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DIET IN THE MANAGEMENT OF PSORIATIC DISEASE: KETOGENIC OR MEDITERRANEAN DIET? PRELIMINARY DATA

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ABSTRACT – *Objective:* Psoriatic Disease (psoriasis - psoriatic arthritis) is an inflammatory systemic condition associated to obesity. Weight loss improves clinical severity. Mediterranean Diet (MD) has been considered a model of healthy and a very low-calorie ketogenic diet (VLCKD) is more effective for losing weight fast in obese. The study aims to determine the effectiveness of the MD and the VLCKD in the treatment of patients with inflammatory disease.

Patients and Methods: Twenty patients were identified as overweight and obese from 1st to 3rd degree using Body Mass Index (BMI). MD has been proposed to overweight patients while obese patients could choose between MD and VLCKD, according to their attitudes. Then, they were divided into two study groups (MD group and KD group).

Results: At baseline and after four weeks, we collected weight, BMI, waist circumference (WC) and body composition through bioimpedance analysis (BIA - Bioelectrical Impedance Analysis). At the end, both of dietary interventions were effective to improve all parameters, but we found a greater and significative reduction of BMI and WC, and more reduction of fat mass (FM) in KD group than MD group.

Conclusions: Preliminary data show that KD could be proposed as a first dietary intervention to obtain a rapid weight loss and maintenance of lean mass.

KEYWORDS: Psoriatic Disease, Mediterranean Diet, Ketogenic Diet.

INTRODUCTION

Psoriatic disease (PsD) is an autoimmune disease that includes two specific inflammatory conditions. These two conditions, psoriasis and psoriatic arthritis, are a result of an overactive immune system. Psoriasis and psoriatic arthritis primarily affect the joints and skin; comorbidities classically associated with psoriasis are Crohn's disease (CD), psychological/psychiatric disorders (DPP) and uveitis. In recent years, obesity and the metabolic syndrome as a whole and its individual components have been associated with psoriasis. The association between obesity and psoriasis is probably bidirectional. The production of inflammatory cytokines in psoriasis, such as TNFα, IL-17, IL-18, IL-6 and VEGF, can induce insulin resistance and contribute to the increase of visceral fat. Similarly, obesity, especially perivisceral abdominal fat, can produce pro-inflammatory factors and predispose to more severe psoriasis and psoriatic arthritis[1,2]. The high prevalence of obesity in patients with PsD represents an important healthcare issue and it requires an update in its standard of care. Management of PsD patients should also include a nutritional

counselling to get the ideal weight for each patient. Weight loss in overweight and obese patients could be the first approach to improve psoriasis, before starting a pharmacological treatment.

Moreover, several studies have found out that PsD patients exhibited significant difference in body composition compared with BMI- matched control groups. On the one hand, PsD patients resulted to have higher body fat percentage, FM (fat mass) and visceral fat rating, on the other hand they showed lower FFM (fat free mass) and skeletal muscle mass percentage[3]. These finding might suggest the presence of sarcopenic obesity in PsD patients and the increase of FM is considered one of major predictor of psoriasis severity. In fact, adipose tissue, especially abdominal fat, releases pro inflammatory cytokines, such as TNFα and IL-17 that increase psoriasis severity and extension.

Previous studies have demonstrated that a long-term weight loss in overweight and obese PsD patients may reduce disease activity and increase the efficacy of systemic therapies[4]. The aim of weight loss should be to reduce the FM and visceral adipose tissue, responsible of systemic inflammation.

The choice of the right hypocaloric regimen is important because in many cases a rapid weight loss is associated to an undesired reduction in lean mass.

Many studies have evaluated the association between food or nutrients and chronic diseases and have found out a significant role of nutritional factors into the pathogenesis of chronic diseases.

