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Effect of Calorie Restriction and Exercise on Type 2 Diabetes

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EFFECT OF CALORIE RESTRICTION
AND EXERCISE ON TYPE 2 DIABETES

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ABSTRACT

Type-2 diabetes (T2D) is a chronic condition, generally regarded as an irreversible, that is among the top 10 causes of death globally. The hallmark of T2D is hyperglycemia, which results from disturbances in insulin sensitivity, insulin secretion, β-cell dysfunction and insulin resistance. Several clinical and lifestyle factors are involved in the progression of T2D, such as obesity and physical inactivity. A high-calorie diet is the main contributor to the development of obesity, which results in T2D, as obesity or increased intra-abdominal adipose tissue is related to insulin resistance. Technological advances have contributed to individuals having a more sedentary lifestyle, leading to obesity and T2D. T2D can be treated with lifestyle interventions, such as diet and exercise. Herein, we highlight the positive impact of a very low-calorie diet (VLCD) and lifestyle modalities in the treatment and prevention of T2D. An inclusion of VLCD 400-800 kcal/day for 8 weeks and $\geq$ 150 minutes exercise 5 times a week as lifestyle interventions can decrease glucose levels to normal, reduce HbA1c and improve insulin resistance and sensitivity. Therefore, a potential mechanism in maintaining glucose homeostasis and remission of T2D by VLCD and exercise reduces body weight.

Keywords: Hyperglycemia, very low-calorie diet, insulin sensitivity, insulin resistance, type 2 diabetes

INTRODUCTION

Type-2 Diabetes (T2D) is a complex metabolic disorder characterized by hyperglycemia due to an impairment in macronutrient metabolism. T2D is associated with a high risk of micro- and macrovascular co-morbid disease [1]. The first known reference to T2D comes in Egyptian manuscripts from 3000 years ago [2], and in the modern era is amongst the top 10 causes of death worldwide. Globally, 425 million people are affected by T2D, which is forecasted to increase to 693 million by 2045 [3]. This increasing trend in diabetes incidence is a significant economical burden, and currently, about US $727 billion are being spent annually on those suffering from T2D equating to one in every eight dollars spent on healthcare [3]. T2D was first considered as one of the central components of metabolic syndrome. However, it is now recognized as a complex endocrine and metabolic

disorder that results in hyperglycemia secondary to advancing insulin resistance [4].

Calorie restriction and exercise are known to promote healthy aging and decrease hyperglycemia; hence, it is central to the management of T2D [5]. Studies show that very low-calorie diets (VLCD) for short durations are effective in managing T2D [6,7]. VLCDs cause significant weight loss with reductions of 5-10% body weight improving blood glucose, lipid profile and blood pressure [8]. However, adhering to chronic and extreme diets like VLCD is challenging for this population, and has some negative consequences on health [5]. This review focuses on the therapeutic potential and challenges of VLCD and exercise for the management of T2D.

METHODOLOGY

A literature search was conducted using a Science Direct, PubMed, Web of Science, SCOPUS, Springer and Google Scholar databases. Search terms included "Diabetes" OR "Type 2 Diabetes" OR "Hyperglycemia" OR "Hyperinsulinemia" OR "Insulin Resistance" AND "Pathogenesis" OR "Inflammation" OR "Cytokines" OR "β-cells dysfunction" AND "Dietary Intervention" OR "Calorie Restriction" OR "Low-Calorie Diet" OR "Very Low-Calorie Diet" OR "Fasting" AND "Lifestyle Intervention" OR "Physical Activity" OR "Exercise" OR "Aerobic" OR "En-

durance Training" OR "Resistance Training" OR "Combined Training." Although many articles are available that discuss the effects of dietary restriction and exercise individually on diabetes, the current review primarily focused on the combined effect of the two on T2D outcomes. Studies that focus on human studies were identified and those articles containing relevant data were thoroughly reviewed (Fig. 1). The reviewing process considered the modification of lifestyle (calorie restriction and exercise) and how this modality reduces the burden of T2D.

PATHOGENESIS OF TYPE 2 DIABETES

Diabetes is condition characterized by disruption in the balance between plasma glucose levels and glucose uptake by the tissues, with resultant hyperglycemia. High plasma glucose concentrations stimulate insulin secretion from the β-cells of the pancreas, which in turn stimulates glucose uptake by the peripheral tissues, most notably the liver, muscle and fat tissue. Insulin also acts to suppress muscle glycogenolysis, adipose lipolysis and hepatic gluconeogenesis to maintain glucose homeostasis [9]. In diabetic patients, chronic hyperglycemia, with resultant hyperinsulinemia leads to progressive insulin resistance, impairing glucose uptake. A positive cycle of insulin resistance and hyperglycemia leads to persistent hyperinsulinemia. Over time, the pancreatic
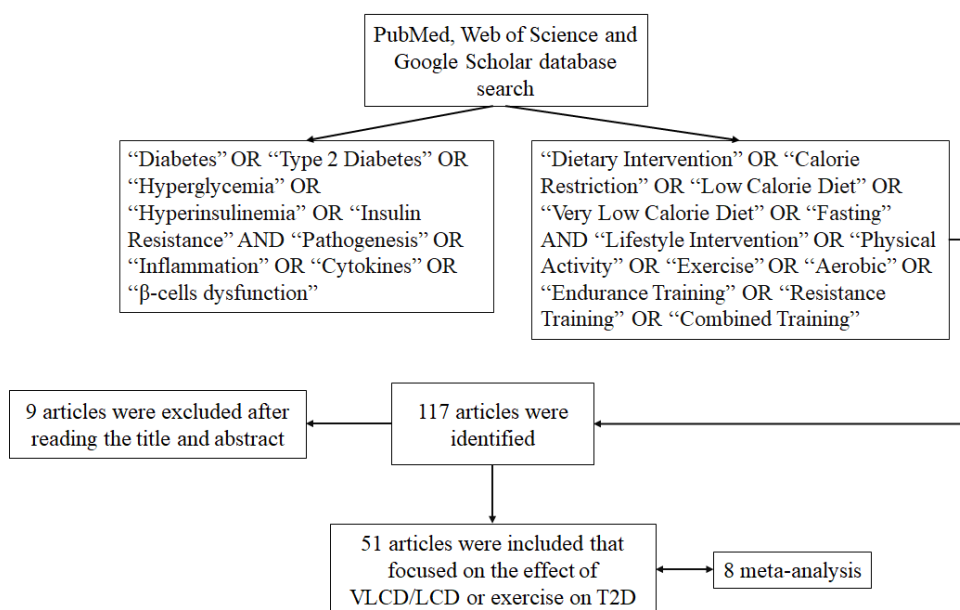

