

A Pilot Study of the Spanish Ketogenic Mediterranean Diet: An Effective Therapy for the Metabolic Syndrome

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ABSTRACT The “Spanish Ketogenic Mediterranean Diet” (SKMD) has been shown to promote potential therapeutic properties for the metabolic syndrome. The purpose of this study was to evaluate the potential therapeutic properties under free-living conditions of the SKMD in patients with metabolic syndrome (following the International Diabetes Federation consensus guidelines) over a 12-week period. A prospective study was carried out in 22 obese subjects with metabolic syndrome (12 men and 10 women) with the inclusion criteria whose body mass index of $36.58 \pm 0.54 \text{ kg/m}^2$ and age was 41.18 ± 2.28 years. Statistical differences between the parameters studied before and after the administration of the SKMD (week 0 and 12, respectively) were analyzed by paired Student’s *t* test. There was an extremely significant ($P < .001$) improvement in low-density lipoprotein cholesterol (from 126.25 mg/dL to 103.87 mg/dL) and all the parameters studied associated with metabolic syndrome: body weight (from 106.41 kg to 91.95 kg), body mass index (from 36.58 kg/m^2 to 31.69 kg/m^2), waist circumference (from 111.97 cm to 94.70 cm), fasting plasma glucose (from 118.81 mg/dL to 91.86 mg/dL), triacylglycerols (from 224.86 mg/dL to 109.59 mg/dL), high-density lipoprotein cholesterol (from 44.44 to 57.95 mg/dL), systolic blood pressure (from 141.59 mm Hg to 123.64 mm Hg), and diastolic blood pressure (from 89.09 mm Hg to 76.36 mm Hg). The most affected parameter was the triacylglycerols (51.26% reduction). After the diet all the subjects were free of metabolic syndrome according to the International Diabetes Federation definition, and 100% of them had normal triacylglycerols and high-density lipoprotein cholesterol levels, in spite of the fact that 77.27% of them still had a body mass index of $>30 \text{ kg/m}^2$. We conclude that the SKMD could be an effective and safe way to cure patients suffering from metabolic syndrome. Future research should include a larger sample size, a longer-term use, and a comparison with other ketogenic diets.

KEY WORDS: • *ketogenic diet* • *ketosis* • *lipolysis* • *low carbohydrate diet* • *metabolic syndrome* • *obesity* • “*Spanish Ketogenic Mediterranean Diet*” • *triacylglycerols* • *weight loss*

INTRODUCTION

THE METABOLIC SYNDROME is a set of the most dangerous heart attack risk factors: abdominal obesity, high blood pressure, high cholesterol, raised fasting plasma glucose, and diabetes.^{1–3}

It is estimated that around a quarter of the world’s adult population have the metabolic syndrome, and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome. In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes.⁴ The underlying cause of the metabolic syndrome continues to challenge the experts, but both central obesity and insulin resistance are considered significant factors.^{5,6} The role of genetics, aging, physical inactivity, hormonal changes, and

the pro-inflammatory state may vary depending on ethnic group.^{7,8} In most people with glucose intolerance or type 2 diabetes, there is a multiple set of risk factors that commonly appear together, forming what is now known as the “metabolic syndrome.” This “clustering” of metabolic abnormalities that occur in the same individual appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality.^{9,10}

The diagnosis of metabolic syndrome would be useful to identify individuals at high risk of both type 2 diabetes and cardiovascular disease. For that reason, several expert groups have attempted to produce diagnostic criteria. The first attempt was by a World Health Organization diabetes group in 1999, which proposed a definition that could be modified as more information became available; the definition of the syndrome required the presence of type 2 diabetes, impaired glucose tolerance, or insulin resistance (based on no specific criteria) as well as at least two of the following: hypertension, obesity, raised triglycerides or low high-density lipoprotein cholesterol (HDLc), and microalbuminuria.¹¹ The European Group for the Study of Insulin