The traditional Mediterranean diet, characterized by a high intake of vegetables, legumes, fruit, cereals and olive oil with a low intake of saturated lipids, has been recommended as a model of healthy diet for many years, even though it is not considered a specific diet program, but rather a set of eating healthy habits to achieve a long-term weight loss. The MD recommends a moderately high intake of fish, a low-to-moderate intake of dairy products (preferably cheese or yogurt), a low intake of meat and poultry, and a regular but moderate intake of wine, generally during meals. It is considered a healthy model with a correct balance between protein, carbohydrates, and fat, which can be daily used to prevent systemic inflammation and metabolic syndrome[5]. An association between adherence to MD and the severity of psoriasis has been also demonstrated[6,7].

The ketogenic diet is a dietary hypocaloric regimen, low in carbohydrates, which forces the body to utilize fat as its primary source of energy and induce and maintain a chronic state of ketosis, a metabolic condition which use ketone bodies as energy source. Ketone bodies are three acid compounds (acetone, acetoacetic acid, beta-hydroxybutyric acid), physiologically circulating in the blood in very low quantities.

The ketogenic diet produces a condition like that occurring during fasting: as a consequence, liver cells start producing ketone bodies, used as alternative energy source.

During ketogenic diet, a low carbohydrate regimen (less than 50 g/day) must be adopted to obtain ketosis. Carbohydrate restriction makes the body to draw energy from triglycerides and fatty acids. The metabolic processes of triglycerides release ketone bodies, which become the main energy source. In the classic ketogenic diet (adopted in some neurological diseases such as pediatric epilepsy, refractory to drug treatment), fat food represents the source to produce ketone bodies[8]. In the VLCKD, ketone bodies, instead, are produced by the metabolism of fat contained in the adipose tissue. The synthesis of ketone bodies in the liver starts only when the blood sugar drops because blood glucose inhibits their formation. However, during the ketogenic diet the blood sugar remains at physiological levels since blood glucose is ensured from two sources: from the gluconeogenesis of aminoacids and from glycerol released by triglycerides lysis. The main advantages of ketogenic diet consist of the considerable rapid weight loss, the absence of hunger feeling, due to the anorexigenic power of ketone bodies and preserving muscle mass, since weight loss involves only fat mass[9,10].

For that reason, the VLCKD has been proposed as a promising option to achieve a significant weight loss in a short time period with a significant improvement on FFM, providing an adequate amount of protein. It has been evaluated in overweight and obese patients with a fast and consistent reduction of fat mass, total cholesterol and triglycerides, reporting any changes in lean mass parameters[11,12]. A recent Italian study has investigated the VLCKD in naïve overweight psoriatic patients as an efficacious first line treatment to improve disease severity[13].

We performed a pilot study to compare the effect of the VLCKD and MD on BMI and body composition parameters in PsD patients after a 4-week period.

PATIENTS AND METHODS

Study design

This is a preliminary study, carried out at Psoriasis and Nutrition Center of IDI-IRCCS of Rome (Italy) according to the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of our Institution. All the participants gave written informed consent before enrolment.

Twenty patients with PsD were enrolled between September 2020 and February 2021; all the patients showed a nutritional status of overweight and obesity of first, second and third grade, according to the BMI criteria. The age range of the participants was between 37 and 74 years and all had been on traditional drug treatment for psoriasis (acitretin and methotrexate) or biologic drugs for at least 6 months. The exclusion criteria were: 1) age <18 years; 2) pregnancy or breastfeeding status; 3) initiation of pharmacological or biological treatments for less than 6 months; 4) presence of severe comorbidities such as nephropathy, liver disease, psychiatric disorders, type 1 diabetes, porphyria, myocarditis, recent cardiovascular events, alcoholism and eating disorders.

At the beginning, the age, sex, and height of each patient were recorded. The study aims to determine the effectiveness of the MD and the VLCKD in the treatment of patients with inflammatory disease after a nutritional treatment followed for four weeks. Therefore, the following parameters were measured at baseline (T0) and after 28 days (T28) of treatment: weight, BMI, WC expressed in cm and the data on body composition through bioimpedance analysis (BIA - Bioelectrical Impedance Analysis) corresponding to fat mass expressed in Kg (FM Kg), lean mass (Fat-Free Mass) expressed in Kg (FFM Kg), metabolically active cell mass of FFM (Body Cell Mass) expressed in Kg (BCM Kg) and skeletal muscle expressed as a percentage of weight (SM%).

