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Chapter 3

Very Low-Calorie Diets in Type 2 Diabetes Mellitus: Effects on Inflammation, Clinical and Metabolic Parameters

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Abstract

Type 2 diabetes mellitus (DM) is a chronic and multifactorial disease strongly linked to a low-grade inflammatory process. Thus far, type 2 DM is generally regarded as an incurable disease by common therapies. However, very low-calorie diet (VLCD) regimens have demonstrated beneficial and rapid effects on glucose metabolism in subjects with type 2 DM. These beneficial effects include improvement of diabetes complications, insulin sensitivity and reduction in glycaemia, glycated hemoglobin (HbA1C), and triglyceride levels. VLCD regimens commonly comprise no more than 800 kcal/day and are therefore associated with rapid weight loss in overweight and obese individuals. This group of diets positively affects local/systemic inflammation and oxidative stress (OS) by modulating inflammatory cytokines, adipokines and endogenous antioxidant levels. The investigation of VLCDs in the field of type 2 DM treatment is progressively augmenting due to the multiple benefits in cardiometabolic health of overweight/obese subjects with type 2 DM. Here, we gather and review the evidence regarding the role of inflammation and OS in individuals with type 2 DM under VLCD regimens.

Keywords: very low-calorie diet, obesity, type 2 diabetes mellitus remission, oxidative stress, adipokines

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1. Introduction

Thus far, type 2 diabetes mellitus (DM) is recognized as an incurable metabolic disease by common therapies. Obesity and type 2 DM are intrinsically correlated, and low-grade chronic inflammation at a local and systemic site has been suggested as a key component in the progression toward the disease [1, 2]. In this regard, very low-calorie diet (VLCD) regimens, providing <800 kcal/d, have demonstrated to exert a beneficial and rapid effect on glucose metabolism in individuals with type 2 DM, which are not seen with pharmacological therapies [3]. Since 1970, VLCD has been used to induce rapid weight loss with a favorable safety profile [4]. Benefits of VLCD in T2DM patients with obesity include weight loss, fat mass reduction, reversion of hyperglycemia, elimination of pharmacologic treatment and normalization of both beta cell function and hepatic insulin sensitivity [3, 5]. The main mechanism by which VLCD regimens exert their beneficial effects on metabolism of type 2 DM subjects appears to be their capacity to induce weight loss and modulate inflammation via cytokines and adipokines [6–8]. However, there are considerable limitations of VLCD regimens in certain individuals. The most common issue to resolve in clinical trials evaluating VLCD regimens is noncompliance of patients due to previous dietary patterns, psychological aspects, vitamin deficiency manifestations and renounce to undergo lifestyle changes [9, 10]. In addition, initial weight loss by VLCD treatment is associated with greater weight regain; thus, long-term weight maintenance after VLCD has been an elusive goal when compared to surgical procedures like bariatric surgery [11, 12].

The purpose of the present chapter is to focus on the metabolic and clinical effects of VLCD regimens in type 2 DM subjects as well as on the role of inflammation and oxidative stress (OS).

2. Clinical outcomes with VLCDs in type 2 DM

The most common way to measure effectiveness among different medical treatments is by the assessment of clinical outcomes. A clinical outcome may refer to any measurable variable that is dependent on the assigned treatment [13]. With regard to type 2 DM, the most important and common outcomes evaluated in clinical trials assessing for therapy effectiveness are glycemia, glycated hemoglobin (HbA1C) levels, insulin sensitivity/resistance and elimination of antidiabetic drugs (also known as "diabetes remission"). However, current therapies, other than bariatric surgery, have failed to demonstrate significant effects on the ultimate goal of type 2 DM therapy, disease remission [14, 15]. Hence, this metabolic pathology is commonly referred, thus far, as an incurable and progressive disease.

