Chapter 15

Medical Nutrition Therapy in Lipedema

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Abstract

Lipedema is a chronic adipose tissue disorder that mostly affects women, including changes in adipose tissue and vascularity anomalies, although its pathology is not known exactly. Lipedema adipose tissue (LAT) leads to chronic systemic inflammation in the body. Since there is no clear proven cure, the main goal is to alleviate the symptoms associated with the disease. Traditional dietary approaches are ineffective on LAT, but dietary models in which carbohydrate intake is restricted and antioxidant-containing food intake is increased can be a therapeutic approach in reducing inflammation and symptoms caused by lipedema. The ketogenic diet, with its low carbohydrate content, is the most frequently studied dietary approach in lipedema and is thought to be the most appropriate for patients. By improving blood glucose profile and insulin resistance, it prevents hyperglycemia induced inflammation supported by lipedema. It also suppresses pain caused by inflammation by causing a decrease in C-reactive protein (CRP) level. The Mediterranean diet, which is high in antioxidants, is another nutritional model that has been reported to have positive effects on lipedema. It is stated that it can be applied to patients with lipedema because of the abundance of anti-inflammatory foods in the diet and the minimum level of components that can lead to pro-inflammatory cytokine production in the body. On the other hand, vitamins and minerals, which have important roles in ensuring the physiological functioning of the body, should be considered as supplementation according to their levels in the body in order not to worsen the negative clinical

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picture caused by LAT. In conclusion, there is still a need for more studies to understand the mechanism of lipedema and to provide the treatment methods it requires. The aim of this chapter is to provide information to the readers about the medical nutrition therapy that can be applied in lipedema according to the current literature.

Introduction

Lipedema is a painful adipose tissue disorder that usually occurs in the extremities and is characterized by abnormal subcutaneous fat accumulation (Crescenzi et al., 2018). It is frequently seen in women (it is thought to be 11-19% of the female population, with the possibility of being even more) due to hormonal changes with the increase in the expression of estrogen, which plays a role in lipid metabolism, with puberty, and it has a genetic predisposition (Buso et al., 2019; Herbst et al., 2021). Since estrogen may be associated with subcutaneous adipose tissue accumulation in the gluteal and femoral regions, it has been stated that adipose tissue dysfunction due to the change in estrogen receptor alpha (Erα) and estrogen receptor beta (Erβ) ratios in areas of involvement may be a possible mechanism responsible for lipedema (Krotkiewski et al., 1983; Kruppa, 2020; Katzer et al., 2021). In addition, although its pathophysiology is not fully known, it has been noted that it may also result from microangiopathy of blood and lymphatic vessels and microvascular dysfunction (Al-Ghadban et al., 2019a). On the other hand, lipedema causes angiogenesis and increased capillary permeability as a result of hypoxia caused by unregulated adipogenesis. It is examined in 5 different types (Figure 1) according to its anatomical location and in 4 stages (Figure 2) according to its severity (Herbst, 2012).

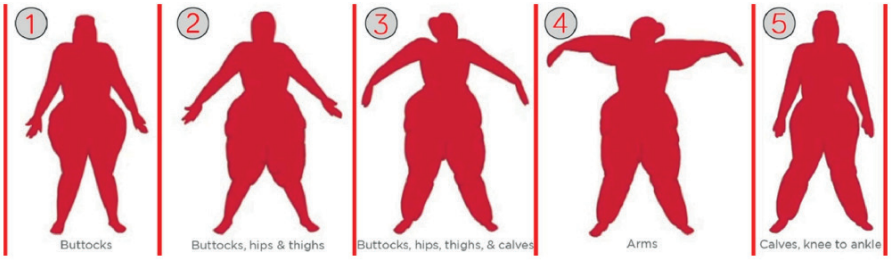

Figure 1. Lipedema types (Keith et al., 2021)

Figure 2. Lipedema stages (Keith et al., 2021)

