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VLCKD IN THE MANAGEMENT OF METABOLIC DISEASE: FOCUS ON TYPE II DIABETES, OBESITY, NON-ALCOHOLIC FATTY LIVER DISEASE AND CARDIOVASCULAR DISEASES

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Abstract

In this review we analyze the recent scientific evidence about, benefits and risks of VLCKDs, and provide recommendations on the correct use of this therapeutic approach for weight loss and management of metabolic diseases.
Over the last decades, the worldwide prevalence of obesity and type 2 diabetes (T2D) has dramatically risen, resulting in a global epidemic.
The transition to high calorie-low fiber diets and processed foods have contributed to this trend.
High carbohydrate intake has been related to higher risk of total mortality, whereas total fat and specific types of fat have been associated with lower total mortality, thus challenging the definition of a healthy diet.
In this context, weight loss is important in the prevention of chronic diseases, associated with high morbility and mortality in industrialized countries.

Keywords: *obesity, type 2 diabetes, cardiovascular diseases, VLCKD.*

Introduction

Over the last decades, the worldwide prevalence of obesity and type 2 diabetes has dramatically risen, resulting in a global epidemic. High carbohydrate intake has been related to higher risk of total mortality, whereas total fat and specific types of fat have been associated with lower mortality. In this contest, VLCKD has recently gained growing interest for the management of obesity and its comorbidities [1].

VLCKD

Ketogenic diets are high-fat, adequate-protein, low-carbohydrate diets and have been primarily used to treat refractory epilepsy in children since the 1920s. In the 1970s the low-carbohydrate high-fat ketogenic diet "Atkins" reached popularity for weight loss. Then, pioneering studies by George Blackburn introduced the concept of "protein-sparring modified fast", forming the basis of VLCKD.

VLCKD is a nutritional protocol characterized by a reduction in energy intake with a relative increase in protein and lipid content resulting in an important glucose reduction, less than 50g/day.

The diet program is structured in different phases. At the beginning patients are allowed to eat protein preparation or natural protein meals (meat/fish/eggs/soy) and low-carbohydrate vegetables. The ketogenic period providing about 600-800 kcal/day and is variable in time (8-12 weeks). During this period patients must be monitored through physical examination (anthropometric measurement, blood pressure, heart rate, etc) and laboratory analysis.

Furthermore, proper water intake (at least 2 l), vitamin/electrolyte and omega 3 supplementation are mandatory, especially in this first phase.

In the following phases, carbohydrates are gradually reintroduced, starting from foods with the lowest glycemic index (fruit – dairy products), followed by foods with moderate and high glycemic index. The daily calorie intake in the reintroduction period ranges between 800 and 1500 kcal/day.

The reintroduction of food allows for a progressive nutritional education that supports long-term weight-loss maintenance [2].

VLCKD in severe obesity

VLCKD is a dietary strategy to assist patients affected by obesity in losing weight rapidly. It is a therapeutic option for patients with severe obesity or moderate obesity associated with others risk factors. VLCKD is suggested for a maximum of 12 weeks in a context of multidisciplinary intervention associated with lifestyle modifications and psychological counselling [3,4,5].

Most of the studies on obesity have shown that intervention with VLCKD is effective in terms of weight loss, visceral fat reduction and improvement of metabolic parameters and inflammation markers, but they are short term. Further studies long time are needed to attribute a stronger level of evidence to this approach.

The use of VLCKD in combination with other dietary approaches could be the solution. The controlled transition to the reintegration of carbohydrate intake allows the body to slowly get used to the glucose consumption and influences the weight regain avoiding spikes of insulin.

Hypocaloric Mediterranean diet remains the most prescribed first-choice diet in Italy, but it is penalized by the high incidence of dropouts due to the difficulty in controlling hunger. The development of a controlled ketosis, which effectively inhibits hunger and increases satiety, makes VLCKD a valuable option for intermittent treatments in combination with other dietetic approach.

In conclusion, there is evidence that VLCKD approach is effective in weight-loss and visceral fat reduction in severe obesity in the short-term. The evidence of a long-term efficacy of VLCKD is sporadic and needs more long-term studies. Lifestyle intervention and VLCKD approach used together for the management of severe obesity are more successful than interventions used alone and without specialized supervision.

VLCKD in type 2 Diabetes and insulin resistance

VLCKD should be considered to obtain an early efficacy on glycemic control, particularly in patients with short duration of the disease.

In obese patients with T2D, exposure to VLCKD for 1 week resulted in a significant improvement of beta-cell function.

The reduction in carbohydrate intake was associated with a decrease in hepatic triacylglycerol content; consequently, higher suppression of hepatic glucose production was observed as a consequence of improved hepatic insulin sensitivity [6].

