Effect of a Ketogenic Diet on Body Weight and Lipid Profile

Nabeela Kanwal¹, Seemin Kashif², Muhammad Kashif³, Allaudin⁴, and Gulalai Rehman⁵*

¹Dept. of Dermatology, PIMS hospital G8/3 Islamabad, Pakistan; ²Dept. of Environmental Design & Nutritional Sciences, Allama Iqbal Open University, Islamabad, Pakistan; ³Dept. of Anesthesia, Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia; ⁴Dept. of Surgery, Bolan Medical College Quetta and Fellow Bariatric Surgery Shifa International Hospital, Islamabad, Pakistan; and ⁵Dept. of Nutrition, Baluchistan Institute of Nephro-Urology, Quetta, Pakistan.

*Correspondence: drgulalai@yahoo.com (Dr. Gulalai Rehman, Consultant Nutritionist, Department of Nutrition, Baluchistan Institute of Nephro-Urology, Quetta, Pakistan).

ABSTRACT
This review article aimed to study the effects of a ketogenic diet on obesity-related measures, and lipid profiles. Total 22 articles were included in the review. Anthropometric measures included in the review were total body mass (Wt), fat mass (FM), body mass index (BMI), and waist circumference (WC). Lipid profile included in this review was serum cholesterol level, serum HDL, serum LDL, and serum triglycerides (TAG). The shortest intervention in these studies lasted for 4 days, and the longest intervention lasted for 12 months. There was a significant Wt loss in all studies. Significant reduction in BMI, FM, and WC was also observed in many studies. In most studies, variable effects on lipid profile were observed. Serum TC level fell in 10 studies and serum TAG levels decreased in 13 studies, but this reduction was statistically insignificant in most studies. Serum LDL level fell in 10 studies and increased in 3 studies, and serum HDL levels fell in 7 studies and increased in 6 studies, but these changes were also not statistically significant in most studies. This review article found beneficial effects of ketogenic diet weight loss and lipid profile, but the studies in this review included dietary intervention of a period≤12 months. Studies for extended periods (at least ≥2 years) should be done to observe long-term effects of a ketogenic diet.

Keywords: Ketogenic diet, high-fat diet, BMI, weight loss, HDL, lipid profile, Type2 DM, and NAFLD.

INTRODUCTION:
Ketogenic diet (KD) is a diet characterized by a very low carbohydrate content i.e. 5%-10% of total daily intake, or 20-50 g per day (Watanabe et al., 2020). A very-low-calorie ketogenic diet (VLCKD) plan is divided into phases. The first phase is with a calorie intake of 600-800 kcal/day and restricted carbohydrates, resulting in a ketosis state. This state is pursued until 80-90% of the normal weight is obtained. The second phase includes the progressive introduction of carbohydrates. Calorie intake is increased from 800 to 1500 kcal/day until the normal weight is achieved. The last maintenance phase is with an intake of 1500-2000 kcal/day. The second and third phases are not ketogenic (Perticone et al., 2019). Rapid weight loss associated with KD makes it one of the most popular diets. Along with being a tough diet due to strict carbohydrate restrictions, it is also an expensive diet as cheaper carbohydrates are exchanged by expensive meat, low-carb flours, and specific types of fats like MCT, butter, and nuts. Adverse health consequences of a ketogenic diet are believed to be due to its high saturated fat content. Some researchers have reported lipid profile derangements following this diet (Batch et al., 2020; Muscogiuri et al., 2019), which is expected to happen following a very high-fat diet. But contrary
to this expectation, many studies reported an improvement in lipid profile (Batch et al., 2020; Ministrini et al., 2019; Valenzano et al., 2019).

This review article was aimed at studying outcomes of KD and VLCKD on obesity-related measures, and on lipid profile. It also discussed the effects of KD on certain obesity-related diseases.

