

# Very-low-calorie ketogenic diet with aminoacid supplement versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study

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**Abstract.** – **OBJECTIVE:** Obesity plays a relevant pathophysiological role in the development of health problems, arising as result of complex interaction of genetic, nutritional and metabolic factors. We conducted a dietary intervention case-control randomized trial, to compare the effectiveness on body composition of two nutritional protocols: a very-low-carbohydrate ketogenic diet (VLCKD), integrated by an aminoacid supplement with whey protein, and very low restricted-calorie diet (VLCD).

**PATIENTS AND METHODS:** The clinical study was conducted with a randomized case-control in which twenty-five healthy subjects gave informed consent to participate in the interventional study and were evaluated for their health and nutritional status, by anthropometric, and body composition evaluation.

**RESULTS:** The results of this pilot study show that a diet low in carbohydrates, associated with a decreased caloric intake, is effective in weight loss. After VLCKD, versus VLCD, no significant differences in body lean of the trunk, body lean distribution (android and gynoid), total body lean were observed ( $p > 0.05$ ). After VLCKD, no increasing of sarcopenia frequency, according ASSMI, was observed.

**DISCUSSION:** Many studies have shown the effectiveness of the ketogenic diet on weight loss; even if not know how to work effectively, as some researchers believe that the weight loss is due to reduced calorie intake, satiety could also be induced by the effect of the proteins, rather than the low-carbohydrates.

**CONCLUSIONS:** Our pilot study showed that a VLCKD was highly effective in terms of body weight reduction without to induce lean body mass loss, preventing the risk of sarcopenia. Further clinical trials are needed on a larger population and long-term body weight maintenance and risk factors management effects of VLCKD. There is no doubt, however, that a proper dietary approach would impact significantly on the reduction of public expenditure costs, in view of prospective data on increasing the percentage of obese people in our nation.

Key Words:

Obesity, Ketogenic diet, Low carbohydrate diet, Body weight, Sarcopenia.

## Introduction

Obesity is defined by the World Health Organization (WHO) as "a condition in which percentage body fat (PBF) is increased to an extent in which health and well-being are impaired". Due to the alarming incidence and prevalence increase, it has been declared as a "global epidemic"<sup>1</sup>. Obesity can be considered mainly as a multifactorial disease dependent on environmental factors, such as diet and poor physical activity, genetic and metabolic factors<sup>2</sup>.

A cross-talk between skeletal muscle and adipose tissue has been proposed and linked with the control of body weight, both fat stores and muscle mass. Sarcopenia has profound physiologic and clinical consequences, including but not limited to impaired protein turnover, mobility loss, osteoporosis, increased fracture risk, dyslipidemia, insulin resistance, overall frailty, and increased mortality. The combination of sarcopenia and obesity, defined as sarcopenic obesity, is an important public health problem that induces fragility in the elderly, and it is associated with functional limitations and increased mortality<sup>3,4</sup>.

The effects of diet on metabolic pathways related diabetes, cardiovascular diseases, and other chronic non-communicable diseases (CNCD) is currently under investigation.

Obesity, cardiovascular diseases, diabetes mellitus, chronic kidney disease, osteoporosis, sarcopenia, Alzheimer's disease, and many cancers can be grouped as non-transmissible CNCD.

A therapeutic life style changes for health status and wellbeing, that included dietary habitus and physical activity, represent an important approach to prevent and treat the metabolic imbalance.

According to the position of the Academy of Nutrition and Dietetics, the successful treatment of obesity requires adoption and maintenance of therapeutic life style changes, in terms of dietary intake and physical activity<sup>5</sup>.

The primary determinant of weight loss is energy deficit. The physician with a patient in the condition of insulin resistance, metabolic inflexibility and inflammation, must be able to choose between several options of diet therapy.

The best diet for losing weight and maintaining good health is the Mediterranean diet<sup>6,7</sup>. However, in the strategy of weight loss there are several dietary approaches available, divided between low calories diet (LCD, 800 kcal day<sup>-1</sup>) and very low-calorie diets (VLCDs, < 800 kcal day<sup>-1</sup>)<sup>8</sup>. Moreover, the choice of the physician should be based on the effectiveness of the loss of fat mass and the patient safety during dietary intervention.