Fig. 1. *Search Methodology*

β-cells cannot maintain insulin production, leading to dysfunction [10]. Additionally, insulin is a powerful inhibitor of lipolysis; even mild elevations of insulin in the plasma cause a remarkable reduction in free fatty acid levels [11].

When glucose homeostasis is disrupted, the risk of T2D increases. The pathophysiology of T2D centres on two main factors: progressive peripheral resistance to insulin and pancreatic β-cell dysfunction with their eventual failure.

Insulin *resistance*

Chronic hyperglycemia due to factors such as poor diet and obesity leads to ongoing insulin release, and eventually the tissues lose responsivity to the hormone. Resistance to insulin action leads to the impairment of insulin-mediated glucose uptake in peripheral tissues (particularly the muscle and fat); impairment of triglyceride uptake by the adipose tissue and incomplete suppression of hepatic glucose output. To maintain glucose homeostasis in these conditions, β-cells secrete more insulin, leading to hyperinsulinemia [16]. Chronic hyperinsulinemia causes a reduction in the sensitivity of insulin, known as resistance. The main outcome of insulin resistance is to reduce glucose uptake and utilization by most body cells, with the exception of neuronal and endothelial cells. Consequently, this decrease in the uptake and utilization of glucose results in hyperglycemia 21. Additionally, obesity and intra-abdominal adipose tissue are also related to insulin resistance, with evidence suggesting that in T2D it increases in parallel with adiposity [19]. Adipose tissue is sequestered in different locations throughout the body, with varied physiological impacts, with the primary two forms being subcutaneous fat under the skin, and visceral fat surrounding the abdominal organs. Subcutaneous fat is considered to be less active, with lower adipokine secretion and less macrophage infiltration [20]. Visceral adipose tissue is a highly active secretory organ, releasing adipokines (such as adiponectin, leptin, interleukin [IL-6] and tumor necrosis factor-α) directly into the portal circulation affecting hepatic glucose and lipid metabolism. High levels of adipokines induce a pro-inflammatory and oxidative state, further reducing insulin sensitivity and exacerbating insulin resistance [21]. Together, insulin resistance and β-cell dysfunction eventually lead to T2D (Fig. 2).

Pancreatic *β-cells*

In T2D, the early stages of β-cell dysfunction are characterized by impairment of the secretion of insulin and ultimately leads to the onset of glucose intolerance [13]. In the first phase of the
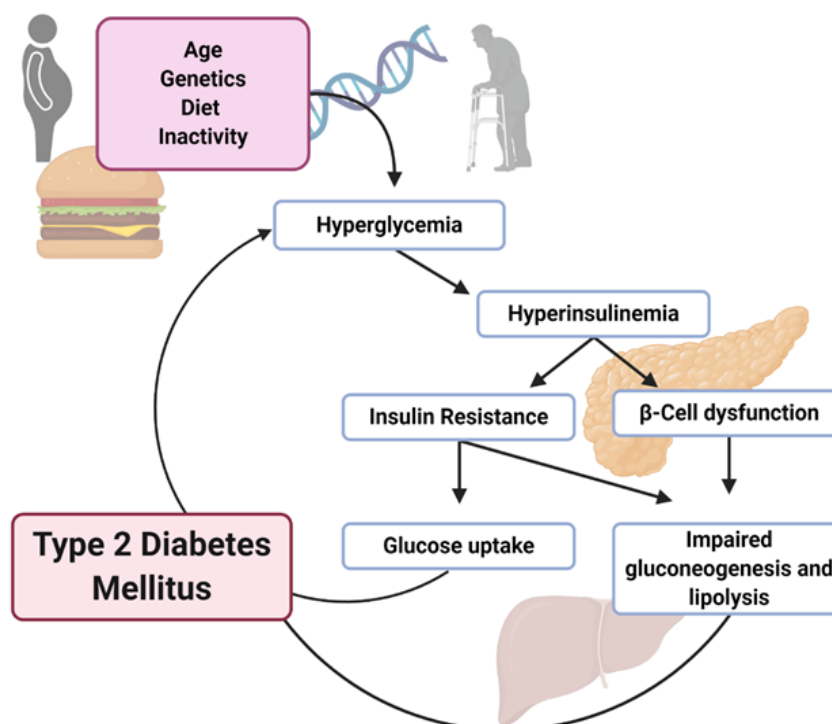

Fig. 2. *Pathophysiology of type-2 diabetes*

progression of diabetes, insulin secretion is elevated to maintain glucose homeostasis in the face of insulin resistance and the resulting hyperglycemia [14]. However, in the second phase, when the disease progresses, there is an impairment of newly synthesized insulin. This condition is reversible in some patients by ongoing glycemic control. On the other hand, if hyperglycemia persists, it will lead to the inhibition of glucose mediated insulin release. Moreover, it can cause accumulation of glycogen in the β-cells due to sustained hyperglycemia, leading to a phenomenon known as β-cell glucotoxicity or desensitization [15].