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Resistance then produced a modification of the World Health Organization criteria; their definition released in the same year required insulin resistance plus two or more of the following: central obesity, with a waist circumference of 94 cm in men and 80 cm in women; dyslipidemia, again which is based on raised triglycerides or low HDLc; hyperglycemia excluding diabetes; and blood pressure >140/90 mm Hg or treatment for hypertension.¹² The National Cholesterol Education Program Adult Treatment Panel III simplified the definition to require three of the following five components: waist circumference >102 cm in men and 88 cm in women; HDLc <40 mg/dL in men and <50 mg/dL in women; triglycerides >150 mg/dL, counted as a criterion in addition to HDLc; blood pressure >130/85 mm Hg; and fasting serum glucose >110 (later 100) mg/dL.¹³ The problem with the World Health Organization and the Adult Treatment Panel definitions has been their applicability to different ethnic groups, especially as relates to obesity cutoffs. For that reason, the International Diabetes Federation (IDF) consensus group met in 2004, with representatives from the organizations that had generated the previous definitions and members from all IDF regions, and developed a new global definition that includes ethnic groups and would be useful to clinicians worldwide for identifying people at increased risk. Their recommendations are now available (Table 1).¹⁴ We considered this definition as the most appropriate for identifying people with metabolic syndrome in our study.

Ketogenic diets have shown to display healthier properties than conventional high carbohydrate/low fat diets.^{15–17} In the same way, the Mediterranean diet has evident health benefits; nevertheless, it is difficult to define which are the healthiest constituents of the Mediterranean diet because it is a very varied diet that can change among the Mediterranean countries. For example, in Spain fish is an important component as well as the olive oil, red wine, and vegetables that are three essential components of such diet in all the countries.¹⁸ Combining the concept of protein ketogenic diet and the four essential components of the Spanish Mediterranean diet started the concept of the “Spanish Ketogenic Mediterranean Diet” (SKMD). So this diet is a protein ketogenic diet with the incorporation of high doses of virgin olive oil and ω -3 fatty acids from fish as the main source of fat, fish as the main source of protein, green vegetables/salads as the main source of carbohydrate, and

moderate red wine intake. Such a diet has been shown to promote potential therapeutic properties for the metabolic syndrome because it is a safe, effective way of losing weight, promoting non-atherogenic lipid profiles, lowering blood pressure, and improving fasting blood glucose levels in healthy obese subjects.¹⁸

The purpose of this study was to evaluate these potential therapeutic properties under free-living conditions in patients with metabolic syndrome (following the IDF consensus guidelines) over a 12-week period. Therefore, the present study was carried out to demonstrate the changes in body weight, waist circumference, body mass index (BMI), blood pressure, lipid profile, and fasting glucose that might occur after administration of the SKMD throughout the period of study.

SUBJECTS AND METHODS

Subjects

A prospective study was carried out at a general medicine consultation in Córdoba, Spain, in 22 overweight subjects with metabolic syndrome (12 men and 10 women) whose BMI and age were $36.58 \pm 0.54 \text{ kg/m}^2$ and 41.18 ± 2.28 years, respectively. None of the patients from this study come from our previous study.¹⁸

Subjects were selected with the cooperation of a database from a medical weight loss clinic. Inclusion criteria were as follows: a diet based on carbohydrate foods (>50% of daily energy intake), achievement of desired weight loss, normal liver and renal function, not to have antecedents of gout or high uric acid, not to have exercise, alcoholic, and smoking habits, not to be pregnant or lactating, BMI $\geq 30 \text{ kg/m}^2$, age ≥ 18 years and ≤ 65 years, and not to be taking medication.