Obesity is a well-known risk factor for type 2 DM [16]; therefore, several treatment approaches have been implemented to induce weight loss in obese individuals with type 2 DM. It is worth mentioning that since 1970, several studies have documented the capacity of a restricted diet to exert a rapid weight loss in overweight/obese subjects in a positive manner [4]. These types of diets comprise no more than 800 kcal/day and are known as VLCDs. VLCD regimens have been evaluated as diet treatments for type 2 DM based on their capacity to induce rapid weight

loss. In 1997, Capstick et al. performed a clinical trial in 14 patients with obesity and type 2 DM aiming to evaluate the effects of a VLCD (425 kcal/day) regimen for 12 weeks on weight and metabolic control. In this clinical trial, body weight (from 108.9 to 94.5 kg), waist circumference (from 116 to 103 cm) and systolic blood pressure (SBP) (−8 mmHg) were reduced. The authors also reported a total reduction in exogenous insulin utilization by 50% in the VLCD cohort individuals who were taking a high dose of insulin per day at baseline, accompanied by a decrease in the number of oral antidiabetic drugs (8–2, median tablets/day). In addition, this regimen was well tolerated with a favorable safety profile [17]. Since then, several studies have implemented a diet treatment for type 2 DM. In 2011, Lim et al. evaluated the clinical effects of a 600 kcal/day VLCD regimen for 8 weeks in 11 middle-aged patients with obesity and type 2 DM. Results showed an average weight loss of 15.3 kg, equivalent to 15% of their initial body weight, with a sustained reduction of 3 kg after a 12-week follow-up [18]. Nevertheless, the majority of these studies have been pursued for <6 months, with limited evidence on their long-term efficacy in the treatment of diabetes.

In regard to the long-term study of VLCD regimens, Paisey et al. compared the clinical effects of a VLCD regimen with an intensive conventional diet plus exercise for 5 years in obese type 2 DM subjects. Fifteen patients in both cohorts finished the program. After 3 years of therapy, subjects in the VLCD regimen lost more body weight (mean ~15 kg weight loss) than their counterparts; however, by 5 years of follow-up, most of the weight was regained. On the other hand, the intensive group had a more sustained and progressive weight loss than the VLCD. The authors demonstrated that VLCD was safe to perform but difficult to follow for more than 6 months and showed a relative low patient compliance rate of ~60% in those individuals [19].

Similarly, Lim et al. showed a persistent beneficial effect on weight control after 6 months of an 8-week VLCD [20]. However, there could be some concerns about the tolerability and safety of VLCD in the long term based on the limited calorie content of these types of diets. Interestingly, Rolland et al. performed a study comparing weight loss and safety in obese subjects of three types of restricted calorie diets: VLCD, low-carbohydrate/high-protein diet and low fat, reduced-energy diet. At 3 months, a greater loss in body weight, total cholesterol, low-density lipoprotein cholesterol (LDL), fasting glucose and diastolic blood pressure in the VLCD cohort was observed. At 9 months, there were no significant differences, with the exception of fasting glucose, among the VLCD (average 550 kcal/day) and low-carbohydrate/high-protein diet (800–1500 kcal/day) regimens. Dropout rates were similar in the VLCD and low-carbohydrate/high-protein diet groups and no adverse effects were reported at 3 and 9 months in both groups [21]. Thus, at least for 9 months, VLCD seems to possess a favorable safety profile compared to less intense restricted calorie diets (>800 kcal/day).

A recent systematic review and meta-analysis compared weight loss following VLCD (<800 kcal/day) and low-energy liquid-formula regimens (>800 kcal/day) in people with and without type 2 DM [5]. The analysis of five studies varying from 4 to 52 weeks in length revealed no significant differences in weight loss among both regimens. Further, data showed that the efficacy on weight loss depended on several factors, including duration of diet and clinical characteristics of the subjects. In addition to effects on body weight, VLCD regimens were associated with a lack of adverse effects.

It is worth mentioning that reduction in body weight by VLCD regimens may trigger beneficial effects on diverse clinical alterations caused by certain pathologies where obesity is linked to their development and/or severity. Indeed, some studies have shown improvements on autonomic nervous system over reactivity (as per changes in heart rate variability) and stage 2 chronic kidney disease (as per changes in glomerular filtration rate) present in obese individuals with type 2 DM by VLCD regimens [22, 23]. Altogether, these studies suggest that weight loss, in the short term, is more rapid and pronounced by VLCD regimens but is also accompanied by more noticeable weight regain in the long term when compared to less restricted calorie diets. However, the long-term effects on body weight by VLCD remain unclear. Weight maintenance and education programs are needed for those individuals willing to follow a VLCD regimen if long-term weight loss is desired.