VLCDs are generally used as part of a comprehensive intervention that includes medical monitoring and a program of lifestyle modification, and they are considered safe and effective when used by appropriately selected individuals under careful medical supervision<sup>9</sup>.

As it is important to preserve lean body mass, VLCD is based on 70 to 100 g/day of protein or 0.8 to 1.5 g protein/kg of ideal body weight<sup>10</sup>.

Moreover, VLCDs includes the very-low-carbohydrate diet (VLCKD) can lead to a state of ketosis, in which the concentration of blood ketones (acetoacetate, 3- $\beta$ -hydroxybutyrate, and acetone) increases due to increased fatty acid breakdown and activity of ketogenic enzymes.

It has been demonstrated that a very low-calorie ketogenic diet (VLCKD) was more effective than Mediterranean Diet in significantly decreasing carbon dioxide body stores, which may theoretically be beneficial for patients with increased carbon dioxide arterial partial pressure due to respiratory insufficiency or failure<sup>10</sup>. However, VLCDs are considered to be appropriate only for those patients with a body mass index<sup>11</sup> (BMI) >30 kg/h<sup>2</sup>, that are at risk of cardio-metabolic diseases, needing a sudden weight loss. As the adipose tissue and skeletal muscle have a role in lipid and glucose metabolism, due to the large number of bioactive proteins, secreted by those tissue and related to some cardiovascular risk factors, limitation would be based only on weight and BMI, without taking into account the body composition, in terms of ratio between body fat and body lean, because it is an increase in morbidity and mortality related to the percentage of adiposity<sup>12</sup>. Since it is possible to identify obese subjects based on the amount of fat mass also in the classes of normal and overweight according to the BMI<sup>13</sup>, it seems important to use the percentage of body fat (PBF) for the diagnosis of obesity, and to choose a personalized dietary intervention with the aim of reducing total fat body mass (TBFat), while preserving lean body mass (TBLean).

As the role of VLCKD in the lean body mass preservation is not well established, we conducted a dietary intervention case-control randomized trial, to compare the effectiveness on body composition of two nutritional protocols: a VLCKD, in which 50% of protein intake is integrated by an aminoacid supplement, and VLCD.

We have assumed that VLCKD can better preserve lean body mass during weight loss, saving from diet-induced sarcopenia.

Given the clinical significance of sarcopenia and obesity, as well as their close relationship in terms of body composition, we comprehensively analyzed TBFat, TBLean, and anthropometric parameters in obese patients after weight loss.

## Patients and Methods

### *Clinical Study Design*

The clinical study was conducted with a randomized case-control design between October 2015 to November 2015.

The study started at T0 with the enrollment of thirty obese subjects, consecutively recruited within a program of routine medical check-up at the Section of Clinical Nutrition and Nutrigenomic, at the University of Rome “Tor Vergata”, and at “Nuova Annunziata” Clinic, Rome, Italy.

Twenty-five healthy subjects gave informed consent to participate in the interventional study, which was performed. All the subjects were evaluated for their health and nutritional status, by anthropometric, and body composition evaluation.

Subjects eligible for the study met the following inclusion criteria: age between 18 and 65 years, with a BMI  $\geq 25$  kg/m<sup>2</sup>, percentage of body fat (PBF)  $\geq 25$  for male, and  $\geq 30$  for female.

Exclusion criteria were as follows: pregnancy, breast-feeding, type 1 diabetes, heart failure, endocrine disorders, liver, kidney, autoimmune, viral chronic (hepatitis C, B, HIV), and neoplastic disease; serum creatinine level of 2 mg per deciliter (177  $\mu$ mol per liter) or more, liver dysfunction (an increase by a factor of at least 2 above the upper limit of normal in GOT and GPT), corticosteroid and chronic inflammatory therapy; participating in another diet trial.

Subjects, who were eligible for the study, were randomly (R) divided into two groups (X and Y).

The group X received the VLCKD, and the group Y received the VLCD.

The study was conducted in double-blind.

It was asked to the subjects not to change their lifestyle habits. Any adverse effect has been properly signed.

