muscles and may induce muscle atrophy and also a catabolic state. Glucocorticoids act in several ways to retard growth and promote muscle protein breakdown (35). Some strategies that could possibly be undertaken to counteract these negative effects of glucocorticoids are discussed later.

4.3. Role of Exercise

The catabolic effect of glucocorticoids on muscle tissue is likely to contribute to muscle wasting in patients with myositis who are also affected by catabolism from the muscle inflammation and from physical inactivity as well. In patients who have undergone renal transplant, the negative effect of low or moderate doses (10–12 mg per day) of glucocorticoids on muscles was reversed by physical exercise. Whether this is true for patients with myositis is not known (36,37).

Physical exercise was, until recently, believed to be harmful for patients with chronic inflammation in muscles, but during the 1990s, it was determined that instead of being harmful, it could even be beneficial for patients with myositis to exercise with improved performance and health-related quality of life (38,39). There are numerous benefits of exercise in terms of nutritional status in healthy individuals. Although many of these effects have not been evaluated specifically in patients with myositis, they could be assumed to be attributable to these patients.

Beneficial effects of exercise in healthy individuals include the following:

- improvement of insulin sensitivity and glucose uptake (40–42);
- increased angiogenesis (blood vessel growth) (43–45), which improves blood flow, oxygen and nutrient supply to the muscle;
- improved endothelial function (46);
- altered stress, immune, and inflammatory mediators and cytokine production (47);
- counteracts muscle protein wasting (48,49); and
- improved function (50,51).

In healthy individuals, the muscle protein metabolism after exercise is negative and food intake is needed in order to gain muscle mass. Because patients with myositis already experience a catabolic state owing to glucocorticoid treatment, the post-exercise meal could be even more important to prevent further muscle protein breakdown. This is best achieved by digesting a combination of carbohydrates and protein after the exercise bout (52). For most rapid availability, a liquid, dietary shake can be used but also dietary carbohydrates with a high glycemic index, like rice cakes, with some protein-rich cottage cheese, suits the purpose fine. It seems as if early post-exercise ingestion of a nutrient supplement, as opposed to ingestion 2 hours after training, enhances the anabolic effect of whole-body protein (53,54). The fact that patients with myositis are in a catabolic state caused by inflammation and steroid use, this approach, otherwise mostly used by athletes, might be of use in these patients.

4.4. Dietary Management

A diet achieving energy balance with a content of approx 30% fat, 50 to 60% carbohydrates and 10 to 20% protein of total energy is recommended for healthy individuals in Nordic European countries and is likely to be appropriate for patients with myositis as well (52,55). Dietary supplements have become popular and some of these have been tested in clinical trials in patients with various chronic inflammatory diseases. There are a few reports on effects of supplements in patients with polymyositis or dermatomyositis.

4.4.1. GLUTEN

Celiac disease or gluten-sensitivity is a chronic intestinal disorder where the upper small intestine is damaged, leading to impaired nutrient uptake in these patients. The predominant antigen triggering an autoimmune response in celiac disease has been identified as the enzyme transglutaminase 2 (TG2). Several studies have established a close association between celiac disease and other autoimmune disorders, such as SS and SLE.

An elevated expression of TG2 has been found in muscle tissue from patients with myositis compared to normal muscle, and TG2 is suggested to be a marker of idiopathic inflammatory myopathies (56–58). There have been reports of an increased frequency of gluten-sensitivity among patients with myositis but screening for autoantibodies against TG2 in serum has so far been negative and needs to be further investigated.

Anti-gliadin, another antibody associated with celiac disease, has been found with increased frequency in patients with myositis. Thus, celiac disease should be considered in patients with myositis who experience intestinal problems such as diarrhea or weight loss that cannot be explained otherwise. Celiac disease is diagnosed by presence of anti-TG2 autoantibodies or anti-gliadin autoantibodies and a small bowel biopsy. Implementation of a gluten-free diet is important in these cases to avoid malnutrition (59).