MATERIALS AND METHODS:
Review of Literature
A systematic literature search Google scholar was performed to identify various studies published since 2017. Only those studies were included which were done on “human subjects”, with overweight or obesity. Studies were included which evaluated the effects of KD and VLCKD on blood sugar control, decrease in fat mass, and lipid profile as main measures. The search terms were composed of a combination of keywords “ketogenic diet or high-fat diet”, “weight loss”, “lipid profile”, “NAFLD”, and “Type2 DM”. Reference lists of review articles were also screened to identify eligible studies. A total of 49 articles were extracted. Two articles were removed because they were animal studies. Other 17 articles were removed because 12 of them were review articles, one was an editorial, 3 were opinions, and one was a case report. Three more articles were removed because they included only one gender. Further 5 articles were removed because they did not contain desired outcome variables. Hence total 22 articles were selected (Fig. 1).

Inclusive/exclusive criteria
Inclusive criteria were: (1) studies including ketogenic diet (KD) or very-low-calorie ketogenic diet (VLCKD), (2) studies including obese patients, with or without any chronic disease, and (3) studies carried out on humans. Exclusive criteria were: (1) case report studies, (2) meta-analysis or review studies, (3) editorials and opinions, (4) studies on animals, (5) studies on one gender only, and (6) studies not having desired outcome variables.

Outcome measures
Outcome measures included anthropometric measures and biochemical measures. Anthropometric measures included in the review were total body mass (weight=W), fat mass (FM), body mass index (BMI), and waist circumference (WC). Biochemical measures included lipid profile i.e. serum total cholesterol (TC), serum high-density lipoprotein (HDL), and serum low-density lipoprotein (LDL), and serum triglycerides (TAG).

RESULTS:
In our review, the dietary intervention lasted for ≤5 weeks in 10 studies, and for >5 weeks in 12 studies. The shortest intervention in these studies lasted for 4 days, and the longest intervention lasted for 12 months (Table 1).

Anthropometric measures
A significant change in Wt was observed in most studies in the review (Table 1). This decline in Wt actually reflected total fat loss, which included loss of visceral fat also. The studies which did not mention body weight, reflected fat loss in form of change in

Fig. 1: Study selection flow-diagram.
BMI, fat mass (FM), or waist circumference (WC). Out of total 22 studies, 18 studies showed a significant reduction in body weight (total body mass). Similarly, there was a significant loss of fat in 12 studies, a significant reduction in BMI in 13 studies, and a significant reduction in WC in 7 studies. Only 2 studies were shorter than a week duration (Luukkonen et al., 2020), still a significant decrease in Wt and other anthropometric measures was observed.

**Biochemical measures**
KD affected lipid profile variably. In most studies, the effects were present but were not statistically significant. Serum TC level fell in 10 studies, though this reduction was not statistically significant in many of these studies. Similarly, serum LDL level fell in 10 studies, however, it was found to increase in 3 studies, and serum HDL levels fell in 7 studies and increased in 6 studies. Shifts in HDL, LDL, and TAG levels were also not statistically significant in most studies. The influence of length of interventions was also overviewed. Only 2 studies were shorter than a week duration (Luukkonen et al., 2020; Myette-Côté et al., 2018), still significant decrease in Wt and other anthropometric measures was observed. In one of these studies (Luukkonen et al., 2020), insignificant fall in TC, HDL, and LDL levels, but in the other study (Myette-Côté et al., 2018), insignificant rise in serum triglyceride levels was observed. Significant decrease in weight and/or other anthropometric measures in all other studies of 2-5 weeks duration were observed. In 3 of these studies, a decline in lipids was observed which was significant. The remaining studies showed an insignificant decrease in lipid levels. Two studies had insignificant increase in HDL level. Like the short duration studies, longer duration studies (=>5 weeks) also showed significant decline in weight and/or all anthropometric measures. Out of 12 studies, 8 studies included lipid profile. TC level fell statistically significantly in 4 out of 8 studies and insignificantly in one study, and TAG level fell significantly in 6 out of 8 studies, and insignificantly in one of these studies. In a study, HDL level fell significantly, and in other two studies fell insignificantly.

**Table 1:** Characteristics of trials of ketogenic diet published in last five years and their effects on obesity and lipid profile.