The complications of type-2 diabetes

People living with T2D are at elevated risk of both micro- and macrovascular diseases. Common macrovascular outcomes include peripheral vascular disease, coronary heart disease and stroke, and common microvascular complications include polyneuropathy, retinopathy and nephropathy. There are also a number of diabetic outcomes related to both micro- and macrovascular damage such as diabetic foot (Fig. 3). The risk of mortality and morbidity is more closely related to macrovascular degeneration compared to microvascular complications in older people. Generally, complications of T2D are divided into two categories:

1. Acute metabolic complications, which are generally short term, such as ketoacidosis, hypoglycemia and hyperglycemia.

2. Late systemic complications, which are long term chronic complications including polyneuropathy and cardiovascular disease. [22]

Microvascular complications are strongly related to hemoglobin A1c (HbA1c), whereas macrovascular complications may develop earlier but do not correlate closely with HbA1c. Glucotoxicity and lipotoxicity secondary to hyperglycemia, hyperinsulinemia and β-cell dysfunction, underlie the complications of T2D, and these early pathophysiologic events are at least partially reversible. However, the management of hyperglycemia in the later stages of T2D is unlikely to reverse macrovascular damage and resulting cardiovascular disease. This highlights the impact of early intervention to improve hyperglycemia and prevent/delay long-term microvascular and macrovascular complications [23].
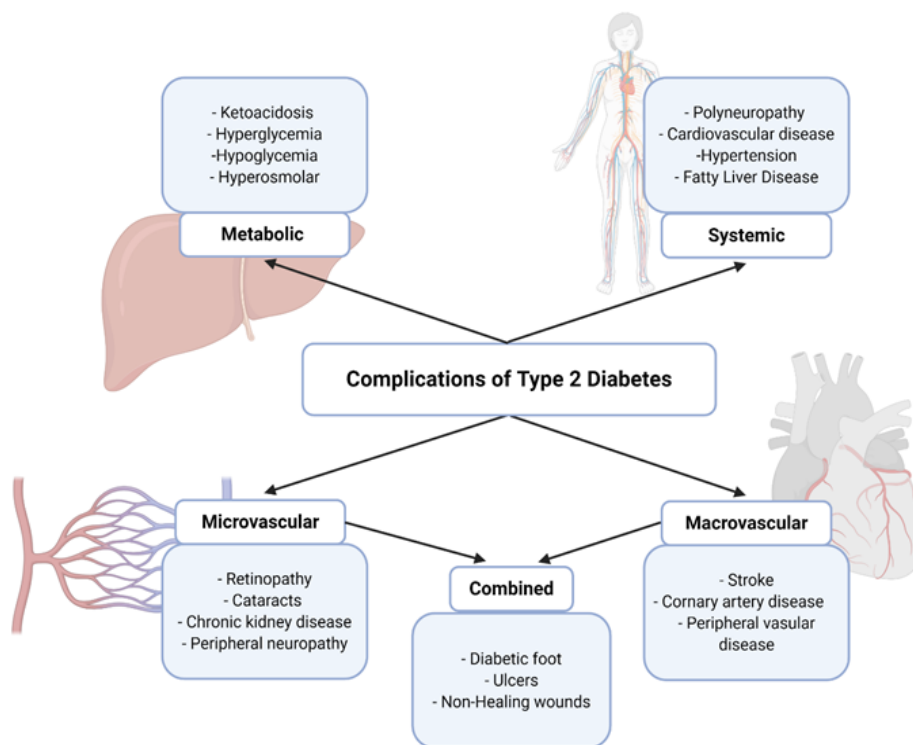