The participants received no financial compensation or gifts. Each participant provided written informed consent.

Analysis were performed at the Section of Clinical Nutrition and Nutrigenomic, Department of Biomedicine and Prevention of the University of Rome “Tor Vergata”.

### *Anthropometric Measurements*

At T1, after a 12-hour overnight fast, all subjects underwent anthropometric evaluation. Anthropometric measurements for all participants according to standard method were carried out<sup>14</sup>. All the individuals were instructed to take off their clothes and shoes before undergoing the measurements.

Waist and hip circumferences were taken using a flexible steel metric tape to the nearest 0.5 cm. Hip circumference was measured according to International Society for the Advancement of Kin anthropometry protocol taken at the greatest posterior protuberance of the buttocks. Waist circumference was measured just above the iliac crest as recommended in the National Institute of Health Guidelines Body weight (kg)<sup>15</sup> was measured to the nearest 0.1 kg, using a balance scale (Invernizzi, Rome, Italy). Height (m) was measured using a stadiometer to the nearest 0.1 cm (Invernizzi, Rome, Italy). BMI was calculated using the formula: BMI = body weight / height<sup>2</sup> (kg/m<sup>2</sup>).

### *Dual X-ray Absorptiometry (DXA)*

To assess body composition analysis, that gives the possibility to measure total body fat (TBFat) and total body lean (TBLean), DXA (i-DXA, GE Medical Systems, Milwaukee, WI, USA) evaluation was performed at baseline<sup>16</sup>.

The technique combined a total body scanner, an X-ray source, an internal wheel to calibrate the bone mineral compartment, and an external lucite/aluminum phantom to calibrate soft mass. Calibration and verification of the reproducibility of the data were daily performed. The subjects have received instructions before attending to the medical views. Individuals were asked to remove all clothing except for undergarments including shoes, socks and metal items prior to begin DXA examination in the supine position, with the scan from the head and moving in a rectilinear pattern down the body to the feet. The average measurement time was 20 min. The effective radiation dose from this procedure is about 0.01 mSv. The coefficient of variation (coefficient of variation = 100 x SD/mean) intra and inter subjects ranged from 1% to 5%. The coefficient of variation for bone measurements is less than 1%; coefficient of variation on this instrument for five subjects scanned six times over a nine months period were 2.2% for total body fat (TBFat), and 1.1% for total body lean (TBLean).

Total body fat percentage (PBF) was calculated as TBFat mass divided by total mass of all tissues, considering also the total body bone (TBBone), as the follow:  $PBF = (TBFat + TBLean + TBBone) \times 100$ .

Appendicular Skeletal Muscle Mass Index (ASMMI) = (Legs Muscle Mass (kg) + Arms Muscle Mass (kg))/Height (m<sup>2</sup>) (Men < 7.59 kg/m<sup>2</sup>, Women < 5.47 kg/m<sup>2</sup>).

### Dietary Treatment

The very-low-carbohydrate ketogenic diet (VLCKD) aimed at an energy intake of 450-500 kcal per day for female and 650-700 kcal per day for male, with 35-40% of calories from fat, < 10% of calories from saturated fat, 5% of calories from carbohydrates (< 6 g), and 55-60% of calories from protein, corresponding to 1.2 g (female) or 1.5 g (male) / kg of body weight, and an intake of 25 mg of fiber per day. The half of the amount of daily protein was reached using amino-acid supplement, called Amin 21K (Italfarmacia, Rome, Italy). The correct administration of diet was evaluated by urinary keto-stick. The powder of aminoacid was dissolved in water and drunk at the breakfast and lunch or dinner.

The very low restricted-calorie diet (VLCD) aimed at an energy intake of 450-500 kcal per day for female and 650-700 kcal per day for male, with 35-40% of calories from fat, < 10% of calories from saturated fat, 15-20% of calories from carbohydrates (< 20 g (female) or < 30 g (male)), and 45-50% of calories from protein, corresponding to 0.9 g (female) or 1.1 g (male) / kg of body weight, and an intake of 25 mg of fiber per day.

In all cases, a capsule of multivitamin, proper integration of mineral salts and an alkalizing product were prescribed. The correct administration of diet was evaluated by urinary keto-stick.

