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Effect of a Ketogenic Diet on Body Weight and Lipid Profile

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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; Min-istrini *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).

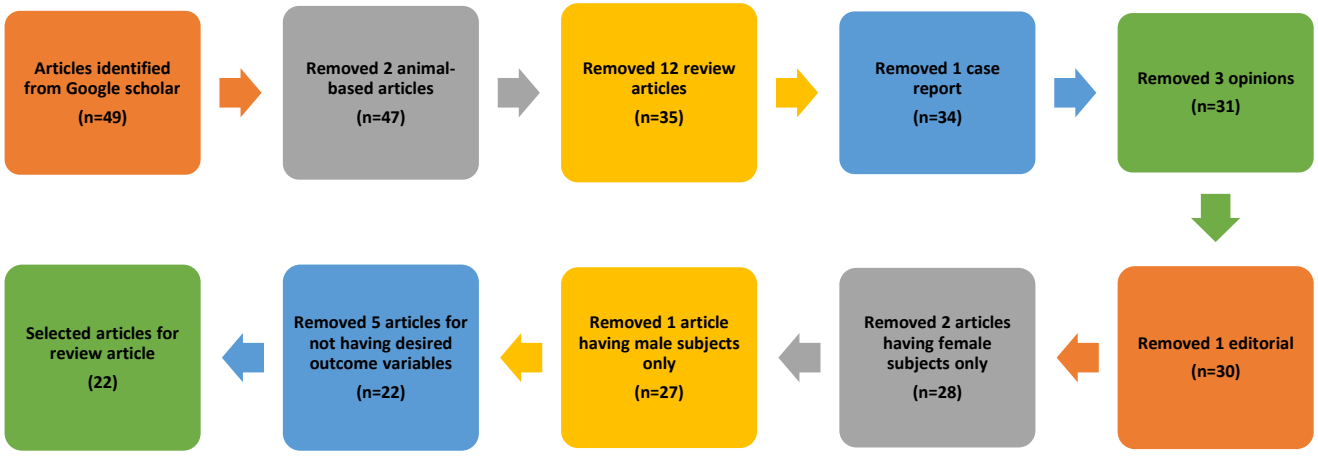


Fig. 1: Study selection flow-diagram.

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

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 of 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.

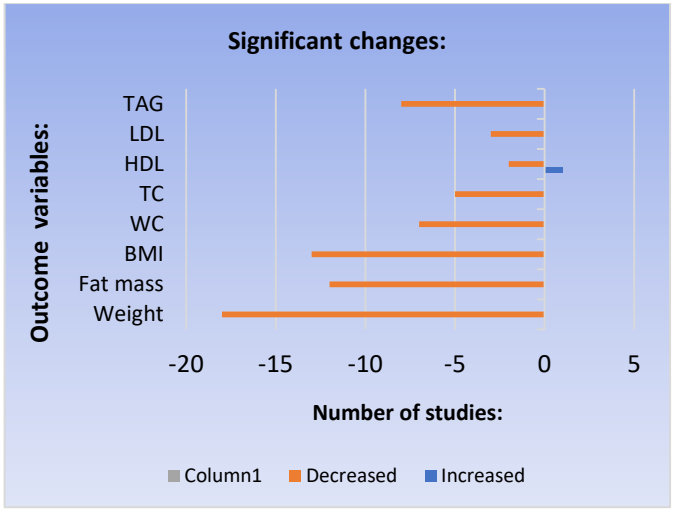
Table 1: Characteristics of trials of ketogenic diet published in last five years and their effects on obesity and lipid profile.