Fig. 3. *Complications of type-2 diabetes*

INFLAMMATION AS A RISK FACTOR FOR TYPE 2 DIABETES

The innate immune system is the first line of defense against chemical, or physical injury, and microbial invasion, which works to restore homeostasis by eliminating threats and repairing tissue damage. The systemic component of the innate immune response is known as the acute phase response which relies upon a diverse range of inflammatory mediators known as cytokines. Cytokines are small proteins that are involved in cell signaling pathways for interaction and communication. Cytokines stimulate the production of acute-phase proteins from the liver, such as C-reactive protein (CRP), serum amyloid A, alpha-1-acid glycoprotein, complement and fibrinogen. The level of these acute-phase proteins, may increase or decrease during injury and inflammation. Interestingly, these inflammatory markers are also known to increase in metabolic syndrome as well as in T2D [24]. In T2D, high CRP levels are related to advanced stages of atherosclerosis, particularly in patients with elevated HbA1c levels and a high concentration of advanced glycation end products [25]. Additionally, in a range of chronic conditions including T2D, tumor necrosis factor (TNF)-α levels are known to increase. There are several factors including nutrition, physical inactivity and age which contribute to the activation of the innate immune system underlying the increased secretion of cytokines and associated inflammation. However in those living with diabetes, the chronic inflammation has important consequences. Inflammatory proteins, CRP, interleukin-6 (IL-6) and TNF-α are all known to exacerbate insulin resistance, T2D and metabolic syndrome. Additionally, high IL-6 and TNF-α are also associated with obesity, T2D, heart disease and endothelial dysfunction [25]. Individuals with impaired glucose tolerance or impaired fasting glucose show higher levels of IL-6 compared to healthy individuals [26], and others have noted that inflammatory markers are related to insulin resistance, but not to insulin secretion [27]. Inhibiting IL-6 signaling through administration of anti-IL-6 receptor monoclonal antibodies results in improved insulin sensitivity and decreased HbA1c levels providing evidence for a therapeutic benefit in countering chronic inflammation in T2D [28]. However, it has also been shown that a combination of calorie restriction to 500 kcal/day, sibutramine (appetite suppressant drug) and an exercise program for 12 weeks in obese individuals leads to meaningful decrease in IL-6 levels [29]. Calorie restriction and regular exercise also improve insulin action, insulin sensitivity and fasting blood glucose levels by reducing body fat, macrophage accumulation and inflammatory cytokine concentrations, with broad anti-inflammatory effects [30] as illustrated in (Fig.4).
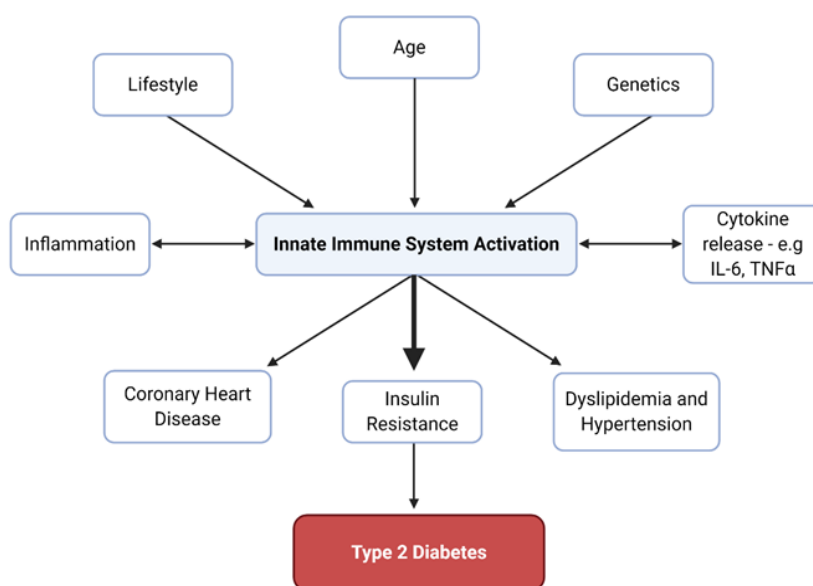

Fig. 4. *Activation of innate immune system and progression of diabetes*

OBESITY AS A RISK FACTOR FOR TYPE 2 DIABETES

Obesity results from a chronic imbalance between energy intake and expenditure, with multifactorial contributions from genetic, epigenetic, physiological, behavioral, socio-cultural and environmental factors [31]. Obesity is related to a wide range of adverse effects on health, including increased risk of disease, disability and death. Obesity has been recognized as a medical disorder since the height of ancient Greece, and the Hindu physician Sushrut (500-400BC) identified that obesity is linked with other diseases including T2D [32]. Obesity is involved in an increased risk of various diseases, including metabolic syndrome, nonalcoholic fatty liver, autoimmune disorders, gout, osteoarthritis, obstructive sleep apnea and cancer [33].

Obesity causes alterations to both the metabolic and endocrine functions of adipose tissue [34]. Increased macrophage accumulation in adipose tissue causes metabolic complications of obesity including insulin resistance and T2D [35]. Obesity leads to high levels of fatty acids and hormones, low lipid turn-over and an increase in inflammatory macrophages that cause activation of pro-inflammatory cytokines (TNF-α, IL-6) [36]. This pro-inflammatory milieu contributes to insulin resistance, T2D, cardiovascular disease, and other co-morbid disorders [34], therefore, obesity is a known risk factor that causes the development of T2D.

Obesity is thought to contribute to approximately 70% of diabetes cases [37]. In the last decade, dietary patterns have shifted towards unhealthy food (junk and fast foods) worldwide [38]. However, this is contrary to modern nutritional science, which emphasizes a varied diet rich in fresh food. It is known that poor diet has a widespread impact on cardiometabolic risk factors that not only include obesity and dyslipidemia but also blood pressure, glucose-insulin homeostasis, lipoprotein concentrations and function, oxidative stress, inflammation, endothelial health, hepatic function, adipocyte metabolism, cardiac function, metabolic expenditure, pathways of weight regulation, visceral adiposity, and the microbiome [39]. Therefore, a healthy diet and active lifestyle is suggested to decrease the risk of life-threatening disease. For greater health benefits, general dietary guidelines main-

ly focus on reducing the intake of dietary fats, particularly saturated and trans, cholesterol, refined grains, sodium, and added sugar [39]. Physical activity and a balanced diet decrease intra-abdominal fat, and reduce the impact of its metabolic effects [40] thereby improving insulin sensitivity and reducing the progression of T2D. Studies have shown that a hypocaloric diet reduces body mass, BMI, body fat percentage, waist to hip ratio, and leptin production [41]. A study of 60 obese women who ate a very low-calorie diet that included four phases (Intensive: 450–680 kcal, transition: 800–880 kcal, maintenance: 1000–1400 kcal, stabilization: 1200 kcal). This was delivered alongside an exercise intervention of 60 minutes of moderate exercise, 20–30 minutes of aerobic training, followed by 20–30 minutes of resistance exercise. They found an improvement in body composition, quality of life and cardiovascular risk factors [42]. Another cohort of 191 obese, nondiabetic patients were provided with 800-1000 kcal/day for 8 weeks. Transcriptome profiling of participant showed improvements in genes related to weight, lipid profile and glucose level [43].