<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Participants of intervention/Control groups</th>
<th>Intervention</th>
<th>Duration of ketogenic Phase (weeks)</th>
<th>Inclusion criteria</th>
<th>Study objective</th>
<th>Parameters with effects &amp; Significance</th>
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<tbody>
<tr>
<td>Myette-Côté, 2018</td>
<td>Canada</td>
<td>Randomized crossover study</td>
<td>11/11</td>
<td>Low-carb, high-fat diet</td>
<td>4 days</td>
<td>Adults with Type2 DM, age 40-75 years, both genders</td>
<td>Effect of low-carbohydrate, high-fat diet with/without post-meal walks on type2 DM patients</td>
<td>Wt↓¹, TAG↑²</td>
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<tr>
<td>Luukkonen, 2020</td>
<td>Finland</td>
<td>Nutritional interventiona l study</td>
<td>10/None</td>
<td>KD</td>
<td>6 days</td>
<td>Over weight/obese adults, both genders</td>
<td>KD reverses NAFLD and insulin resistance despite increasing circulating non-esterified fatty acids (NEFA)</td>
<td>Wt↓¹, FM↓¹, BMI↓¹, WC↓¹, TC↓¹, HDL↓¹, LDL↓¹</td>
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<td>Choi, 2018</td>
<td>Korea</td>
<td>Randomized controlled trial</td>
<td>19/11</td>
<td>KD</td>
<td>2 weeks</td>
<td>Age 19-49 years, BMI&gt;25, both genders</td>
<td>Effects of low-calorie ketogenic nutrition drinks</td>
<td>Wt↓¹, FM↓¹, BMI↓¹, WC↓¹, TC↓¹, HDL↓¹, LDL↓¹, TAG↓¹</td>
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<tr>
<td>Author(s)</td>
<td>Country</td>
<td>Study Type</td>
<td>Participants</td>
<td>Design</td>
<td>Duration</td>
<td>Intervention</td>
<td>Outcome Measures</td>
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<tr>
<td>Merra, 2017</td>
<td>Italy</td>
<td>Crossover randomised double-blind trial</td>
<td>54/54</td>
<td>VLCKD</td>
<td>3 weeks</td>
<td>18-65 years, BMI ≥25, both genders</td>
<td>VLCKD and KD used as part of lifestyle modification, Wt↓, FM↓, BMI↓, WC↓, TC↓, HDL↓, LDL↓, TAG↓</td>
<td></td>
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<tr>
<td>Buscemi et al., 2021</td>
<td>Italy</td>
<td>Cohort</td>
<td>31/20</td>
<td>VLCKD</td>
<td>10-12 weeks</td>
<td>Both genders, 18-65 years, BMI 27-39.9, and non-diabetic or type 2DM from &lt;6 years with HbA1c ≤ 10%</td>
<td>VLCKD and vitamin D levels, Wt↓, FM↓, BMI↓, WC↓, TC↓, HDL↓, LDL↓, TAG↓</td>
<td></td>
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<tr>
<td>Gomez Arbelaez, 2018</td>
<td>Spain</td>
<td>Nutritional interventional study</td>
<td>20/None</td>
<td>VLCKD</td>
<td>4 months</td>
<td>Age 18-65 years, BMI ≥30, both genders</td>
<td>Changes in RMR, and associated hormonal alterations in patients with a VLCK-diet, Wt↓, BMI↓</td>
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<td>Sajoux, 2019</td>
<td>Spain</td>
<td>Cohort</td>
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<td>VLCDK</td>
<td>2-3 months</td>
<td>Overweight/obese adults, both genders</td>
<td>VLCK diet can change body composition, Wt↓, BMI↓</td>
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<td>Bruci, 2020</td>
<td>Italy</td>
<td>Observational prospective study</td>
<td>92/None</td>
<td>VLCKD</td>
<td>3 months</td>
<td>Obese patients coming to High Specialization Centre for the Care of Obesity, Sapienza University of Rome, both genders</td>