The effects of VLCKD on beta-cell function may be responsible for the significant percentage of patients showing remission of T2D. Indeed, remission of diabetes may be expected in a relevant percentage of patients with early diagnosis of the disease after 3 months of VLCKD [6, 7].

A longer observation reveals a persistent remission in almost half of the patients [6, 8], despite weight regain [6].

Long-lasting remission was observed in particular in patients with lower fasting plasma glucose, younger age and a shorter duration of diabetes [8]. Improvements in glycemic control during intervention with VLCKD have been found, despite discontinuation of anti-diabetes therapy [8, 9].

Continuous or intermittent use of VLCKD is associated with an important reduction in insulin and oral glucose-lowering medication requirements.

VLCKD in non-alcoholic fatty liver disease

NAFLD is the most common liver disorder in industrialized countries, where obesity and T2DM are the major risk conditions for this disease and for its progression towards non-alcoholic steatohepatitis (NASH) and liver cirrhosis or hepatocellular carcinoma.

Given the tight association of NAFLD with obesity, even modest weight loss significantly reduces liver fat while improving hepatic insulin resistance [10,11].

In humans 2 weeks of dietary intervention with a VLCKD reduced hepatic triglycerides in subject with NAFLD; reductions were significantly greater with VLCKD than with standard caloric restriction. A similar study showed that liver total volume was rapidly decreased by a short-term (6 days) VLCKD, probably due to glycogen depletion, and such decrease was higher than with a standard hypocaloric diet [12].

A 2-year study reported that increasing the content of protein in the diet may reduce liver fat and lower the risk of T2D in people with NAFLD. Finally, more than half of the patients, who were previously diagnosed with NAFLD, no longer had fatty liver [13].

A 12-week intervention research showed that intrahepatic triglyceride content is lower after a high protein-low carbohydrate diet than a low protein-high carbohydrate diet. This suggests that high protein-low carbohydrate diets may limit intrahepatic triglyceride in healthy humans. High-protein intake stimulates hepatic lipid oxidation due to the high energetic demand for amino acid catabolism and ketogenesis. Protein-induced glucagon secretion inhibits *de novo* lipogenesis and stimulates hepatic ketogenesis [14].

Although these evidences, lack of results limit the validation of VLCKD use in patients with NAFLD.

VLCKD and cardiovascular diseases

Obesity is associated with increased risk of cardiovascular morbidity and mortality [15]. Overweight status has also been found associated with increased risk of developing cardiovascular disease (CVD) at an earlier age [16].

Cardiovascular diseases are pathological process that affect the arterial system and determine the progressive narrowing of the arteries until they are completely obstructed.

The rapid impact of VLCKD in reducing visceral fat shows beneficial effects on risk factors for CVD.

VLCKD could be part of a multidisciplinary strategy for cardiovascular rehabilitation in obese patients.

Studies by Blackburn showed marked effects of VLCKD in the reduction of body weight, systolic and diastolic blood pressure, fasting plasma glucose and triglyceride levels [17].

The anti-inflammatory effects of VLCKD could play an important cardioprotective role.

In fact, 12-week-long VLCKD has been reported to reduce pro-inflammatory cytokines (tumor necrosis factor alpha, TNF-α; interleukin 6, IL-6; interleukin 8, IL-8; monocyte chemoattractant protein 1, MCP-1; E-selectin; intercellular adhesion molecule 1, ICAM-1; plasminogen activator inhibitor 1, PAI-1) [18].

Others pre-clinical studies demonstrated that β-hydroxybutyrate blocks NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome [19], supporting a direct anti-inflammatory role of VLCKD beyond its effects on metabolic parameters [20].

Conclusions

Despite the short and middle term benefits of VLCKD in terms of weight loss, improvement of insulin resistance with potential remission of T2D, reduction of intrahepatic triglyceride content and reduction in cardiovascular risk factor are widely documented, some concerns exist about its use in the long-term period due to the paucity of studies.

Few studies have demonstrated that VLCKD is safe and effective in the long term, although additional clinical trials are needed.

VLCKD is a highly effective therapeutic tool in patients who needed rapid weight loss over a short-term period, such as individuals with moderate to severe obesity and cardiovascular risk factors. The potential of this diet in determining remission of T2D, particularly in obese patients with short disease duration, should be taken into consideration.

Once an ideal body weight is achieved, VLCKD should be necessarily followed by a long-term multifactorial strategy aimed at weight-loss maintenance.

One of the open questions is related to the ideal duration and frequency of use of VLCKDs. In the past, the use of VLCKDs without proper medical supervision generated therapeutic failures and side effects that led to their default for many years.

In conclusion VLCKD is an important therapeutic tool to associate with others approach and lifestyle changes, a lot of evidences shows its efficacy and its safety, but more long-term studies are requested.

At the end it should be emphasized that the use of VLCKD requires a clear clinical indication under strict medical supervision.

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