MANAGING TYPE 2 DIABETES

Calorie restriction and weight reduction
Dietary interventions that provide adequate nutrition but are low in energy are known as calorie restriction (CR). As there are a number of intrinsic links to calorie intake, glucose homeostasis and obesity, calorie restriction aids in the prevention and management of T2D. Evidence has shown that calorie restriction in obese individuals increases insulin sensitivity and decreases acute insulin response to glucose [44]. In fact, calorie restriction improves insulin sensitivity by as much as 40%, as well as assisting in improved β-cell responsiveness of to glucose [45]. Very low calorie diet (VLCD) treatment for weight reduction consist of four phases: (1) initial phase: patients consume a balanced LCD of 1200 to 1500 kcal daily for 1 to 4 weeks; (2) modified fast phase: consumption of VLCD only; (3) refeeding phase: reintroducing solid food; and (4) stabilization/ maintenance phase: which focuses on nutritional education and behavior modification that help to sustain weight loss [1]. VLCD treatment can results in achiev-

ing an average weight loss of 1 to 2 kg/week for women and 1.5 to 2.5 kg/week for men [2,3]. It was observed that rapid weight reduction could increase the risk of gallstones that results in cholecystectomy [4]. Therefore, it is advised that the rate of weight loss should not exceed an average of 1.5 kg/week [5] to minimize the adverse effect of VLCD. Likewise, a study included seven obese patients with non-insulin-dependent diabetes mellitus (NIDDM) underwent four periods of low-calorie intake: (i) baseline weight maintenance diet for seven days, (ii) followed immediately by a calorie restriction diet (800 kcal/day) for seven days, (iii) followed by weight loss program for two months comprising of a very low-calorie diet (400 kcal/day) then four weeks of gradual refeeding and weight maintenance diet for seven days, (iv) a final week of calorie restriction of 800 kcal/day. This calorie restriction was associated with significant reductions in weight and BMI of the obese individuals, which decreased from 32.8 ±2 to 27.5 ±1.3 kg/m2. Even the short duration of calorie restriction (800 kcal/day) caused substantial reductions in fasting plasma glucose, hepatic glucose production, fasting plasma triglycerides, and increased insulin sensitivity and secretion. Additionally, the four different calorie intake periods demonstrated that restriction had an important regulatory effect on the metabolism of obese patients with NIDDM which was independent of weight loss [46].

Interestingly, a systematic review and meta-analysis identified six randomized control trials where VLCDs showed greater weight reduction in the short term but similar weight loss in the long term compared to LCD diets [47]. This is likely due to challenges in compliance on both diets, but particularly VLCDs. VLCDs has been used over the past 40 years, and the management of obesity and weight loss has been recognized in various nutritional guidelines. A longitudinal qualitative study of 18 participants showed that very low energy diets of <800 kcal/day for 8 weeks, reduced weight and led to diabetes remission [48]. An early study also showed that insulin-treated T2D patients with on the VLCD diet approach had significant weight reduction, which leads to the cessation of insulin treatment in some patients [49]. However, have VLCD shown some side effects such as dizziness, constipation, diarrhea, flatulence, sensitivity to cold, fatigue, dry skin, halitosis, gallstones and hair loss, with LCD better tolerated [50].

Effects of physical activity in the management of diabetes

Physical inactivity is a significant risk factor for T2D, thought to play a role in as many as 90% of cases [51]. According to World Health Organization reports and recommendations, exercise improves both physical and mental well-being and regular moderate-intensity exercise reduces cardiovascular disease, T2D and cancer [52] making exercise imperative in the management and prevention of diabetes. Physical activity as also a cost-effective therapeutic approach with few known side effects, significantly improving life quality, immune function and reducing the risk of various life-threatening diseases [53]. Most of the clinical studies that have evaluated exercise interventions in T2D have used an exercise frequency of three times per week, [54,55] however current physical activity guidelines recommend five sessions of moderate activity weekly [56,57]. Aerobic exercise for 45 minutes, three times per week over eight weeks at 50-70% heart rate, demonstrated a reduction in insulin resistance [58]. However, the effect of a single bout of exercise on insulin sensitivity lasts for 24-72 hours, depending upon the duration and intensity of the activity [59]. Generally, the duration of insulin sensitivity is not more than 72 hours, and so this should guide prescription or use, with no more than 72 hours elapsing between successive exercise sessions [60]. Four international diabetes associations, Diabetes UK, the Canadian Diabetes Association, the American Diabetes Association, and the European Association for the Study of Diabetes have reported training recommendations for T2D and are summarized in Table 1. These associations recommend a moderate to moderate intensive activity for T2D patients.