Unlike lymphedema, there is bruising, severe pain, non-pitting edema, and hypersensitivity to pressure in the lower extremity areas where the involvement is present (Buso et al., 2019). In advanced levels, it can lead to deterioration in the lymphatic system and cause lipolymphedema (Herbst, 2012; Gould et al., 2020). Crescenzi et al. (2018) revealed that even women with less severe lipedema have high sodium accumulation in muscle, skin, and subcutaneous adipose tissue (SAT). This suggests that the disease may adversely affect lymphatic capillary drainage even at mild levels. Lipedema patients are often misdiagnosed for obesity in the diagnosis because they appear to be overweight, but the localization of fat accumulation, hormonal changes thought to be the main trigger of the disease, the affected population, and the time of onset of the disease constitute characteristic features for the diagnosis of lipedema (Forner-Cordero et al., 2012; Kruppa et al., 2020). The diagnosis is made by family history, clinical observation and physical examination, and the main criterion is bilateral fat involvement extending from the hip to the ankle (Wold et al., 1951). In the treatment, it is aimed to reduce the inflammation caused by lipedema adipose tissue by increasing the level of physical activity and to alleviate symptoms such as severe pain, which is thought to be caused by inflammation (Crescenzi et al., 2018; Al-Ghadban et al., 2019a). In addition, it is aimed to prevent the worsening of other pathological conditions such as obesity, lymphedema and venous insufficiency in the prognosis of this disease (van la Parra et al., 2023). Current treatment options include conservative decongestive therapy, physical rehabilitation, liposuction, and certain dietary approaches whose effectiveness has been frequently studied in recent years.

1. Medical Nutritional Treatment of Lipedema

Patients with lipedema have a different adipose tissue distribution and content than obese individuals without lipedema. Lipedema adipose tissue is resistant to exercise, traditional calorie-restricted diets, and weight loss with bariatric surgery in the treatment of obesity (Crescenzi et al., 2018; Herbst et al., 2021). On the other hand, this tissue causes low-level chronic inflammation in the body. Although it is known that most of the patients with lipedema have obesity, which is also a chronic inflammation condition, it has been stated that the inflammation in these individuals is independent of obesity (Okhovat and Alavi, 2015; Al-Ghadban et al., 2019a). This reveals that the inflammation caused by lipedema adipose tissue cannot be alleviated by approaches in the treatment of obesity. Since the symptoms seen in patients are thought to be caused by the systemic inflammation caused by LAT, the main goal for treatment is to eliminate this condition (Suga et al., 2009; Al Ghadban et al., 2019a). For this reason, it has been revealed that some diet types with high antioxidant and anti-inflammatory content, especially the ketogenic diet, can have a positive effect on the clinical picture of the disease by reducing the current inflammatory status and preventing the possible increase in LAT induced inflammation (Masino and Ruskin, 2013; Roberto and Cione, 2020; Di Renzo et al., 2021).

The aim of the present review is to provide readers with information about medical nutrition therapy and various dietary approaches in patients with lipedema.

1.1. Low-Carb Ketogenic Diet

The ketogenic diet (KD) is a diet approach with very low carbohydrate (<50 g/day), very high fat and sufficient protein content (Ułamek Kozioł et al., 2019). There are 4 main types: classic long chain triglyceride (LCT) KD, medium chain triglyceride (MCT) KD, modified Atkins diet (MAD) and low glycemic index diet. Among these, the most commonly applied is the 4:1 LCT type, which defines 1 gram of protein and carbohydrate against 4 grams of fat (Paoli, 2014; Kossoff et al., 2018). The main target is the formation of ketosis in the body by the production of ketone bodies (acetone, acetoacetate, β hydroxybutyrate), which is confirmed by a beta-hydroxybutyrate (BHB) value of ≥0.5 mmol/L in the blood (McKenzie et al., 2017). In ketosis, fatty acid oxidation is provided and ketone bodies are used as the body's main energy source instead of glucose (Valenzuela et al., 2021). Due to the effects of ketogenic diet such as reconstruction of damaged myelin sheaths, improvement of impaired metabolic events of

neurons, suppression of reactive oxygen species (ROS) production, and thus prevention of neuronal inflammation, this diet is used in the clinic, especially in the management of epilepsy that does not respond to antiepileptic drugs and in the nutritional treatment of various other neurological diseases (Ułamek Kozioł et al., 2019; Dyńka et al., 2022).