### Statistical Analysis

A paired *t*-test or a non-parametric Wilcoxon test were performed to evaluate differences at baseline and after nutritional intervention.

The differences between parameter at baseline and after diet were calculated as the follow:  $\Delta\% = [(Z-W)/W] \times 100$ , where  $\Delta\%$  is the percentage variation of each parameter, calculated as ratio of absolute variation to the base value.

In all statistical tests performed, the null hypothesis (no effect) was rejected at the 0.05 level of probability.

### Results

Of the 25 subjects enrolled, four of them did not meet the inclusion criteria; therefore, 21 participants were resulted eligible for the study. Three subjects declined to participate after one week, so eighteen patients completed the study, with a mean age of  $47.54 \pm 14.38$  years. The mean age of X group was  $45.40 \pm 16.39$ , of the Y group was  $49.33 \pm 13.78$  ( $p = 0.68$ ). The population was represented by the 72.72% of female and 27.28% of male.

At baseline (T0), the mean of BMI was  $33.69 \pm 3.51$  kg/m<sup>2</sup>. According to BMI, the 54.54% of the population was overweight, the 45.46% was obese. In the X group the 80% was obese. In the Y group the 16.67% was obese.

All the subjects were obese according to PBF estimated by DXA (> 30% for female, > 25% for male).

The characteristics of the participants at baseline (T0) after 3 weeks of each dietary treatment (T1) are shown in Table I (VLCKD) and Table II (VLCD).

**Table I.** Comparison between the body composition before and after administration of very-low-carbohydrate ketogenic diet for 3 weeks.

n = 9	Baseline (T0) media (SD)	After 3 weeks of VLKD (T1) media (SD)	p
Weight (kg) <sup>a</sup>	99.78 (4.57)	92.80 (4.78)	0.00*
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	33.69 (3.51)	31.36 (3.59)	0.00*
Waist circumference (cm) <sup>a</sup>	103.90 (5.98)	98.40 (5.91)	0.00*
Abdomen circumference (cm) <sup>a</sup>	111.82 (5.42)	108.20 (6.73)	0.03*
hip circumference (cm) <sup>a</sup>	114.30 (6.42)	111.30 (7.73)	0.01*
Trunk Body Fat (kg) <sup>a</sup>	20.37 (5.59)	19.78 (4.99)	0.59
Trunk Body Lean (kg) <sup>a</sup>	25.06 (5.55)	26.23 (4.74)	0.69
Android Body Fat (kg) <sup>a</sup>	3.3046 (1.11)	3.2078 (0.92)	0.76
Android Body Lean (kg) <sup>a</sup>	3.75 (1.09)	3.92 (0.61)	0.75
Gynoid Body Fat (kg) <sup>a</sup>	6.01 (1.50)	5.70 (1.10)	0.30
Gynoid Body Lean (kg) <sup>a</sup>	8.06 (2.18)	8.59 (1.81)	0.67
Total Body Fat (kg) <sup>a</sup>	37.24 (9.31)	34.79 (9.38)	0.02*
Total Body Lean (kg) <sup>a</sup>	53.01 (12.86)	54.93 (8.96)	0.75
Percentage Body Fat (%) <sup>a</sup>	40.30 (8.25)	37.52 (9.63)	0.30

Paired *t*-test <sup>a</sup> or a non-parametric Wilcoxon test<sup>b</sup>.

**Table II.** Comparison between the body composition before and after administration of very low restricted-calorie diet for 3 weeks.

