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Efficacy and Tolerability of the Ketogenic Diet Compared to the Mediterranean Diet in a Cohort of Overweight/Obese Patients: Effects on Anthropometric and Metabolic Parameters

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***Abstract*— *Background**: According to the World Health Organization (WHO) and the Global Burden of Disease Study, a healthy and balanced diet could significantly reduce the incidence and prevalence of the main chronic-degenerative diseases. Scientific studies show that following a varied and balanced diet, characterized by the balanced intake of all nutrients, offers countless benefits. Therefore, a healthy diet combined with an active lifestyle helps prevent and treat many chronic diseases such as obesity and overweight, arterial hypertension, metabolic diseases and some forms of cancer. Obesity is now widely regarded as a global epidemic and, for this reason, there is a need to resort to less invasive interventions, such as nutritional therapy and physical activity, even before resorting to more invasive interventions, such as bariatric surgery. **Objectives**: Leaving aside pharmacological and surgical interventions, the aim of our study is to evaluate the efficacy and tolerability of two types of diets, Mediterranean Diet and Ketogenic Diet, in a cohort of overweight / obese patients and evaluate the effects that these have on anthropometric and metabolic parameters. **Methods**: The study includes a population of 60 subjects divided into two groups; a first group consisting of 30 subjects followed a Mediterranean diet (MetDiet) while the other group, also composed of 30 subjects, followed a ketogenic diet (KetoDiet). In this study, the mean age was 53 ± 14 years, and 75% of the population was female. All subjects were reviewed after 3 weeks and after 4 months of nutritional therapy. Data were reported as mean ± standard deviation (SD). The differences between the means in the two treatment groups were compared using a Student's t-test for independent samples. All analyzes were conducted using SPSS 25.0 statistical software for Windows. A two-sided p-value <0.05 was considered statistically significant. **Results**: There is a higher prevalence of subjects suffering from arterial hypertension, type 2 diabetes mellitus, treated with diuretics and oral hypoglycemic agents, in participants who followed the Mediterranean diet compared those who followed a ketogenic diet. After 3 weeks of nutritional therapy, individuals treated with the ketogenic diet have a greater reduction in body weight, body mass index (BMI), waist circumference (CV), waist-hip ratio (WHR), fat mass (FM), visceral fat mass (FMV) compared to subjects who followed the Mediterranean diet. **Conclusions**: The results of this study suggest, after 4 months of nutritional therapy, a greater compliance of the ketogenic diet compared to the Mediterranean diet in limiting some anthropometric parameters (such as: body weight, degree of obesity, CV, WHR, FM and FMV) and some parameters metabolic (such as: reduction of Tot-col, LDL-col and uric acid, glycaemia, HbA1c and triglycerides). Therefore, very low calorie diets have shown better results than the MetDiet, but maintenance nutritional therapy or the possible worsening of obesity complications still require careful analysis and more in-depth studies*.

***Keywords*—** *Obesity, Europan guidelines, Weight maintenance, obesity onset, mediterranean diet, ketogenic diet*.

I. INTRODUCTION

In the last 40 years, the eating habits of Italians have changed considerably. This change is due to the development of the economy, social changes, a higher standard of living, a more sedentary lifestyle and incorrect eating habits (1). All this has led on, the one hand to the disappearance of nutritional deficiencies of the past, but on the other hand it has led people to eat more, and consequently these people will face more serious health problems. Currently, in higher-income countries, the gradual transition towards a diet that is too rich in processed and refined foods, especially of animal origin, in saturated fats, cholesterol and simple sugars and at the same time low in foods of plant origin, has contributed to generating over 2.1 billion overweight or obese people (2). Body weight represents the tangible expression of the balance between caloric income and expenditure. Excess body fat can be classified as overweight, followed by moderate obesity and severe obesity (3). Therefore, a healthy diet combined with an active lifestyle helps prevent and treat many chronic diseases such as obesity and overweight, arterial hypertension, metabolic diseases and some forms of cancer (4). In recent years, the prevalence of overweight and obesity has increased alarmingly in many countries around the world, so much so that today we are talking about a global epidemic. Severe obesity, or BMI >35 kg / m2, is rapidly growing within the epidemic (5, 6). According to data provided by the World Health Organization (WHO), the number of obese people doubled after 1980; in 2014, more than 1.9 billion adults were overweight and of these, over 600 million were obese (7). In Italy there are surveillance systems, coordinated by the Istituto Superiore di Sanità (ISS), which collect data on the weight of the population and on modifiable risk factors and which will be able to provide their own contribution to the platform proposed by the WHO. Among these: OKkio alla Salute, for