Ketone bodies formed in the body with KD may be effective in the nutritional treatment of lipedema by having anti-inflammatory properties and reducing oxidative stress (Dupuis et al., 2015; Puchalska and Crawford, 2017; Di Renzo et al., 2021). Even though the exact mechanism is not known, it has been stated that the pain caused by lipedema is alleviated by this antioxidative and anti-inflammatory effect of KD (Suga et al., 2009). Cannataro et al. (2021) revealed that, in addition to a weight loss of 41 kg in the lipedema patient on a ketogenic diet, a decrease in CRP (C-reactive protein) level compared to baseline, a decrease in general pain complaints and an improvement in other biochemical parameters. Similarly, Sørlie et al. (2022) noted a significant reduction in both weight loss and chronic pain in women with lipedema following a 7-week ketogenic diet. At the end of the KD diet, the women who consuming the Scandinavian diet for the following 6 weeks continued to lose weight while their chronic pain returned. This result reveals that the ketogenic diet can reduce pain with its anti-inflammatory effect independent of weight loss (Suga et al., 2009; Strath et al., 2020).

High carbohydrate consumption (more than 45% of total energy) and proinflammatory effects of postprandial hyperglycemia are considered as possible causes for the development of lipedema (Gregersen et al., 2012; Nankam et al., 2022). Conversely, the ketogenic diet has a very low carbohydrate content and therefore lowers the level of oxidative stress, leading to a reduction in inflammation. In addition, it induces an increase in the amount of adenosine, a natural analgesic, which is a possible mechanism that suppresses pain sensation in lipedema (Masino and Ruskin, 2013; Lusardi et al., 2015; Strath et al., 2020). In addition, although lipedema does not reduce adipose tissue, its coordinated application with exercises such as swimming, yoga and pilates that can help lymphatic drainage can improve the pain caused by these, as a result of eliminating edema, hypoxia and inflammation in patients (Al-Ghadban et al., 2019b). In a study examining the effectiveness of two diets with different carbohydrate and fat contents in patients with lipedema, a high antioxidant and low carbohydrate high fat (LCHF) diet was found to be more effective in reducing lipedema induced pain and swelling compared to a medium carbohydrate medium fat diet consisting of low glycemic index foods. It has been shown to be

more effective in reducing weight and correcting impaired body proportion (Jeziorek et al., 2022) (Figure 3 and 4).

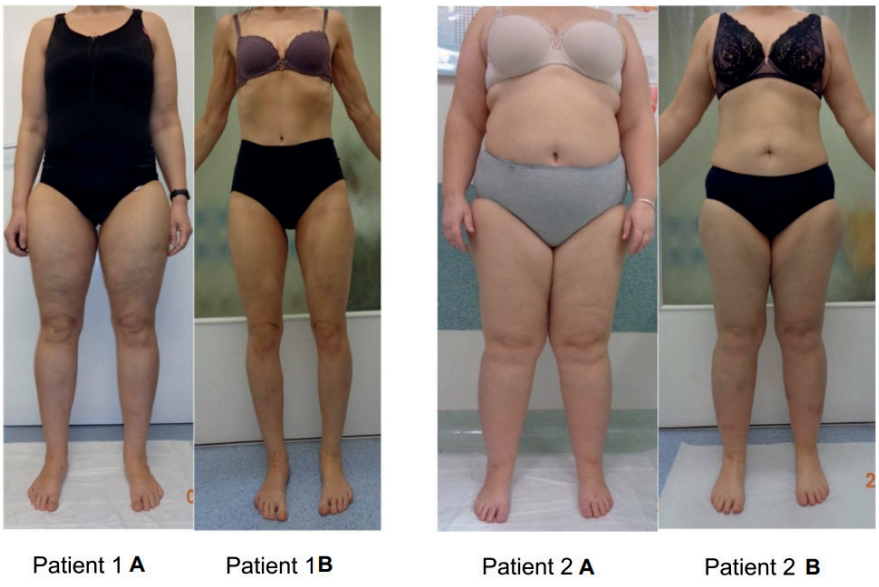

Figure 3. Pre-treatment (1A and 2A) and post-treatment (1B and 2B) body views of patients following a low carbohydrate high fat (LCHF) diet (Jeziorek et al., 2022)