Materials for clinical data assessment

The body composition was obtained by impedance analysis using the BIA Light instrument - single frequency 50 kHz, with "Dietosystem - Nutritional Suite on Demand software" (DS Medica srl Milan, Italy). The anthropometric measurements were collected according to the common method (with a measuring tape and a scale).

Sample groups and dietary intervention

The patients were initially identified based on BMI as overweight patients, with BMI <30 Kg/m^2, and with obesity, with BMI ≥ 30 Kg/m^2, from first to third grade.

Due to the exploratory nature of the study and the small sample size, the twenty patients were divided in two clusters of ten participants based on the nutritional status: the first group (MD group), ranging from overweight to 1^{st} grade obesity, followed a balanced low-calorie diet of the Mediterranean type for four weeks (overweight = 6 patients; obese 1^{st} grade = 4 patients). The second group of ten patients (KD group), in a mixed state of obesity between 1^{st}, 2^{nd} and 3^{rd} grade, followed a VLCKD regimen for four weeks (1^{st} grade = 3 patients; 2^{nd} grade = 4 patients; 3^{rd} grade = 3 patients). After 28 days of follow-up (T28), we measured all parameters (weight, WC, BMI, FM, FFM, BCM, SM) that were compared to the baseline data (T0).

Mediterranean Diet (MD) group: 10 patients (4 females and 6 males), age 37 - 74 years. This group followed a balanced low-calorie Mediterranean diet of 1200 - 1400 Kcal/die; distribution of macronutrients: ≤ 60% carbohydrates, 12 - 18% proteins, 20 - 35% fats. Macro and micronutrients, water and alcohol have been divided following the LARN 2014 guidelines. A meal plan was administered including the consumption of two servings of vegetables and three servings of fruit per day, three servings of meat per week, three servings of fish per week, carbohydrates from whole sources, use of extra virgin olive oil (EVOO) and, if desired, a glass of wine a day.

Ketogenic Diet (KD) group: 10 patients (9 females and 1 male), age 42 - 61 years. This group followed a ketogenic diet of the VLCKD type of 600 - 880 Kcal/die with an intake of 0.5 - 0.9 gr/Kg/die of carbohydrates (for a total of maximum 50 gr/die), 1.2 - 1.4 gr/Kg /die of protein and 0.2 - 0.5 gr/Kg/die of fat. The 70% of protein intake was from food and the rest by supplementation of soluble whey proteins enriched with inositol, potassium, L - citrulline, L - ornithine, L - carnitine, L - cystine, magnesium and niacin (protocol PROTEONORM DietoSystem DS Medica srl Milan, Italy; http://dsmedica.info).

Statistical analysis

All data were analyzed using GraphPad Prism 9.0.1 software (La Jolla, CA, USA). The normal distribution of observations for each parameter was assessed by the Kolmogorov - Smirnov test. For the "before - after" comparison of the paired data at T0 and at T28 within each group and for each parameter, a double-tailed Student's *T*-test for paired data was used and a *p*-value ≤ 0.05 was considered significant. For the comparison of the results obtained by the two diets, the double-tailed Mann - Whitney U test was used, due to the low number of observations, and a *p*-value ≤ 0.05 as a threshold for statistical significance.

RESULTS

All patients (n = 20) followed and completed the nutritional treatment for four weeks without reporting side effects, obtaining an improvement in all the parameters related to weight loss.

Data analysis within groups

In the group of patients who followed MD (Table 1) we obtained a significant reduction of BMI (p = 0.0002), WC (p = 0.0006) and FM (p = 0.01). About the FFM and BCM parameters, a small decrease is observed which is not significant; although the percentage of SM increased in the observation time, but the statistical analysis did not return a significant value.

Table 1. Anthropometric measures and body composition evaluated by BIA parameters of PsD patients who followed the Mediterranean Diet at baseline (T0) and after 28 days (T28).