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children aged 6 to 10; HBSC, for 11, 13 and 15 year olds; STEPS, for adults 18-69 years old; PASSI d'Argento, for the elderly over 65 (8). Overweight and obesity are conditions characterized by an excessive accumulation of body fat and have negative consequences on health. Obesity represents an important public health problem and imposes an economic burden on society through the increase in health costs for the medical treatment required, for the treatment of associated pathologies (direct costs), the loss of productivity due to absenteeism and premature mortality (indirect costs), psychological problems and poor quality of life (9, 10). Obesity could lead Europe towards a very serious crisis by 2030 and towards an unprecedented public health challenge, hitherto underrated and not accepted as a strategic governance problem associated with significant economic implications (11). The clinical significance of excess body fat is influenced by other factors such as familiarity with other chronic diseases (metabolic, cardiovascular, neoplastic, etc.), the distribution of body fat, the age of onset and the presence of complications and / or morbid associations. The clinical significance of excess body fat is influenced by other factors such as familiarity with other chronic diseases (metabolic, cardiovascular, neoplastic, etc.), the distribution of body fat, the age of onset and the presence of complications and / or morbid associations. In light of the epidemiological data on the complications of obesity, it is however necessary to intervene on the reduction of cardiovascular risk and on the overall improvement of health (12, 13). Various therapeutic strategies are used for the treatment of obesity ranging from lifestyle modification, pharmacotherapy and, ultimately, obesity surgery, also called bariatric surgery. Despite the enormous advances in pharmacology, not always effective and not easy to use, the most effective first-line therapeutic interventions to reduce comorbidities and costs related to obesity are: the correct combination of nutrition, physical activity and support psychological (14, 15). But lifestyle modification programs aren't always successful, especially in patients with severe obesity. However, patients often return to previous behaviors and regain weight. We must not forget that the COVID-19 pandemic has worsened the situation especially in the lockdown, which saw a restriction of people's movements, an increase in food portions, and difficulties in accessing treatment services (16, 17, 18). On the other hand, the drug therapy of obesity is currently limited by costs, potential side effects and contraindications that cannot make them suitable for all subjects with obesity (19, 20). Although multiple therapeutic options are available for the treatment of patients with obesity, bariatric surgery is regarded as the most effective method of achieving weight loss and reduction of comorbidities and mortality in patients with severe obesity (21, 22). But surgical procedures are invasive procedures, expensive and not without side effects such as: nausea, vomiting, dumping syndrome, constipation, diarrhea, deficiency or reduced intake or reduced absorption. Therefore, despite its effectiveness, it can lead to several irreversible complications related to surgical procedures and its availability is limited. It should be remembered that the management and treatment of obesity have broader objectives than simple weight loss. For this reason, the basic treatment of the obese subject should include "counseling", a correct educational protocol aimed at modifying the lifestyle (23). Often overweight and obese patients are looking for quick solutions to solve their problem, such as drastic diets that allow rapid weight loss or the search for "miracle" drugs. These strategies are not effective, because they do not allow adequate and stable weight reductions over time.

The ability to communicate with the patient, the ability to listen, empathy, are important elements in the relationship with the overweight / obese patient, often returning from numerous and frustrating dietary attempts (24, 25). The diagnosis of overweight and obesity is essentially clinical and is based on the evaluation of some anthropometric parameters, rather simple to calculate, and some metabolic parameters. The path dedicated to the diagnosis and treatment of overweight / obese patients includes a multidisciplinary team involving the specialist doctor and also the figure of the dietician, in order to improve the effectiveness of nutritional treatment (26). Regarding the composition of the diet, according to the literature, it is clear that the option of a low- carbohydrate diet should be considered in the obese patient. According to the 2014 NICE guidelines, very low calorie diets can be used for up to 12 weeks. Currently, after years of heavy criticism of low calorie and ketogenic diets (VLCKD), some studies are proving their usefulness (27, 28). Therefore, the dietary approach will have to focus on effective and visible results in a not too long time, so that the patient feels motivated to continue in his effort. For these reasons, the objective of our study is to evaluate the efficacy and tolerability of two different types of diets, in a cohort of overweight / obese patients, in order to evaluate which of the two has given greater results in terms of loss of body weight and changes in anthropometric parameters. Furthermore, given that obesity has a wide range of repercussions on health (such as metabolic diseases, dyslipidemia, cardiovascular diseases, diseases of the digestive system and others), we also wanted to analyze some metabolic parameters (such as lipid profile, liver enzymes, glycaemia, HbA1c, uricemia and creatinine), in order to evaluate which of the two diets improved these parameters and their return to normal ranges.

II. Materials and Methods

A. Description of the sample

The subjects were recruited at the S.O.C. Endrocrine diseases of metabolism and nutrition of the "Pugliese-Ciaccio" Hospital of Catanzaro, from January 2020 to September 2021. The sample, object of our study, was composed of 60 Caucasian subjects, with an average age of 53 ± 14 years and 75% of the population was female. These 60 subjects were divided into two groups, a first group consisting of 30 subjects followed a Mediterranean diet while the second group consisting of 30 subjects followed a ketogenic diet. All subjects signed an informed consent at the time of inclusion.

