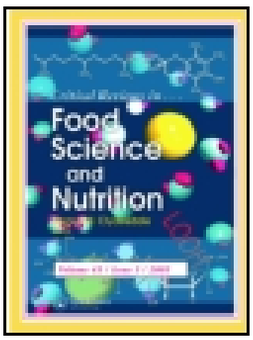

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Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Luigi Barrea , Matteo Megna , Sara Cacciapuoti , Evelyn Frias-Toral , Gabriella Fabbrocini , Silvia Savastano , Annamaria Colao & Giovanna Muscogiuri (2020): Very low-calorie ketogenic diet (VLCKD) in patients with psoriasis and obesity: an update for dermatologists and nutritionists, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1818053

To link to this article: https://doi.org/10.1080/10408398.2020.1818053

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1818053

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REVIEW

Very low-calorie ketogenic diet (VLCKD) in patients with psoriasis and obesity: an update for dermatologists and nutritionists

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ABSTRACT

Psoriasis is a chronic skin immune-mediated disease with systemic pro-inflammatory activation; both genetic and lifestyles factors contribute to its pathogenesis and severity. In this context, nutrition plays a significant role, *per se*, in psoriasis' pathogenesis. Obesity is another important risk factor for psoriasis, and weight reduction may improve psoriasis' clinical severity. The excess body weight, particularly visceral fat mass, can affect both drug's pharmacokinetics and pharmacodynamics. Therefore, psoriasis and obesity share a certain degree of synergy, and the chronic inflammatory state represents the basis of this vicious cycle. Evidence reported that nutrition has different impact on the clinical severity of psoriasis, though some specific diets have been more investigated in clinical studies compared to others. Diets with systemic anti-inflammatory properties seem to have a higher effect on improving the clinical severity of psoriasis. Of interest, very-low-calorie ketogenic diet (VLCKD), through the production of ketone bodies, has been associated with both a significant reduction of body weight and inflammatory state. VLCKD leading to both weight loss and reduction of systemic inflammation may decrease the exacerbation of the clinical manifestations or even it may block the trigger of psoriatic disease. This dietary pattern could represent a potential first-line treatment in psoriatic patients with obesity. The review aims to summarize the current evidence regarding VLCKD and psoriasis with specific reference to antioxidant and anti-inflammatory effects of this dietary pattern.

KEYWORDS

Diet; inflammation; obesity; psoriasis; very low-calorie ketogenic diet (VLCKD)

Introduction

Among the top 20 causes of death reported for 2017 (Roth et al., 2018), eleven of them were directly related to inflammation (Yilmaz et al. 2020), that is the most important biological process that controls the interaction between organisms and the environment (Bordoni et al. 2017). Nonetheless, there is a small division between the favorable and adverse effects of inflammation. Acute inflammation is usually a short-term immune response that is reduced after the elimination of pathogens. However, an uncontrolled acute immune response can lead to an allergic response or lethal anaphylactic shock. Conversely, inadequate immune response or insufficient inflammation can cause deferred wound repair and repeated infection of pathogens. The correct and controlled response of the inflammation modifies its beneficial or destructive result. Therefore, it results that extended and deregulated chronic inflammations are the common cause of several chronic diseases (Furman et al. 2019), such as obesity (Pessentheiner, Ducasa, and Gordts 2020), type 2 diabetes mellitus (Banerjee and Singh 2020), cardiovascular diseases (Hamjane et al. 2020), pulmonary diseases (Rondanelli et al. 2020), immunological diseases (Francisco et al. 2019), cancers (Murata 2018), neurological irregularities (Rea et al. 2018), arthritis (Scanzello 2017), psoriasis (Coimbra, Catarino, and Santos-Silva 2016), vitiligo (Harris 2016), and type I diabetes (Eizirik, Colli, and Ortis 2009). Nowadays, there is an increasing number of immune-mediated inflammatory diseases; among them, psoriasis has a prominent position because it is one of the most prevalent immune-mediated inflammatory diseases worldwide (Ellis et al. 2019; Knox et al. 2019; Parisi et al. 2013). It is a systemic inflammatory disease (Korman 2020) which is nowadays considered as a systemic disease with a prevalent skin and joints (psoriatic arthritis) involvement. In addition, psoriasis is directly related with other diseases (Takeshita et al. 2017a), such as chronic inflammatory bowel diseases (Nehring and Przybyłkowski 2020), chronic kidney disorders

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(Grandinetti et al. 2020; Lee et al. 2019), obesity (Barrea et al. 2016a), metabolic syndrome (Peralta et al. 2019), cardiovascular diseases (Casciano et al. 2018), and type 2 diabetes mellitus (Mamizadeh, Tardeh, and Azami 2019).

Psoriasis, as a T-cell-mediated immune-mediated inflammatory diseases is characterized by activation of antigen-presenting cells, and activation and expansion of Th-1 and Th-17 T cells (Deng, Chang, and Lu 2016). The inflammatory cytokines from those cells are increased in the skin and blood of psoriatic patients and are essential to recruiting more T cells to the skin and joints, boosting angiogenesis and epidermal hyper proliferation (Deng, Chang, and Lu 2016). Simultaneously these cytokines have pleiotropic effects on different mechanisms such as angiogenesis, insulin signaling, adipogenesis, lipid metabolism and immune cell trafficking (Deng, Chang, and Lu 2016).

There are several risk factors for psoriasis that may be responsible for its onset: genes well-identified such as HLA-Cw*06 allele (Davidovici et al. 2010), and environmental factors (Barrea et al. 2016a) which include injuries, infections, certain medical treatments, stress, and nutritional habits. As they have a complex interaction, there are several evidence focused on nutrition since it has a deep impact not only on psoriasis but also on several chronic inflammatory diseases and immune-mediated inflammatory diseases (Barrea et al. 2016a; Ruiz-Canela, Bes-Rastrollo, and Martínez-González 2016). In fact, it has been vastly documented how nutrients can modify human's inflammatory status and, consequently, achieve the control of several diseases (Calder et al. 2013; Gioia et al. 2020; Zahedi et al. 2020).

Additionally, it is noteworthy the deep impact of nutritional interventions on both dermatological and metabolic outcomes such as weight loss in patients with obesity and the improved response to psoriasis therapies (Carrascosa et al. 2014; Upala and Sanguankeo 2015). It has been reported that obesity in psoriatic patients can affect the psoriasis drug's pharmacokinetics and pharmacodynamics (Barrea et al. 2016a). Gisondi et al. highlighted a possible increased risk of liver and renal toxicity from methotrexate and cyclosporine in psoriatic patients with obesity (Gisondi, Del Giglio, and Girolomoni 2016). Many of these chronic diseases, including cardiovascular, cerebrovascular and neurodegenerative diseases, and cancer (MacDonald et al. 2020), have an ever-increasing risk factor, the low-grade inflammation because of its low-grade continuous systemic production of inflammatory factors (León-Pedroza et al. 2015). Through this activity, low-grade inflammation has been related to many misbalances and disturbances in several physiological (León-Pedroza et al. 2015), metabolic process including insulin resistance and type 2 diabetes mellitus, obesity, atherosclerosis, endothelial dysfunction, and Parkinson's disease (Chao, Wong, and Tan 2014). From these conditions, obesity has been studied thoroughly, and recent evidence pointed out that obesity predisposes patients to psoriasis and promotes psoriatic inflammation (Carrascosa et al. 2014; Jensen and Skov 2017; Snekvik et al. 2017).