<td>Efficacy of VLCKD in mild kidney failure, Wt↓, FM↓, BMI↓, TC↓, HDL↓, LDL↓, TAG↓</td>
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<tr>
<td>Pilone, 2018</td>
<td>Italy</td>
<td>Nutritional interventional study</td>
<td>119/None</td>
<td>VLCKD</td>
<td>30 days</td>
<td>Age 18-62 years, BMI ≥ 40, both genders</td>
<td>Evaluation of effect of VLCKD, Wt↓, FM↓, BMI↓, WC↓, TC↑, HDL↑, LDL↓, TAG↓</td>
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<td>Valenzano, 2019</td>
<td>Italy</td>
<td>Nutritional interventional study</td>
<td>20/None</td>
<td>VLCKD</td>
<td>8 weeks</td>
<td>Obese adults, age 20-60 years, both genders</td>
<td>Effect of VLCKD, Wt↓, FM↓, BMI↓, TC↑, HDL↓, LDL↓, TAG↓</td>
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<td>McKenzie, 2017</td>
<td>USA</td>
<td>Nutritional interventional study</td>
<td>238/None</td>
<td>VLCKD</td>
<td>10 weeks</td>
<td>Type 2DM, age 21-65 years, both genders</td>
<td>Individuals with T2D could achieve weight loss, Wt↓, BMI↓, TC↑, HDL↑, LDL↑, TAG↑</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Type</td>
<td>Participants</td>
<td>Duration</td>
<td>Interventions</td>
<td>Outcome Measures</td>
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<td>Volek, 2019</td>
<td>USA</td>
<td>Nutritional interventional study</td>
<td>14/15 KD</td>
<td>12 weeks</td>
<td>Healthy adults from various military branches, both genders</td>
<td>Meta- and performance responses of KD</td>
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<td>Walton, 2019</td>
<td>USA</td>
<td>Nutritional interventional study</td>
<td>11/None Low-carb, high-fat diet</td>
<td>90 days</td>
<td>Age 18-45 years, females, type 2 DM Low-carbohydrate diets are effective to improve insulin resistance</td>
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<tr>
<td>Castro, 2018</td>
<td>Spain</td>
<td>Nutritional interventional study</td>
<td>20/None VLCKD</td>
<td>4 months</td>
<td>Age 18-65 years, BMI ≥ 30, both genders Weight loss FM↓</td>
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<tr>
<td>Greene, 2018</td>
<td>Australia</td>
<td>Randomized, crossover design</td>
<td>12/12 LCKD</td>
<td>6 months</td>
<td>14 power lifters and weight lifters, both genders, age range 18-55 years LCKD could be used by weightlifters Wt↓</td>
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<tr>
<td>Perticone, 2019</td>
<td>Italy</td>
<td>Nutritional interventional study</td>
<td>28/28 VLCKD</td>
<td>12 months</td>
<td>Overweight/obese adults, both genders Ketogenic diet effect on vitamin D levels WC↓</td>
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<tr>
<td>Saslow, 2017</td>
<td>USA</td>
<td>Randomized controlled trial</td>
<td>16/18 VLCKD</td>
<td>12 months</td>
<td>Aged ≥18 years, BMI ≥ 25, HbA1c &gt; 6.0% Compare LCK and moderate carbohydrate diet. Wt↓</td>
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1significant values in **bold letters**, 2insignificant values in *italics*, KD = ketogenic diet, LCKD = low-carbohydrate ketogenic diet, VLCKD = very low-calorie ketogenic diet, Wt = body weight, FM = fat mass, BMI = body mass index, WC = waist circumference, TC = serum total cholesterol, HDL = serum high-density lipoprotein, LDL = serum low-density lipoprotein, TAG = serum triglycerides

