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Ketogenic diet and phytoextracts

Comparison of the efficacy of Mediterranean, zone and tisanoreica diet on some health risk factors

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ABSTRACT: The purpose of this work was to test the efficacy of three kind of different diet on some health risk factors. The primary objective of the present study was to examine the effects of diets, amount of carbohydrate intake and use of phytoextracts on weight loss, body composition and related risk factors and on metabolic values as Resting Energy Expenditure (REE) and Respiratory Ratio (RR).We tested 44 subjects randomly assigned to one of 3 groups of diet: Mediterranean (MED), Zone (ZON) and Tisanoreica® i.e. ketogenic diet plus phytoextracts (TIS). Anthropometry, blood chemistry and urine analysis were performed. After 40 days TIS led to a significant average weight and fat loss compared to ZON and MED. Moreover TIS showed a significant reduction in fasting glucose whilst there weren't significant differences in creatinine, uric acid and urea. A significant reduction in the Respiratory Ratio in the TIS group was observed. In conclusion our data shows that the TIS diet, using supplements that mimic the look and taste of carbohydrates and phytoextracts enhance weight reduction, improved lipid profile and mitigate the side effects of ketosis.

KEYWORDS: ketogenic diet, Mediterranean diet, zone diet, phytoextracts, tisanoreica, weight loss.

INTRODUCTION

Obesity is a leading public health problem in the western countries (1) and it is related to high health care costs (2). Obesity, and in particular abdominal obesity, contributes to cardiovascular risk factors such as dyslipidaemia, hypertension and diabetes (3, 4). Although weight loss is a desired objective of many of obese and overweight subjects, and the health benefits of weight loss have been well established (5-8), actually there are no definite data useful in order to ascertain the safeness and usefulness of long-term weight loss eating patterns (9). Dietary strategies supported by the majority of physicians and dieticians, who highlight restriction in fat intake, are associated with only a modest weight loss and a poor long-term compliance (10-12). Obese and overweight subject's compliance to a low-fat and high complex-carbohydrate diet is often a problem because this population has been shown to prefer a high-fat diet. Indeed, these subjects eat highly processed foods, rich in fat and simple sugars (13, 14). Moreover, the recommendation of low fat – high carbohydrate diet may even promote the intake of sugar and highly refined starches, which may lead to obesity and dyslipidaemia, especially among insulin resistant subjects (15). For this reason, in recent years, several dietary strategies have spread promising to be effective weapons in fighting obesity. Among these, to contest the primacy of the classic low-calorie diet, there are the Zone diet and VLCD (Very Low Charbohydrate Diets). The use of low carbohydrate diets (VLCD very low carbohydrate diets) for weight loss, despite their efficacy, has been an area of controversy. In the last years an increase amount of evidence about positive effects on short term weight loss, metabolic profile with regards to insulin sensitivity, glycemic control and serum lipid values has accumulated (10, 13-16). There are conflicting hypothesis about the mechanism of action of VLCD. Some authors suggests that there are no metabolic advantage of low carbohydrate diets. Suggesting that Weight loss results from decreased caloric consumption, likely due to the greater satiation effects of higher protein intake (16).

Zone diet was invented by B. Sears and popularized by the book "Zone diet" (17) and has become a popular food strategies used among those who want to lose weight and among athletes. Despite its popularity some severe concerns has been done by scientific community (18-22) and there is no evidence that the particular "structure" of the "Zone diet" could lead to further advantages compared to LC (low carbohydrate) and HF (high fat) diets (23). In recent years, Dansinger (24) compared different kinds of diets, like Atkins, Ornish, Weight Watchers and Zone but he did not find differences in weight loss between the different diets, while the weight loss was related to the adherence to dietetic treatment. Adherence to dietary treatment has demonstrated itself to be the limiting factor in the effectiveness of VLCD. Thus, the challenge is the developing of a palatable diet with low refined sugar and starches capable to generate enough satiety in order to tolerate a decreased amount of carbohydrates. So, over the past few years, there has been an increase of interest in the role of VLCD on weight loss (25) and their effects on metabolism. Some data have shown that a ketogenic diet produces a less efficient metabolic effect than a high fat non-ketogenic diet (26). So, it's improper the expression "a