In the same way, it has been demonstrated that a correct diet and physical exercise positively impact on psoriasis by reducing oxidative stressors, modifying directly the Psoriasis Area and Severity Index (PASI) scores (Alotaibi 2018; Torre-Alonso et al., 2017), and reducing the severity of psoriasis (Upala and Sanguankeo 2015). In order to achieve weight loss, there have been proposed several nutritional strategies (Barrea et al. 2016a; Upala and Sanguankeo 2015; Zuccotti et al. 2018) and different diets such as formula food-reducing diets (Leeds 2014), gluten-free diet (Bhatia et al. 2014), very low-calorie ketogenic diet (VLCKD) (Castaldo et al. 2016a), vegetarian diets (Upala and Sanguankeo 2015), and Mediterranean diet (Barrea et al. 2015a), among others.

Among them, VLCKD has been demonstrated to reduce inflammation more significantly than the others (Forsythe et al. 2008). The current evidence on the efficacy of VLCKD in the context of psoriasis are scarce, indeed two studies have reported the clinical benefits of VLCKD in psoriatic patients (Castaldo et al. 2020; Castaldo et al. 2016a). It could be hypothesized an indirect effect of VLCKD mediated by weight loss; in fact reducing mostly visceral fat could be associated to an improvement of low grade inflammation and in turn of psoriasis. However, VLCKD may also have a direct effect on psoriasis, not mediated by weight loss.

This review aims to summarize the current evidence regarding the efficacy of VLCKD as potential treatment of psoriasis, mostly in the context of obesity, highlighting antioxidant and anti-inflammatory properties of this dietary pattern.

Psoriasis, inflammation and oxidative stress

Psoriasis is a chronic inflammatory skin disease affecting around 2% of the population in Western countries (Boehncke and Schön 2015). It has significant impacts on both physical and emotional health-related quality of life comparable to other major illnesses. Although the pathogenetic mechanisms underlying psoriasis need to be completely clarified, it is considered an autoimmune disease, with intense cross talk between components of the innate and the adaptive immune system, triggering inflammation cascade (Capon et al. 2012). Inflammation is maintained by an abnormal activation of T lymphocytes (Th-1 and Th-17) which are involved in the production of several pro-inflammatory cytokines such as interleukins (IL) like IL-1, IL-6, IL-17, IL-18, IL-22, IL-23, and IL-33, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) (Balato et al. 2012; Gangemi et al. 2003; Karbach et al., 2014; Mitsui et al. 2016).

Inflammation can be considered a cardinal point in psoriasis pathogenesis being a trigger factor for hyper proliferation and angiogenesis, which drive the development of psoriatic lesions. Moreover, inflammation can be considered the primary cause of all skin and articular psoriasis signs: erythematous scaly plaques affecting different body regions can be the only clinical manifestation of psoriasis or they can be associated with articular involvement (psoriatic

Table 1. Oxidative stress markers and anti-oxidants in psoriasis.

Psoriasis and oxidative stress	
Increased oxidative stress markers	Decreased anti-oxidants
Low-density lipoprotein-cholesterol	Paraoxonase-1
ROS	CAT (erythrocyte and plasma)
Malondialdehyde	SOD (erythrocyte and serum)
Lipoprotein(a)	Vitamin E
Nitric oxide	
Thiobarbituric acid reactive substances	

ROS, reactive oxigen species; CAT, catalase; SOD, superoxide dismutase.

arthritis). However, psoriasis cannot be regarded as isolated cutaneous or articular inflammation, but rather represents a chronic systemic inflammatory disease (de Oliveira et al. 2015; Lai and Yew 2016; Takeshita et al. 2017b). An increasing number of studies in various populations and settings supports the association between psoriasis and other diseases with shared inflammatory pathways: cardio-metabolic disease, obesity, gastrointestinal disease, kidney disease, malignancies, infections, and mood disorders (Lai and Yew 2016; Takeshita et al. 2017a). To better clarify the link between skin and systemic inflammation, several groups have identified biomarkers of inflammation in the blood of psoriasis patients, which correlate with psoriasis severity, such as C-reactive protein (Strober et al. 2008), erythrocyte sedimentation rate (Kanelleas et al. 2011), and the platelet activation marker P-selectin (Garbaraviciene et al. 2010). On the other hand, epidemiological evidences confirm the association between psoriasis and cardiovascular comorbidities such as atherosclerosis.

Atherosclerosis and psoriasis are both inflammation-driven phenomenon (Hansson 2005, 2017). Späh F. was among the first who discussed a potentially common inflammatory pathway and the idea of an integrated treatment approach (Späh 2008). Many more shared mechanisms of atherosclerosis and psoriasis have been studied in detail in more recent years: Th-1 lymphocytes role has been established in atherosclerosis as well as psoriasis (Frostegård et al. 1999; Methe et al. 2005; Stemme et al. 1995); high circulating levels of Th-17 lymphocytes and IL-17 have been observed in patients with acute coronary syndrome; similarly, the role of Th-17 lymphocytes is well known in psoriasis and documented by the high clinical efficacy of therapies targeting the IL-17 pathway (Cheng et al. 2008; Hashmi and Zeng 2006). On the other hand, systemic inflammation may contribute to atherosclerosis and psoriasis progression (Korman 2020), being associated with elevated production of oxygen free radicals, which in turn induce vascular endothelial cell damage, with a self-amplifying pathogenetic processes (Incalza et al. 2018). Interestingly, psoriatic and cardiopathic patients seem to share the disbalances of the oxidative stress and the inflammation status that characterizes both diseases (Incalza et al. 2018). This observation introduces us to another phenomenon involved together with chronic inflammation in both psoriasis and its comorbidities (especially metabolic and cardiovascular ones): oxidative stress (Lin and Huang 2016). If physiological inflammation is an essential response in protecting against injurious stimuli, chronic and pathological inflammation can result in an aberrant response with additional tissue damage, generating an abnormal oxidative stress overload and resulting in cellular damage (Lin and Huang 2016).