B. Inclusion / Exclusion Criteria

All subjects who presented: Triglycerides> 400 mg / dl, forms of secondary obesity (endocrinopathies, genetic

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abnormalities of the central nervous system, iatrogenic forms), eating disorders, type 1 diabetes mellitus, pregnancy were excluded from the population examined in this study. , breastfeeding, kidney failure, chronic pancreatitis, history of ongoing cancer, alcohol or drug abuse, chronic inflammatory diseases, use of psychiatric drugs and corticosteroids.
The subjects included in our study were: men and women aged >18 years, diagnosed with type 2 diabetes mellitus (T2DM), overweight subjects, subjects with I ° and II ° obesity, who used oral lipid-lowering agents, diuretics, hypoglycemic and oral hypouricemic drugs, smokers.

C. Dietary Treatment: Mediterranean Diet Sample

The concept of the Mediterranean diet (Metdiet) was first introduced by Ancel Keys and Francisco Grande in 1957, and has been considered as the traditional dietary pattern found in the olive growing areas of the Mediterranean, mainly Greece, Italy and France, to between 1950 and 1960. To date, the Mediterranean diet has become the gold standard of reference for a healthy and correct diet as several studies show that this diet is effective in preventing overweight, obesity and metabolic diseases, whose multifactorial pathogenesis involves environmental, genetic, behavioral factors, etc. (29, 30, 31, 32). The benefits have been attributed to the macro and micronutrients of which it is composed. This type of diet is characterized by the high consumption of fruit and vegetables, whole grains, dried fruit, medium-low consumption of white and red meats, fish, dairy products, eggs, wine and oil (33, 34). The Mediterranean diet followed by the study sample was a low-calorie diet of about 1300 Kcal. The basal metabolic rate was calculated with the Harris-Benedict formula, whose formula provided for the use of the ideal weight, obtained with the Lorenz formula. The goal was a calorie deficit of about 500 Kcal / day. The protein intake was about 0.8 g / kg / day with a high biological value using meat, fish, milk and yogurt with a reduced fat and legume content. Carbohydrates, recommended as complex carbohydrates (cereals, bread and pasta) represented about 55% of the total energy. The fats consisted mainly of monounsaturated fatty acids (extra virgin olive oil) and represented 25-30% of the total energy. The diet was organized into 3 main meals (breakfast, lunch and dinner) and 2 snacks; snacks included the consumption of fresh or dried fruit (20 grams of almonds as a mid-morning snack and 1 serving of fresh fruit as a mid-afternoon snack). Breakfast included the consumption of partially skimmed milk or a jar of low-fat yogurt plus 3 rusks and possibly a bitter coffee. Lunch included a plate of pasta (about 60 g) or rice (70 g) to be seasoned in a simple way plus a vegetable side dish and 15 grams of extra virgin olive oil, to be divided between the pasta and the vegetable side dish. Instead, dinner included the consumption of a protein dish (meat or fish, or eggs, or dairy products or legumes) plus a side dish of vegetables and 15 grams of extra virgin olive oil, to be divided between the protein plate and the vegetable side dish. Furthermore, after dinner it was recommended to consume a small seasonal fruit. The consumption of fish at least 2 times a week was recommended, the consumption of cheese and eggs 2 times a week and the consumption of sugary drinks and alcoholic beverages was not recommended, with the exception of half a glass of red wine at lunch. At the end of the 4 months, the subjects were given a maintenance diet of about 1400 kcal.

D. Dietary Treatment: Ketogenic Diet Sample

The ketogenic diet is a diet that induces the body to form substances called "ketone bodies", the production of which occurs when a very low amount of carbohydrates are taken, as in the case of fasting or a very high-fat diet. So, it is a diet high in fat, low in carbohydrates and with sufficient protein for growth that mimics the metabolic changes that occur during hunger. In this case, the body, and in particular the brain, use ketone bodies as a source of energy. The periods in which fasting was used to treat epilepsies date back to 500 BC, but starting from the 1920s other dietary regimens were used in addition to fasting to treat epilepsies and then were little used with the modern era of antiepileptic drug treatment.
The ketogenic diet is a last resort treatment for subjects with resistant epilepsies in fact, even today, it continues to be used in pediatrics in children with refractory and drug-resistant epilepsies (35, 36, 37, 38). In the classic protocol of the ketogenic diet, lipids represent 87-90% of calories, carbohydrates less than 10% of the total energy with a moderate / low protein content. It is a biochemical model of fasting that directs the organs, especially the brain, to use ketone bodies more as a source of nutrition in place of glucose (39). All this should not cause concern for the body because the body can adapt to a diet low in carbohydrates, as the body has the ability to synthesize glucose from amino acids and glycerol; therefore the energy needs can also be satisfied by lipids and proteins. Although there has been talk of ketogenic diets since the 1920s as a medical strategy for treating refractory epilepsy, studies of its healing properties have scientifically few studies in other medical areas. Recently, its applicability and efficacy have been addressed in diseases such as obesity (40, 41), polycystic ovary syndrome (42) and T2DM (43, 44). Given the extensive studies of the Mediterranean diet and the recent studies of the ketogenic diet on the state of overweight and obesity (45, 46, 47,48, 49), in our study we wanted to demonstrate how anthropometric and metabolic parameters change in the short / medium term, using a low-calorie Mediterranean diet and a ketogenic diet. The subjects who followed a ketogenic diet used a therapeutic protocol that included 6 phases: the first two phases consisted in the entry of ketosis and in the greater loss of weight and body fat, while the phases from 3 to 6, from the standard duration of two weeks, were the stages of food reintroduction where there was less weight and body fat loss (Figure 1).