calorie is a calorie"; in ketogenic conditions, the metabolic rate per calorie is effectively increased (25). Although several recent trials compared VLCD vs. traditional low fat, high carbohydrate weight loss diets (10, 13-15, 25), data suggest that VLCD were at least as effective as low fat high carbohydrate diets in the induction of weight loss for up to 1 year (27). However, most of these trials were limited by a combination of small sample size, high rates of dropout, or limited diet assessment. There is a little amount of data about VLCD with food substitutes and there are no researches about weight loss in ketogenic diet with the help of phytoextracts. The primary objective of the present study was to examine the effects of diets, amount of carbohydrate intake and use of phytoextracts on weight loss, body composition and related risk factors and on metabolic values as resting energy expenditure (REE) and respiratory exchange ratio (RR).

Subjects

Through email advertisements, 60 healthy overweight or obese volunteers were recruited (Table 1). Inclusion criteria were: age between 25 and 65 years, BMI >25, the desire to lose weight and the absence of serious diseases. Exclusion criteria were the use of drugs in the previous 2 months, pregnancy, lactation, existing weight-loss diet, assumption of drugs for weight loss in the previous 5 months, and presence of ketonuria. The subjects were interviewed on their ability to follow a low caloric diet. Eight subjects dropped out before randomization, and 8 during the study: a total of 44 subjects completed the trial(BMI: MED mean 29.81 ±2.88, min 27.55, max 35.91; ZON mean 29.87 ±3.3, min 25.22, max 35.91; TIS mean 29.87 ±3.54, min 25.78, max 36.42). Protocol, potential risks, and benefits were widely explained and a written informed consent to participate in the study was signed by all participants. The ethics committee of the Department of Human Anatomy and Physiology of the University of Padua approved the study.

Intervention

We considered three kinds of diets: Mediterranean diet (MED – 65 percent CHO, 15 percent PRO, 30 percent FAT), zone diet (ZON – 30 percent PRO, 40 percent CHO, 30 percent FAT) and Tisanoreica diet® (TIS). Subjects were randomly assigned to one of the 3 groups of diet. There were no significant differences in the amount of calories and fibres related to a different approach to the diet between the three groups. All participants completed the recall of the previous 24 hours and the 7-days diary of eaten foods. The participants were informed how to record food intake. The diaries were collected at each visit in the course of the study, in order to analyse the food intake. Successively a prescriptive, fixed-menu plan was given to all participants together with explanations of the different kinds of diets. For all diets the total daily caloric intake was divided into 5 meals.

Mediterranean diet (MED)

The Mediterranean Diet was prescribed using the guidelines based upon a large number of scientific researches spanning more than 25 years (28). The dietary plans was built to achieve a dietary macronutrient distribution of approximately 55 percent of energy derived from carbohydrate, 15 percent from protein and 30 percent from fat during the day (Table 2).

Zone diet (ZON)

Zone diet was calculated applying the methodology described by Sears in the book "The Zone" (10) The Zone Diet (ZON) comprises of 40 percent energy from carbohydrates, 30 percent from protein and 30 percent from fat and advocates only slight use of grains and starches (Table 2). The precise 0.75 protein to carbohydrate ratio required with each meal is suggested to reduce the insulin to glucagon ratio, which is supposed to affect eicosanoid metabolism and ultimately produces a cascade of biological events. Zone theory suggest that this dietary manipulation leading to a reduction in chronic disease risk, enhanced immunity, maximal physical and mental performance, increased longevity and permanent weight loss.

Tisanoreica diet® (TIS)

Tisanoreica diet® is a ketogenic diet with the support of phytoestracts.

The TIS diet was ketogenic in the first 20 days with less than 30g of CHO daily, using a low carbohydrates high-protein dishes and herbal teas (Table 1 and 2). At the time of the first visit a detailed menu containing permitted and not permitted foods was provided to each participant. Briefly, it was explained that during the first three weeks it was necessary to totally exclude carbohydrates and a detailed menu containing permitted and not permitted foods was provided to each participant.