We excluded people with exercise habits in order to minimize the potential confusion effect associated with its potential positive impact on the metabolic syndrome. In connection with exercise performance, ketogenic diets are a controversial subject because some authors consider they could affect negatively athletic performance, whereas some studies indicate that the use of ketogenic diets does not imply a limitation in physical activity, with the only exception being reduced performance in anaerobic activities such as weight lifting or sprints. Some authors go even further, showing that ketogenic diets increase performance in aerobic physical activities such as cycling, because the

TABLE 1. THE NEW INTERNATIONAL DIABETES FEDERATION DEFINITION FOR THE METABOLIC SYNDROME

Component	Value
Raised triglycerides	$\geq 150 \text{ mg/dL}$ or specific treatment for this abnormality
Reduced high-density lipoprotein cholesterol	$< 40 \text{ mg/dL}$ (1.03 mmol/L) in males $< 50 \text{ mg/dL}$ (1.29 mmol/L) in females or specific treatment for this abnormality
Raised BP	Systolic BP ≥ 130 or diastolic BP $\geq 85 \text{ mm Hg}$ or specific treatment for this abnormality
Raised fasting plasma glucose	$\geq 100 \text{ mg/dL}$ or specific treatment for this abnormality

According to the new International Diabetes Federation definition, for a person to be defined as having the metabolic syndrome they must have central obesity (body mass index $> 30 \text{ kg/m}^2$ or waist circumference in Europeans for men of $\geq 94 \text{ cm}$ and for women of $\geq 80 \text{ cm}$) plus any two of the previous factors.

BP, blood pressure.

organism is better prepared to use fat as a source of energy since a metabolic adaptation occurs in which fat becomes the main source of energy without affecting blood glucose levels; thus a glycolytic metabolism becomes a lipolytic metabolism.^{15,17,19}

Because obesity increases the risk for alterations in hepatocyte function that lead to accumulation of lipid in hepatocytes and hepatomegaly (non-alcoholic fatty liver disease), we consider higher liver transaminase levels as a variant of normality in such obese patients (hepatic transaminases less than or equal to twice normal values [serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase values ≤ 80 mU/mL]). Chronic hepatitis B or C was ruled out in such patients by negative serologies. We determined normal renal function as measured by plasma urea nitrogen and plasma creatinine: creatinine ≤ 1.3 mg/dL and urea ≤ 26 mg/dL. Subjects with the inclusion criteria were selected for eligibility by phone, and 40 eligible subjects were invited to attend an orientation session during the week prior to the study. Patients measured their body's ketosis state every morning by ketone strips. During the study, the participants were phoned by the same person weekly, in order to assure the correct performance of the protocol and the ketosis state. If the subjects failed to maintain adequate compliance with the clinical trial protocol, they would be dropped from the study.

Subjects received no monetary compensation for their participation and provided a voluntary written consent form before initiating the diet.

The Ethics and Clinical Investigation Committee of the "Spanish Medical Association of the Proteinic Diet" approved the study protocol, informed consent form, and subject informational materials. Patient anonymity was preserved.

Diet

This protein ketogenic diet was called the SKMD because of the incorporation of virgin olive oil and ω -3 fatty acids from fish as the principal sources of fat, moderate red wine intake, green vegetables and salads as the main source of carbohydrates, and fish as the main source of proteins. It was an unlimited calorie diet; nevertheless, subjects were encouraged to consume per day a maximum of 30 g of carbohydrates in the form of green vegetables and salad, a minimum of 30 mL of virgin olive oil, 200–400 mL of red wine, and no limit of the protein block.

Participants were permitted three portions (200 g per portion) of vegetables daily: two portions of salad vegetables (such as alfalfa sprouts, lettuce, escarole, endive, mushrooms, radicchio, radishes, parsley, peppers, chicory, spinach, cucumber, chard, and celery) and one portion of low carbohydrate vegetables (such as broccoli, cauliflower, cabbage, artichoke, eggplant, squash, tomato, and onion). Three portions of salad vegetables were allowed only if the portion of low carbohydrate vegetables was not consumed. Salad dressings allowed were garlic, olive oil, vinegar, lemon juice, salt, herbs, and spices.