Oxidative stress is a disproportionate increase of oxidants versus antioxidants, leading to a disruption of redox signaling and control and/or molecular damage (Luo et al. 2017). Reactive oxygen species (ROS) mediated oxidative damage involves a vast number of biological molecules since it causes lipid peroxidation, DNA modification, and secretion of inflammatory cytokines (Baek and Lee 2016; Yadav et al. 2018). The cellular redox balance is tightly regulated by several (enzymatic) antioxidants and pro-oxidants. One important line of defence is a system of enzymes, including glutathione peroxidase, superoxide dismutase (SOD), and catalase (CAT), which decrease the concentration of the most harmful oxidants (Liguori et al. 2018; Pham-Huy, He, and Pham-Huy 2008). In patients with chronic inflammation, the antioxidant system may be depleted, and prolonged oxidative stress develops. Inadequate antioxidant protection or excessive ROS production creates a condition known as oxidative stress, contributing to the development of different skin and systemic diseases (Baz et al. 2003; Houshang et al. 2014).

Several authors investigated the alterations of oxidative stress markers in psoriatic patients compared to healthy controls. Table 1 summarizes the main oxidative stress and antioxidant markers in psoriasis. Nemati et al. (Nemati et al. 2014) determined psoriatic patients' antioxidant status. They showed that increased levels of lipids and lipoproteins and decreased levels of antioxidants as paraoxonase-1, SOD, CAT, bilirubin and uric acid could lead to an accumulation of oxidized low-density lipoprotein-cholesterol and ROS in patients with psoriasis (Nemati et al. 2014). This phenomenon may have an important role in inflammatory immune events, resulting in progressive skin cell damage or atherosclerosis in patients with psoriasis (Nemati et al. 2014). Barygina et al. (Barygina et al. 2013) suggested that the redox imbalance found in patients's blood and skin plays an important role in psoriasis pathogenesis. Moreover, several authors observed significantly increased levels of oxidative stress markers in psoriatic patients. Pujari et al. (Pujari 2014) showed significantly increased levels of serum malondialdehyde and significantly decreased serum vitamin E and erythrocyte catalase activity in psoriasis patients as compared to controls. Similarly, several other studies (Akbulak et al. 2018; Aktürk et al. 2012; Skutnik-Radziszewska et al. 2020) reported significant increased levels of oxidative stress markers with concomitant reduced antioxidant activity levels in psoriatic patients (Table 1). Among oxidative stress markers found increased in psoriasis, there are lipoprotein(a) and markers of lipid peroxidation (Ferretti et al. 2012), nitric oxide and its end products (Aktürk et al. 2012), thiobarbituric acid reactive substances (Woźniak et al. 2007). Among antioxidant markers found decreased in psoriasis, there are erythrocyte CAT (Pujari 2014), plasma CAT (Nemati et al. 2014), erythrocyte SOD (Lin and Huang 2016), serum SOD (Gabr and Al-Ghadir 2012). Interestingly, some authors reported a positive correlation between

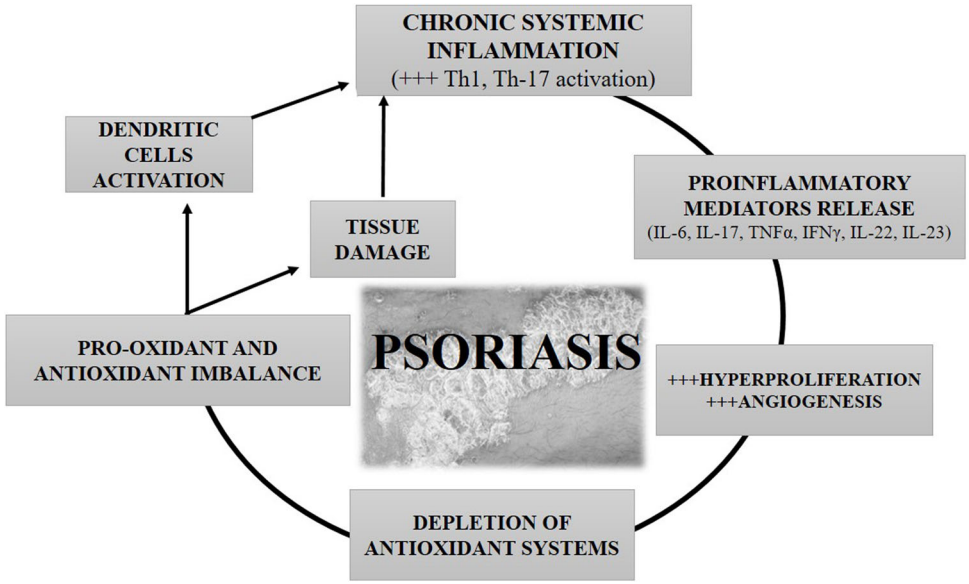

Figure 1. Pathophysiological model of the self-sustaining loop connecting inflammatory processes and oxidative stress in psoriasis pathogenesis.
Chronic systemic inflammation and oxidative stress are closely related to each other. Chronic systemic inflammation through the stimulation of immunologic cells promotes the generation of pro-inflammatory cytokines and other ROS. In addition, oxidative stress can trigger DCs activation and inflammatory cascade, resulting in further amplification of the inflammatory response, hence creating a self-sustaining loop.
Th, T helper cells; IL, interleukin, TNF, tumor necrosis factor, IFN, interferon.

oxidative stress markers and PASI values and a negative correlation between antioxidant markers and PASI values in psoriasis patients (Gabr and Al-Ghadir 2012; Nemati et al. 2014; Pujari 2014). These data provide evidence that oxidative stress may play a critical role in the pathogenesis of psoriasis, promoting inflammation directly through not only tissue damage, but also indirectly triggering pro-inflammatory cytokines release. It is noteworthy, among pro-inflammatory cytokines, the production of which is up-regulated by oxidative stress, TNF-α is currently considered a critical mediator of psoriatic inflammation (Kyriakou et al. 2014). Indeed, Barygina et al. (Barygina et al. 2013) also observed that anti-TNF-α therapy effectively contrasts high levels of ROS in psoriatic patients. Dendritic cells (DCs) play another crucial role of the link between inflammation and oxidative stress in psoriasis. It is well known that DCs are very central pathogenic players in psoriasis: they express inflammatory molecules and secrete mediators involved in downstream activation of T cells and keratinocytes (Johnson-Huang, Lowes, and Krueger 2012). Rutault et al. observed that the ROS-treated DCs are more efficient in promoting T-cell proliferation than normal DCs (Rutault et al. 1999). These evidence suggest that oxidative stress could enhance the capacity of DCs to promote T-cell activation, proliferation, and pro-inflammatory cytokine production, with a self-amplifying loop, able to perpetuate the cutaneous inflammatory process. However, it is not clear if there is an intrinsic oxidative stress condition in psoriatic skin independently from the pro-inflammatory intrinsic or extrinsic condition. Some authors (Dimon-Gadal et al. 2000; Xian et al. 2019) reported that fibroblasts in the lesion free skin of psoriasis patients show increased oxidative damage even before the formation of characteristic psoriatic lesions. Considering the several influences, mentioned above, of oxidative stress on systems operative in the immune-mediated inflammation present in psoriasis, drugs inducing antioxidative mechanisms should have therapeutic potential. In fact, during the recent years, several studies on treating psoriasis with antioxidants and drugs possessing antioxidative activity have been published. Xiran et al. (Lin and Huang 2016) reviewed the published studies on treating psoriasis with antioxidants and drugs with antioxidant activity, concluding that antioxidants may be effective in the prevention and/or treatment of diseases when the right antioxidant is given to the right subject at the right time for the right duration. Among antioxidants studied for potential therapeutic activity in psoriasis, vitamin D is one of the most investigated (Barrea et al. 2017a; Megna et al. 2020). It seems to be able to perform various immunomodulatory, anti-inflammatory, antioxidant and anti-fibrotic actions (Megna et al. 2020). A more recent and extensive review of oxidative stress involvement in psoriasis by Cannavò et al. (Cannavò et al. 2019) confirmed the importance of redox imbalance in psoriasis pathogenesis. The authors also proposed to use serum malondialdehyde as a candidate for clinical screening of psoriasis patients since it is intimately linked to PASI.