The allowed foods were: cooked or raw green vegetables (200g/meal), meat, fish and eggs (2 times/day), olive oil 5 g/day. Integration with a dish composed of high quality proteins and zero carbohydrates that mimics the taste of carbohydrates (PAT®) equivalent to 18 grams of protein, was provided for every meal, for a maximum of four per day. During the last three weeks there was the introduction of complex carbohydrates (50-80g/day), cheese (100g/day), and the reduction of PAT (from four to two), while the other indications remained unchanged. The distribution of

nutrients (proteins, carbohydrates and fats) in terms of percentage of total caloric intake was 36, 12 and 52 percent, respectively (weeks 1 to 3) and 31, 25 and 44 percent (weeks 4 to 6). During the 6 weeks, the patients in the TIS group took 20ml of extract A, 20ml of extract B and 50ml of extract C (Table 3). In the first three weeks, before breakfast and lunch they also took 40ml of extract D (Table 3).

Characteristics	MED group Mean (SD)	ZON group Mean (SD)	TIS group Mean (SD)
Age, years	35.29 (±7.43)	41.14 (±6.96)	41.44 (±8.03)
Gender, n	Female, 8 Male, 5	Female, 8 Male, 7	Female, 10 (59) Male, 7
BMI	29.81 (±2.88)	29.87 (±3.3)	29.87 (±3.54)

Table 1. General characteristics of subjects recruited in the three groups: Mediterranean (MED), Zone (ZON) and Tisanoreica (TIS) diet.

	MED	ZON	TIS Week 1-3	TIS Week 4-6
Energy Kcal	**1175**	**1138**	**1098**	**1186**
Protein, g/day (% daily Energy)	45(14)	85 (30)	99 (36)	91 (31)
Carbohydrate, g/day (% daily Energy)	170 (53)	114 (40)	34 (12)	74 (25)
Fat, g/day (% daily Energy)	35 (25)	38 (30)	63 (52)	58 (44)
			Mean Kcal/die of the two phases of TIS	
			1138	

Table 2. Diet composition in Mediterranean (MED), Zone (ZON) and Tisanoreica (TIS) diet.

Plant extracts	Week 1-2	Week 3-5	Composition
Extracts A, ml/day	20	20	Durvillea antarctica, black radish, mint, liquorice, artichoke, horsetail, burdock, dandelion, rhubarb, gentian, lemon balm, chinaroot, juniper, spear grass, elder, fucus, anise, parsley, bearberry, horehound
Extracts B, ml/day	20	20	Serenoa, Red clover, Chervil, Bean, Elder, Dandelion, Uncaria, Equisetum, Horehound, Rosemary
Extracts C, ml/day	50	50	Horsetail, asparagus, birch, cypress, couch grass, corn, dandelion, grape, fennel, elder, rosehip, anise
Extracts D, ml/day	40	0	Eleuthero, eurycoma longifolia, ginseng, corn, miura puama, grape, guaranà, arabic coffee, ginger

Table 3. Plant extracts in TIS group.

Measurements

We weighted the subjects every 20 days, after an overnight fast. The height was measured with a stadiometer and BMI was calculated. Before and after the training period, percentage of body fat was assessed by skinfold measurement using Fitnext® (GSA-Tea, Caldogno; Vicenza, Italy) software that utilises 9 skinfolds (triceps, biceps, pectoral, subarmpit, subscapulare, iliocristale, mid-abdominal, anterior thigh, medial calf), 6 bone circumferences (arm, forearm, waist, hip, thigh, calf), 4 bone diameters (elbow, wrist, knee, ankle), and waistline measurement (29).

It was used Bioelectrical impedance (Soft Tissue Analyser® of Akern Bioresearch, Pontassieve, FI, Italy) was used to obtain a better definition of the body composition in order to analyse how the diet-related body fluids loss influenced the total weight loss. BIA for calculating total body water has a high accuracy with a mean bias of 0.5 (30).

Biochemical analyses (glucose, triglycerides, uric acid, cholesterol, urea, transaminases, creatinine, electrolytes) were performed on an empty stomach at the baseline, at 20th and 40th day, taking cubital blood test strips immediately examined by a Reflotron® Roche (Roche Diagnostics, Basel, Switzerland) analyser (31-33). This analysys shows a high overall between-laboratory precision (32) with a day-to-day mean imprecision with the control materials of of 4.4 percent (33).