4.5. Supplements

In healthy individuals, it is crucial to support the body with adequate nutrients in order to optimize physical exercise and increase muscle mass or muscle endurance. Body builders, fitness competitors, and marathon runners have, for decades, been using dietary and nutritional supplements to sculpt massive muscles or to be able to undertake strenuous endurance exercise. Supplements have become an enormously profitable industry and the effect of most supplements on the market can be questioned. Through basic research, the safety of several different supplements for use in healthy people has been established (60). There is limited information available that is specific to patients with polymyositis and dermatomyositis; information that is available is presented further on in this chapter.

4.5.1. CREATINE

A commonly used supplement among athletes is creatine. A large number of studies have been published on the subject, describing the ergogenic outcome on muscle strength and size when using creatine in combination with resistance training [61–64].

As mentioned earlier, energy is stored as CP in muscle cells. The effect of creatine supplements in exercise is the result of increased muscle creatine levels that make it

possible to perform more repetitions during weight training by increasing the resynthesis of ATP. This provides the ability to work out at an enhanced level and results in a greater gain in muscle mass (65).

Some patients with myositis have a metabolic disturbance that gives them significantly lower levels of stored creatine in muscles and a defect in the production of ATP, impairing their muscle energy supply (66,67). Creatine supplements have recently been evaluated in a placebo-controlled trial in patients with myositis, in combination with stable immunosuppressive treatment and/or steroids (68). The creatine and the placebo groups performed the same home exercise program. The creatine-supplemented group had a significant improvement, compared with the placebo group, in the primary outcome that reflected the ability to undertake high-intensity exercise.

Side effects of creatine supplements, for example, muscle cramps and heat intolerance, have been described. These side effects may be related to an increase in water retention during the initial days of supplementation. Water retention and an increase in muscle mass may cause weight gain while supplementing with creatine (69). The use of creatine supplements with exercise among patients with myositis was without significant side effects and was considered effective and inexpensive (68,70).

In animal models with arthritis, it was suggested that creatine supplementation might have an anti-inflammatory action; similar suggestions have been made based on research using cell cultures in which creatine supplementation also had an anti-inflammatory action on endothelial cells. These effects may arise from the ability of creatine-supplemented cells to inhibit endothelial permeability and expression of adhesion molecules, decreasing the traffic of proinflammatory cells and mediators from the bloodstream into the tissue (71).

The optimal duration of creatine supplementation during exercise is not known. In the controlled trial, a beneficial effect of creatine, in combination with exercise, was observed after 3 months, and no significant side effects were reported over 5 months.

Regarding creatine supplementation in general, the literature is based on adults, so there is a lack of data regarding safety of creatine use in growing adolescents. Therefore, no conclusions can be drawn for patients with juvenile dermatomyositis and creatine supplementation (72). In a placebo-controlled study including 50 boys between ages 4 and 10 years diagnosed with Duchenne muscular dystrophy (DMD), creatine supplementation was well tolerated (73). Although creatine is a common supplement, commercially marketed creatine products might not meet the same quality control standards as pharmaceuticals, and because of possible impurities or differences in dosage, caution is urged. Patients should always discuss use of any dietary supplement with their physician.

4.5.2. ANABOLIC STEROIDS

Anabolic steroids increase muscle mass and strength, and have been used by athletes for decades. The use of anabolic steroids in sports was banned by the International Olympic Committee in 1974. Use of these hormones may generate several side effects, such as severe acne, increased body hair, and aggressive behavior that may occasionally trigger violent behavior (74).

Until the 1990s, anabolic steroids were manufactured solely by pharmaceutical companies, but the variety of prohibited anabolic steroids in sports has expanded

because of steroid production by nonpharmaceutical companies (75). Without a prescription from a doctor, anabolic steroids are an illegal drug, and the use of hormones without a physician's surveillance could involve major risks.

In recent years, anabolic steroids have been investigated in terms of possible benefits for patients with disease-related muscle wasting. Testosterone administration has had positive results in different patient populations, but because it is a natural androgen hormone, it possesses virilizing effects, which limits the population that can be treated. An alternative is oxandrolone, a synthetic testosterone analog, that also can be used in treating women and children with chronic muscle-wasting conditions (76).