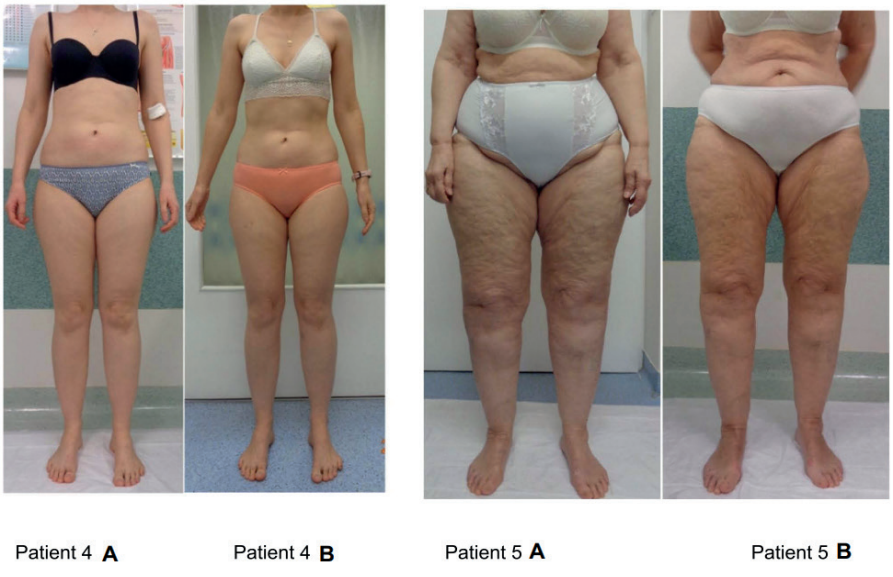

Figure 4. Pre-treatment (4A and 5A) and post-treatment (4B and 5B) body appearances of patients following a diet with moderate carbohydrate moderate fat (MCMF) content (Jeziorek et al., 2022)

The glycogen stores in the body also require water retention (Lorenzo et al., 2019). Since increased glycogen stored with diet applications with high carbohydrate content will lead to more fluid retention, this can be considered as a possible cause of edema and increased tissue fluid in lipedema, apart from all the other mechanisms described so far (Gould et al., 2020). For this reason, it has been stated that KD application may contribute to both the destruction of storage glycogen and the alleviation of edema caused by excessive fluid accumulation due to excess amount of storage glycogen (Keith et al., 2021).

It has been shown that lipedema adipose tissue may be closely related to insulin resistance due to its hypertrophic adipocyte structure (Gustafson et al., 2015; Faerber, 2018). Insulin resistance and high insulin levels promote lipogenesis and are among the main causes of systemic chronic inflammation (Bertsch et al., 2020). For this reason, diets with low carbohydrate content are important in patients with lipedema to prevent hyperinsulinemia and provide glycemic control (Goss et al., 2020; Michalczyk et al., 2020; Rasmussen et al., 2020). In a study, in type 2 diabetes patients using insulin and other antidiabetic drugs, although the drug doses used by some patients were halved, the application of a low carbohydrate ketogenic diet (LCKD) for 24 weeks reduced blood glucose and glycosylated hemoglobin (HbA1c) to normal levels and was more effective than low-calorie diet. (Hussain et al., 2012). In another study, it was revealed that the low-carbohydrate Atkins diet applied for 2 years in diabetes patients decreased the blood insulin value and caused a significant decrease in HbA1c and CRP levels (Shai et al., 2008). In a recent study, it was stated that feeding with a low carbohydrate high fat (LCHF) diet caused a decrease in fasting insulin level and triglyceride concentration, and this diet may be a suitable nutritional approach for patients with lipedema (Jeziorek et al., 2023). On the other hand, in addition to low carbohydrate content, a low glycemic index diet prevents insulin levels from increasing by balancing blood glucose (Reich-Schupke et al., 2017; Buso et al., 2019; Jeziorek et al., 2022). Westman et al. (2008) compared the effects of LCKD and low glycemic index diet (LGID) in type 2 diabetes patients, and stated that although they noted improvements in HbA1c, blood glucose and blood insulin levels in both groups, the effectiveness of LCKD was more dominant than LGID. This suggests that the low carbohydrate content of the ketogenic diet is a more important factor in inhibiting the formation of high insulin levels that cause lipogenesis stimulation. In addition, due to its low carbohydrate content, it may be a more effective option in suppressing lipedema adipose tissue

increase in terms of blood glucose, insulin level and various other biochemical parameters.