The urinalysis was performed at baseline, 10, 20, 30 and 40 days from the beginning, after an overnight fast, in the midstream, with the use of chromatic reagents through the Combur Test® Roche (Roche Diagnostics, Basel, Switzerland) (34). The total repeatability of this system is between 98 and 100 percent (34). Specific weight, pH, leukocytes, nitrite, protein, glucose, ketone bodies, urobilinogen, birilubina, blood were analysed. The analysis does not provide exact values but a reference range. Despite these limits, this qualitative analysis was chosen for its simplicity to of use and for the possibility to enable subjects to perform the test at home.

The energy expenditure (REE) was analyzed by oxygen consumption (VO_2) and respiratory ratio (RR) with ergospirometer Ergocard® (Pacific Medical Systems, Hong Kong, S.A.R), a "pitot tube" pneumotacograph. Basal Respiratory Ratio and Energy Expenditur was made between 7am and 8am after an overnight fast. The subjects were placed in supine position in a well-ventilated quiet room with dim lights, a temperature around 24°C and after a 30 minutes period of rest RR and REE were measured for 30 minutes.

Nutritional characteristics (amount of energy, carbohydrates, fats, protein and fibres) of diets were analyzed using the crude mean.

Statistics

The dietary intake differences between groups were tested through the analysis of variance (ANOVA). For body weight and other secondary measures, analysis was performed using all points and all diets and was tested for interaction between diet groups and time in a mixed model using a covariance structure. Triglycerides were transformed with logarithms to obtain a normal distribution. For these data, the representations in the table and figures are rough and not processed in order to make them easier to interpret. From the beginning, the differences between diets were designed for ANOVA. If an interaction was found, a post hoc Tukey test between the differences was performed. The significance has been placed at $p<0.05$. All the data are presented as mean ± standard deviation (SD).

RESULTS

Regarding the weight reduction, the TIS group experienced a significant decrease (8.08 Kg: from 89.3 ± 13.8 Kg to 81.3 ± 12.5 Kg), compared with ZON group (4.5 Kg: from 84.2 ± Kg 11.9 to 79.7 ± 10.9 Kg) and MED group (3.5 Kg: from 85.2 ± 9.6 Kg to 81.7 ± 9.5 Kg) meaning in percentage terms MED – 4.07 percent, ZON -5.31 percent, TIS – 9.07 with a significant difference of TIS vs. MED ($P<0.005$) and TIS vs. ZONE ($p<0.05$).

Concerning the fat there was a reduction of 5.5 Kg (from 22 ± 6.9 Kg to 16.5 ± 5.9 Kg) in the TIS group, of 2.3 kg (from 21.5 ± 10.6 Kg to 19.2 ± 9.7 Kg) in the ZON group and 2.1 Kg (from 23.7 ± 6.3 Kg to 21.6 ± 6 Kg) in the MED group, with a significant difference of TIS vs. ZON and MED ($p<0,05$).
Changes in lean body mass did not differ in a statistically significant manner, although there is a tendency of the ZON group to maintain more muscle mass. The BIA data present a significant ($p<0.05$) reduction in total body water (TBW) in the TIS group respect to MED and ZON groups. Concerning the biochemistry, a significant reduction ($p<0.05$) in fasting blood glucose was found in the TIS group compared to the MED group from 103.6 ± 19.5 mg/dl to 89.1 ± 8,3 mg/dl in the TIS; from 103.9 ± 11.1 mg/dl to 104.1 ± 17.5 mg/dl in MED. There were no significant changes in blood parameters of liver function (ALT, GGT). There was a significant increase and difference in HDL cholesterol ($p<0.05$) between TIS and ZON and between TIS and MED (TIS from 32.9 ± 10.9 mg/dl to 38.4 ± 12.4 mg/dl; ZONE from 31.9 ± 9.2 mg/dl to 33 ± 8.3 mg/dl; MED from 33.9 ± 11.1 mg/dl to 34.1 ± 17.5 mg/dl) (Figures 1 and 2). Triglycerides (TG) also showed a significant reduction ($p<0.05$) in the TIS group compared to MED and ZON: TIS from 108.2 ± 20.9 mg/dl to 85.2 ± 10.5 mg/dl, MED from 120 ± mg/dl to 125 ± mg/dl, ZON from 124.2 ± mg/dl to 122.6 ± mg/dl. There are no changes in transaminases, uric acid, creatinine, electrolytes in blood. Differences in CK, UA and urea were not significant. Urine tests did not show any significant change in specific weight, pH, leucocytes, nitrite, protein, glucose, ketone bodies, urobilinogen, bilirubin, blood. We only observed an increase in the ketonemia of the TIS group the tenth day that normalized to the twentieth day. There was a high significant reduction ($p<0.005$) in RR in the TIS group compared to the MED (TIS from 0.88 ± 0.02 to 0.83 ± 0.016; MED from 0.89 ± 0.022 to 0.88 ± 0.02) while the REE was super imposable with no significant differences between groups and before and after the experimental period (MED 3,3 ml/Kg/min; ZON 3,5 ml/Kg/min; TIS 3,3 ml/Kg/min). Regarding the compliance is notable that only 1 subjects withdrawal during the experiment in TIS group whilst 2 in ZON and 5 in MED. None of subjects performing the TIS diet reported the typical syntom of ketogenic diets as halitosis, numea and constipation.