	T0 Mean± SD	T28 Mean ± SD	Differences T28 – T0		*p*-values
BMI	29.38 ±3.00	27.71 ±3.07	-1.67	-5.58%	0.0002***
WC CM	102.70 ±10.73	97.70 ±10.49	-5.00	-4.87%	0.0006***
FM KG	29.97 ±4.98	26.58 ±6.51	-3.39	-11.31%	0.01**
FFM KG	53.05 ±11.74	52.65 ±11.26	-0.40	-0.75%	0.64
BCM KG	28.40 ±8.22	27.97 ±7.65	-0.43	-1.51%	0.53
SM%	31.42 ±5.05	32.95 ±5.19	+1.53	+4.87%	0.25

Legend: MD (Mediterranean Diet) group. Data are expressed as mean ± standard deviation recorded at T0 and T28 (after 4 weeks of nutritional treatment). ***p-value < 0.001; **p-value < 0.01; p-value was obtained with Student's T-test calculating the differences between T0 and T28 for each parameter.

Among the patients who followed the KD (Table 2) we obtained a significant reduction in BMI (p = 0.0001), WC (p = 0.0001) and FM (p = 0.002). KD did not significantly affect the FFM and BCM parameters, while the percentage of SM showed a significant increase (p = 0.014).

Table 2. Anthropometric measures and body composition evaluated by BIA parameters of PsD patients who followed the VLCKD at baseline (T0) and after 28 days (T28).

	T0 Mean± SD	T28 Mean ± SD	Differences T28 – T0		*p*-values
BMI	38.57 ±4.83	35.67 ±4.71	-2.90	-7.52%	0.0001***
WC CM	116.30 ±12.8	109.20 ±12.6	-7.10	-6.10%	0.0001***
FM KG	45.84 ±7.67	40.21 ±8.45	-5.63	-12.28%	0.002**
FFM KG	55.95 ±10.33	53.99 ±9.33	-1.96	-3.50%	0.12
BCM KG	28.76 ±6.28	28.49 ±5.98	-0.27	-0.94%	0.67
SM%	25.07 ±2.75	26.42 ±2.27	+1.35	+5.38%	0.014*

Legend: KD (Ketogenic Diet) group. Data are expressed as mean ± standard deviation recorded at T0 and T28 (after 4 weeks of nutritional treatment). ***p-value < 0.001; **p-value < 0.01; *p-value < 0.05; p-value was obtained with Student's T-test calculating the differences between T0 and T28 for each parameter.

Data analysis between groups

To compare the results achieved with the two nutritional regimens and to investigate whether the effects were significant, we compared the values corresponding to the differences between the T28 and T0 time-points for each single parameter using the two-tailed Mann Whitney U test, considering $p \leq 0.05$ as significant threshold value. We showed the averages of the differences for each parameter of both diets.

KD showed more and significant effects on BMI (p = 0.0037) and WC (p = 0.016), compared to MD. About the other parameters, the loss of FM is consistent, indicating that both diets were able to determine a loss of fat mass. KD appears to have resulted in a greater loss of FFM than MD, but the reduction of the metabolically active component of lean body mass, BCM, is lower. The percentage of skeletal muscle increased similarly in both diets (Table 3 and Figure 1).

Table 3. Comparison between the action of the MD and VLCKD on PsD patients.

	MD	KD	*p*-values
BMI	-1.67 ±0.8	-2.9 ±0.7	0.0037**
WC cm	-5.00 ±3.0	-7.10 ±1.3	0.016*
FM Kg	-3.39 ±3.4	-5.63 ±4.0	0.33
FFM Kg	-0.40 ±2.7	-1.96 ±3.6	0.25
BCM Kg	-0.43 ±2.1	-0.27 ±1.9	0.69
SM%	+1.53 ±4.0	+1.35 ±1.4	0.39