First Author, year	Country	Study design	Participants of intervention/ Control groups	Intervention	Duration of ketogenic Phase (weeks)	Inclusion criteria	Study objective	Parameters with effects & Significance
Myette-Côté, 2018	Canada	Randomized crossover study	11/11	Low-carb, high-fat diet	4 days	Adults with Type2 DM, age 40-75 years, both genders	Effect of low-carbohydrate, high-fat diet with/without post-meal walks on type2 DM patients	**Wt↓**[1] *TAG↑*[2]
Luukkonen, 2020	Finland	Nutritional interventional study	10/None	KD	6 days	Over weight/ obese adults, both genders	KD reverses NAFLD and insulin resistance despite increasing circulating non-esterified fatty acids (NEFA)	**Wt↓** **FM↓** **BMI↓** **WC↓** *TC↓* *HDL↓* *LDL↓*
Choi, 2018	Korea	Randomized controlled trial	19/11	KD	2 weeks	Age 19-49 years, BMI>25, both genders	Effects of low-calorie ketogenic nutrition drinks	**Wt↓** **FM↓** **BMI↓** **WC↓** *TC↓* *HDL↓* *LDL↓* *TAG↓*

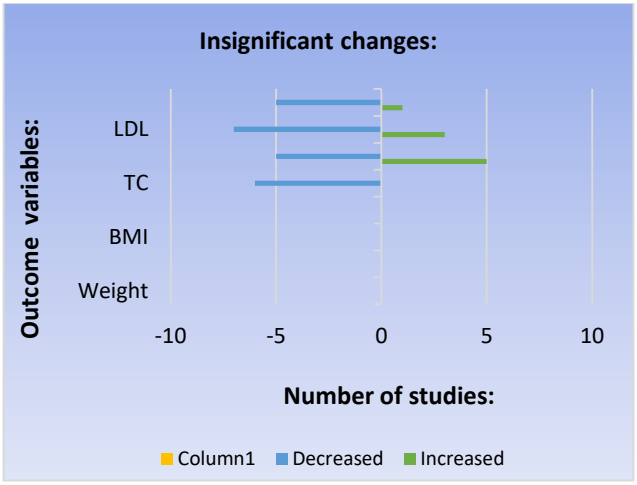
Merra, 2017	Italy	Crossover randomized double-blind trial	54/54	VLCKD	3 weeks	18-65 years, BMI ≥25, both genders	VLCKD and KD used as part of lifestyle modification	**FM↓** **BMI↓** **WC↓** *TC↓* *HDL↓* *LDL↓* *TAG↓*
Buscemi *et al.,* 2021	Italy	Cohort	31/20	VLCKD	10-12 weeks	Both genders, 18–65 years, BMI 27–39.9, and non-diabetic or type 2DM from<6 years with HbA1c≤10%	VLCKD and vitamin D levels.	**Wt↓**[1] **FM↓** **BMI↓** **WC↓** TC↓ HDL↓ TAG↓
Gomez Arbelaez, 2018	Spain	Nutritional interventional study	20/None	VLCKD	4 months	Age 18-65 years, BMI ≥30, both genders	Changes in RMR, and the associated hormonal alterations in patients with a VLCK-diet	**Wt↓** **BMI↓**
Sajoux, 2019	Spain	Cohort	20/59	VLCDK	2-3 moths	Overweight/obese adults, both genders	VLCK diet can change body composition	**Wt↓** **FM↓**
Bruci, 2020	Italy	Observational prospective study	92/None	VLCKD	3 months	Obese patients coming to High Specialization Centre for the Care of Obesity, Sapienza Uni-versity of Rome, both genders	Efficacy of VLCKD in mild kidney failure.	**Wt↓** **FM↓** **BMI↓** **TC↓** *HDL↓*[2] *LDL↓* **TAG↓**
Pilone, 2018	Italy	Nutritional interventional study	119/None	VLCKD	30 days	Age 18-62 years, BMI ≥ 40, both genders	Evaluation of effect of VLCKD	**Wt↓**[1] **FM↓** **BMI↓** **WC↓** *TC↓*[2] *HDL↑* *LDL↓* *TAG↓*
Valenzano, 2019	Italy	Nutritional interventional study	20/None	VLCKD	8 weeks	Obese adults, age 20-60 years, both genders	Effect of VLCKD	**Wt↓** **FM↓** **BMI↓** **TC↓** *HDL↓* **LDL↓** **TAG↓**
McKenzie, 2017	USA	Nutritional interventional study	238/None	VLCKD	10 weeks	Type 2DM, age 21-65 years, both genders	Individuals with T2D could achieve weight loss.	**Wt↓** **BMI↓** **TC↓** *HDL↑* *LDL↑* **TAG↓**