In conclusion, data suggest that chronic inflammation and oxidative stress are closely related to each other. Chronic inflammation with the stimulation of immunologic cells promotes the generation of pro-inflammatory cytokines and other ROS. On the other hand, oxidative stress can trigger DCs activation and inflammatory cascade, resulting in further amplification of the inflammatory response, hence creating a self-sustaining loop (Figure 1). Although future studies should investigate the role of antioxidant supplements in psoriatic patients, a healthy lifestyle and a diet rich in antioxidants can be considered an integrant part of pharmacologic therapy in the management of psoriatic patients.

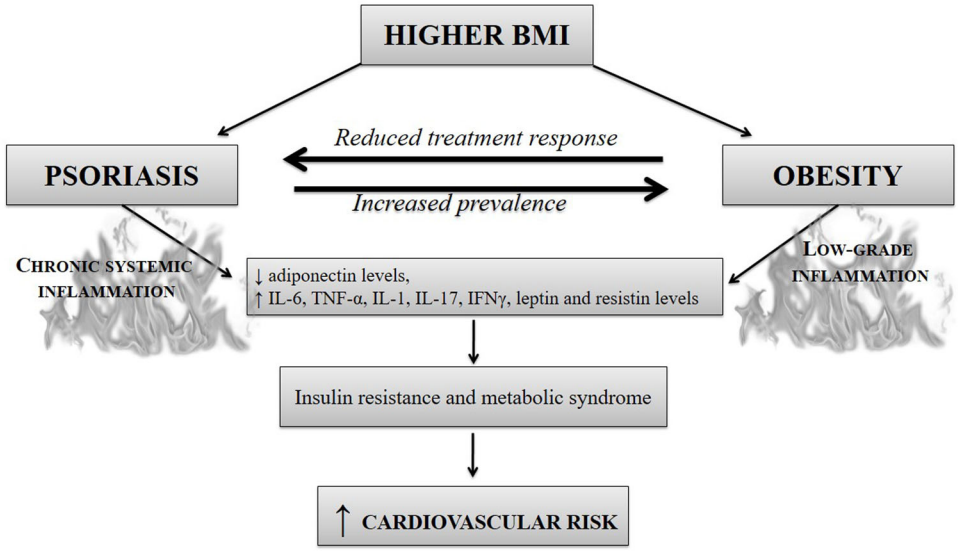

Figure 2. Relationship between obesity and psoriasis.
Obesity and psoriasis are strictly linked by shared pro-inflammatory pathways. The relationship between obesity and psoriasis is bidirectional: obesity, mainly visceral, predispose to psoriasis and psoriasis itself may favor obesity onset. The low-grade inflammation and chronic systemic inflammation associated with obesity and psoriasis, respectively, through the pro-inflammatory cytokines produced by the adipose tissue in patients with obesity and from psoriasis itself, lead to the development of insulin resistance, metabolic syndrome and cardiovascular diseases. In addition, obesity increasing the risk of adverse effects of systemic drugs with a negative impact on the treatment of psoriasis.
BMI, body mass index, IL, interleukin, TNF, tumor necrosis factor, IFN, interferon.

Obesity and psoriasis

The worldwide prevalence of obesity in adults increased in the last 3 decades of 27.5%. Obesity is the result of complex relationships between genetic factors and environmental factors, including diet, and socioeconomic influences (Apovian 2016; Barrea et al. 2019a). In addition, also obesogenic endocrine disruptors are potentially involved in weight gain by altering lipid metabolism and promoting adipogenesis and fat accumulation (Muscogiuri et al. 2017; Nappi et al. 2016). Obesity is a risk factor for the development of several comorbid conditions, including sleep disturbances and hypovitaminosis D (Muscogiuri et al. 2019a; Muscogiuri et al. 2019b; Pugliese et al. 2020).

Psoriasis and obesity are strictly linked, sharing genetic and environmental risk factors as well as a common chronic inflammatory state (Reich 2012). It is well known that obesity prevalence is significantly higher in psoriasis subjects than the general population, with obesity being one of the most common comorbidities of psoriatic disease (Herron et al. 2005; McGowan et al. 2005). Moreover, epidemiological studies indicate that obesity leads to a higher risk of developing psoriasis and poorer long-term clinical outcome with increased psoriasis morbidity (Davidovici et al. 2010; Herron et al. 2005; G. G. Krueger and Duvic 1994). Increased body mass index (BMI) is also strictly linked to psoriasis. BMI values correlate with longitudinal spleen diameter, disease duration and severity in psoriasis patients, negatively impacting treatment options (Balato et al. 2015a; Di Lernia et al. 2012; Gisondi et al. 2008; Naldi et al. 2008). Several studies showed that obesity reduces anti-TNF-α agents' efficacy in psoriasis (Bardazzi et al. 2010; Shan and Zhang 2019), probably due to pharmacokinetics implications with Di Lernia et al. (Di Lernia et al. 2012) also showing that anti-TNF-α long-term survival rate is affected by BMI, which can be considered a potential predictor of drug discontinuation. Also, Gisondi et al. reported in a case control study that a moderate weight loss (i.e. 5–10% of the body weight) was able to increase the response of patients with obesity with moderate-to-severe psoriasis to low-dose cyclosporine, highlighting the importance of including lifestyle modifications such as low-calorie diet, in supplementing the pharmacologic treatment of psoriatic patients with obesity (Gisondi et al. 2008). In this *scenario*, physical exercise has shown as an important lifestyle intervention that can reduce psoriasis severity, further underlying the link between psoriasis and body weight (Balato et al. 2015b; Naldi et al. 2014). Indeed, it is well known that central obesity is associated with greater amounts of inflammatory visceral fat, which is more hypertrophied, contains more macrophage infiltration, has an increased presence of activated T cell populations and expresses a more pro-inflammatory cytokine profile, marked by increased TNF-α, IL-6, and IL-17, and decreased adiponectin (Ahmed and Gaffen 2010; Lumeng, Bodzin, and Saltiel 2007; Reich 2012). To note, a similar inflammatory state of activated T cells and increased pro-inflammatory cytokines have been described in psoriasis and is thought to be responsible for the induction of psoriatic plaque formation, supporting the strong pathophysiological link between obesity and psoriasis (Krueger 2012).