n = 9	Baseline (T0) media (SD)	After 3 weeks of VLKD (T1) media (SD)	p
Weight (kg) <sup>a</sup>	74.77 (5.04)	68.80 (4.24)	0.00*
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	29.21 (1.07)	26.90 (1.34)	0.00
Waist circumference (cm) <sup>b</sup>	84.72 (2.73)	83.75 (7.05)	0.34
Abdomen circumference (cm) <sup>a</sup>	99.92 (3.18)	96.67 (3.34)	0.02*
Hip circumference (cm) <sup>a</sup>	109.42 (3.61)	105.98 (2.61)	0.00*
Trunk Body Fat (kg) <sup>b</sup>	16.20 (1.86)	15.32 (2.11)	0.1
Trunk Body Lean (kg) <sup>b</sup>	18.32 (1.09)	16.98 (1.25)	0.03*
Android Body Fat (kg) <sup>a</sup>	2.76 (0.41)	2.39 (0.45)	0.00*
Android Body Lean (kg) <sup>a</sup>	2.70 (0.21)	2.38 (0.20)	0.00
Gynoid Body Fat (kg) <sup>b</sup>	6.71 (2.05)	5.42 (0.64)	0.03*
Gynoid Body Lean (kg) <sup>a</sup>	5.85 (0.57)	5.53 (0.46)	0.04*
Total Body Fat (kg) <sup>a</sup>	33.06 (3.60)	30.59 (3.65)	0.00*
Total Body Lean (kg) <sup>a</sup>	39.00 (3.03)	35.70 (3.09)	0.00*
Percentage Body Fat (%) <sup>a</sup>	44.37 (3.35)	44.53 (4.14)	0.74

Paired *t*-test <sup>a</sup> or a non-parametric Wilcoxon test<sup>b</sup>.

After 3 weeks of diet (T1), according to BMI, the 72.72% of the population was overweight, the 27.28% was obese. In the X group the 60% was obese. In the Y group, no subject was classified as obese.

All groups had a significant decreased in BMI: after VLCKD the  $\Delta\%$  of BMI was = -6.91, ( $p = 0.00$ ), and after VLCD the  $\Delta\%$  of BMI was = -7.91 ( $p = 0.00$ ).

Both groups lost weight, but the reduction was greater in the VLCD ( $\Delta\% = -7.98$ ;  $p = 0.00$ ) compared to VLCKD ( $\Delta\% = -6.99$ ;  $p = 0.00$ ).

However, in both groups no significant reduction of PBF was observed ( $p > 0.05$ ).

After VLCKD, no significant differences in body fat of the trunk, body fat distribution (android and gynoid) were observed, whereas, abdomen circumference ( $\Delta\% = -3.23$ ), hip circumference ( $\Delta\% = -7.98$ ), waist circumference ( $\Delta\% = -5.29$ ), and total body fat ( $\Delta\% = -6.57$ ) were significantly different ( $p < 0.05$ ).

After VLCD, no significant differences in waist circumference, body fat of the trunk were observed. However, abdomen circumference ( $\Delta\% = -3.25$ ), hip circumference ( $\Delta\% = -3.14$ ), android body fat ( $\Delta\% = -13.40$ ) and gynoid body fat distribution ( $\Delta\% = -19.22$ ), total body fat ( $\Delta\% = -7.47$ ) were significantly different ( $p < 0.05$ ).

Moreover, after VLCD a significant decrease of total body lean of the trunk ( $\Delta\% = -7.31$ ), android lean body distribution ( $\Delta\% = -11.85$ ), gynoid lean body distribution ( $\Delta\% = -5.47$ ), and total body lean ( $\Delta\% = -8.46$ ) were highlighted ( $p < 0.05$ ).

After VLCKD, no significant differences in body

lean of the trunk, body lean distribution (android and gynoid), total body lean were observed ( $p > 0.05$ ).

Moreover, the frequency of sarcopenia at baseline according to ASMMI was 20% in the X group; after VLCKD, no sarcopenic subject was highlighted.

## Discussion

Many research have shown the effectiveness of the ketogenic diet on weight loss<sup>17</sup>; even if not know how to work effectively, as some researchers believe that the weight loss is due to reduced calorie intake, satiety could also be induced by the effect of the proteins, rather than the low-carbohydrates<sup>20</sup>. Others, however, believe that in fact there is a metabolic gain, based on the first law of hemodynamics or law of conservation of energy<sup>11</sup>. However, other authors still have remarked old considerations for which little would be important macronutrients present in the diet, only effective for the reduction of calories<sup>22</sup>. Contrary to these opinions, the majority of studies has shown that people who follow a diet low in carbohydrates lose more weight in the first 3-6 months compared to those who follow balanced diets<sup>23-25</sup>, perhaps because the proteins of the ketogenic diet represent a wasteful process for the human body which allows a greater weight loss<sup>21,26,27</sup>. The energy cost of gluconeogenesis has been confirmed<sup>18,20</sup> and it has been calculated at ~400-600 Kcal/day (due to both endoge-