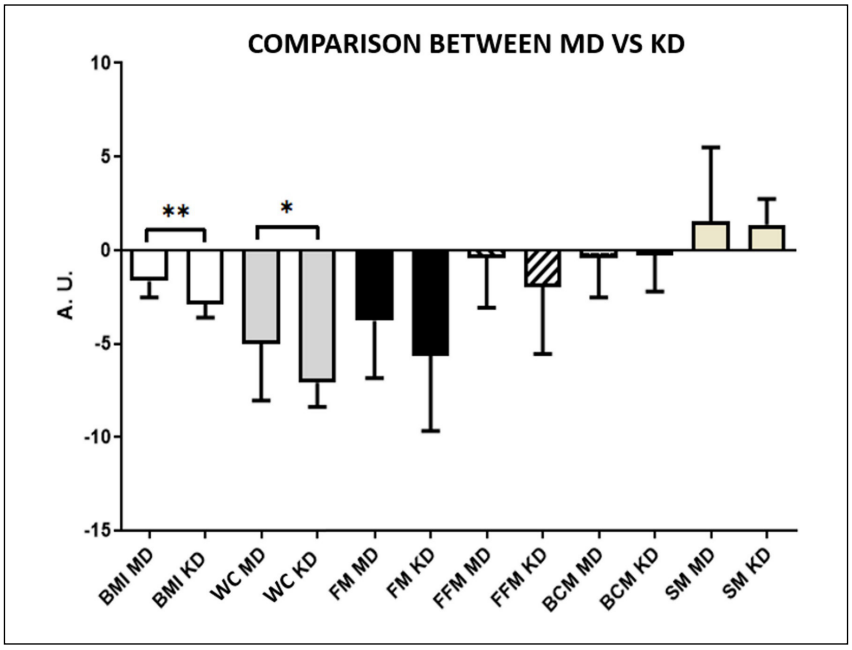

Figure 1. Comparison of MD and KD diet parameters after 4 weeks of nutritional regimen. The elements of the graph represent an average of the differences between T0 - T28 values for each parameter with the relative standard deviations. A decrease of BMI, WC, FM, FFM and BCM was obtained during the observation time (T0-T28). While SM values indicate an increase in skeletal muscle mass (T0-T28). The p-values resulted from the two-tailed Mann - Whitney U test. ***p*-value <0.01; **p*-value <0.05; A.U. = arbitrary unit.

DISCUSSION

MD can be considered a model of healthy nutritional habits to follow daily overtime and could be an adjuvant therapy in all the chronic inflammatory diseases such as psoriasis and psoriatic arthritis, due to its anti-inflammatory and antioxidant properties[14-16]. It provides a large amount of polyunsaturated fatty acids (PUFAs), in particular ω-3, and monounsaturated fatty acids (MUFAs), which are a valid support for the pharmacological treatment, reducing the systemic inflammation[17].

On the contrary, KD must be considered as a dietary therapy to be applied for a specific and well-defined period in selected patients. Recently KD has also found application as “nutritional therapy” in different therapeutic areas. For instance, it is used in the treatment of rare metabolic diseases such as GLUT 1 deficiency, in neurological diseases such as epilepsy, in the treatment of severe obesity or be-

fore bariatric surgery, in metabolic syndrome, insulin resistance and other related diseases[18,19]. There were different kind of KD, according to the therapeutic area. The ketogenic protocol we applied in this pilot study was the VLCKD type. In the short term, VLCKD can determine a consistent reduction in body weight and abdominal adiposity and a significant improvement in metabolic profile and body composition, providing adequate amount of protein. Considering the VLCKD type, low-carbohydrate protein-sparing ketogenic regimens have attracted several researchers over the last few years due to their important impact on body weight, visceral adipose tissue (VAT), glucose homeostasis and metabolic syndrome, as well as the absence of major safety concerns. Another interesting aspect that has been shown is the anti-inflammatory properties of ketone bodies[20,21].

Bioelectrical impedance analysis (BIA) is a simple, safe, inexpensive, and non-invasive method to estimate body composition parameters: body hydration and lean mass, fat mass and metabolic components. FM represents a deposit of energy with a significant physiological metabolic function. FM, especially VAT, is associated to many diseases such as hypertension, dyslipidemia, diabetes and even cancer[22,23]. FFM consists of muscles, bones, minerals, and other fat-free tissues, which include BCM and Extracellular Mass (ECM). BCM is the metabolically active component of FFM, and it includes muscle tissue, internal organs, intracellular and extracellular water and bone tissue. The reduction of BCM can be considered as one of the criteria for evaluating protein loss. BCM is considered as one of the most important factors related to energy expenditure, protein needs and metabolic response to stress. In fact, chronic inflammation, and increased cytokine production, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, can determine BCM alterations[24].