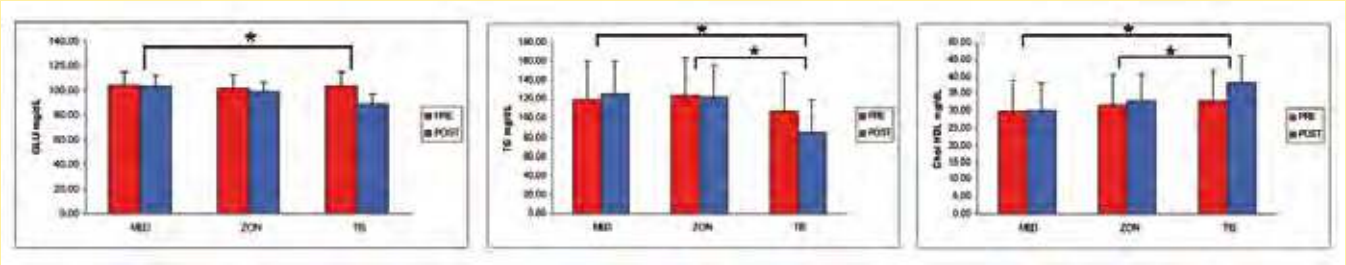

Figure 1. Variations of Body weight and Body fat pre vs post treatment between Mediterranean (MED), Zone (ZON) and Tisanoreica (TIS) diet.
* = P<0.05; ** = P< 0.005

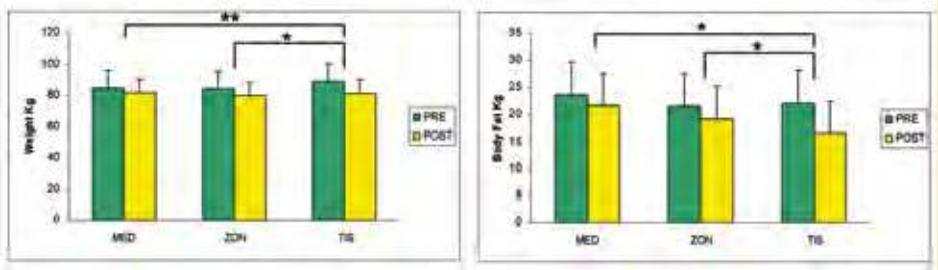

Figure 2. Variations of Blood Glucose (GLU), Blood HDL Cholesterol (HDL) and Tryglicerides (TG) values pre vs post treatment between Mediterranean (MED), Zone (ZON) and Tisanoreica (TIS) diet.
* = P<0.05; ** = P< 0.005