Different types of training:

a) Moderate intensity is generally classified as 55-69% of maximum heart rate (HRmax) and 55-69% of maximum oxygen consumption (VO2 max); vigorous training exercise is defined as 70-85% HRmax, (70-85% of VO2 max); and intensive exercise is defined as having greater than 85% of HRmax, (>89% of VO2 max) [61]. In one systematic review, 47 randomized trials with over 8500 participants were selected to determine the effect of physical activity on glycemic control. It was noted that the exercise of

Table 1. *Exercise recommendations for type 2 diabetes by international associations*

Associations	Training type	Frequency (per week)	Duration (min/week)	Intensity
American Diabetes Association (ADA)	ET, RT, CT	≥ 5	≥ 150	Moderate intensity
Canadian Diabetes Association (CDA)	ET, RT, CT	≥ 5	≥ 150	Moderate to moderate intensive
European Association for the Study of Diabetes (EASD)	ET, RT, CT	–	≥ 150	Moderate to moderate intensive
Diabetes UK	ET	3–5	15–60 min/session	Moderate

Endurance training (ET), Resistance training (RT), Combined training (CT)

more than 150 min/week was effective for cardiovascular health and improved T2D outcomes [62]. Therefore, it is recommended to have 150 min/week of moderate activity or 75 min/week of vigorous activity.

b) Strength training is an effective form of exercise for building bones, muscle strength, burning fat and increasing general metabolism. Evidence shows that physical activity during menopause prevents weight gain and reduces the risk of heart disease, T2D and cancer [63,64]. Aerobic exercise has been reported to result in a greater reduction in HbA1c when compared to resistance training. However, combined resistance and aerobic exercise training was significantly better than only aerobic exercise. Similarly, some long term endurance training intervention studies showed a significant reduction in HbA1c, which indicates that endurance training is associated with reducing T2D risk [65,66].

In a systematic review and meta-analysis, it was shown that 3,600 Metabolic Equivalent (MET) minutes/week reduced the risk of T2D by 19% [67]. Another study of 98 participants, receiving lifestyle intervention of 5-6 aerobic and combined aerobic and strength training sessions for 30-60 minutes a week for 12 months found remission of diabetes in 23% of participants [68]. Similarly, 98 participants with T2D who performed 5 to 6 aerobic training sessions of 30-60 minutes per week alongside 2 to 3 of resistance training showed reductions in HbA1c, glycemic control and need for glucose-lowering medications [69].

Combination of very-low-calorie diet and exercise in improving the biomarkers of type-2 diabetes

Insulin resistance is related to the etiology of T2D in both aging and obesity. However, the exact causes for the development of insulin resistance are still unclear but it is thought that overnutrition, overweight and obesity are the major contributing factors [70]. Sedentary lifestyle, and alterations in glucose metabolism due to aging and mitochondrial function are also believed to cause insulin resistance [71]. Combination of both calorie restriction and exercise have been shown to significantly decrease insulin levels in the plasma and improve insulin sensitivity in middle-aged obese and elderly overweight individuals [72]. The insulin-dependent glucose transporters are associated with specific classes of skeletal muscle oxidative metabolism. Skeletal muscle is of two types: low oxidative skeletal muscle (type 1 slow-twitch), the main fuel source are triglycerides, fatigue slowly and use aerobic respiration; fast oxidative skeletal muscle (type 2 fast-twitch), in which the main fuel source is glycogen, break down ATP quickly, contraction force is greater and while also using aerobic respiration. Low oxidative type skeletal muscle tissue has less glucose transporters 4 (GLUT4); and hence, shows a decrease in insulin sensitivity compared to high oxidative fibers [73]. Exercise helps increase both mitochondrial and GLUT4 content in skeletal muscle, improving glucose transport and utilisation in the muscle.

Evidence shows that exercise increases mitochondrial content and electron transport chain activity, whereas calorie restriction improves insulin sensitivity in overweight older adults [74]. Weight reduction secondary to calorie restriction also improves tyrosine kinase activity, the enzyme responsible for the transfer of a phosphate group from the ATP molecule to a protein in skeletal muscle insulin receptors [75], thus increasing the concentration and function of GLUT4 receptors, however it is unable to activate muscle glycogen synthase by insulin. Different mechanisms, such as the depletion of muscle glycogen, are involved in improving insulin sensitivity with calorie restriction, however the undelying mechanisms require further investigation [46]. Thus, taken together the evidence suggests that the combination of VLCD and physical activity results in weight loss and a decrease in T2D risk. A systematic review of studies showed that aerobic activity and diet combination resulted in greater reductions in weight and fasting glucose level [76]. Likewise, the long-term effect of exercise and VLCD for 16 weeks in twenty-seven obese, insulin-dependent T2D participants was observed. Patients followed a combination of VLCD, consisting of 450 kcal/day, with a weekly exercise program of 30 min aerobic exercise for four months at 70% of maximum heart rate. Bodyweight and the glucoregulatory parameters significantly improved after the four-month intervention period compared to the baseline value. Body weight (kg) in this group decreased from 114 ± 5 to 86 ± 4 and HbA1c (%) from 7.8 ± 0.4 to 6.3 ± 0.4 [77]. Studies that report a reduction in the risk of T2D through the combination of a low calorie diet and physical activity have been summarized in Table 2.

T2D and excess adiposity are linked with one another. Recent evidence shows that weight reduction through medical interventions or bariatric surgery can cause remission in T2D in young people and in those with recent onset of disease [78]. The Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) study is a current, non-blinded, pragmatic, randomized, controlled, parallel-group trial. It includes 138 subjects, younger adults with T2D, in the early stage of diabetes (≤ 3 year duration) who have undergone intensive lifestyle intervention changes (i.e., 800 kcal/day intake and 150 min/week exercise for 12 weeks) and results are hoped to identify a path to reversal of

T2D [78]. Recent evidence has also reported that low-calorie diet and lifestyle interventions resulted in a significant improvement and T2D remission [79]. For, instance, An open-label cluster-randomized primary care trial, (the DiRECT study), of 49 primary care practices in Scotland and the Tyneside region of England, demonstrated the impact of a low energy diet (LED) for T2D remission. This study followed the participants for 12 months, and it was shown that 24% of the LED intervention group achieved 15 kg weight loss, with nearly half (56%) achieving full remission [79]. Similarly, evidence showed that calorie restriction combined with exercise improved blood pressure, glucose level, lipid profile, inflammatory cytokines, reduce insulin resistance, HbA1c, circulating level of leptin, weight and waist circumference [80,81].