Our study has analyzed the effect of 4 weeks nutritional treatment, comparing a hypocaloric MD and a VLCKD, using the measure of BMI, weight and body composition parameters, in patients with psoriasis, which embody a target of patients with chronic inflammatory disease and dysmetabolism. In our preliminary results, KD showed more and significant effects on BMI and WC, compared to MD. For this reason, KD could be proposed as an alternative tool to manage obese patients. It has been hypothesized that major weight loss can be consequent to the suppressive effect of KD on appetite and to controlled hunger, due to the satiety effect of proteins. In fact, during KD there are changes in circulating level of ghrelin and leptin, hormones which control appetite. The severe reduction in body weight was mainly a result of FM reduction, as assessed by BIA. The reduction of FM is similar in the two groups, although BMI reduction was superior in KD group. KD appears to have resulted in a greater loss of FFM than MD, but the reduction of the metabolically active component of lean body mass, BCM, is lower. This indicates that KD is able to determine weight loss without causing protein loss and sarcopenia. The percentage of skeletal muscle increased similarly in both diets. SM represents the largest body compartment in most adults, except for obese patients who have more significant percentage of adipose tissue mass. Loss of SM mass is present in different pathologic conditions including cancer, diabetes and obesity, as well as being a general feature of ageing. The maintenance of SM mass and its integrity is necessary for proper functioning of the musculoskeletal system and to provide efficient nutrient uptake and storage. Evidence from several studies suggests that circulating levels of saturated and unsaturated fatty acids (FA) may affect SM mass and its function: a larger amount of circulating saturated FA has been shown to decrease myotube diameter and suppress insulin signaling[25]. Currently, new evidence reveal that unsaturated FA may act to counter pro-atrophic mediators, including those triggered following exposure to saturated FA. For example, MUFAs and PUFAs have been reported to prevent palmitate-induced reductions in insulin sensitivity as well as to convey anti-inflammatory effects in SM cells.

It is commonly assumed that in obese patients, the weight loss is associated to an important loss of SM mass, following in parallel fat reduction. KD has been shown to maintain SM consistently and significantly. Consequently, KD could be considered a valid therapeutic option in overweight and obese PsD patients because it can induce a rapid and well tolerated weight loss. The VLCKD was used, however, to maintain muscle mass and to prevent weight regain. The maintaining of muscle mass plays an important role to preserve physical functionality and to improve cardiometabolic risk. A recent systematic review and meta-analysis confirmed that men and women aged 50 years and older can retain lean mass while losing fat mass when they consume energy-restricted higher-protein rather than normal-protein diets. According to this evidence, older overweight and obese adults should consume protein intakes ≥1.0 g/kg/d to preserve lean mass during a successful weight-loss intervention[26].

CONCLUSIONS

A nutritional counselling could be always proposed to all the PsD patients as a first line therapeutic strategy. VLCKD could be proposed as a first dietary intervention to all the obese patients to obtain rapid weight loss and maintenance of FFM, BCM and SM. After a short period to obtain the ideal weight,

patients could be instructed to continue MD, which maintains weight loss and reduce systemic inflammation. Our preliminary study was conducted on a small number of patients, with non-homogeneous characteristics for which our results should be confirmed in larger studies with a longer follow up period.

Conflict of interest:

The authors have no conflict of interest to declare.

Ethics Committee:

This is a preliminary study, carried out at Psoriasis and Nutrition Center of IDI-IRCCS of Rome (Italy) according to the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of our Institution (N. Prot. 475/2016).

Informed consent:

All the participants gave written informed consent before enrolment.

Authors contribution:

(I) Conception and design: R. Laurenti, E. Gubinelli; (II) Administrative support: R.Laurenti, S. Pallotta; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: R. Laurenti, E. Gubinelli, M.Fioretti; (V) Data analysis and interpretation: M.Fioretti; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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