Hence, it is not surprising that diet and physical exercise may lead to an improvement in psoriasis severity and increased response to treatments since they are both able to reduce the size and, consequently, the inflammatory activity of hypertrophied adipocytes which join psoriasis and obesity.

Physical activity is mainly known to decrease chronic inflammation and specifically lowers levels of pro-inflammatory cytokines (TNF-α and IL-6) and leptin whose expression is reported to be elevated in psoriasis (Kondo, Kobayashi, and Murakami 2006; Nicklas et al. 2008; Zhu et al. 2013). Moreover, physical activity can also elevate anti-inflammatory cytokines, including adiponectin, whose expression is significantly lower than controls in psoriasis, independently of BMI (Kondo, Kobayashi, and Murakami 2006; Li et al. 2014; You and Nicklas 2008). Further pieces of evidence demonstrated that progressive weight loss can produce significant improvements in the severity of psoriasis, as it happens with bariatric surgery procedures, a consolidated treatment option for obesity (Barrea et al. 2020a; Velazquez and Apovian 2018). Indeed, several studies supporting the fact that obesity may be causal in psoriasis, are represented by evidence that bariatric surgery can produce rapid remission from psoriasis (Higa-Sansone et al. 2004; Hossler, Maroon, and Mowad 2011; Pérez-Pérez et al. 2009). This is probably due to the low-grade systemic inflammation state, which links obesity and psoriasis pathogenesis with numerous adipokines secreted by adipocytes playing a significant role in both diseases. Notably, they are not limited to IL-1, IL-6, IL-17, and IFN-γ, but also to other factors recruited and stimulated in obesity such as leptin. Indeed, leptin levels are elevated in psoriasis and obesity, playing an essential role in predisposing to cardio-metabolic comorbidities, which further link obesity and psoriasis with diabetes and metabolic syndrome (Çerman et al. 2008; Liu et al. 2019; Myers et al. 2010). Even if leptin also correlates with psoriasis severity and favors IL-6 and TNF-α production (Çerman et al. 2008), there are other several adipokines which are both deregulated in obesity and psoriasis. In particular, resistin, adiponectin, chemerin, and vaspin, provide other indirect evidence that the immunological and metabolic alterations associated with obesity may be linked with the pathophysiology of psoriasis (Balato and Megna 2017). Additionally, the importance of vitamin D in both obesity and psoriasis should not be neglected. Many significant links exist between low vitamin D status, psoriasis, and increased risk of obesity (Barrea et al. 2017a; Megna et al. 2020). Higher BMI positively correlates with psoriasis risk (every increase in BMI results in a 9% higher risk of psoriasis onset and a 7% higher risk of increased PASI score) and a lower vitamin D status (Barrea et al. 2017a; Fleming et al. 2015). Moreover, as a chronic inflammatory disease, psoriasis was reported as a vitamin D deficient state where low $1,25(OH)_2D$ levels were associated with visceral adipose volume, vascular uptake of F-fluorodeoxyglucose (FDG), coronary plaque burden and increased cardiometabolic risk independent of traditional risk factors (Playford et al. 2019). Metabolic syndrome and cardiovascular disease occur at a higher frequency in patients with psoriasis than those of the general population (Barrea et al. 2018a; P. Gisondi et al. 2007; Playford et al. 2019). This may also be due to overlapping genetic predispositions between metabolic disease and psoriasis, which involve genes that may act as risk factors common to psoriasis and metabolic diseases such as cytokines, cytokine receptors, and metabolic markers (Reich 2012). A model has been proposed that illustrates several potential functional interplays between shared genetic risk factors that drive both psoriasis and obesity, and in turn, may promote the development of cardiovascular comorbidities (Davidovici et al. 2010). In this context, insulin-resistance can play an important role (Napolitano, Megna, and Monfrecola 2015). Indeed, the altered amount of adipocytokines secreted by the adipose tissue of a patients with obesity contributes to insulin resistance and psoriasis pathogenesis (Davidovici et al. 2010; Napolitano, Megna, and Monfrecola 2015). For example, adipocytokines such as leptin and adiponectin can regulate and affect insulin sensitivity through modulation of insulin signaling and the molecules involved in glucose and lipid metabolism. These adipocytokines are deregulated in a very similar way in both psoriasis and obesity, highlighting the mechanisms of the possible common association with insulin resistance observed in those patients (e.g., plasma levels of adiponectin are decreased in obesity, psoriasis, insulin resistance, and type 2 diabetes mellitus) (Davidovici et al. 2010; Napolitano, Megna, and Monfrecola 2015; Reich 2012). Therefore, it is not surprising that some authors supported the theory that psoriasis and obesity may drive a joint pathogenetic march, the so called 'psoriatic march' where the systemic inflammation that associate psoriasis and obesity may cause insulin resistance, which in turn triggers endothelial cell dysfunction, leading to atherosclerosis and finally myocardial infarction or stroke (Boehncke et al. 2011). Hence, this theory provides strong scientific support to the significant increased cardiovascular diseases and related mortality found in psoriasis disease (Davidovici et al. 2010; Reich 2012).

In conclusion, obesity and psoriasis are strictly linked to genetic factors and shared pro-inflammatory pathways. Both conditions are also likely to deeply interact at a functional level: higher BMI and obesity can lead to the up-regulation of pro-inflammatory mediators that support psoriasis pathogenesis, thus increasing psoriasis risk and disease severity. On the other hand, also psoriasis appears to influence adipocyte homeostasis and perpetuate systemic inflammation, with increased release of inflammatory mediators which have pleiotropic effects on diverse processes such as angiogenesis, insulin signaling, adipogenesis, lipid metabolism, and immune cell trafficking with the metabolic aspects of this chronic Th-1 and Th-17 inflammation having the potential to impact other conditions such as obesity, diabetes, thrombosis and atherosclerosis (Carrascosa et al. 2014). In this context, the relationship between obesity and psoriasis is probably bidirectional: obesity, mainly visceral, predispose to psoriasis and psoriasis itself may favor obesity onset; Figure 2.

Nutrition, diet, and psoriasis

Among the environmental risk factors for psoriasis, studies suggesting that diet and nutrition play a critically important role, *per se*, both in the psoriasis pathogenesis and in affecting drug pharmacokinetics and pharmacodynamics

(Barrea et al. 2016a; Rodríguez-Cerdeira et al. 2019). Nevertheless, in the vast majority of evidence, it is not easy to separate dieting from weight loss *per* se. Several nutritional deficiencies are often found in the psoriatic patients due to an accelerated loss of nutrients from the hyper-proliferation and desquamation of the epidermal layer of skin (Pona et al. 2019; Wolters 2005).