Volek, 2019	USA	Nutritional interventional study	14/15	KD	12 weeks	Healthy adults from various military branches, both genders	Metabolic, and performance responses of KD	**Wt↓** **FM↓**
Walton, 2019	USA	Nutritional interventional study	11/None	Low-carb, high-fat diet	90 days	Age 18-45 years, females, type 2 DM	Low-carbohydrate diets are effective to improve insulin resistance	**Wt↓**[1] **BMI↓** **HDL↑** *LDL↓*[2] **TAG↓**
Castro, 2018	Spain	Nutritional interventional study	20/None	VLCDK	4 months	Age 18-65 years, BMI ≥ 30, both genders	Weight loss	**FM↓**
Greene, 2018	Australia	Randomized, crossover design	12/12	LCKD	6 months	14 power lifters and weight lifters, both genders, age range 18- 55 years	LCKD could be used by weightlifters	**Wt↓**
Perticone, 2019	Italy	Nutritional interventional study	28/28	VLCKD	12 months	Overweight/obese adults, both genders	Ketogenic diet effect on vitamin D levels	**WC↓** *TC↓* *HDL↑* *LDL↓* **TAG↓**
Saslow, 2017	USA	Randomized controlled trial	16/18	VLCKD	12 months	Aged ≥18 years, BMI≥25, HbA1c >6.0%	Compare LCK and moderate carbohydrate diet.	**Wt↓** **BMI↓** *HDL↑* *LDL↑* *TAG↓*

[1]significant values in **bold letters,** [2]insignificant 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



(a)



(b)

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

Continued Table 1 -

First Author, year	Country	Study design	Participants of intervention/ Control groups	Intervention	Duration of ketogenic Phase (weeks)	Inclusion criteria	Study objective	Parameters with effects & Significance
Albanese, 2019	Italy	Nutritional interventional study	72/106	VLCKD	3 weeks	Patients with morbid obesity undergoing lap-aroscopic sleeve gastrectomy, both genders	Weight loss in candidates und	**Wt↓**[1]
Ministrini, 2019	Italy	Nutritional interventional study	52/20	VLCKD	25 days	18-65 years age, both genders, BMI ≥ 40 or a BMI ≥ 35 with comorbidities (type 2 DM, HTN, obstructive sleep apnea etc)	Low activity of lysosomal acid lipase (LAL) could be involved in NAFLD	**Wt↓** **FM↓** **BMI↓** **LDL↓** **TAG↓**
D'Abbond-anza, 2020	Italy	Nutritional interventional study	70/None	VLCKD	25 days	Age 18-65 years, Both genders, BMI ≥ 40 or BMI ≥ 35 with obesity-related comorbidities.	Effects of sex differences on weight loss and NAFLD in obese patients	**FM↓** **WC↓**
Hall, 2020	USA	Randomized, crossover design	20/20	KD	28 days	Overweight/ob ese adults, both genders	Compare low-carbohydrate diet with low-fat diet	**Wt↓** *TC↓*[2] **HDL↓** *LDL↑* *TAG↓*
Schiavo, 2018	Italy	Nutritional interventio nal study	27/None	Ketogenic micronutrie nt-enriched diet	4 weeks	Morbidly obese patients undergoing bariatric surgery, both genders	Effect of micronutrient-rich KD in reducing body weight	**Wt↓** **BMI↓** **TC↓** *HDL↑* **LDL↓** **TAG↓**

[1]significant values in **bold letters,** [2]insignificant 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

Similarly, HDL level increased significantly in a study, and insignificantly in 3 studies. Significant rise in HDL level occurred in 90 days intervention (Walto*n 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).

Effecton 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

differences in calorie intake. In experimental groups, the top reduction of body weight was recorded after six months, but the weight loss slowed down after twelve months, regardless of the diet followed. The diets were effective even after two years (Albanese *et al.,* 2019; Batch *et al.,* 2020; Drabińska *et al.,* 2021). VLCKD also showed achievement of a significant decline in body weight in patients. Results were obtained during the ketogenic phase and weight remained stable over the next two years (Castellana *et al.,* 2020). Our review of literature revealed that there was significant weight loss even in dietary intervention as short as four days.