3. Metabolic parameters with VLCDs

The main goal pursued by pharmacological and nonpharmacological treatments in type 2 DM is to normalize the blood glucose levels. Diabetes remission, defined, as achieving glycemia below the diabetic range in the absence of active pharmacologic or surgical therapy [24] is lamentably rare by common therapies, including exercise, diet and antidiabetic drugs [14]. However, even a small decrease in high blood glucose levels is associated with a significant reduction in microvascular [25] and macrovascular [26] complications in subjects with type 2 DM. Until now, the only therapy that has compelling evidence in inducing long-term (up to 10 years) diabetes remission is bariatric surgery [27]. Interestingly, VLCD regimens have shown metabolic benefits in type 2 DM individuals, in the short term, similar to those observed by bariatric surgery. For instance, in 1979, Savage et al. evidenced a restoration of normal fasting plasma glucose levels by a VLCD regimen (500 kcal/day), for at least 4 weeks, in obese and type 2 DM individuals [28]. Such effects were attributed to the weight loss induced by the diet. Notably, all individuals presented a short duration of diabetes, 2–24 months. In 2004, Jazet et al. performed a clinical trial in 17 obese individuals with type 2 DM, with the purpose to identify the factors that could predict the blood glucose lowering effect induced by a VLCD regimen. After a 30-day treatment with 450 kcal/day, all individuals lost weight, but not all of them (i.e., nonresponders) achieved a reduction in blood glucose levels. But those who did (i.e., responders) had a shorter duration of type 2 DM and preserved the capacity of β-cells to secrete insulin [29]. This evidence provided key information in regard to diabetes remission that was later investigated by other groups. In 2011, the Newcastle Counterpoint study demonstrated reversal in 11 people with type 2 DM (<4 years of diagnosis) using a VLCD consisting of 600–800 kcal/day. A rapid decrease in liver and pancreas fat content derived from weight loss was linked to the glucose-lowering effects elicited by VLCD [18]. Later on, the same group of researchers showed that a higher baseline plasma insulin levels, preserved β-cell function and lower duration of diabetes were linked to diabetes remission following a VLCD regimen (624–700 kcal/day) for at least 6 months [20]. Despite being regarded as progressive and incurable, type 2 DM appears to be reversible by means of VLCD regimens. Nonetheless, long-term diabetes remission remains to

be investigated and ongoing clinical trials are in the run [30] to provide more solid and clear evidence, as to if diabetes remission is possible by considerably changing the way people eat, without the necessity of invasive procedures (i.e., bariatric surgery).

