Very Low-Calorie Diets and Diabetes

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Very low-calorie diets (VLCD) are hypocaloric dietary regimens of approximately 400–800 kcal/day that result in 20–30% reductions in body weight, sometimes in just 12–16 weeks. A body of evidence demonstrates that adherence to VLCD in adults with type 2 diabetes (T2D) can result in marked improvements to glycemic control and even full T2D remission, challenging the convention that T2D is a lifelong disease. Although these data are promising, the majority of VLCD studies have focused on weight loss and not T2D remission as a primary endpoint.

Keywords: type 2 diabetes ; remission ; very low calorie diets ; hypocaloric diets

1. Introduction

Type 2 diabetes (T2D) and its comorbidities have reached epidemic proportions globally [1], largely driven by high rates of obesity in adults and children. With less than 2% of cases of T2D entering spontaneous remission [2], the current clinical paradigm is that T2D is irreversible. Although current standard clinical care is effective in maintaining normoglycemia in T2D [3], long-term studies show that intensive glycemic control is not sufficient in halting T2D progression and decline in pancreatic β-cell function, or in mitigating the risk of cardiovascular disease [4][5]. Weight loss is the primary approach for nutritional management of T2D [6][7], and evidence shows that, compared to standard care, intensive multicomponent lifestyle interventions, including behavior change, physical activity and dietary energy restriction produce superior weight loss and improvement to glycemic control [8][9].

Dietary energy restriction approaches for management and treatment of T2D have largely focused on weight reduction through the use of either low-calorie diets (LCD) (1200–1500 kcal/day) [10][11][12], or very low-calorie diets (VLCD) (approximately 400–800 kcal/day) [13][14][15][16][17][18][19][20][21][22]. VLCD approaches have shown to be the most effective in producing rapid weight loss, improvement to pancreatic insulin secretory capacity, and reduction of hemoglobin A1c (HbA1c) to pre-diabetic and non-diabetic levels, sometimes within days [13][14][15][16][17][18][19][20][21][22][23][24][25]. However, despite this body of evidence [13][14][15][16][17][18][19][20][21][22][23][24][25], the long-term efficacy of VLCD for reversing T2D remains unclear, as many of these studies have been of short duration (< 12 weeks), did not have T2D remission as a primary endpoint, and varied greatly in their VLCD protocols, follow up duration, and definitions of T2D remission.

A recent body of evidence has demonstrated that with VLCD approaches, clinically defined and sustained (6–24 months) [22][25], show that a VLCD intervention led to significant reductions in body weight and sustained T2D remission in 45–60% of subjects after 12 months, and in 35% of individuals at 24 months [22][25]. However, data also showed that approximately 30% of individuals with relatively longer duration T2D (3.8 years since diagnosis) did not achieve remission despite significant weight loss (i.e., non-responders) [26]. Also, consistent with numerous VLCD weight loss studies [27], approximately 25% of individuals who achieved remission from T2D, regained a significant proportion of their lost weight and had their T2D relapse at 24 months [23][26].

Collectively, these data demonstrate that it remains unclear what the efficacy and durability of T2D remission is, using VLCD approaches, and, equally important, a better understanding is needed of which individuals with T2D would most likely respond and benefit from VLCD approaches for T2D remission.

This narrative review will provide an overview of the studies which share similar VLCD approaches that specifically sought to measure T2D as a primary endpoint. This narrative review will also address who is likely to benefit, what the risks are, and how a VLCD approach compares to other less restrictive hypocaloric diets on remission of T2D.