The protein intake of this protocol was calculated using the Blackburn formula, recommending 1.2 g/ kg / day of protein for women and 1.5 g / kg / day of protein for men. While the intake of carbohydrates, which came from products and vegetables, was less than 50 g / day during the first two phases. The first phase lasted about a month and consisted of the consumption of 4 substitute meals and included the consumption of vegetables for both lunch and dinner.

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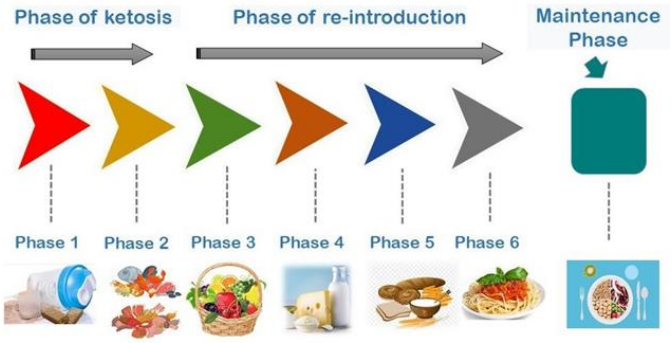

Fig. 1. Representation of the phases of the ketogenic diet

Subjects were advised to consume a tablespoon of oil at both lunch and dinner, drink at least 2 liters of water, and take a mineral salt supplement and a vitamin supplement. After this month, the subjects moved on to phase 2, whose phase differed from phase 1 only for the elimination of a replacement meal for lunch or dinner, a protein dish was provided in its place. This phase lasted about 2 months and subsequently the subjects moved on to phase 3, which differed from phase 2, for the reintroduction of two fruits per day. From phase 3 we moved on to phase 4, in which the reintroduction of legumes at lunch was foreseen in place of the replacement meal or in place of the protein dish and then the reintroduction of dairy product at breakfast or as an alternative to legumes, meal replacement or protein dish. Furthermore, from phase 3 to phase 6 it was no longer recommended to use mineral salts supplementation but only vitamin supplementation.
From phase 4 the subjects passed in phase 5 and phase 6 in which the reintroduction of whole grains and pasta was foreseen. It was decided to use meal replacements for the high content of essential amino acids, to get as close as possible to a normal diet, to increase the palatability, to offer a wide choice of products (from wafers, bread, breadsticks, crepes, omelettes, soups, drinks, etc.), to overcome the monotony of the diet and to ensure the right protein intake as foods are subject to changes related to cutting, the presence of visible fat, intramuscular fat and more. The proteins used in the replacement meals were proteins derived from whey, egg, soy and peas. At the end of the 6 phases, the dietician gave the patient a maintenance diet, of about 1400 kcal, which differed from patient to patient based on eating habits and compliance at the end of the ketogenic diet.

E. Anthropometry

At the time of inclusion, all 60 subjects underwent a general medical history, pathological history, drug history and food history. The general medical history also included the anthropometric assessment (BMI, waist and hip circumference, WHR). The body mass index (BMI) was calculated as body weight, expressed in kg, divided by the square of the height, expressed in m2. Height and weight were measured to an approximation of 0.05 m and 0.1 kg respectively. The circumference of the abdomen was measured, in an upright position, with an approximation of 0.5 cm, in the midpoint between the iliac crests, placing the metric tape, inelastic, around the abdomen, just above the upper portion of the lateral edge of the crest. iliac, without forcing it. The hip circumference was obtained by placing the tape measure at the widest point above the greater trochanters, maintaining the erect position. The Waist-Hip ratio (WHR) was calculated directly by the software of the TANITA instrument, used for the bioimpedance analysis. The same subjects were reviewed after 3 weeks and after 4 months and during these follow-ups the following were measured: BMI, waist and hip circumference, WHR).