One placebo-controlled study performed mainly on male subjects with inclusion body myositis (IBM), another subset of chronic muscle inflammation, showed some effect in improving whole-body and upper extremity strength (77). Under the controlled conditions of the trial, the adverse effects were minimal and the drug was considered safe and classified as a treatment of possible benefit (77).

No controlled studies have been performed in patients with polymyositis or dermatomyositis, so whether oxandrolone has any effect in these disorders is not known. Results similar to those in the IBM trial were documented in boys with DMD with the conclusion that oxandrolone may have some beneficial effect in slowing the progress of weakness (78). Patients with chronic obstructive pulmonary disease (COPD) also experience muscle wasting, which is further enhanced by glucocorticoid therapy. A study using another anabolic steroid, nandrolone decanoate, for supplementary treatment in patients with COPD, resulted in a significant increase in fat-free mass and an overall positive effect on body composition relative to placebo (79).

4.5.3. GLUTAMINE

Glutamine is a conditionally essential amino acid, meaning that it is essential during conditions of trauma, sepsis, or cancer. The majority of free glutamine is synthesized and stored in skeletal muscle. Glutamine provides the body with new precursors for energy substrates, antioxidants (mostly glutathione), and acute-phase proteins found in the blood shortly after onset of an infection (80). This mobilization leads to an intramuscular glutamine depletion, resulting in a decrease in lean muscle mass (81).

Patients in intensive care may develop severe myopathies and muscle biopsies from these patients show low levels of muscle glutamine (82). The previously mentioned proinflammatory cytokines IL-1 and TNF that are upregulated in myositis, mediate a decrease in protein synthesis and an increase in protein degradation in skeletal muscles. Muscle infusions of glutamine in an animal model of sepsis attenuated the expression of proinflammatory cytokines by suppressing the signaling pathway of NF- κ B, and might therefore have therapeutic potential for various inflammatory diseases (83).

Patients with myositis are treated primarily with glucocorticoids, which induce the release of glutamine into the blood at the expense of muscle protein degradation. Branched chain amino acids (BCAA; valine, leucine, and isoleucine) serve as precursors of glutamine (84), and contribute to approx 20% of the amino acids released during muscle protein breakdown, the major part of which is used for glutamine synthesis.

The systemic availability of dietary glutamine is reduced by uptake in the gut and liver; thus, the whole-body glutamine availability largely depends on the rate of

glutamine synthesis in skeletal muscle. Supplementation of either glutamine or BCAA might counteract the muscle degradation caused by inflammation, steroid treatment, and physical inactivity, but the field has to be further investigated. No studies have been performed in patients with myositis, but glutamine, as well as amino acid supplementation, over 10 days inhibited whole-body protein degradation in patients with DMD (85).

4.5.4. FATTY ACIDS

Fat is the most calorically dense food component and is known as the most efficient way for the body to store excess energy. Fat is more than just energy storage, however, because every cell within the body has a membrane around the surface and surrounding the nucleus. These membranes are built of fatty acids, called phospholipids, which can be released from the membrane by different enzymes and used for multiple tasks, depending on the fatty acid type. Arachidonic acid (AA), the precursor of the proinflammatory PGE₂, is an omega-6 (n-6) polyunsaturated fatty acid (PUFA) and is metabolized from linoleic acid, found in nuts, seeds, and vegetable oils, such as corn oil (86).

Fish oil and flaxseed oil are rich sources of anti-inflammatory omega-3 (n-3) PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA/DHCA), both metabolized from α -linolenic acid. Both linoleic and α -linolenic acid are essential fatty acids, which means that the body cannot synthesize them .

In a modern Western diet the ratio between n-6 and n-3 fatty acids is about 20 to 1, and this may have an effect on eicosanoid synthesis. A diet containing a higher intake of n-3s may shift AA-derived proinflammatory mediators to the more anti-inflammatory properties of EPA and DHA metabolites. A number of animal trials have been performed showing that diets containing a higher intake of n-3, or fish-oil supplements, reduces AA content in cell membranes and inhibits the synthesis of proinflammatory prostaglandins. Prior to consuming any dietary supplements, patients should consult with their physician and with their nation's dietary guidelines (86,89–91).