1.2. Anti-inflammatory Mediterranean Diet

Given the LAT induced infection in lipedema patients, feeding a diet high in anti-inflammatory content may help alleviate symptoms caused by inflammation. The Mediterranean diet, which is one of them, is a nutritional approach that is stated to have positive results in individuals with lipedema due to its antioxidant, anti-inflammatory, antihyperglycemic and antidiabetic effects. Although the results of studies examining the effects of this diet directly on individuals with lipedema are very limited, the available data in the literature reveal that this diet has positive effects on patients (Di Renzo et al., 2021).

The Mediterranean diet consists of a diet with a high seasonal fruit and vegetable content, rich in seafood, limited in red meat, unrefined whole grains, consuming olive oil as a lipid source, and increasing nuts consumption (Schwingshackl et al., 2020). Fish, red wine, fruit and vegetables, flavonoids and other foods rich in antioxidants, which make up the diet, strengthen the body's endogenous antioxidant system and prevent the increase in proinflammatory cytokines and oxidative stress levels (Holt et al., 2009). Studies have proven that it plays a role in the reduction of inflammatory biomarkers, especially CRP and Interleukin-6 (IL-6) (Estruch, 2010; Schwingshackl and Hoffmann, 2014). Haghighatdoost and Hariri (2019) revealed that the consumption of grapes and the resveratrol it contains causes a decrease in CRP levels and has a protective effect against inflammation. Granado-Serrano et al. (2012) stated that Quercetin, an antioxidant flavonoid found mostly in onions, vegetables and fruits such as apples, strawberries, and red leaf lettuce, mediates the inhibition of free radical production by increasing intracellular glutathione levels. Prasad et al. (2013), on the other hand, showed that Quercetin plays a role in the scavenging of reactive oxygen species (ROS) and hydroxyl radicals formed in hypoxic state.

Fish, which has an important place in the Mediterranean diet, contains plenty of omega-3 (w-3) fatty acids, which have anti-inflammatory properties and suppress inflammation in various diseases (Alexander and Supp, 2014). Together with W-3 polyunsaturated fatty acids (PUFA), Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), it reduces the levels of inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α) and IL-6 (McDaniel et al., 2008). Olive oil, on the other hand,

replaces animal and refined oils in the diet, contributes to the development of sirtuin 1 gene (SIRT1) expression, which provides the resistance of cells to oxidative stress with its polyphenols in its structure, and leads to inhibition in proinflammatory cytokine production (Schwingshackl et al., 2020).

The Mediterranean diet provides improvement in high blood glucose and insulin resistance, which have a proinflammatory effect and increase lipedema symptoms (Bertsch et al., 2020). Restriction of sugar, fructose, refined carbohydrates, processed foods and sweeteners, high vegetable content and high fiber consumption (>25 g/day) in the diet lead to suppression of hyperinsulinemia induced insulin resistance and proinflammatory cytokine production (Faerber, 2018; Venter et al., 2022). In addition, reducing saturated fat intake and increasing consumption of olive oil, nuts and fish rich in w-3 also help prevent inflammation (Faerber, 2018). On the other hand, it was stated that this dietary approach in diabetic patients caused a decrease in HbA1c due to its anti-inflammatory properties, and because it is rich in MUFA, it regulates glycemic control and lead to insulin sensitivity (Shen et al., 2015; Martín-Peláez et al., 2020). Zhu et al. (2017) revealed that resveratrol, which is found in large amounts in fruits such as grapes, mulberries, blackberries and strawberries, improves high blood glucose, HOMA-IR and insulin resistance.

Vitamins and minerals in the foods that make up the content of the Mediterranean diet and other anti-inflammatory diets also play an important role in strengthening the antioxidant system and correcting the inflammatory condition. For example, selenium, which is found at high levels in the structures of seafood and oilseeds in the diet, participates in the structure of enzymes that play a role in the prevention of oxidative stress and helps to increase the antioxidant capacity (Mehdi et al., 2013). Nuts, which are rich in monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), contain plenty of vitamin E, vitamin B2, folate and magnesium. Their consumption is inversely related to CRP, IL-6 and other inflammatory biomarkers, whose levels are expected to increase due to chronic inflammation in lipedema patients (Yu et al., 2016). Hong et al. (2018) stated that nut decreased oxidative load and serum proinflammatory cytokine levels, while increasing antioxidant enzyme levels. In addition, the Mediterranean diet rich in foods with anti-inflammatory properties may also promote a reduction in pain caused by inflammation in individuals with lipedema. Ortola et al. (2022) revealed that the Mediterranean diet provides suppression of pain sensation in older adults and this may be due to the anti-inflammatory effect of high consumption of fruits and vegetables rich

in potassium, phosphorus, calcium, magnesium minerals and vitamins B, E, A and K.