F. Bioimpedance Analysis

At the time of inclusion, all 60 subjects, after the anamnestic part, underwent bioimpedance analysis using the Tanita InnerScan®, Radio Wireless Body Composition Platform, BC-1000 model. This monitor is a precision instrument utilizing state-of-the-art technology. The subject was asked to remove metal objects, shoes, and any socks, and then to get on the “Tanita”, taking care to position the sole and the heels of the feet well on the electrodes of the instrument. The exam, lasting a few seconds, was recorded wirelessly on the outpatient computer, after installing the "GMON Pro - Tanita" version 3.1 software. Bioimpedance analysis showed alipid lean mass (FFM), muscle mass (MM), fat mass (FM) and visceral fat mass (FMV) expressed in kg, body weight expressed in kg, BMI, body water as a percentage (not shown in the statistics), the waist and hip circumference and the WHR. All subjects were reviewed after 3 weeks and after 4 months and during these follow-ups the bioimpedance analysis was performed again to assess the change in FFM, MM, FM, FMV, body weight, BMI, circumferences and WHR.

G. Blood Chemistry Tests

Also on the same day, at the time of inclusion, all 60 subjects exhibited their blood chemistry tests, carried out at the same facility where the study was carried out or carried out privately. After three weeks, at the first follow-up, only the bioimpedentiometric examination was carried out and compliance with the delivered diet was assessed but no control blood chemistry tests were delivered, as it is difficult to repeat the analyzes after only three weeks. It should be remembered that in the study, there were subjects with low income, such that they could not afford to carry out examinations in such a short time. Therefore, for this reason, we asked the subjects to repeat the blood chemistry tests after 4 months. We were thus able to assess a difference with those exhibited during the first visit and the effectiveness of the diet on metabolic parameters. The blood tests required were: Tot- col (ml / dl), HDL-Col (ml / dl), Triglycerides (ml / dl), glycaemia (ml / dl), creatinine (ml / dl), uric acid (ml / dl); HbA1c (%) and liver enzymes (IU / L). LDL-Col was calculated in the clinic using the Friedewald formula (50).

H. Statistical Analysis

Data are reported as mean ± standard deviations (SD). All variables were normally distributed. The differences between the means in the two treatment groups were compared using a Student's t-test for independent samples. The $\chi 2$ test was used to compare the prevalences of categorical variables.

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The generalized linear model (GLM) was used to correct the differences between the means in the two treatment groups for confounding factors, i.e. all those variables that were statistically significant on the Student's t-test and on the $\chi 2$ test (such as levels baseline serum glucose, HbA1c, HDL-cholesterol, triglycerides, prevalence of arterial hypertension, use of diuretics and oral hypoglycemic agents). All analyzes were conducted using SPSS 25.0 statistical software for Windows (S. Wacker Drive, Chicago, IL, USA). A two-sided p-value <0.05 was considered statistically significant.

III. Results

The demographic and clinical characteristics of the study participants are shown in table 1. In this study, the mean age was 53 ± 14 years, and 75% of the population was female. The prevalence of severe obesity status at baseline was 35%. The prevalence of subjects with arterial hypertension was 48% and with diabetes mellitus 35%. The demographic, anthropometric and clinical characteristics of the population classified according to the dietary treatment at baseline, i.e. subjects who followed a Mediterranean-type diet and subjects who followed a ketogenic diet, are indicated in table 2.

TABLE 1. Demographic, anthropometric and clinical characteristics of the cohort.

	Participants (*n* = 60)
Age (years)	53 ± 14
Female gender (%)	75
Body weight (Kg)	91.9 ± 16
BMI (Kg/m^2)	34.4 ± 6
CV (cm)	110.6 ± 13
WHR	0.99 ± 0.1
Smokers (%)	13
Lipid-lowering (%)	30
Hypertension (%)	48
Diuretics (%)	33
Diabetes (%)	35
Oral hypoglycemic agents (%)	32
Hypouricemic agents (%)	10
Obesity I (%)	47
Severe Obesity (%)	35
Bioimpedance analysis	
FFM (Kg)	52.7 ± 9
MM (Kg)	50.8 ± 9
FM (Kg)	37.6 ± 11
FMV (Kg)	13.8 ± 6
Blood chemistry tests	
Glucose (mg/dL)	114 ± 34
HbA1c (%)	5.9 ± 0.9
Creatinine (mg/dL)	0.81 ± 0.2
Total Cholesterol (mg / dL)	200 ± 37
HDL cholesterol (mg / dL)	48 ± 13
LDL cholesterol (mg / dL)	125 ± 36
Triglycerides (mg / dL)	132 ± 58
Uric Acid (mg / dL)	5.6 ± 0.9
AST (IU/L)	23 ± 7
ALT (IU/L)	27 ± 12
γGT (IU/L)	24 ± 11

Data are presented as mean ± SD or prevalence as appropriate. BMI, body mass index; CV, waist circumference; WHR, waist circumference to hips ratio; Severe obesity, obesity ≥ II; FFM, alipidic lean mass; MM, muscle mass, FM, fat mass; FMV, visceral fat mass; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate transaminase; ALT, alanine amino transferase; γGT, gamma glutamyl transpeptidase.