The minimum 30 mL of olive oil was distributed as 10 mL per principal meal (breakfast, lunch, and dinner). Red wine (200–400 mL/day) was distributed as 100–200 mL per lunch and dinner. The protein block was divided in "fish block" and "no fish block": the "fish block" included all the types of fish except larger, longer-living predators (swordfish and shark), and the "no fish block" included lean meat, fowl, eggs, shellfish, and cheese. Both protein blocks were not mixed in the same day and were consumed individually during its day under the condition that at least 4 days of the week were for the "fish block."

Trans fats (margarines and their derivatives) and processed meats with added sugar were not allowed.

No more than two cups of coffee or tea and at least 3 L of water were consumed each day. Infusions and artificial sweeteners were allowed (saccharin, cyclamate, acesulfame, aspartame, and sucralose), although we recommended avoiding sweeteners.

Supplements

Monounsaturated fats from olive oil and ω -3 fatty acids from fish are the predominant fats in the Spanish Mediterranean diet. The four most consumed fishes (68.3% of the total fish consumption) during our previous study with the SKMD were salmon, mackerel, sardine, and trout. We estimated during the first 4 weeks of this study that the average edible fish consumption per subject during the "fish block" day was approximately 1.12 ± 0.41 kg/day. With these results we estimated that the ω -3 intake during the "fish block" day was approximately 14.56 ± 5.37 g/day. In order to assure a high intake of ω -3 fatty acids every day, the day of the "no fish block" were given 9 g of ω -3 salmon oil (three capsules of 1 g, 3 times a day).

Micronutrients (vitamins and minerals) were given daily to each subject in the form of two tablets of a polyvitamin–mineral supplement and one tablet of calcium carbonate (1,500 mg). Each tablet of the polyvitamin–mineral supplement contained the following: vitamin A, 680 μ g; β -carotene, 720 μ g; vitamin D, 5 μ g; vitamin E, 10 mg; vitamin C, 60 mg; vitamin B1, 1.4 mg; vitamin B2, 1.6 mg; vitamin B6, 2 mg; folic acid, 200 μ g; vitamin B12, 1 μ g; niacin, 18 mg; biotin, 150 μ g; pantothenic acid, 6 mg; vitamin K, 30 μ g; calcium, 120 mg; potassium, 40 mg; phosphorus, 126.3 μ g; iron, 8 mg; magnesium, 45 mg; copper, 0.9 mg; zinc, 8 mg; manganese, 1.8 mg; iodine, 75 μ g; molybdenum, 45 μ g; boron, 70 μ g; chlorine, 21 mg; chromium, 25 μ g; molybdenum, 45 μ g; nickel, 5 μ g; selenium, 55 μ g; silicon, 3 mg; tin, 10 μ g; and vanadium, 10 μ g.

Measurements

Subjects' weight, adverse effects, waist circumference, and systolic/diastolic blood pressure were measured at weeks 0, 4, 8, and 12, at the same time (depending on the subject) and using always the same digital scale (model 703, Seca, Hamburg, Germany), side effects questionnaire, tape measure, and mercury sphygmomanometer (model 03-225, Labtron, Colonia, NJ, USA), respectively. The side effects

questionnaire was a checklist of side effects commonly mentioned during weight loss studies. If the patient was worried about any side effect during the study, a telephone number was given to report it.

Fasting venous blood samples were collected at weeks 0 and 12 for HDLc, triacylglycerol, and glucose. Venous blood samples for glucose, lipid, and lipoprotein analysis were collected into EDTA-containing (1 g/L) tubes from all subjects after a 12-hour overnight fast at the beginning of the study and at the end of each dietary period. Plasma was obtained by low-speed centrifugation for 15 minutes at 4°C within 1 hour of venipuncture. Plasma triacylglycerol levels were determined by enzymatic techniques. HDLc was determined after precipitation with phosphotungstic acid. Plasma glucose was measured by the glucose oxidase method. To reduce interassay variation, plasma was stored at -80°C and analyzed at the end of the study.