4. Cytokines and adipokines in obesity and type 2 DM

Evidence has shown that a prolonged positive energy balance (more calories consumed than those expended) above that required for normal growth and development leads to overweight and obesity [31], which is a well-known risk factor for the development of type 2 DM [16]. Although a high proportion of individuals with type 2 DM are overweight/obese [32], not all of the overweight/obese individuals develop type 2 DM. The anatomical site where the excess calories are preferentially stored as triglycerides plays a pivotal role in the occurrence of metabolic abnormalities [33]. The adipose tissue has been recognized as the main site for lipid accumulation when excess calories are ingested [34]. However, studies have also shown that a positive energy balance over time leads to an increased accumulation of lipids (in the form of triglycerides) in various organs, including the liver, skeletal muscle and pancreas [35]. The abnormal fat accumulation in those organs has been linked to various derangements in the metabolism, including insulin resistance and β-cell failure (core defects of type 2 DM) [3]. Additionally, inflammation is a common feature of both obesity and type 2 DM. Indeed, studies have shown that obese individuals present an increase in adipose tissue macrophages and other immune cell infiltration [1]. These cells are key drivers of inflammation via overproduction of inflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor-α (TNF-α) and IL-6, which are strongly associated with the progression of the obese phenotype and metabolic traits of type 2 DM [36, 37]. In addition, the abnormal infiltration of immune cells in adipose tissue has deleterious long-term consequences on the biology of this tissue, as adipocytes are major targets of the pro-inflammatory effects of cytokines released by immune cells [38]. It is suggested that adipocytes secrete more than 600 potential hormones and signaling molecules (and the list grows every year), also known as adipokines, some of them are also produced by immune cells [39]. This group of molecules possesses a myriad of effects on diverse tissue/organs, including but not limited to the control of inflammation, fat distribution, insulin sensitivity and secretion, energy balance, appetite and satiety [39–42]. Some of the best studied and relevant adipokines in obesity and type 2 DM are leptin, adiponectin, TNF-α, IL-6, IL-1, resistin, dipeptidyl peptidase IV, apelin, monocyte chemotactic protein-1 (MCP-1), and so on [40, 41]. Interestingly, adipokines can act as either pro-inflammatory or anti-inflammatory signaling molecules. For instance, in lean individuals, adipocytes release anti-inflammatory adipokines (e.g., IL-4, IL-10, IL-13, apelin, etc.), while in obese subjects, pro-inflammatory molecules (e.g., TNF-α, leptin, IL-6, resistin, etc.) are predominantly released. The imbalance of cytokines and adipokines homeostasis in overweight/obese individuals leads to chronic low-grade systemic inflammatory state, a process that is a key driver of insulin resistance and ultimately to the development type 2 DM [2]. Thus, therapeutic strategies targeting cytokine and adipokine levels may favorably influence both obesity and type 2DM.

The most studied adipokines in type 2 DM subjects with VLCD are adiponectin and leptin. Adiponectin is a 244-amino acid hormone synthesized by mature white adipose tissue in subcutaneous, visceral and perivascular adiposity [42]. Adiponectin increases as fat mass decreases, and some of its functions are adipogenesis, adipocyte lipid storage (a "healthy" expansion of adipose tissue) and adipocyte insulin sensitivity via increased GLUT4-mediated glucose uptake [43]. The beneficial metabolic effects of adiponectin are in part related to its capacity to modulate the energy sensor 5′ adenosine monophosphate-activated protein kinase (AMPK) [44]. The regulation of adiponectin is a very complex system; however, low plasma adiponectin levels are associated with overweight, obesity and type 2 DM [43, 45]. The exact mechanisms involved in downregulation of adiponectin are not fully understood. Dietary restriction regimens in all its varieties (e.g., VLCD, calorie restriction, intermittent fasting, etc.) have been documented to exert beneficial metabolic effects in patients with type 2 DM derived from weight loss and concomitant modulation of adipokine levels. VLCD appears to have the most profound and rapid positive effect on weight loss, insulin resistance, β-cell function, inflammation and OS than other calorie-restricted regimens [3, 46–49]. However, the majority of studies performed, thus far, have failed to demonstrate significant changes in adiponectin serum levels after VLCD regimens in obese and type 2 DM individuals, despite improvements on metabolism [6, 8, 50].

Conversely, leptin is a 167-amino acid hormone secreted mainly by white adipose tissue and is positively correlated with body fat content [51]. Leptin regulates energy homeostasis by inhibiting appetite (anorexigenic effects), thereby inducing the weight loss. In obese subjects, circulating levels of leptin are increased [52]. Interestingly, after a three-week regimen with VLCD in obese women, Anderlová et al. demonstrated a significant reduction on leptin serum levels and an increase of soluble leptin receptor levels, with no significant effects on adiponectin [6]. In addition, Lips et al. directly compared the effects between VLCD and bariatric surgery (Roux-en Y gastric bypass) on systemic inflammation markers in obese women. Three months after both interventions such as leptin and adiponectin serum levels were reduced and increased, respectively, by both regimens, although a more favorable inflammatory profile was observed in the VLCD cohort [53]. Noteworthy, VLCD has also been shown to positively affect inflammatory markers in obese type 2 DM subjects. Mraz et al. evidenced that a two-week VLCD regimen (~600 cal/day) decreased body weight and fasting glycemia accompanied by decreased C-reactive protein and IL-6 plasma levels in obese type 2 DM women. Moreover, these subjects experienced a reduction in inflammatory markers at the mRNA level, including chemokine receptors (e.g., CCR-1, CCR-2, CCR-5, IL-6 receptor) in peripheral monocytes and chemokines (CCL-8 and CXCL-10) in subcutaneous adipose tissue [8].