nous and food source proteins<sup>26</sup>. Except this, no experimental evidences support this hypothesis, on the contrary, a recent work has shown that there are no changes in energy expenditure after a VLCKD<sup>28</sup>. Certainly the effects of the loss of weight of the VLCD depend on various factors: decreased appetite for satiety provided protein<sup>20,30</sup>, effects on appetite control hormones<sup>29</sup> and to a possible direct appetite-suppressant action of the KBs<sup>21</sup>; reduction in lipogenesis and increased lipolysis<sup>18,19</sup>; reduction in the resting respiratory quotient and, therefore, greater metabolic efficiency in consuming fats<sup>28,32</sup>; increased metabolic costs of gluconeogenesis and the thermic effect of proteins<sup>21,26</sup>.

There are several evidence support about using of whey protein to increase anabolic hormones, like insulin and GH. However, whey protein has potential as a functional food component to contribute to the regulation of body weight by providing satiety signals<sup>27</sup>. Whey protein appears to have a blood glucose lowering effect partly mediated by incretins. Effects of whey protein on metabolic mechanism seem be in muscle protein synthesis<sup>18</sup>. Several results in different studies proved the importance of protein quality as a determinant of lean body mass responses during resistance training<sup>44</sup>. So we supposed, during weight lost, biological value of protein is constitutive. In contrast, there are no clear-cut effects shown on blood lipids and lipoproteins, blood pressure and vascular function.

The results of this pilot study show that a diet low in carbohydrates, associated with a decreased caloric intake, is effective in weight loss. Although compliance with the diets was assessed primarily by dietary records, these data are supported by more objective measures. Thus, we believe that the outcomes of this study can be attributed primarily to differences in the prescribed diets of the two groups and are applicable to the large number of obese. Also, the amount of body water plays an important role as the weight loss may be due to diuresis consequent to caloric restriction or reduction of body water followed presumably by the reduction of glycogen stores<sup>33,34</sup>. However, these studies were of very short duration, from 2-3 weeks in length. Most diets that have a significant restriction of calories cause a sodium diuresis that occurs over the first week or 3 of their use, and in fact, we noted the most rapid weight loss in both groups over this period. Our body composition analysis revealed a similar percentage of body fat as in

low-fat diet group. Because we think it is far-fetched to think that the change of weight in the groups at 3 and 6 months is due to the variation in body water in the diet low in carbohydrates, but the reduction of caloric consumption<sup>35</sup>. Although the inaccuracy of dietary records for obese individuals is well documented<sup>36,37</sup>, not easy to think that reducing the weight in the two groups is only due to a different calorie intake but probably also to a different exercise. Not very clear, moreover, it appeared to be the reduction of food intake in the group of patients in a diet low in carbohydrates to a level equal to VKLCD group were following a prescribed restriction of calories. This suggests the possibility that the diet low in carbohydrates gives a greater sense of satiety. Several reports have suggested, in fact, that the protein satisfies the appetite more than carbohydrates and fats<sup>38,39</sup>. Although it is known as ketosis secondary to increased protein intake results in reduced appetite, this does not seem likely based on our data. At the end of this paper it is important to emphasize certain points. First, a single study cannot define criteria for safety and effectiveness, also because our results are still limited by the lack of durability, but with the certainty that a diet low in carbohydrates will produce weight loss and reduction of cardiovascular risk factors and cancer in analysis periods longer<sup>41</sup>. Care must be taken, for the low intake of calcium and fiber in the diet with reduced carbohydrate content and the fact that ketosis has been shown to be related to myocardial dysfunction in children<sup>42</sup>. Finally, the observed preservation of muscle mass brought about during a VKLCD is possible at least four possible mechanisms<sup>43</sup>. May be involved as the surge of low levels of blood sugar are a stimulus for its secretion and it could be that the protein mass of skeletal muscle affected by adrenergic influences. The liver produces ketone bodies during a VKLCD and they flow from the liver to extra-hepatic tissues (e.g., brain, muscle) for use as a fuel. As low blood sugar increases GH secretions, one could speculate that a VKLCD increases GH levels. A VKLCD is almost always relatively high in protein and there is evidence that high protein intake increases protein synthesis by increasing systemic amino acid availability<sup>44</sup>, which is a potent stimulus of muscle protein synthesis<sup>45</sup>. During weight loss, higher protein intake reduces loss of muscle mass and increases loss of body fat<sup>46</sup>. Can interact with the insulin to

regulate the control of protein synthesis to support the muscle mass during periods of reduced caloric intake<sup>47</sup>.