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**Fig. 2:** Significant and insignificant changes after ketogenic diet.

(a) Significant changes:

(b) Insignificant changes:
Similarly, HDL level increased significantly in a study, and insignificantly in 3 studies. Significant rise in HDL level occurred in 90 days intervention (Walton et al., 2019), and two insignificant increases in HDL level occurred in 12 months interventions (Perticone et al., 2019; Saslow et al., 2017). LDL levels fell significantly in one study (Valenzano et al., 2019), and insignificantly in 3 studies, but increased insignificantly in only 2 studies. There was no significant increase in LDL levels in any study.

**DISCUSSION:**

All studies constituting this review revealed a statistically significant reduction in body fat in terms of weight, fat mass, BMI, and WC. Our review also found correction of lipid profile in most studies. In this review, a variable effect of ketogenic diet was observed on lipid profile. It was expected that a very high-fat diet would lead to derangements in the lipid profile. However, contrary to this expectation, a shift of lipid levels was found towards the healthy side. Serum TC declined in all the studies in which it was measured. Serum LDL and TAG levels increased insignificantly in some studies but fell in majority of the studies, but HDL levels increased in about 50% of these. Our pre-sent review, however, found a decrease in LDL levels in most studies, and even at 12 months of dietary intervention (Perticone et al., 2019).

**Effect on fat loss**

According to literature, ketogenic diet caused double the reduction of Wt on the 15th day of the intervention as compared to a diet with restricted calories only (Drabińska et al., 2021). This could be related to the

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<th>Duration of ketogenic Phase (weeks)</th>
<th>Inclusion criteria</th>
<th>Study objective</th>
<th>Parameters with effects &amp; Significance</th>
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<tr>
<td>Albanese, 2019</td>
<td>Italy</td>
<td>Nutritional interventional study</td>
<td>72/106</td>
<td>VLCKD</td>
<td>3 weeks</td>
<td>Patients with morbid obesity undergoing laparoscopic sleeve gastrectomy, both genders</td>
<td>Weight loss in candidates and</td>
<td>Wt↓¹</td>
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<tr>
<td>Ministri, 2019</td>
<td>Italy</td>
<td>Nutritional interventional study</td>
<td>52/20</td>
<td>VLCKD</td>
<td>25 days</td>
<td>18-65 years age, both genders, BMI ≥ 40 or a BMI ≥ 35 with comorbidities (type 2 DM, HTN, obstructive sleep apnea etc)</td>
<td>Low activity of lysosomal acid lipase (LAL) could be involved in NAFLD</td>
<td>Wt↓</td>
</tr>
<tr>
<td>D’Abbondanza, 2020</td>
<td>Italy</td>
<td>Nutritional interventional study</td>
<td>70/None</td>
<td>VLCKD</td>
<td>25 days</td>
<td>Age 18-65 years, both genders, BMI ≥ 40 or BMI ≥ 35 with obesity-related comorbidities.</td>
<td>Effects of sex differences on weight loss and NAFLD in obese patients</td>
<td>FM↓</td>
</tr>
<tr>
<td>Hall, 2020</td>
<td>USA</td>
<td>Randomized, crossover design</td>
<td>20/20</td>
<td>KD</td>
<td>28 days</td>
<td>Overweight/obese adults, both genders</td>
<td>Compare low-carbohydrate diet with low-fat diet</td>
<td>Wt↓</td>
</tr>
<tr>
<td>Schiavo, 2018</td>
<td>Italy</td>
<td>Nutritional interventional study</td>
<td>27/None</td>
<td>Ketogenic micronutrient-enriched diet</td>
<td>4 weeks</td>
<td>Morbidly obese patients undergoing bariatric surgery, both genders</td>
<td>Effect of micronutrient-rich KD in reducing body weight</td>
<td>Wt↓</td>
</tr>
</tbody>
</table>

¹significant values in **bold letters**, ²insignificant values in *italics*, KD = ketogenic diet, LCKD = low-carbohydrate ketogenic diet, VLCKD = very low-calorie ketogenic diet, Wt = body weight, FM = fat mass, BMI = body mass index, WC = waist circumference, TC = serum total cholesterol, HDL = serum high-density lipoprotein, LDL = serum low-density lipoprotein, TAG = serum triglycerides
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... 8 mM/L, and hence the possibility of ketoacidosis in these patients is limited (Fig. 2) (Drabińska et al., 2021).

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... a normo-caloric high-fat ketogenic diet (HFKD) has been found to inhibit lipogenesis and induce fatty acid oxidation, leading to weight loss and reduced hepatic fat. Conversely, a hypercaloric but proper diet diminishes fat oxidation in liver and increases lipogenesis from carbohydrates, causing NAFLD (Watanabe et al., 2020). At very low caloric intake, macro-nutrient disposition is not important in improving liver pathology. It is rather caused by weight loss itself. Whereas at higher calories, the macronutrient ratio seems to become more important. Carbohydrate restriction plays a primary role in the efficacy of KD on NAFLD. Ketosis might affect NAFLD pathogenesis, apart from carbohydrate restriction. Ketone esters reduced glycolysis and increased muscle fat oxidation in the absence of a carbohydrate-restricted diet when administered to athletes (Watanabe et al., 2020). Our review found improvement in lipid profile in most studies, and even a reduction in liver size and statuses in NAFLD patients (Pilone et al., 2018).