5. VLCD and OS

OS is a condition of imbalance between oxidative species and antioxidant defense [54]. Several lines of evidence suggest a close relationship between inflammation and OS [55–57]. Indeed, various OS markers are up regulated in subjects with type 2 DM [58–60], where a chronic low-grade inflammation state is present. Regimens with calorie-restricted diets have been reported

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to positively affect OS in obese and type 2 DM individuals via modulation of recognized OS markers. For instance, a study performed with obese individuals (with and without metabolic syndrome diagnosis) evidenced a reduction of oxidized LDL plasma levels after a VLCD for 3 months. In another study, a VLCD regimen for 8 days was associated with improved oxidative status, defined as increase in superoxide dismutase (SOD) and reduction in malondialdehyde (MDA) levels, in obese individuals with and without type 2 DM [61]. Although such effects were only reported in nine patients, surprisingly, a seven-day period was enough to demonstrate significant reductions in those parameters in addition to reductions in fasting plasma glucose, total cholesterol and LDL levels. Likewise, Heilbronn et al. documented reduced DNA damage (a marker of OS) in blood samples from overweight individuals after 6 months of a VLCD regimen compared to individuals who had followed a weight maintenance diet [49]. There exists a link between OS and inflammation in type 2 DM, and in this regard, VLCDs have shown the capacity to attenuate both processes.

6. Future directions and recommendations

There is no doubt about the beneficial metabolic effects linked to VLCD regimens in type 2 DM. Such beneficial effects by VLCD go beyond glycemic and lipid control, since VLCD has shown to reduce OS and inflammation. Perhaps, in addition to its associated safety profile, VLCD regimens are now taking a privileged position in the treatment of type 2 DM, because of their capacity (in part) to exert rapid and substantial weight loss without the common risks associated with bariatric surgery. However, particular points that need to be addressed in VLCD trials are whether these types of diets are viable treatments for long-term diabetes remission and these regimens are applicable in primary care settings. Specifically, there is a need for more evidence related to the VLCD-associated benefits and safety, in longer and larger studies, which fortunately may be available soon because of current ongoing clinical trials evaluating this scenario.

Indeed, the Diabetes Remission Clinical Trial (DiRECT) is an ongoing trial intended to determine whether a weight management program (i.e., consisting in a VLCD regimen, food reintroduction and long-term weigh loss maintenance steps) delivered in a routine primary care setting and is a practical and successful treatment to achieve type 2 DM remission after 2 years [32]. This study started in 2016 and the obtained results are promising.

It has been manifested that individuals under VLCD regimens may suffer from psychological stress (e.g., increase in cortisol levels), which may be associated with weight regain after the discontinuation of VLCD regimens [62]. Interestingly, the Prevention of WEight Regain in diabetes type 2 (POWER) was designed to evaluate the effectiveness of adding a psychological intervention to a VLCD regimen in overweight type 2 DM individuals [63].

Clear recommendations for individuals with type 2 diabetes who would like to improve or reverse their condition by VLCD regimens await further studies. Nevertheless, all individuals with newly diagnosed type 2 DM should be informed about the possibility of reversing their disease by a diet regimen, not commonly offered as a treatment by general practitioners. This

will bring hopes and motivation to individuals who are categorized as possessing an incurable disease. It is important to mention that not all individuals are capable to execute a task that comprises a relative drastic change to their lifestyle that has been maintained for years. Hence, structured programs that involve groups of dieticians, nurses, doctors and psychologists are required in order to treat this disease and lead to disease remission. Health Services around the globe will continue to suffer from the cost burden of type 2 DM as its incidence is projected to increase worldwide [64]. Even if a small proportion of type 2 DM individuals reverse their condition, the savings in health programs, particularly in developing countries, will be substantial.

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