2. Effect of Very Low-Calorie Diets on Remission of T2D

We summarized five (5) VLCD studies that specifically examined VLCD for T2D remission, and defined T2D remission parameters in their methods [17][20][21][22][23][24][25] (Table 1). The Counterpoint study (Counteracting Pancreatic Inhibition by Triglyceride) Lim et al. [17], was among the first studies to comprehensively explore T2D remission with VLCD. More

specifically, it sought to examine the relationship between excess pancreatic lipid and impaired insulin responses in the reversal of T2D, and to test the twin cycle hypothesis for the onset of T2D (reviewed in [28]). The Twin Cycle hypothesis purports that in obesity and pre-diabetes, fatty liver and hepatic overproduction of triglyceride-rich very-low density lipoprotein (VLDL) has a spillover effect, leading to ectopic pancreatic fat accumulation, impaired β-cell function and onset of T2D [28]. The Counterpoint study used an 8-week VLCD protocol of 600 kcal/day (25% of energy requirement) in 11 obese subjects with T2D who had relatively short-duration disease of less than 4 years since diagnosis [17].

All metabolic parameters were compared to baseline recruitment values and against those of age and sex-matched non-diabetic controls [17]. They reported that, after 7 days of the VLCD, participants had reductions in fasting plasma glucose (FPG) to non-diabetic levels (<100 mg/dL), as well as significant reductions in fasting plasma insulin ($p < 0.05$), and triglyceride ($p < 0.01$). The normalization of FPG to non-diabetic levels after just 7 days occurred with a modest weight loss of approximately 4% of initial body weight, but a 30% decrease in ectopic pancreatic and hepatic triglyceride [17]. At the completion of 8-weeks, the VLCD intervention resulted in a body weight reduction of 15 kg, and all subjects maintained the 30% reductions in intrahepatic and pancreatic lipid levels, with 73% of subjects maintaining non-diabetic FPG levels [17]. The Counterpoint study provided proof of concept that with VLCD normalization of glycemic control in T2D is possible, and evidence that short-term VLCD promotes marked improvement in hepatic insulin resistance and normalization of β-cell function [17].

Given the positive results of the Counterpoint study in participants with relatively new onset of T2D [17], a larger and longer follow-up study by Steven et al. [21] sought to examine the effects VLCD in subjects with relatively longer T2D disease duration. Coined the Counterbalance study (Counteracting BetA cell failure by Long term Action to Normalize Calorie intakE), this study expanded the VLCD protocol from Lim et al. in three phases: 8 weeks of VLCD liquid formula (624–700 kcal/day), followed by 2 weeks of an isocaloric solid food diet, and then by a structured and individualized 6-month weight maintenance program. Subjects that achieved non-diabetic T2D remission were categorized as “responders”, defined by achievement of a FPG of <125 mg/dL and HbA1c levels of <6.5% (<48 mmol/mol) at the 2-month and 6-month follow-up periods. They found, similar to Lim et al. [17], that in some individuals FPG levels were rapidly reduced to non-diabetic levels within 7 days after the onset of the VLCD [21]. After 8-weeks on the VLCD, mean weight loss was approximately 15% of baseline body weight among both responders and non-responders, which then remained unchanged in both groups over the 6- month duration of the study. However, after 8 weeks of VLCD, 87% of subjects with relatively shorter T2D duration (<4 years since diagnosis) had non-diabetic FPG levels, whereas just 50% of the long- duration T2D group (8–23 years since diagnosis) achieved non-diabetic FPG. At a 6-month follow up, during the weight maintenance phase, 40% of the participants in the VLCD intervention arm were classified as responders and in T2D remission [21]. Compared to non-responders, 60% of responders had relatively shorter duration disease of <4 years at baseline, lower FPG, HbA1c, and higher first phase insulin responses [21]. Also, consistent with findings in Lim et al. [17], improvements to β-cell function in responders occurred with concomitant reduction in pancreatic fat levels [21]. The 10-year Q-RISK score, a metric used to assess cardiovascular disease (CVD) risk [29], was reduced from 23% to 7% in responders from the Counterbalance study, which is consistent with a large body of data demonstrating significant reductions in CVD with weight loss and glycemic control in T2D [30][31].