4.5.5. VITAMIN D

Osteoporosis and fractures are common consequences of glucocorticoid therapy and of physical inactivity. Thus, patients with polymyositis and dermatomyositis are at high risk for developing this complication. Prevention of bone loss should be considered as part of the therapy for these patients.

Prevention of steroid-induced bone loss is based on calcium and vitamin D supplementation, adequate protein intake, and regular physical exercise (92). The classic function of vitamin D is to regulate bone formation and resorption through regulating calcium homeostasis. For children and adolescents, glucocorticoid treatment may cause failure to reach a normal peak bone mass with an increased risk for hip and spine fractures later in life, which makes supplementation of calcium and vitamin D even more important in this population (93,94).

Vitamin D is also an important immune system regulator. The vitamin D receptor is present on various immune cells, producing and releasing the active hormone. Vitamin D status has been linked to autoimmune diseases in humans where low vitamin D intake is associated with increased susceptibility to develop autoimmune diseases such as multiple sclerosis and RA (93,95). Moreover, vitamin D insufficiency can lead to

disturbed muscle metabolism (96). In different animal models of autoimmune disease, it has been shown that supplementation with vitamin D or treatment with D-hormone analogs acts in an immunosuppressive way, decreasing the disease symptoms (93,95,97,98).

Major dietary sources of vitamin D are fortified dairy products, fatty fish, and fish liver oils. The main supply of D hormone is obtained through sun exposure of the skin where the UV light converts a pro-vitamin to the active D vitamin. The sunlight exposure is significantly less in northern climates and especially low during winter months (93,99). The serum level of vitamin D is the best indicator for defining any deficiency, insufficiency, or toxicity. Concentrations below 40 to 50 nmol/L reflect vitamin D insufficiency and intoxication levels are clearly above 200 nmol/L. There have been no reports of intoxication from sunlight exposure; all of the observed cases are owing to excessive oral intake (96).

Most dietary guidelines for vitamin D are based on maintaining bone health, and differ throughout a lifetime. Important variables are season, latitude, and the food fortification of the country *per se* (100). To our knowledge, no reports of vitamin D effects on the immune system in patients with polymyositis or dermatomyositis have been published, but as patients with dermatomyositis may be sensitive to UV light exposure, they are at risk of vitamin D deficiency and as a consequence at high risk to develop osteoporosis. This is another strong indication for vitamin D supplementation in patients with dermatomyositis.

4.5.6. VITAMIN E

Aggressive distribution of vitamin E was used for treatment of polymyositis and dermatomyositis during the early 20th century for several decades. An explanation for this could probably be that one of the primary manifestations of vitamin E deficiency is myopathy (101,102).

Reversible human myopathy caused by vitamin E deficiency has been described in a couple of cases (103,104). Vitamin E is a soluble lipid that acts primarily as an antioxidant and as a scavenger of products from lipid peroxidation preventing cell damage, but in recent years, non-antioxidant functions such as signaling and gene regulation have been discovered (105).

Vitamin E covers eight structurally related isomers, the most active of which is α -tocopherol. Rich sources of vitamin E are vegetable oils, such as sunflower oil. Nuts are also a good source of vitamin E, whereas fruits, vegetables, and meat contain lesser amounts.

Vitamin E deficiency is rare in humans and does not occur as a result of a dietary deficiency, but rather, from genetic abnormalities, or secondary to fat malabsorption syndromes such as chronic cholestasis, cystic fibrosis, and celiac disease. Another aspect to consider in determining the need for vitamin E supplementation is the antioxidant needs during exercise. Reactive oxygen species are generated in contracting muscles and mediate muscle damage and inflammatory responses after a demanding exercise bout. Dietary supplementation with vitamin E in order to negate this contraction-induced muscle damage has been controversial because of dissimilar test parameters including age and fitness of the subjects, dose and duration of the antioxidant, and type of exercise performed (106–108). As myositis therapy, vitamin E is no longer used because it is not considered effective (109).

4.5.7. HERBAL SUPPLEMENTS

Herbal supplements are widely used and among the most popular products are supplements with immune-stimulatory properties. The field of research evaluating alternative medicine and autoimmunity is limited but there have been some cases reported.