As can be seen from the table 2 there were no differences between the two groups on gender (p = 0.23), on the age of the participants (p = 0.80), nor on body weight (p = 0.40), nor in the prevalence of severe obesity (p = 0.58). However, there is a higher prevalence of subjects with arterial hypertension (p<0.001), type 2 diabetes mellitus (p <0.001) and on treatment with diuretics (p = 0.013) and oral hypoglycemic agents (p = 0.005) in participants who have followed the Mediterranean diet compared to those who followed a ketogenic diet (table 2). Furthermore, these same subjects also had higher levels of blood glucose, HbA1c, triglycerides and lower blood levels of HDL-cholesterol (table 2).

TABLE 2. Demographic, anthropometric and clinical characteristics at baseline of the cohort divided according to dietary treatment.

	MetDiet (*n* = 30)	**KetoDiet (*n* = 30)**	*p-value*
Age (years)	54 ± 16	53 ± 13	0.80
Female gender (%)	67	83	0.23
Body weight (Kg)	93.7 ± 18	90.3 ± 14	0.40
BMI (Kg/m^2)	35.3 ± 6	33.5 ± 5	0.21
CV (cm)	111.8 ± 14	109.3 ± 12	0.46
WHR	1.01 ± 0.1	0.97 ± 0.1	0.29
Smokers (%)	13	13	1
Lipid-lowering (%)	37	23	0.39
Hypertension (%)	73	23	<0.001
Diuretics (%)	50	17	0.013
Diabetes (%)	60	10	<0.001
Oral hypoglycemic agents (%)	50	13	0.005
Hypouricemic agents (%)	17	3	0.19
Severe Obesity (%)	40	30	0.58
Bioimpedance analysis			
FFM (Kg)	52.5 ± 10	52.9 ± 9	0.86
MM (Kg)	50.6 ± 9	50.9 ± 8	0.89
FM (Kg)	38.7 ± 11	36.4 ± 11	0.42
FMV (Kg)	14.8 ± 7	12.7 ± 4	0.15
Blood chemistry tests			
Glucose (mg/dL)	129 ± 39	100 ± 19	0.001
HbA1c (%)	6.3 ± 1.0	5.5 ± 0.6	0.002
Creatinine (mg/dL)	0.87 ± 0.3	0.75 ± 0.1	0.053
Total Cholesterol (mg / dL)	200 ± 41	201 ± 33	0.91
HDL cholesterol (mg / dL)	44 ± 9	52 ± 15	0.020
LDL cholesterol (mg / dL)	126 ± 40	125 ± 33	0.94
Triglycerides (mg / dL)	149 ± 63	116 ± 49	0.028
Uric Acid (mg / dL)	5.6 ± 0.8	5.7 ± 1.1	0.61
AST (IU/L)	23 ± 8	23 ± 7	0.98
ALT (IU/L)	27 ± 12	28 ± 12	0.81
γGT (IU/L)	27 ± 9	22 ± 13	0.13

Data are presented as mean ± SD or prevalence as appropriate. BMI, body mass index; CV, waist circumference; WHR, waist circumference to hips ratio; Severe obesity, obesity ≥ II; FFM, alipidic lean mass; MM, muscle mass, FM, fat mass; FMV, visceral fat mass; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate transaminase; ALT, alanine amino transferase; γGT, gamma glutamyl transpeptidase.

Table 3 shows the changes in anthropometric and clinical parameters of the population after 3 weeks and 4 months of dietary interventions. After 3 weeks of nutritional therapy, individuals treated with the ketogenic diet had greater reductions in body weight, BMI, CV, WHR, FM and FMV than those who followed the Mediterranean diet. The generalized linear model (GLM) indicates that differences in weight, BMI, CV, WHR, FM and FMV persist even after adjustment for the baseline prevalence of arterial hypertension,