Some vitamins, including A, E, and C, and oligoelements, like selenium, copper, zinc, manganese and iron, for their antioxidant properties, can reduce the oxidative stress and the production of ROS (Pona et al. 2019; Wu and Weinberg 2019). Among fat-soluble vitamins, vitamin D is considering an essential therapeutic option in the treatment of patients with psoriasis (Barrea et al. 2017a), due to its bi-directional role in both proliferation and maturation of keratinocytes that in comorbidities linked to inflammation, obesity and psoriasis (Barrea et al. 2017a; Barrea et al. 2017b; Savastano et al. 2017; Barrea et al. 2018b), including cardiovascular diseases (Masson, Lobo, and Molinero 2020). Among nutrients, healthy dietary fats such as monounsaturated fatty acids (MUFA) mainly contain extra virgin olive oil and protect lipoproteins and cellular membranes from oxidative damage (Clark et al. 2019). Recently, it has been reported that patients with psoriasis consumed total fat and omega (ω)-6/ω-3 polyunsaturated fatty acids (PUFA) ratio, and showed a lower consumption of MUFA and ω-3 PUFA. This lowest consumption of MUFA was negatively associated with the highest clinical severity of psoriasis (Barrea et al. 2015b). Finally, relationships with individual foods and psoriasis were also studied; in particular, fish oil, fruits, vegetables, and coffee were negatively associated with the clinical severity of psoriasis (Afifi et al. 2017; Barrea et al. 2018a). It should also be considered that diet is a complex combination of different foods from various groups and nutrients, and these are highly correlated to each other, making it difficult to divide the effect of a single nutrient from that of others in free-living populations (Hu 2002).

The rationale for dietary intervention in patients with psoriasis a double-action should represent it: reduction of body weight, in particular fat mass and visceral adipose tissue, resulting in the reduced inflammatory milieu and consequently of the clinical severity of psoriasis (Barrea et al. 2016b). The prescription of targeted dietary interventions in conjunction with personalized medical therapies are currently recommended (Ford et al., 2018; Gamret et al. 2018). Furthermore, evidence reports that psoriatic patients are highly motivated to carry out dietary modification because these changes are perceived as natural, safe and patient-initiated (Afifi et al. 2017; Magin et al. 2006). Unfortunately, there is a lack of knowledge on the different effects of diet treatments in psoriatic patients due to the lack of clinical trials and specific guidelines summarizing evidence on psoriasis and diet (Bhatia et al. 2014; Clark et al. 2019; Debbaneh et al. 2014; Peralta et al. 2019). Different dietary changes can serve as an essential adjunct to medical treatment in psoriatic patients, among dietary pattern Mediterranean diet, gluten-free diet, vegetarian diet, and intermittent fasting are among the most studied dietary approaches (Adawi et al. 2019; Damiani et al. 2019; Debbaneh et al. 2014; McCusker and Sidbury 2016; Wu and Weinberg 2019).

Of interest, the Mediterranean diet is characterized by foods with anti-inflammatory and antioxidant actions, including extra-virgin olive oil, vegetables, fruits, legumes, nuts, whole-grain cereals, and red wine at meals (Mazzocchi et al. 2019). The high adherence to the Mediterranean diet has been associated with several inflammatory diseases, including inflammatory skin diseases as hidradenitis suppurativa (Barrea et al. 2019b), polycystic ovary syndrome (Barrea et al. 2019c), type 2 diabetes mellitus (Muscogiuri et al. 2019c), obesity (Barrea et al. 2017c; Barrea et al. 2017d) and obesity-related diseases such as breast cancer (Laudisio et al. 2020), endocrine dysfunction (Muscogiuri et al. 2019d), gut diseases (Barrea et al. 2019d) and menopause (Barrea et al. 2020b).

Recent evidence reported an association between adherence to the Mediterranean diet and clinical severity of psoriasis. One cross-sectional study showed that lower adherence to the diet was positively associated with the clinical severity of psoriasis, and the consumption of extra-virgin olive oil was found to be an independent predictor of PASI score (Barrea et al. 2015b). Similar results were demonstrated in a second cross-sectional study in a larger population of 3.557 patients, highlighting low levels of adherence to the Mediterranean diet were associated with clinical severity of psoriasis (Phan et al. 2018). These two studies pointed out the potential impacts of pro-inflammatory and anti-inflammatory foods on psoriasis.

Beyond observational studies, also some randomized clinical trials in overweight or patients with obesity have shown the benefits of dietary interventions in both reductions of body weight and the clinical severity of psoriasis when combined with systemic treatments (Al-Mutairi and Nour 2014; Gisondi et al. 2008; Guida et al. 2014; Jensen et al. 2013; Mahil et al. 2019; Naldi et al. 2014). Considering that all investigated dietary treatments are heterogeneous in terms of total energy intake (obtaining variable changes in body weight), in clinical severity of psoriasis (different variation of PASI score), and study duration and efficacy (over 16 to 24 week) (Al-Mutairi and Nour 2014; Gisondi et al. 2008; Guida et al. 2014; Jensen et al. 2013; Mahil et al. 2019; Naldi et al. 2014), no dietary intervention should be preferred compared to another (Ford et al., 2018). However, all these studies reported a positive correlation between body weight loss and decreased clinical severity of psoriasis (Al-Mutairi and Nour 2014; Gisondi et al. 2008; Jensen et al. 2013; Mahil et al. 2019; Naldi et al. 2014).

The Medical Board of the National Psoriasis Foundation recently published a systematic review on the dietary recommendations for adults with psoriasis or psoriatic arthritis strongly recommending body weight reduction with a hypocaloric diet in psoriatic patients with overweight and obesity (Ford et al., 2018). A gluten-free diet was weakly recommended only in psoriatic patients with serologic markers of gluten sensitivity positive. All the dietary changes should not be considered as the sole source of treatment but should

always be used in conjunction with standard medical therapies for psoriasis (Ford et al., 2018).

Ketogenic diet

In the last few years, the ketogenic diet has achieved considerable interest in managing several diseases, including overweight and obesity (Muscogiuri et al. 2019e; Trimboli et al. 2020). Very recently, Caprio et al. published a consensus statement of the cardiovascular endocrinology club of the Italian Society of Endocrinology (SIE) (Caprio et al., 2019). There are different ketogenic diets whose common purpose is inducing ketosis, among these, we have classic ketogenic diet, Atkins diet, high-fat ketogenic diet, very-low-carbohydrate diet and VLCKD (Castellana et al. 2020; Hussain et al. 2012). In VLCKD daily calorie intake is up to 700–800 kcal/day, lipids intake can be up to 30–40 g/day and about 0.8 to 1.2 g/day of proteins *per* each kg of ideal body weight are provided (Castellana et al. 2020; Muscogiuri et al. 2019e).