Effect on Type2 DM
Studies found that ketogenic diet could reduce fasting blood glucose and glycosylated hemoglobin, along with improving lipid metabolism and reducing body weight (Yuan et al., 2020). It also improved weight and metabolic parameters in Type2 DM patients (Choi et al., 2018; Di Raimondo et al., 2021). Although the ketogenic diet showed a favorable effect on HDL levels, there was an accompanying increase in amounts of LDL and very-low-density lipoproteins in the literature. Hence, it is recommended that those wishing to start a ketogenic diet, especially those with comorbidities like type2 DM, and liver disease should consult their physicians for risks and benefits (Blanco et al., 2019; Di Raimondo et al., 2021; Gupta et al., 2017).

Effect on cardiovascular diseases
Obesity, hypertension, type2 DM, and NAFLD are all connected, and all are major risk factors for cardiovascular diseases (Watanabe et al., 2020). KD results in decreased bodyweight, TAG, and diastolic blood pressure, and an increment in HDL levels as well (Gupta et al., 2017). All these changes are beneficial for the cardiovascular system.

Effect on polycystic ovary syndrome (PCOS)
PCOS is accompanied by obesity, insulin resistance, LH/FSH ratio, and androgen excess. KD helped treat PCOS by improving body weight, testosterone levels, luteinizing hormone/ follicle-stimulating hormone ratio, and insulin levels (Gupta et al., 2017). KD is not free of adverse events, if not carried out with proper care (Watanabe et al., 2020). If present in large amounts, β-hydroxybutyrate, and acetoacetate can result in a decreased blood pH (acidemia). A third ketone, acetone, is neutral, which does not alter blood pH. Acetone can pass through lungs into one’s breath, and can make it a ketone biomarker (Blanco et al., 2019). One case report narrated that KD offers short-term weight loss, but it can have potentially harmful side effects like ketoacidosis (Blanco et al., 2019). But this diet can be considered safe for weight loss in diseases like DM, because the ketosis during this diet does not go beyond 7 to 8 mM/L, and hence the possibility of ketoacidosis in these patients is limited (Fig. 2) (Drabińska et al., 2021).
KD was found to have positive effects on body weight, BMI, waist circumference, HDL levels, triglyceride levels, blood sugar level, hemoglobin A1c (HbA1c), and insulin levels. However, there was not enough record to support ketogenic diet for long time because most of the studies were of shorter duration, i.e., ranging from 3 months to 3 years. Although most studies mentioned the shift in lipid profile to be favorable, increases were also found in TC and LDL (Batch et al., 2020). Some studies showed that significant differences were found in the first 6 months of intervention, but this statistical significance decreased after one to two years. Meager sample sizes, brief study durations, and absence of control diets decrease validity of these studies (Drabińska et al., 2021). Majority of the studies in the present review had fewer than 50 participants, were of about 3 months duration, and about half of the studies did not have controls. As there is restrained number of strong studies depicting the potential risks of KD, recommendations to support ketogenic diet in patients without comorbidities, should be done by the nutritionist (Batch et al., 2020). VLCKD is a great therapy for people with obesity and especially for those who have already been unsuccessful in losing weight in the past, and/or have an urgency to lose weight. Once the target weight is achieved, it is compulsory to suggest an appropriate healthy lifestyle i.e. physical activity and a balanced nutritional pattern (Drabińska et al., 2021).

CONCLUSION:
Our literature review found considerable favorable effects of both KD and VLCKD on fat mass and lipid profile, though the studies included in the review included 12 months dietary intervention only. More studies need to be done for extended periods of time (at least ≥2 years) to observe effects of these diets after long duration.

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CONFLICTS OF INTEREST:
There is no conflict of interest.

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