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use of diuretics and oral hypoglycemic agents, blood glucose levels, HbA1c, triglycerides and HDL-cholesterol (weight: p <0.001; BMI: p = 0.006; CV: p = 0.003; WHR: p = 0.021; FM: p = 0.001; and FMV: p = 0.041). Furthermore, after 3 weeks there is a statistically significant reduction in muscle mass which is greater in subjects who followed the ketogenic diet compared to the Mediterranean diet (p = 0.009). However, after adjusting for the baseline prevalence of arterial hypertension, use of oral diuretics and hypoglycemic agents, blood glucose levels, HbA1c, triglycerides and HDL-cholesterol, there was no statistically significant difference in the change in muscle mass between the two groups (Metdiet: -0.004 ± 0.7 kg vs Ketodiet -2.1 ± 0.7 kg, p = 0.083; respectively). After 4 months of treatment the results obtained are comparable to those demonstrated after 3 weeks, i.e. a greater reduction in body weight, BMI, CV, WHR, FM and FMV in subjects treated with the ketogenic diet compared to those who followed the Mediterranean diet. (table 3). These results remain statistically different, on GLM analysis, between the two groups even after adjustment for confounding variables (weight: p <0.001; BMI: p <0.001; CV: p <0.001; WHR: p = 0.002; FM: p < 0.001; and FMV: p = 0.010). However, after 4 months there is a statistically significant reduction in lean mass which is greater in subjects who followed the ketogenic diet compared to the Mediterranean diet (p = 0.035). After adjustment there was no statistically significant difference between the two groups on this parameter (Metdiet: 1.6 ± 1.2 kg vs Ketodiet: -1.3 ± 1.2 kg, p = 0.13; respectively). Furthermore, as shown in table 3, after 4 months there is a lower prevalence of severe obesity in subjects treated with the ketogenic diet compared to subjects treated with the Mediterranean diet (33% vs 7%, p = 0.021; respectively). As for the biochemical parameters, after 4 months of treatment, individuals treated with the ketogenic diet have a greater reduction in blood levels of total cholesterol, LDL-cholesterol and uric acid compared to those treated with the Mediterranean diet (table 4). After adjustment for the baseline prevalence of arterial hypertension, use of oral diuretics and hypoglycemic agents, blood glucose levels, HbA1c, triglycerides and HDL-cholesterol, there is still a statistically significant difference in the change in total cholesterol and uric acid between the two groups. (Col-Tot: Metdiet: -10.6 ± 5 mg / dL vs Ketodiet: -26.6 ± 5 mg / dL, p = 0.039; Uric acid: Metdiet: 0.6 ± 0.1 mg / dL vs Ketodiet: -0.7 ± 0.1 mg / dL, p <0.001; respectively). GLM, in relation to the reduction in blood levels of LDL-cholesterol indicates a reduction trend (Metdiet: -10.2 ± 5 mg / dL vs Ketodiet: -24.7 ± 5 mg / dL, p = 0.07; respectively). A very interesting fact is that there is a greater reduction in blood glucose, after adjustment for the baseline values of glycemia, triglycerides, HDL-cholesterol, HbA1c, which is greater in subjects treated with the ketogenic diet than in those treated with the Mediterranean diet. (glycemia: Ketodiet: -15.4 ± 2 mg / dL vs Metdiet: -8.9 ± 2 mg / dL, p = 0.039; respectively). We therefore wanted to analyze the response to the two dietary treatments also on the basis of gender. Between males and females who followed the Mediterranean diet, both after 3 weeks and after 4 months, there were no statistically significant differences in the variation of anthropometric and haematochemical parameters (data not shown). It was found that men who followed the Mediterranean diet compared to women had a greater reduction in WHR after 4 months of treatment (Women -0.005 ± 0.5 vs Men: -0.08 ± 0.8, p = 0.028; respectively). Between males and females who followed the ketogenic diet, both after 3 weeks and after 4 months, there were no statistically significant differences in the variation of anthropometric and blood chemistry parameters (data not shown). It is found, however, that women than men have a greater reduction in BMI after 4 months, and that men have a greater reduction in serum AST levels than women after 4 months of treatment (Women, BMI: - 6.02 ± 2 kg / m2 vs Men, BMI: -3.6 ± 1 kg / m2, p = 0.004; Women, AST: -4.0 ± 4 IU / L vs Men, AST: -6.2 ± 0.8 IU / L, p = 0.019; respectively).

TABLE 3. Change in anthropometric and clinical characteristics of the split cohort based on dietary treatment after 3 weeks and after 4 months.

	3 weeks		**4 months**			
	MetDiet (*n* = 30)	**KetoDiet (*n* = 30)**	**MetDiet (*n* = 30)**	**KetoDiet (*n* = 30)**	***p-value 3 weeks***	***p-value 4 months***
Body weight (Kg)	-3.5 ± 2.4	-9.0 ± 4.6	-5.7 ± 4.0	-15.4 ± 5.3	<0.001	<0.001
BMI (Kg/m^2)	-1.7 ± 2.6	-3.3 ± 1.9	-2.6 ± 3.0	-5.6 ± 2.4	0.009	<0.001
CV (cm)	-2.1 ± 2.2	-8.0 ± 6.9	-4.7 ± 5.2	-16.7 ± 7.7	<0.001	<0.001
WHR	-0.02 ± 0.04	-0.05 ± 0.05	-0.03 ± 0.07	-0.09 ± 0.05	0.005	<0.001
Severe Obesity (%)	33	20	33	7	0.38	0.021
Bioimpedance analysis						
FFM (Kg)	-0.3 ± 2.5	-1.9 ± 3.8	1.9 ± 7.8	-1.6 ± 4.4	0.06	0.035
MM (Kg)	0.3 ± 3.0	-2.4 ± 4.4	1.5 ± 7.9	-0.9 ± 5.8	0.009	0.16
FM (Kg)	-2.3 ± 2.5	-5.7 ± 3.8	-5.1 ± 4.1	-11.0 ± 5.1	<0.001	<0.001
FMV (Kg)	-0.9 ± 1.3	-2.6 ± 2.9	-2.1 ± 1.9	-4.6 ± 3.2	0.004	0.001

Data are presented as mean ± SD or prevalence as appropriate. BMI, body mass index; CV, waist circumference; WHR, waist circumference to hips ratio; Severe obesity, obesity ≥ II; FFM, alipidic lean mass; MM, muscle mass, FM, fat mass; FMV, visceral fat mass.