The main requirement to be defined as a ketogenic diet is the carbohydrate restriction, usually to less than 30–50 g/day. In the first three to four days of the ketogenic diet, glucose is produced through the biochemical processes of glycogenolysis and gluconeogenesis. After that, there is a metabolic switch to increased glucagon and decreased insulin due to both low glucose and insulin levels, inducing free fatty acids release from the adipose tissue (Muscogiuri et al. 2019e). The fatty acids release in this way serve as a substrate for the synthesis of ketone bodies by the liver and will be used by extra hepatic tissues such as an alternative fuel source. VLCKD was recently reported with an effective management strategy in patients with overweight and obesity (Leslie et al. 2017), with a weight loss up to −15.6 kg with a ketogenic diet of at least four weeks (Castellana et al. 2020; Moreno et al. 2016). It has been reported as VLCKD was more effective for weight loss than not ketogenic ones. Compared VLCKD to no ketogenic diets, with similar energy intake, the first was associated with a higher weight loss following three weeks (Albanese et al. 2019; Cunha et al. 2020). This result was also confirmed in one meta-analysis (Bueno et al. 2013). In this context, VLCKD appear to result in a more consistent reduction in visceral adipose tissue, an improvement in body composition (increased of free fat mass and decreased fat mass), and metabolic profile (Bravata et al. 2003; Crujeiras et al. 2017; Goday et al. 2016; Gomez-Arbelaez et al. 2017; Moreno et al. 2014, 2016; Wycherley et al. 2012). This is because ketone bodies which occur during ketogenesis, likely have antioxidant activity and anti-inflammatory properties (Youm et al. 2015).

Ketogenic diet and antioxidant activity

Mitochondria are the primary source of energy production in cells that through the oxidative phosphorylation leads to the production of ATP (Greco et al. 2016). By the transfer of electrons along the electron transport chain, mitochondria play a key role in the production of ROS and in apoptotic processes (Greco et al. 2016). Unluckily, the ROS accumulation mainly due to the mitochondrial complexes I and III, damage macromolecules, including proteins, lipids and nucleic acids (Andreyev, Kushnareva, and Starkov 2005; Kushnareva, Murphy, and Andreyev 2002). Mitochondrial dysfunction caused by the oxidative stress increased the ROS production in a pathological positive feedback loop (Włodarczyk and Nowicka 2019; Xu et al. 2019). It has been reported that hydroxybutyrate metabolism, the most studied ketone bodies, reduce the oxidative stress (Greco et al. 2016), demonstrating a reduction of ROS production, resulting in improvement of mitochondrial respiration (Achanta and Rae 2017; Tieu et al. 2003). The protective activity of the ketogenic diets on oxidative stress is explained by different mechanisms that include the activation of nuclear factor erythroid-derived 2 (NF-E2)-related factor 2 (Nrf2) (Milder, Liang, and Patel 2010). This factor is a cellular endogenous antioxidant system representing the primary inducer of detoxification genes (Milder, Liang, and Patel 2010). In addition, there is the intracellular modulation of the NAD+/NADH ratio, which protects against ROS and plays a vital role in redox reactions, mitochondrial biogenesis and cellular respiration (Yang and Sauve 2016). Ketogenic diets also play other significant oxidation regulating mechanisms including the increased efficiency of the expression of uncoupling proteins (Sullivan et al. 2004) that reduces the production of ROS and reactive oxygen nitrogen species through reduction the mitochondrial membrane potential (Harper et al. 2004).

Ketogenic diet and anti-inflammatory activity

Obesity and other several diseases, including type 2 diabetes mellitus and cardiovascular diseases, are interconnected by mechanisms related to inflammatory mechanisms (Saltiel and Olefsky 2017). Conversely, the cells have endogenous mechanisms tending to reduce the molecules responsible for inflammatory damage (Verdile et al. 2015). The ketogenic diet is a promising approach for enhancing endogenous anti-inflammatory programs and attempting to block inflammation. Of interest, the ketogenic diet is related to the decrease of systemic inflammation due to the activation of peroxisome proliferator-activated receptor gamma (Jeong et al. 2011). Hydroxybutyrate can provide both energy but also activate the receptor hydroxy-carboxylic acid receptor 2 (HCA2) (Taggart et al. 2005), a G-protein coupled receptor, expressed on macrophages, dendritic cells and microglia (Rahman et al. 2014), that through the inhibition of NF-kB activation, may elicit anti-inflammatory effects (Zandi-Nejad et al. 2013). The HCA2 activation is associated with Prostaglandin D2 (PGD2) production by Cyclooxygenase 1 (COX1) (Zandi-Nejad et al. 2013), with the induction of a protective macrophage phenotype related with decreased of systemic inflammation (Rajakariar et al. 2007). Furthermore, it has been reported that β-hydroxybutyrate can lead to inhibition of NLRP3 inflammasome in lipopolysaccharides (LPS)-stimulated human monocytes by limiting $K+$ efflux from cells, resulting to increased secretion of IL-1β and IL-18 (Youm et al. 2015). It is noteworthy, the inhibition of IL-1beta and IL-18 production from β-hydroxybutyrate were

Table 2. Studies on VLCKD and psoriasis.

Reference	Subjects	Diet	Treatment duration	Outcomes
Castaldo et al. 2015	1 (40 years old woman)	protein-based, ketogenic enteral nutrition liquid of ~300 kcal/day	24 h a day *per* 4 weeks	>80% PASI reduction 11 Kg weight reduction
Castaldo et al. 2020	37 (11 males, mean age= 43.1 years)	-first phase of 4-week of VLCKD (protein sparing) -second phase of a 6 week of hypocaloric Mediterranean-like diet at low glycemic index	10 week of 2-phase: -first phase of 4-week -second phase of a 6 week	Mean change of −10.6 in PASI score 64.9% of subjects reached PASI75 response or more Mean reduction in BSA of −17.4% Mean change in body weight of −12.0 %

BSA, Body Surface Area; PASI, Psoriasis Area Severity Index; PASI75, reduction of 75% of initial PASI value; VLCKD, Very Low-calorie Ketogenic Diet.

dose-dependently (Youm et al. 2015). In this context, Forsytheet al. in a randomized controlled dietary intervention trial in 40 overweight individuals aged 18–55 years, compared the effect of low fat (1.478 kcal:%, carbohydrate:-fat:protein = 56:24:20%) and low carbohydrate diets (1.504 kcal:%, carbohydrate:fat:protein = 12:59:28%) on circulating fatty acid composition and markers of inflammation for 12 weeks (Forsythe et al. 2008). The authors reported that individuals fed with ketogenic diet developed ketosis and weight loss, reduced adiposity, and improved glycaemic control and insulin sensitivity. Although both diets reduced the concentration of inflammatory markers, a more significant anti-inflammatory effect was reported for the ketogenic diet (Forsythe et al. 2008).