DISCUSSION

The efficacy of ketogenic diet on the reduction of fat mass and on the improvement of some blood chemistry parameters is well known (23, 27, 35-37). Doubts that this diet can somehow create a potential risk to the liver and kidneys have been questioned in recent years (38, 39). There is the tendency to consider as high-protein diet as ketogenic diet. Instead, on the bases of the increased demand for amino acids for the neoglucogenesis it is to be considered substantially normoproteic and hypoglucidic. The lack of such an approach to food is based on its immediate effect even if some authors raised doubts regarding the effectiveness in the long term. Some authors actually suggest that LCD is at least effective as low fat diets (40, 41), but there are some evidences that LCD may be more effective in fat loss mostly in the short periods and, more important, may act as a "booster" for the metabolism (42, 43). Moreover Shai et al. (44) shows that, almost during the ketogenic period (10 months) the VLCD was more effectiveness on weight loss than low fat and Mediterranean diet. Actually the effectiveness of low carbohydrate diet is maintained even after a 12 months period, although the efficiency decreases (9). The low compliance often caused by some side effects such as constipation and bad breath is one of the problems of this diet. This fact could partially explain the difficulty to maintain the obtained results (44).
In this study, in addition to comparing the effect of the three types of diets on metabolic parameters, blood chemistry and anthropology, we also set the objective to verify the effect of integration with some products (herbal and proteic) that allow the intake of needed proteins without feeling deprived of carbohydrates.
The use of low carbohydrates high-protein foods that imitate the palatability and appearance of carbohydrates and the use of herbal products that reduce the side effects of ketosis in order to accelerate and enable the full use of ketone bodies may explain the increased compliance of the TIS compared to other types of diets and also with classical ketogenic diet. Although an increased fluid loss induced by the exhaustion of stocks of glycogen could explain the greater weight reduction compared to fat reduction in the TIS group, the values of the weight decrease still remain highly significant mainly due to the reduction of fat both as absolute (kg) and relative (percent) values as confirmed by several other studies (45-48). This data are highly significant also considering the substantially equivalence in term of caloric input in the three diets, MED 1175 Kcal/die, ZON 1138 Kcal/die, TIS (mean) 1138 Kcal/die).

These results confirm the influences of the thermic effect of nutrition on metabolism (49, 50). Moreover the present study confirms the findings of other researchers about blood chemistry profiles i.e. a significant reduction in ketogenic diet of triglycerides and an improvement of HDL serum cholesterol, due to an increased activity of lipase and lipid catabolic pathways of insulin, following the introduction of foods with low or no carbohydrates (22). The reduction in lean body mass and muscle didn't present significant differences between the three diets. The renal function and the blood values remained unaltered, except those already mentioned among the significant results. The raise of urinary ketone values is a common result in the ketogenic diets while its lowering after 20 days may suggest that the herbal products improved the use of peripheral ketone bodies with a reduction of urinary excretion. It's possible that a better utilization of ketone bodies by peripheral tissues, muscle, brain and kidneys led to a reduction in their amount in the urine. As directly mentioned by subjects, the side effects of ketosis, like nausea, vomiting, headache, bad breath and constipation, were lightened with the help of phytoextracts, acting to improve the functions of excretory organs. Acidosis and other side effects caused by ketone bodies was thwarted by alanine and glutamine contained in PATE®, which, when oxidized, produce ammonium ions, or bases capable of buffering acidosis. The absence of modification in the liver function tests (ALT, GGT) confirmed the safety of the diet at least in the short-medium term. Moreover, it's to consider the fact that the protein intake is not high in relation to amino acid requirements for neoglucogenesis.

CONCLUSION

This study confirms the efficacy of the ketogenic diet on the reduction of fat mass and on the improvement of the lipid profile and the substantial safety in terms of liver and kidney parameters. Furthermore, it shows that the high-protein dishes help to improve the patient compliance, through a better appearance and taste of carbohydrates. Moreover, the use of phytoextracts is helpful in the reduction of side effects such as halitosis, nausea and constipation, frequently the real causes of dropout of subjects. Within the various types of ketogenic diet (from Atkins to South Beach), where the world's literature seems to confirm the effectiveness in the treatment of many diseases and conditions (Alzheimer, epilepsy, overweight, hypetriglicеridemia, hypercholesterolemia, impaired fasting glucose) the union of a ketogenic diet using meal protein and phytoextracts for a short period of time seems to allow the achievement of good results by reducing the side effects and increasing compliance. In order to confirm these encouraging data, considering the short period of our trial, longer studies on larger population samples are needed.

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