VLCD treatment Safety and Precautions

VLCD therapy is safe for BMI >30 kg/m^2 along with regular medical supervision but for overweight individuals with BMI of 27-30 kg/m2, VLCD should only reserved to those who have any weight-related medical problems [94, 96]. BMI ≥ 30 kg/m2 is a risk factor for cardiovascular morbidity and mortality, therefore substantial weight reduction is necessary to improve quality of life [100]. Generally, National Institute of Health (NIH) recommends to reduce energy intake by 500 kcal/day to those who have class I obesity [101]. Individuals with class II and class III obesity should restrict to 500–1000 kcal/day reduction. By reducing 500 kcal/day energy intake, a person can achieve 0.5 kg/week weight loss [102].

However, VLCD treatment is not advisable for childern and adolescents. VLCD can effect normal body growth, protein intake and increase nitrogen loss [103,104]. Also VLCD terapy is not considered safe for adults older than 50 years. Older people are at higher risk of negative nitrogen balance with weight loss as they have already depleted lean body mass and low immune response [105]. Similarly, VLCD is not appropriate for pregnant and lactating women as they have increased nutritional requirements [106]. Furthermore, other people that should be excluded from VLCD treatment are those suffering from cardiac disease, hepatic disease, renal disease, infectious disease, psychiatric disease (bulimia nervosa or anorex-

Table 2. *Studies showing the effect of very low calorie diet, low calorie diet and exercise on type-2 diabetes*

Characteristics of participants	Diet and lifestyle modification	Duration	Primary outcomes	Results
11 participants with type 2 diabetes	600 kcal/day and habitual level of physical activity	8 weeks	Normalization of both beta cell function	Normalized Fasting plasma glucose and improve hepatic insulin sensitivity [99]
30 individuals with T2D	Very low calories diet 624–700 kcal/day	8 weeks with VLDL	weight loss in 40% of repondent	HbA1c fell significantly from 7.1 ± 0.3 to $5.8 \pm 0.2\%$ in responders and plasma glucose of <7 mmol/L [82].
10 participants with obesity	Very low calorie diet 800kcal/day divided into 4-5 meal per day and 45min/week exercise	12 weeks	Body weight and body fat significantly decreased	Leptin to adiponectin ratio improve which is a biomarker for the insulin sensitivity [83].
70 participants with coronary artery disease	800-1000 kcal/day 12 week aerobic interval training 3 times/week followed by 40 weeks AIT 2 times a week	8-10 weeks	Weight and central body fat loss	Lower, total cholesterol, triglycerides, and inflammation [84]
145 overweight or obese patients with T2D	1200 to 1800 kcal per day, 175 minutes of moderate intensity physical activity every week	1 year	Reduce weight	Reduce HbA1c and cardiovascular risk factors [85]
306 individuals with T2D	825–853 kcal/day formula diet	3–5 months	Reduction in body weight. Some patients complaint about the biliary colic and abdominal pain	Remission of T2D in 46% of participants [79].
278 obese adults	810 kcal/day formula diet	12 weeks	weight change at 12 months	Improve the risk of cardio-metabolic disease [86].
19 patients with diabetes and obesity	600 kcal/day	8 weeks	Reduce weight, insulin resistance and increase beta cell function	First 2 weeks of VLDL improve glycemic control. 8th and 12th weeks of VLDL leads to diabetes remission in 79% participants [87].
383 obese but non diabetic patients	800-100kcal/day	8 weeks	Reduced weight and improve glycemic control	Improve long term metabolic outcomes and prevent T2D [88]
433 obese but non diabetic patients	800 kcal/day	8 weeks	-	Improve insulin sensitivity [89]
2224 individuals	810 kcal/day	8 weeks	Reduce fat free mass, hip circumference, pulse pressure, and insulin resistance.	Following calorie restricted diet cause normal glycemia in 35% of participants [90]

Alternate Days Calories Restriction

Characteristics of participants	Alternate day calorie restriction	Habitual diet days	Duration	Results
63 overweight or obese participants with T2D	2 days severe energy restriction (1670-2500 kJ/day)	5 days of habitual eating	12 weeks	HbA1c and percent body weight reduced $-0.7 \pm 0.9\%$ and $-5.9 \pm 4\%$, (< 0.001) respectively [91]
54 individuals with type 2 diabetes	VLCD for 5 consecutive days (2 weeks) followed by either intermittent VLCD (400-600kcal) for 1 day/week (15 weeks) or 1500−1800 kcal/day diet at other times for 5 consecutive days every 5 weeks (5-day)	Standard behavioral therapy (SBT) with a 1500−1800 kcal/day diet	20 week	VLCD cause reduction of weight and attained a normal HbA_{1c} [92].
35 overweight or obese but healthy adults into 4 groups: Alternate days calorie restriction(ADCR) (n=13), exercise (n=10), exercise plus ADCR (n= 12), and control (n = 10)	VLCD (400–500 kcal) Exercise session: 1) 5 min warm up; 2) 40 minutes resistance training; 3) 20 minutes aerobic exercise; 4) 5 minutes cool-down	Received ad libitum on the remaining 4 days of the week	8 weeks	ADCR and exercise induce beneficial changes in body weight, body composition, glucose, insulin, insulin resistance and triglyceride in overweight and obese adults [93].

VLCD= Very Low Calorie Diet, **LCD=**Low Calorie Diet, **ADCR=** Alternate Day Calorie Restriction

ia nervosa) and type 1 diabetes because of severe ketosis or hypoglycemia [94].