Statistical analysis

Statistical differences between the parameters before and after administration of the SKMD (week 0 and 12) were analyzed by paired Student's *t* test with SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) and are expressed as mean \pm SEM values. The parameters studied were as follows: weight, waist circumference, BMI, systolic blood pressure, diastolic blood pressure, LDLc, HDLc, triacylglycerol, and glucose. Before the Student's *t* test, Kolmogorov-Smirnov and Shapiro-Wilk tests were used for testing normality, and the assumption of homoscedasticity was determined with the Snedecor *F*-test.

RESULTS

Subject attrition

Of the 26 individuals who started the study, data collected from 22 subjects were used in the final analysis. Data were not used from four subjects: three subjects were withdrawn for failure to maintain adequate compliance with the clinical trial protocol, and one subject was lost to follow-up.

Parameters analyzed

Normal distribution and the assumption of homoscedasticity were verified. As there were no significant differences in male and female subjects in all the parameters examined ($P > .05$), the data from men and women in each group are pooled and presented together. The changes in all the parameters studied are shown in Table 2.

There was an extremely significant ($P < .001$) improvement in low-density lipoprotein cholesterol (from 126.25 mg/dL to 103.87 mg/dL) and all the parameters studied associated with the metabolic syndrome (Table 2): body weight (from 106.41 kg to 91.95 kg), BMI (from 36.58 kg/m² to 31.69 kg/m²), waist circumference (from 111.97 cm to 94.70 cm), fasting plasma glucose (from 118.81 mg/dL to 91.86 mg/dL), triacylglycerols (from 224.86 mg/dL to 109.59 mg/dL), HDLc (from 44.44 to 57.95 mg/dL), systolic blood pressure (from 141.59 mm Hg to 123.64 mm Hg), and diastolic blood pressure (from 89.09 mm Hg to 76.36 mm Hg). The most affected parameter was the triacylglycerols (51.26% reduction). The percentages of patients with pathological values of metabolic syndrome according to the new IDF definition were as follows: 77.27% for BMI, 63.64% for waist circumference, 13.64% for fasting plasma glucose, 0% for triacylglycerols, 0% for HDLc, 22.73% for systolic blood pressure, and 9.09% for diastolic blood pressure. After the diet all the subjects were free of metabolic syndrome according to the IDF definition, and 100% of them had normal triacylglycerol and HDLc levels, in spite of the fact that 77.27% of them still had a BMI of >30 kg/m².

Adverse effects ($n = 8$ [36.36% of patients]) were slight, and most of them (75%) appeared and disappeared at the first week of the study. The most common symptoms experienced were asthenia (87.85%), headache (62.5%), constipation (50.1%), sickness (25%), diarrhea (25%), and insomnia (25%).

DISCUSSION

Low carbohydrate diets are, from a practical and physiological point of view, a much more effective way of losing

TABLE 2. CHANGES IN LEVELS OF PARAMETERS ASSOCIATED WITH THE METABOLIC SYNDROME BEFORE AND AFTER THE SPANISH KETOGENIC MEDITERRANEAN DIET

Parameter	Week 0	Week 12
Weight (kg)	106.41 \pm 2.38	91.95 \pm 2.22
BMI (kg/m ²)	36.58 \pm 0.54 (100%)	31.69 \pm 0.54 (77.27%)
Waist circumference (cm)	111.97 \pm 2.49 (100%)	94.70 \pm 2.58 (63.64%)
Glycemia (mg/dL)	118.81 \pm 1.43 (100%)	91.86 \pm 1.45 (13.64%)
Triacylglycerols (mg/dL)	224.86 \pm 9.04 (95.45%)	109.59 \pm 2.68 (0%)
HDLc (mg/dL)	44.44 \pm 1.19 (59%)	57.95 \pm 1.04 (0%)
SBP (mm Hg)	141.59 \pm 1.81 (95.45%)	123.64 \pm 1.71 (22.73%)
DBP (mm Hg)	89.09 \pm 1.03 (90.91%)	76.36 \pm 1.06 (9.09%)
Patients with MS [<i>n</i> (%)]	22 (100%)	0 (0%)

Data are mean \pm SEM values (percentage of patients with pathological values of the metabolic syndrome (MS) according to the new International Diabetes Federation definition). The *P* value was extremely significant ($P < .001$) in all the parameters studied.