Our pilot double-blind study showed that a VLCKD was highly effective in terms of body weight reduction without to induce lean body mass loss, preventing the risk of sarcopenia. Together these data, serve as clinical information to support measure and diet selection for prevention of risks induced during dietary treatment in obesity management.

Further clinical trials are needed on a larger population and long-term body weight maintenance and risk factors management effects of VLCKD. As the full spectrum of metabolic effects induced by VLCKD is not completely characterized, new trials that are specifically designed to assess the combined effects of genotypes and dietary intervention are needed. Nutrigenomic, nutrigenetic and biochemical analysis could be performed to ensure safety during the dietary treatments, before definitive conclusions can be made<sup>48</sup>.

The prospect of personalized medicine may help move obesity prevention and treatment from universal to precision approaches, towards weight-loss programs tailored to a person's genome<sup>49</sup>. The advance in helping obese people to achieve a healthier weight will be the use of behavior, body composition and genetic data to customize diets as an approach known as "precision weight loss".

Public health expenditure in Italy in 2010 amounted to 113.5 billion euro, or 7.3% of GDP<sup>50,51</sup>. The projection of public health expenditure in 2050 has focused on estimating the impact of demographic and economic components. Demographic changes and the growth of disposable income impact to over 168 billion euro on the accounts of health than in 2010<sup>50,51</sup>. At the end of this period, the public health expenditure would amount to a value close to 281.5 billion euro, equal to 9.7% of GDP. This model is based on the assumption of a constant current epidemiological picture. It can, however, be assumed in the forecast model to introduce a change in the epidemiological picture associated to the increase of a risk factor of many diseases (cardiovascular disease, diabetes, some cancers, etc.) such as obesity. The basic assumptions are the following: italian obese children are 11% of the population; it is estimated that the number of obese adults will increase by 2.4% annually until 2025, and by 2.8% annually from 2025 to 2050, taking into account that 70% of obese children remain obese as an adult now, and that on average one third of obese adults had

been obese since childhood; it assumes that the health care cost of an adult obese person is on average 1400 euro more than the average health cost per capita. Crossing the figures for per capita health care costs associated with each obese and the growing number of obese, you can estimate the greatest impact on health care costs. With a forecast for 2050, this simulation leads to more spending, compared to the base case of the model, for about 24.3 billion euro, resulting in a ratio of health expenditure to GDP of around 10.6% (compared with 9.7% of the base case of the forecasting model). The total cost caused the epidemiological picture simulated for the 2010-2050 period is 347.5 billion Euros for the diseases to which effect is subject more frequently than a person of normal weight. Changing the obesity epidemiological assumptions combined with those on the demographic mix brings the number of obese nearly 14 million in 2050 (compared to assumptions) about 5 million that would occur in the event that were modified. So an increase of 1400 Euros more per year for obesity-related diseases for 20 years of survival would produce 28,000 euro per capita in more spending. If these represent 10% of the adult population over 18 years (10% of 50 million people = 5 million people on average) would lead to a higher total expenditure of EUR 140 billion in 20 years, i.e. 7 billion more (or less if you are cured), in practice roughly a 5-6% spending more than the estimates if they are not cared for.

## Conclusions

The prospect of personalized medicine may help move obesity prevention and treatment from universal to precision approaches, towards weight-loss programs tailored to a person's genome<sup>49</sup>. The advance in helping obese people to achieve a healthier weight will be the use of behavior, body composition and genetic data to customize diets as an approach known as "precision weight loss".

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## Conflict of Interests

The Authors declare that they have no conflict of interests

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