Effect on serum lipids

In literature, the ketogenic diet showed a rise in HDL levels, along with a rise in amounts of LDL, and very-low-density lipoproteins (VLDL) in blood (Batch *et al.,* 2020). However, in the present review, a variable effect of ketogenic diet was observed on lipid profile. A shift of lipid levels was found towards the healthy side. Serum TC levels declined in all studies, serum LDL and TAG levels increased insignificantly in some studies, but fell in most, and HDL levels increased in about half of them. Review found a decrease in LDL levels in most studies, even at 12 months (Perticone *et al.,* 2019).

Effect on NAFLD

There is a common belief that increasing dietary fat intake leads to fatty liver and prevents fat mass loss. But 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 heaptic fat. Conversely, a hypercaloric but proper diet diminishes fat oxidation in liver and increases lipogenesis from carbohydrates, causing NAFLD (Wata-nabe *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).

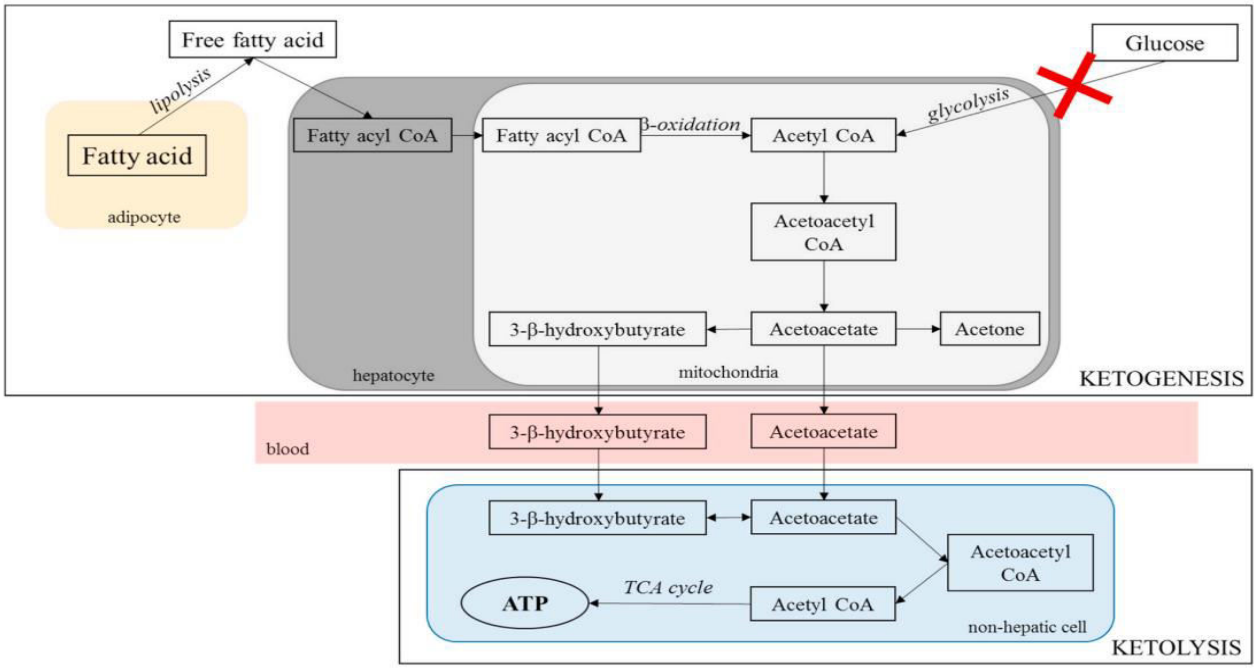


Fig. 3: Simplified pathways of ketone metabolism during KD (Drabińska *et al.,* 2021).

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.

ACKNOWLEDGEMENT:

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CONFLICTS OF INTEREST:

There is no conflict of interest.

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