VLCKD and psoriasis

Only few studies have been conducted on the efficacy of VLCKD in patients with psoriasis (Castaldo et al. 2020; Castaldo et al. 2016a) (Table 2). The scientific rationale of this evidence was based on the inflammatory background associated with both psoriasis, obesity and its related cardiometabolic complications (Kosinski and Jornayvaz 2017; Watanabe et al. 2020).

Castaldo et al. in 2016 evaluated the efficacy of VLCKD on restoring response to systemic therapy in relapsing plaque psoriasis in a case report (Castaldo et al. 2016a). This patient was female and 40 year aged with recurrent plaque psoriasis and psoriatic arthritis, treated up to six months before VLCKD with biologic therapy, in particular subcutaneous adalimumab 80 mg *per* 1 week then, 40 mg every 2 weeks *per* 12 months. Her PASI score was 37 at baseline prior adalimumab treatment, and after 3 months, PASI score fell to zero. At psoriasis' relapse, instead of considering switching to a second-line biologic agent or the use of higher doses of adalimumab, the patient was treated with protein-based, ketogenic enteral nutrition liquid of ~300 kcal/day composed as follows: a total protein content of 1.2 g *per* kg of ideal body weight (with a 10 g of branched-chain amino acids, 5 g glutamine and milk proteins). This protocol was administered 24 h a day *per* 4 weeks (Castaldo et al. 2015; Castaldo et al. 2016b). After this cycle of protocol, the patient showed a significant weight loss (from 92 to 81 Kg, ~12% of initial body weight) and a decrease of visceral adiposity evaluated by aorto-mesenteric visceral fat thickness (from 19 to 12 mm) (Monaco et al. 2014). Of interest, an improvement of skin lesions with a reduction of PASI > 80%, has also been observed (Castaldo et al. 2016a).

Very recently, Castaldo et al. evaluated the efficacy of a ketogenic induction phase as first-line treatment for chronic plaque psoriasis in a single-arm, open-label clinical trial. This study evaluated 37 individuals, 11 males, with a mean age of 43.1 years (Castaldo et al. 2020). All participants were adult with overweight or obesity, and systemic drug-naïve (never treated, excluding the use of topical emollients) with stable (no self-reported change in the last 3 months) chronic plaque psoriasis (diagnosis confirmed by two dermatologists), that involved at least 10% of the body surface area. The dietary intervention consisted of a 10 week of 2-phase, the first phase of 4-week of VLCKD (protein sparing). The composition of VLCKD was as follows: carbohydrates 10 to 20 g (represented by 400-500 g/day of vegetables), extra virgin olive oil 20 to 30 g as the only source of seasoning *per* day, with the addition of an oral liquid formula (<500 kcal/day spread throughout the day, 20% at breakfast and 40% at lunch and dinner) of milk protein providing 1.2 g of protein *per* kg of ideal body weight. Alkalizing substances and a multivitamin-multimineral supplement were complemented to all patients, with a recommended intake of bicarbonate-rich alkaline water in the minimum quantity of 2 L/day (Castaldo et al. 2016c). The second phase instead included a 6 week of hypocaloric Mediterranean-like diet at low glycemic index (Castaldo et al. 2016c), as follows: carbohydrates 54% with use of low glycemic index foods and least 30 to 35 g/day of fiber through the consumption of fruit and vegetables ad libitum; protein 18%, with supplementation of 20 g of milk proteins (10 g at breakfast and 10 g at dinner); and fat 28%, mainly in the form of extra virgin olive oil with saturated fatty acids <7% (Castaldo et al. 2016c). The primary endpoint was the reduction in PASI score while the secondary endpoints were PASI score responses of ≥50% and ≥75%, improvement in itch severity, body surface area involved, and dermatology life quality index score to the tenth week. At week-10 the dietary protocol resulted in a significant reduction in PASI score (with a mean change of −10.6 (95% confidence interval: −12.8 to −8.4; $p < 0.001$), and with a change in body weight of −12.0% (95% confidence interval: −13.7 to −10.4%; $p < 0.001$). In 97.3% (36 patients) and 64.9% 24 (patients), PASI score responses of ≥ 50% and ≥ 75% were recorded, respectively. The dietary protocol also resulted in an improvement in itch severity

(-33.2 points) and dermatology quality of life index score (-13.4 points), and a reduction in the body surface area involved (-17.4%). Of interest, the improvement of PASI scores at week −10 was independent of both weight status ($p = 0.68$) and baseline disease severity ($p = 0.26$). As expected, the protocol resulted in significant improvements in body fat distribution, the metabolic profile including uric acid, glucose and lipid metabolism, and inflammatory parameters (TNF-α, INF-γ, IL-1β, and IL-2). This study evaluated the efficacy of a dietary weight loss intervention the time as a first-line therapeutic strategy in psoriatic patients.

Conclusion

Nutrition is considered a key point factor in the management of chronic inflammatory skin diseases, including psoriasis. Whether it is known that weight loss is associated with amelioration of clinical severity of psoriasis and its comorbidities, less is known about the effect of VLCKD on psoriasis. The evidence suggests that VLCKD, through the reduction of systemic inflammation and obesity, might have beneficial effects *per se*, paving the way for new therapeutic targets and strategies. Of interest, through weight loss and reduction of chronic systemic inflammation, VLCKD in psoriatic patients could also restore a quick response to systemic psoriatic therapy. Dermatologists should always consider in psoriatic patients with overweight and obesity, combining dietary interventions, including VLCKD with the standard psoriatic medical therapies. The preliminary data on VLCKD on reducing clinical severity of psoriasis is promising, but randomized controlled trials are needed to assess the additional benefits of VLCKD versus other not ketogenic diets with the same calorie intake. Altogether, although the clinical studies in the literature are limited, there is evidence that VLCKD may be a reliable option to achieve a significant in both reduction of clinical severity of psoriasis and weight loss in patients with overweight and obesity. Considering the very intense caloric restriction and nutrients, including vitamins and minerals, thus VLCKD should be regarded as a dietary, medical prescription to be proposed to properly specific psoriatic patients, as a part of pharmacological therapy strategy, and under strict Clinical Nutritionist supervision.

Acknowledgements

We are thankful to Panta Rei Impresa Sociale s.r.l. (https://www.pantarei.eu/pantarei/) and Dr Pasquale Antonio Riccio, for their scientific support.

Disclosure statement

The authors have nothing to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not for-profit sectors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations

PASI	Psoriasis Area and Severity Index
VLCKD	very low-calorie ketogenic diet
IL	interleukin
TNF-α	tumor necrosis factor-alpha
IFN-γ	interferon-gamma
ROS	Reactive oxygen species
SOD	superoxide dismutase
CAT	catalase
DCs	Dendritic cells
BMI	body mass index
MUFA	monounsaturated fatty acids
ω	omega
PUFA	polyunsaturated fatty acids
HCA2	hydroxy-carboxylic acid receptor 2.

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