Although there are not enough studies, it is thought that diets with high antioxidant properties, especially the Mediterranean diet, can help prevent inflammation or alleviate existing inflammation with all these mechanisms and thus be effective in lipedema symptoms.

1.3. Nutritional Supplements in Lipedema

Vitamin and mineral losses may occur due to dietary approaches that can be applied to treat lipedema and alleviate its symptoms. Reddy et al. (2002) reported that low carbohydrate diet increases urinary calcium excretion and may pose a risk in terms of bone loss. Adam-Perrot et al. (2006) stated that similar the low-carbohydrate diet is insufficient to provide the micronutrient needs of the body. Additionally, in a systematic review, it was revealed that the intake of thiamine, folate, magnesium, iron and iodine in the body decreased with carbohydrate-restricted diet consumption (Churuangsuk et al., 2019). In another study, it was shown that a 3-month ketogenic diet could not provide the manganese, vitamin D and E requirements needed by the body (Taylor et al., 2019). Therefore, although antioxidative and anti-inflammatory diets, which are important in the medical nutrition therapy of lipedema, can adequately supply the body's vitamin and mineral needs due to their high vegetable and fruit content, low-carbohydrate nutritional approaches such as the ketogenic diet may lead to serious micronutrient deficiencies in patients with lipedema (Castro- Quezada et al., 2014).

According to the available literature data, the efficiancy of any nutritional supplement in lipedema has not been clearly proven (Cannataro and Cione, 2022). However, since micronutrient deficiencies that may occur with dietary approaches that can be applied in the treatment may worsen the inflammatory condition caused by lipedema, additional consumption of nutritional supplements with anti-inflammatory properties should be evaluated in line with the needs of the patients. For example, considering the pain caused by LAT induced inflammation in patients, antioxidant and anti-inflammatory ascorbic acid can be used to relieve pain (Mikirova et al., 2012). Bai et al. (2021) revealed that high vitamin C intake provides a reduction in diabetic neuropathic pain. On the other hand, the levels of micronutrients with anti-inflammatory properties such as vitamin D, which acts as a modulator through various mechanisms in the prevention of systemic inflammation, selenium, which contributes to the alleviation of the inflammatory state by participating in the structure of some antioxidative enzymes, and zinc,

which reduces oxidative stress and suppresses inflammation, should be closely monitored in patients with lipedema as well as in every individual (Mehdi et al., 2013; El-Sharkawy and Malki, 2020; Drożdżal et al., 2021). In addition, vitamins and minerals that are deficient in the body as a result of the diets applied should be determined and supplements at the necessary levels for the continuity of the physiological functioning of the body functions should be arranged together with the physician and dietitian. As a result, although the supplementation of micronutrients in individuals with lipedema has not been proven, at least preventing the deficiencies of these nutrients may allow the dietary approaches that are considered suitable for lipedema patients to be applied for a longer period of time without vitamin and mineral deficiencies (Jeziorek et al., 2022; Cannataro and Cione, 2022).

Conclusion

Considering the current studies in the literature, although it is not a dietary approach that has been definitively proven to be applicable in patients with lipedema, those that are stated to be more suitable than other diets are anti-inflammatory diets, especially the ketogenic diet and the Mediterranean diet, due to their low carbohydrate content and anti-inflammatory properties. It is seen that their mitigating effect on lipedema disease and its symptoms mostly occurs through mechanisms based on low carbohydrate content and antioxidant and anti-inflammatory compounds. Therefore, although there is still a lot of uncertainty about the pathogenesis of lipedema and appropriate treatment options, according to current data, diet applications that target the formation of ketosis in the body and high antioxidant anti-inflammatory content should be considered as the first choice in medical nutrition therapy. In addition, vitamin mineral levels, which have an important place in the prognosis of the disease and the clinical picture of the patients, should be closely monitored and their supplementation should be considered when necessary.

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