4.5.7.1. Polyphenols. Polyphenols are a group of micronutrients with similar molecular structure, found in plants where they act as a defense against pathogens and UV radiation. Dietary polyphenols can be divided into four subgroups: flavonoids, stilbenes, lignans, and phenolic acids (110).

It has been determined both epidemiologically and experimentally that polyphenols have anti-inflammatory activity. The suggested mechanism of this activity is the inhibition of NF- κ B signaling and COX activity, thus reducing PG production (111). One group of polyphenols is the flavonoids that can be found in fruits, vegetables, wine, tea, and dark chocolate. Their presumed beneficial effects are mainly antioxidative in disorders such as stroke, cancer, and inflammatory diseases (111).

Another polyphenol found in green tea extract is epigallocatechin gallate (EGCG). EGCG has not yet been tested in humans, but in an animal model of DMD, supplementation of green tea extract for 5 weeks decreased degenerating muscle fibers and infiltrating immune cells in muscle tissue (112). The researchers also noted that the muscles were more fatigue resistant and concluded that this feature was owing to an improved structure of muscle tissue.

In yet another study, EGCG induced expression of mPGES-1 leading to induction of PGE₂ in pulmonary cells (113). We found no reports on EGCG in inflammatory myopathies, but based on these observations, we believe that some caution should be taken if used for myositis as this EGCG could work in both a proinflammatory as well as an anti-inflammatory manner.

4.5.7.2. Immunostimulatory Preparations. There are herbal supplements with immunostimulatory activity. Potent immune-activating properties have been shown in algae (*Spirulina platensis* and *Aphanizomenon flos-aquae*), both in human (chemoprotective effects) and animal studies (increased macrophage activity (114,115)).

Support for an immunostimulatory property is based on reports that patients suffering from autoimmune skin disorders have experienced flares and discomfort such as blisters after taking supplements containing *Spirulina* or echinacea (purple cornflower), another popular immune-boosting herbal supplement (115). In one case report, a woman taking algae in a combined dietary supplement developed heliotrope rash and was later diagnosed with dermatomyositis. Although this could be a coincidence, the well-known immune-enhancing properties of these algae supplements, in combination with the clinical history of this woman, could indicate that these substances could induce an autoimmune disease (115).

5. CONCLUDING REMARKS AND RECOMMENDATIONS

As a general recommendation, it is of great importance to consume an adequate amount of macronutrients and trace elements for maintenance and improvement of body functions. This is particularly true for patients with polymyositis or dermatomyositis. A well-balanced diet, with moderate intake of all of the food groups, is generally

recommended. There are some additional actions that the patient with myositis can undertake in an attempt to influence the clinical symptoms and treatment-related side effects of this disease. One such recommendation is to supplement with calcium and vitamin D, to reduce the risk of developing steroid-induced osteoporosis. Another suggested supplement is folic acid, in order to counteract deficiencies caused by methotrexate treatment.

Another supplement, although less well studied, is creatine. Creatine has been shown to have a beneficial effect, without negative side effects, on patients with myositis when used as a supplemental treatment in combination with conventional pharmacological treatment and physical exercise.

As a general recommendation, we also emphasize that it is important that people suffering from inflammatory myopathies do not experiment with supplements, trace elements, or excess ingestion of certain foodstuffs without consulting their personal physician first, as there are potential risks of some supplements that may cause adverse events.

Some of the substances mentioned should only be supplemented if there is an existing state of deficiency that can be determined by a blood sample. Some nutrients and trace elements share the same receptors and/or transport molecules in a competitive manner, and an excess intake of one can lead to a deficiency of another, with serious consequences. One compound may affect multiple mechanisms.

Certain foods can also interact with drug metabolism in unfavorable ways, in which case it is absolutely necessary for health care providers to inquire about the intake of any health foods or supplements. The authors do not encourage patients with inflammatory myopathies to undertake unsupervised experiments with any of the above mentioned nutrients. In some instances (i.e., anabolic steroids), possession and distribution is considered a crime. The information presented in this chapter is solely a review of the field of research, based on studies performed primarily on patients suffering from disorders other than myositis, and healthy persons. Thus, the authors cannot be held responsible for any events caused by disuse of this knowledge.

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