BMI, body mass index; DBP, diastolic BP; HDLc, high-density lipoprotein cholesterol; SBP, systolic BP.

weight. Such diets provide metabolic advantages; for example, they help to preserve muscle mass, reduce appetite, diminish metabolic efficiency, induce metabolic activation of thermogenesis, and favor increased fat loss.^{15,16} These diets are also healthier because they promote a non-atherogenic lipid profile, lower blood pressure, and decrease resistance to insulin with an improvement in blood levels of glucose and insulin.^{15,17} The low carbohydrate diet called SKMD has shown therapeutic properties in obese subjects (weight loss, lipid profile, blood pressure, and fasting blood glucose levels) that have been attributed to the synergic effect between the high protein ketogenic nature of the diet and its richness in virgin olive oil, fish, vegetables, and red wine.¹⁸ In this 12-week diet intervention study, the SKMD resulted in an extremely significant reduction in all the parameters associated with the metabolic syndrome. Following the IDF criteria, 100% of the patients were cured of the metabolic syndrome in spite of the fact that 77.27% of them still had a BMI over 30 kg/m² due to the short term of the study. If we consider the results taken in conjunction with the fact that the scientific literature demonstrates that the basic components of the SKMD are effective ways to improve or even treat the metabolic syndrome, we can state that the components of the SKMD may exert a synergic effect indeed. Our statement is founded in the following findings:

1. Carbohydrate restriction improves all of the features of metabolic syndrome, and these beneficial effects do not require weight loss.^{20,21} This may explain why all the patients of our study were cured of the metabolic syndrome in spite of the fact that 77.27% of them still had a BMI over 30 kg/m². Similarly, carbohydrate restriction improves the markers of metabolic syndrome in normal subjects, patients with metabolic syndrome, and those with diabetes.^{20,21} This is not strange if we consider that the ketogenic diet improves glycemic control in patients with type 2 diabetes such that diabetes medications can be discontinued or reduced.²² In *ad libitum* comparisons low carbohydrate diets do better than low fat diets for weight loss and metabolic syndrome, substitution of protein for carbohydrate improves metabolic syndrome, and, in contrast, explicit low fat/high carbohydrate interventions exacerbate the metabolic syndrome.²⁰ For that reason, some authors consider that the metabolic syndrome might be seen as a generalization of the carbohydrate intolerance that characterizes frank diabetes and should be defined as those physiologic markers that respond to reduction in dietary carbohydrate.^{20,21} Nevertheless, we have to clear up that this is may be due to modern diets that are in the context of western omnivorous diets high in carbohydrates because vegetarian and vegan diets also offer significant benefits for the metabolic syndrome²³ and type 2 diabetes.²⁴
2. Although some authors have not found²⁵ a relationship between adherence to the Mediterranean diet and lower metabolic syndrome prevalence, some compo-

nents of such traditional Mediterranean diets have shown an inverse association with metabolic syndrome and its components.²⁵ In fact, it has been suggested that not all the components of the Mediterranean diet are likely to provide the same level of protection.²⁶ In this sense, only some components of the Mediterranean diet might be considered as medicinal agents for the metabolic syndrome. From all these components, the four components of the Mediterranean diet in Spain used in this study exert these anti-metabolic syndrome properties: virgin olive oil,^{25,27–30} fish oil-derived ω -3 fatty acids,^{29,31–34} vegetables/salad,^{25,29} and moderate red wine consumption.^{25,27,35–38}

Explanations and suggestions

We recognize several limitations of our study that may have influenced the study findings:

1. The study sample is small (22 subjects).
2. This is not a random population study, because subjects were selected for eligibility, and their eligibility was related with their compliance to the diet.
3. Although this diet is pretty similar to the “Paleolithic diet,” we thought that it should be more correct to call it the “SKMD” because the pillars of this diet are virgin olive oil, fish, red wine, and vegetables, all them defined as essential components of the Spanish Mediterranean diet. This was properly explained at the Introduction. Thus, it is a Spanish Mediterranean diet without components that block the ketosis state. For that reason the name “SKMD” is used here. We thought that the Paleolithic diet was less appropriate because of the presence of red wine and dairy products. Moreover, the Paleolithic diet could include berries, fruit, nuts, and other components (if the season is favorable for this kind of food) that could block the ketosis state. So, the Paleolithic diet is not always ketogenic, in spite of the fact that it could be.
4. Once the patient has achieved our goals (weight loss and analytical parameters), the diet is less restrictive regarding carbohydrate intake, being easier to adhere to and more similar to the Paleolithic diet, but preserving the pillars of the “SKMD.” For that reason it could be called the “Spanish Mediterranean Paleolithic diet.” The components will be added to this diet progressively and according to this order under strict control by the physician: all kind of vegetables without restriction (except high glycemic or load index tubers), nuts, berries or fruits, yogurt, milk, and legumes. Products with added carbohydrates (any kind of sugar, maltodextrin, starch, syrup, flour, etc.) will not be allowed. Forbidden tubers could be included from time to time, and cereals or their derivatives occasionally or never. The components will be added weekly or monthly, according to the patient’s tolerance. Thus, there are patients who require the “SKMD” (with no tolerance to carbohydrates) continuously and others

who will tolerate legumes even three times a week and some pieces of fruit daily.

5. Weight loss may be related with improvement in all parameters that were studied, although 77.27% of the subjects still had a BMI of $>30 \text{ kg/m}^2$, a criterion that is considered central obesity for the metabolic syndrome. And, as we said, the new IDF definition considers central obesity as the most important and necessary parameter for the diagnosis of metabolic syndrome. Keeping in mind the 77.27% of patients who still have central obesity, we do not know the real role of the weight loss for these results.
6. We did not take into consideration calorie intake before and after the 12 weeks. Although it is known that an equal number of calories are ingested, ketogenic diets are more effective for achieving fat loss than the conventional high carbohydrate/low fat diets,^{15,16} we do not know if our patients take in less food and fewer calories, and if it is the case, this would be correlated with weight reduction and better cardiovascular parameters.
7. Although the effect of vitamins is not clear, especially in short interventions, their possible contribution to better cardiovascular parameters should be possible.
8. Calcium plus vitamin D supplementation has shown a potential anti-obesity role,³⁹ so its potential contribution to the weight loss in our study should be possible. A drawback that has been attributed to high protein diets is that they have a negative effect on the calcium metabolism and are therefore damaging in relation to bone density. There are conflicting studies that state that the consumption of high levels of protein does not affect bone density negatively, that, in contrast, the consumption of low levels of protein has a negative impact on older people's bone density, and that an increase in animal protein intake to 1.55 g/kg of body weight/day has a beneficial effect on the bone mass of older people. Moreover, no link has been found between the consumption of proteins/phosphorus and calcium absorption efficiency, and also the negative effect on bone mass can be avoided when proteins levels are very high, by consuming 20 mg of calcium/g of protein consumed.^{15,17} Having in mind the short duration of this study, the calcium plus vitamin D supplementation we added, and the cheese consumption that was allowed, we supposed bone density would not be a problem in this study.
9. Our study has no control groups to consider the interaction between the components of the SKMD. There is no way to say if the healthy results are due to the ketogenic nature of the diet, the virgin olive oil, the red wine, the higher fish intake, the higher salad intake, or a synergic effect between these components.

All these limitations should be known and accordingly considered by further trials.

We conclude that the SKMD could be an effective and safe way to cure patients suffering from the metabolic syndrome.

Future research should include a larger sample size, a longer-term use, and a comparison with other ketogenic diets.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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