TABLE 4. Changes in blood chemistry parameters of the split cohort based on dietary treatment after 4 months.

	MetDiet (*n* = 30)	**KetoDiet (*n* = 30)**	*p-value*
Glucose (mg/dL)	-13.3 ± 16.5	-11.0 ± 9.3	0.49
HbA1c (%)	-0.41 ± 0.5	-0.36 ± 0.4	0.69
Creatinine (mg/dL)	-0.08 ± 0.12	-0.05 ± 0.08	0.14
Total Cholesterol (mg / dL)	-9.3 ± 24.9	-27.8 ± 21.8	0.003
HDL cholesterol (mg / dL)	3.3 ± 6.0	3.6 ± 9.8	0.89
LDL cholesterol (mg / dL)	-8.4 ± 26.2	-26.6 ± 23.9	0.007
Triglycerides (mg / dL)	-21.2 ± 28.2	-22.3 ± 36.8	0.89
Uric Acid (mg / dL)	-0.12 ± 0.4	-0.53 ± 0.9	0.025
AST (IU/L)	-2.3 ± 5.1	-4.4 ± 3.7	0.07
ALT (IU/L)	-4.7 ± 8.3	-7.6 ± 9.4	0.20
γGT (IU/L)	-4.1± 8.3	-5.6 ± 9.8	0.52

Data are presented as mean ± SD or prevalence as appropriate. HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate transaminase; ALT, alanine amino transferase; γGT, gamma glutamyl transpeptidase.

IV. Discussions

Over the years, food choices, especially in the most industrialized countries, have drastically changed. We have gone from a food model rich in whole grains, legumes, fruit

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and vegetables, towards a diet characterized by high-calorie food, rich in saturated fats and animal proteins, sugars, processed meats (fast food, junk food, etc. .). Unfortunately, the costs of some healthier foods have increased, just think of fish and some cuts of meat but also fruit and vegetables; so a single-income family with more than two children is not always able to manage expenses. It should be remembered that today life is much more hectic and there are people who do more than one job in a day or who do heavy working hours, so these people don't even have time to cook. Another important fact to emphasize is that people have little time to devote to physical activity. Therefore, we can say that there is a close correlation between the cost of food and the adoption of healthier lifestyles. All these factors should not be underestimated because they are precisely the ones that affect people's health. Just think that the least expensive foods are also the most caloric ones, precisely because they are richer in refined and processed cereals, saturated fats, added sugars, hidden salt. While they offer great palatability, on the other hand they are the ones that further strengthen the poverty / obesity relationship. Several studies affirm that the Mediterranean diet is an effective diet against the onset of chronic diseases but nowadays there are no opportunities to follow the Mediterranean diet in the best possible way (51, 52, 53, 54). Here people will face more chronic diseases, just think of diabetes, metabolic syndrome, dyslipidemias, cancer and many others. Especially in southern Italy, where we should lead by example (given the birth of the Mediterranean diet), epidemiological data underline high prevalence of obesity, diabetes, both in children, adolescents and adults. So, leaving aside drug therapies, from a nutritional point of view, how can we implement strategies to avoid, reduce or delay the onset of these diseases as much as possible? That's why we decided to compare two different diets, the Mediterranean diet and the ketogenic diet. Many studies affirm that the Mediterranean diet is effective but there are still few studies comparing these two diets. So, our goal was to demonstrate how, by comparing these two diets, the anthropometric and metabolic parameters could change. Unfortunately, these data suggest an efficacy in the short / medium term. Our goal for future studies will be to evaluate and demonstrate long-term results and to evaluate whether other studies have compared two types of different diets, and to evaluate whether anthropometric and metabolic parameters had the same changes in the ketogenic diet compared to the Mediterranean diet. We want to emphasize that, in our study, the subjects who followed the ketogenic diet did not lose muscle mass (MM) and lean mass (FFM), they reduced the degree of severe obesity more than the Mediterranean diet, they reduced the levels of Tot-Col and triglycerides and increased HDL-Col levels. Furthermore, the use of meal replacements in the ketogenic diet did not increase uric acid levels (55). In conclusion, from the data demonstrated in our study, we can define the ketogenic diet an excellent strategy, compared to the Mediterranean diet, in reducing the degree of severe obesity, some metabolic parameters and the reduction of body weight in the short / medium term and delay as much as possible, more invasive interventions, such as bariatric surgery. Another fact that should not be underestimated is that ketogenic diets have motivated the subjects more and from these we have observed a better compliance, compared to the Mediterranean diet.

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