The VLCD is known to reduce weight while preserve lean body mass, achieved by providing greater amount of dietary protein 0.8 to 1.5 g protein/kg ideal body weight [107]. Protein can be provided in form of milk, soy, or egg-based powder (mixed with water). Vitamins and mineral supplements should be given to fulfill body needs [96,108]. To maintain electrolyte balance, 3 to 5 g of sodium chloride, and 3 g of potassium will be given and patients should be asked to drink 1.5 to 2 L of noncaloric fluid per day[109]. Maintaining proper hydration is very important during VLCD treatment to prevent orthostatic hypotension [110].

Patients receiving VLCD should be monitored during first 2 weeks of rapid weight loss as the side effects from VLCD therapy are common during the first 2 weeks of treatment [111]. It is difficult to maintain weight loss in a long term after VLCD treatment. Maintenance of weight loss can be achieved by active follow up with behavioral therapy, nutrition education and exercise [108]. Unsupervised VLCD can results in serious complications including death of patient [108]. Evidence showed that VLCD for longer duration can even lead to cardiac complication and hence death. No death rate was observed when VLCD has been taken for 8 weeks or less [112].

Weight reduction maintenance with VLCD

VLCD is known to be superior treatment as compared to LCD to achieve short term weight loss but achieving long term weight loss maintenance is difficult. The National Heart, Lung, and Blood Institute (NHLBI) expert panel recommended LCD (1000 to 1500 kcal/day) over VLCD. The panel's decision was based on data from randomized trials that reported no differences in long-term weight losses between VLCDs and LCDs; in fact, greater weight regain was observed after VLCD treatment [113]. However, despite this expert panel's conclusion, the majority of individual randomized trials reported greater long-term weight losses after VLCDs. For instance, in a meta-analysis of long-term studies, demonstrated that VLCD treatment has been association in achieving greater long-term weight loss as compared to LCD [114]. Similar-

ly, Astrup and Rossner illustrated that the larger initial weight loss induced by VLCD is related to greater long-term weight reduction [115], Although, long term weight loss with VLCD can be obtained when combined with behavioral therapy and regular exercise. Considerably, exercise will not increase the weight reduction, but it is helpful in maintaining weight loss [116]. Behavioral therapy (food diaries, shopping strategies, dietary preference) and exercise can help to maintain weight loss for 1- 3 years after VLCD. However, VLDL diets results in increasing psychological stress and hormone level such as cortisol that can eventually induce negative effects on insulin resistance and lower dietary success [117]. Therefore, psychological counselling is very important for patients receiving VLCD. Consequently, total duration VLCD intervention consist of 4-6 months that includes introduction of VLCD for 8 weeks, refeeding and stability phase, is helpful to reduce weight without any further complications. After VLCD treatment (4-6 months), patients should gradually introduce to LCD along with behavioral modification and exercise to sustain body weight.

CONCLUSION

The number of cases of T2D is increasing rapidly worldwide and contributes to enormous social and personal suffering and economic burden. Patients present with hyperglycemia due to the progressive deterioration of glucose metabolism over the years. High-calorie diets and physical inactivity are major contributors to the causes and initiation of T2D. There is a strong evidence that physical activity and dietary modalities reduce the risk of morbidity and mortality in individuals with T2D. Strategies that deal with this global problem of increased rates of T2D and its complications should focus on physical activity and how to reverse the condition at the population level. Moreover, calorie restriction diets also prove to be beneficial in the management of T2D. Therefore, future research is required to include long-term lifestyle interventions including very low-calorie diets and exercise and to analyzed the remission outcomes of patients with T2D.

Disclosure of interest

The authors do not have any conflict of interest.

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Резиме

ЕФЕКТОТ НА ОГРАНИЧУВАЊЕТО НА КАЛОРИИТЕ
И ВЕЖБАЊЕТО ВРЗ ДИЈАБЕТЕС ТИП 2

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Дијабетес тип 2 (T2D) е хронична состојба, општо се смета за неповратна и е меѓу првите 10 причини за смрт на глобално ниво. Карактеристика на T2D е хипергликемијата, што произлегува од нарушувања на чувствителноста на инсулин, секрецијата на инсулин, дисфункцијата на β-клетките и инсулинска резистенција. Неколку клинички фактори и фактори на живот се вклучени во прогресијата на T2D, како што се дебелината и физичката неактивност. Високо-калоричната диета најмногу придонесува за развојот на дебелината, што резултира со T2D, бидејќи дебелината или зголеменото интраабдоминално масно ткиво е поврзано со инсулин-ската резистенција. Технолошкиот напредок придонесе поединци да имаат повеќе седентарен начин на живот, што доведува до дебелина и T2D. T2D може да се третира со интервенции во животниот стил, како што се диета и вежбање. Овде го потенцираме позитивното влијание на многу нискокаличната диета (VLCD) и модалитетите на животниот стил во третманот и пре-венцијата на T2D. Вклучување на VLCD 400–800 kcal/ден за време од 8 недели и ≥ 150 минути вежбање петпати неделно – бидејќи интервенциите во животниот стил може да ги намалат ни-воата на глукоза до нормала, да го намалат HbA1c и да ја подобрат инсулинската резистенција и чувствителност. Затоа, потенцијалниот механизам за одржување на хомеостазата на глукозата и ремисијата на T2D со VLCD и вежбање ја намалува телесната тежина.

Клучни зборови: хипергликемија, нискокалична диета, чувствителност на инсулин, инсулинска резистенција, дијабетес тип 2