Similarly, a small prospective VLCD study by Umphonsathien et al. [24], specifically examined T2D remission in 19 overweight adults (mean body mass index [BMI] 27.7), with an average T2D duration of 2 years (range 0.4–8 years). Subjects were administered a VLCD of 600 kcal/day for 10 weeks, followed by a 4-week gradual solid food reintroduction phase, and an increase in energy intake up to 1500 kcal/day. Dietary compliance was measured using a daily food record and urine ketone levels. They defined T2D remission as FPG level <126 mg/dL, HbA1c <6.5% (<48 mmol/mol), and the discontinuation of all antidiabetic medications. Dietary compliance was reported at 90%, and they reported that at weeks 4, 8 and 12 of the re-feeding phase, approximately 40%, 75% and 70% of subjects were in T2D remission, respectively [24]. Over 12 weeks, those who achieved remission had a mean weight loss of 9.5 kg or 12% of initial body weight. This small study found, similar to the Counterpoint and Counterbalance studies [17][20][21], that improvement in glycemic control was apparent in the first 7 days of onset of the VLCD and that duration of T2D was a predictor of remission (mean duration of 2 years vs. 6 years in non-responders) [24]. While it would have been informative, rates of remission were not reported after the re-feeding period. Although this study, along with Counterpoint and Counterbalance studies, provides proof of concept that VLCD can result in T2D remission with a high response rate, these studies lack the appropriate controls, and had relatively short follow-up of 2-6 months.

The Diabetes Remission Clinical Trial (DiRECT) sought to address these limitations with a rigorous and comprehensive study of a VLCD approach for T2D remission that spanned 24 months [22][23]. DiRECT recruited 306 overweight and obese adults aged 20–65 with a BMI range of 27–45 kg/m, diagnosed with T2D within the past 6 years [22]. Exclusion criteria included diagnosis of very advanced T2D, defined as requiring exogenous insulin or with an HbA1c of 12% (108

mmol/mol) or greater [22]. All subjects were then cluster randomized to either a VLCD protocol, or a standard diabetes care intervention [22]. The VLCD intervention arm involved 3 phases: 1) Total diet replacement phase: a daily liquid formula diet replacement providing 825–853 kcal/day for 3–5 months (duration based on individualized weight loss goals); followed by 2) Food reintroduction phase: a stepped food reintroduction and increase in daily kcal for 6–8 weeks, adjusting individualized caloric intake for maintaining weight loss; and 3) Weight loss maintenance phase: a 24-month, multi-pronged, individualized medical and behavioral support model called the Counterweight-Plus program delivered either by a nurse or registered dietician for long-term weight maintenance [22][23]. The Counterweight-Plus program has been shown to be effective in real-life primary care settings in the community and, because it can be administered either by dietitians or a nurse, it reduced cost VLCD treatment to less than half of the average cost for treating an individual with T2D in the U.K. [32]. Remission from T2D was defined as HbA1c < 6.5% (<48 mmol/mol) after at least 2 months without the need for antidiabetic medications. The attrition rate for the DiRECT intervention group was 25% at 12 months [22], which is superior to the 25–50% dropout rates in the first 3 to 6 months of prior VLCD studies [27][33][34]. Results from the primary outcomes of T2D remission and weight loss were reported based on an intent-to-treat model [22][23].

At 12 months, within the VLCD intervention arm, 46% of participants achieved remission of T2D, mean weight loss was 10 kg, and 25% lost over 15 kg of body weight [22]. Remission rates and weight loss in the standard care arm at 12 months were 4% and 0% respectively [22]. Almost 74% of subjects in the VLCD intervention arm no longer needed antidiabetic medications compared to 18% in the standard care arm at month 12 of the weight maintenance phase [22]. Subjects in the VLCD intervention arm also had marked reductions in blood pressure, with 48% of participants no longer requiring the use of antihypertensive drugs, compared to no reductions in antihypertensive drug use in the standard care arm [22]. A 24 month follow up showed that 35.6% of subjects in the VLCD intervention arm remained in T2D remission, and among those who achieved remission, 70% maintained a weight reduction of over 15 kg [23]. Improvement in quality of life and general well-being were higher in subjects in the VLCD intervention than those in the standard care arm [23].

The Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) trial is another RCT in similar size and scope to the DiRECT that also specifically sought to examine T2D remission as a primary endpoint [25]. DIADEM-I recruited 147 overweight adults aged 18–50 with a BMI 27 kg/m2 or greater, and a mean T2D duration of <3 years (mean of 21.2 months) [25]. DIADEM-I defined T2D remission using a similar parameter as DiRECT, of HbA1c < 6.5% (<48 mmol/mol), and being free of antidiabetic medications for at least 3 months [25]. However, unlike DiRECT, DIADEM-I also included a more rigorous level of remission termed “normoglycemia” defined as HbA1c <5.7% (<39 mmol/mol), with no antidiabetic medications for at least 3 months [25]. All participants stopped use of antidiabetic medications, and were then randomized to receive either a supervised intervention of 12 weeks of a either a total diet replacement of a VLCD liquid formula of 800–820 kcal/day, followed by a structured 12-week food reintroduction phase (n = 70), or standard care (n = 77), based on American Diabetes Associations (ADA) guidelines [35]. Subjects in the VLCD arm also received behavioral support using a multi-component approach called the Specialist Lifestyle Management (SLiM) weight loss program, that was reported to be successful in facilitating weight loss in obesity [36]. The follow up period was 12 months from baseline. Consistent with the DiRECT [22], subjects in the VLCD intervention arm of DIADEM-I had a mean weight reduction of 11.98 kg at month 12, with 15% of subjects achieving a weight loss of greater than 15% of body weight, compared to 3.98 kg of weight loss in the control arm [25]. T2D remission and normoglycemia occurred in 61% and 33% of participants respectively in the VLCD intervention arm, and 12% and 4% of participants in the control arm. Similar to the DiRECT [22], the drop-out rate in the VLCD arm was 18.9%, (15/79), and in the control arm 12.6% (10/77) [25].

3. Comparison between a Very Low-Calorie Diet and a Low-Calorie Diet for T2D Remission

The DiRECT and the DIADEM-I are the only large-scale RCTs of VLCD to examine T2D remission as a primary endpoint. However, it is appropriate to compare their findings to those of the Look AHEAD study [10][37], the largest-RCT to examine the potential of an intensive lifestyle intervention (ILI) of diet, exercise and behavioral support to achieve and maintain long-term weight loss among obese individuals with T2D [10][37]. LookAHEAD randomized 2241 participants to an ILI of a low-calorie diet of 1200–1500 kcal/day, physical activity and intensive behavioral support [10][37]. The ILI group was compared to individuals in a standard care of diabetes support and education intervention (DSE). At the 4-year outcomes assessment, approximately 50% of the ILI group maintained the loss of 5% of their baseline body weight, and 27% lost and maintained 10% of their baseline body weight [10][37]. Although T2D remission was not a primary endpoint, using a definition of FPG of <126 mg/dL, HbA1c of <6.5% (<48 mmol/mol), without requiring any antihyperglycemic medication, post-hoc analysis in the Look AHEAD reported that 11.5% participants in the ILI group had partial or complete remission of T2D by 12 months, and 9.2% had T2D remission at 24 months, compared to 2% remission in the standard care group [10]. Also, individuals that achieved T2D remission in the ILI group, maintained 6.3% of their lost weight, compared to 0.9% weight loss maintenance in the standard care group [10][37]. A follow-up showed a decline in T2D remission rates, with

7.5% of ILI participants in remission after 4 years [38]. Compared to the LookAHEAD, mean weight loss (10 kg vs. 8.6 kg) was similar, but T2D remission rates at 12 months (46% vs. 9.2%), were superior in the DiRECT [10][22]. It is unclear why, despite having less than 15% difference in the mean weight loss reductions after 12 months, that the differences in T2D remission rate in the DiRECT study was markedly greater (>130%) than that of LookAHEAD.

A study by Sarathi et. al. [39] sought to examine T2D remission, but with more moderate calorie restriction of 1500 kcal/day than those typical of VLCD. They recruited 28 adults (mean 24 years of age) with newly diagnosed T2D (<12 months), who were then counseled to consume 1500 kcal/day using solid foods and to undertake daily brisk walking for 1 hour per day with follow-ups at 3, 12 and 24 months. After 3, 12 and 24 months, remission, defined as FPG of <100 mg/dL and HbA1c of <5.7% (< 39 mmol/mol), was reported in 53.1%, 50% and 46.9% of subjects [39]. Mean weight loss at 3, 12 and 24 months was 4.97 kg, 6.56 kg and 7.66 kg, respectively. The 24-month mean was 8.2% of initial body weight, which is similar to the 7.6% weight reduction reported in the VLCD arm in the DiRECT at 24 months [23].

Lastly, a small study (n = 8), by Petersen at al. [40], demonstrated in obese subjects with T2D, that euglycemia and improved insulin sensitivity can be achieved with a modest energy restriction of ~1200 kcal/day for 7 weeks [38]. The authors noted that normalization of T2D parameters occurred in all 8 individuals, and with a body weight reduction of 8 kg, but an 80% reduction of intra-hepatic lipids [40]. These data suggest that T2D remission, albeit at lower rates than observed with VLCD [17][20][21][22][23][24], is possible with even modest calorie restriction and exercise. This opens the possibility that individuals who struggle with the more aggressive calorie restriction of VLCD have alternatives for T2D remission approaches.

4. Degree of Weight Loss Necessary for T2D Remission

The current arguments against the use of a VLCD for weight loss are based on a body of data demonstrating that VLCD approaches are only effective in producing rapid weight loss in the short-term (<12 months), and that after the reintroduction of solid food in the long-term (≥24 months), marked weight regain is typical [27][41][31]. Data from a number of meta-analyses of VLCDs are in agreement that in the long-term (1–5 years of follow up), most individuals fail to maintain the 15–20% weight reductions that are typical of VLCDs [27][32][31]. However, data show that various degrees of T2D remission can occur across a wide range of weight loss, sometimes before any appreciable reduction in body weight occurs [10][15][18][20][23]. For example, a weight loss VLCD study by Henry et. al. [15] of 30 obese adults (mean BMI >35) with T2D, reported that within just 10 days of the VLCD, 87% of intervention subjects (26/30) showed significant reductions ($p < 0.001$) in FPG, insulin levels, and hepatic glucose output (HGO), while losing only ~4% of their initial body weight [15]. In the DiRECT, at 24 months T2D remission in the VLCD arm was reported in 5% of individuals that lost as little as 5 kg of weight, almost 30% of individuals that lost 5–10 kg of weight, and almost 60% of participants that lost 10–15 kg of weight, or 10–15% of their initial body weight [23]. No data on remission within ranges of weight loss was reported in the DIADEM-I study [25]. Evidence that more modest weight loss and T2D remission was also reported in the LookAHEAD study [10], which showed a significant ($p < 0.01$) association between T2D remission across all tertiles of weight loss in the ILI group [10].

Together, these data show that with VLCD, short-term onset of T2D remission can occur with even negligible weight loss, and for some individuals, modest reductions in body weight of 10–15% that have been documented in numerous VLCD studies [27][42], are sufficient for maintaining T2D remission in the long-term. These data also suggest that, unlike typical anti-obesity approaches that emphasize maximum weight loss [27][33], future VLCD practices for T2D remission should favor highly flexible and tailor-made weight loss targets that consider individual responses.

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