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EFFICACY OF A 12-MONTH VERY LOW-CALORIE KETOGENIC DIET (VLCKD) IN GLYCEMIA COMPARED WITH PARAMETERS BEFORE STARTING THE REGIME IN PATIENTS WITH OBESITY AND TYPE 2 DIABETES. A CLINICAL STUDY

Hala Hassan Deeb

Department of Clinical Biochemistry, Faculty of Pharmacy, Al Hawash Private University, Syria- Homs.

Keywords:

VLCKD, Obesity, Diabetes, Body Mass index, Fasting plasma glucose, Lipid profile, Weight-loss

Correspondence to Author:
Hala Hassan Deeb

Research Scholar,
Department of Clinical Biochemistry, Faculty of Pharmacy, Al Hawash Private University, Syria- Homs.

E-mail: hala197944@gmail.com

ABSTRACT: In obese patients with noninsulin-dependent diabetes mellitus (NIDDM), reducing calorie intake improves glycemic control. The present study tested the theory that controlling calorie intake has an important role in long term, independent of weight loss in metabolic regulation of NIDDM patients. 23 women included in this study were selected, Antidiabetic therapy (except metformin) was discontinued concurrently with the start of VLCKD diet and Parameters were collected at starting program and once every 3 months for a year. In result, on T3 (after 9 months) ofVLCKD restriction produced substantial decreases in fasting plasma glucose for (19±9.31), HbA1c % (1±0.34),Weight loss (35.6±9.9), BMI (11.9±2.5), Tri Acyl Glycerol(22.99±19.27) and Total Cholesterol (52.5±4.89), and no significant decreasing in Creatinine is found .While on T4 (after 12 months)there is a significant decreasing in: fasting plasma glucose for (18±8.41), HbA1c % (1±0.5), Weight loss (33.5±10.3), BMI (12.3±2.2), Tri Acyl Glycerol (18±22.1) and Total Cholesterol (46.7±21.5), and no significant decreasing in Creatinine. It is important to noticethe stability of biochemical parameters after nine months of study. These findings indicate that VLCKD restriction has an important regulatory and safe effect on the metabolism of obese patients with NIDDM that is independent of weight loss.

INTRODUCTION: According to WHO, around 9% of adults worldwide had diabetes in 2014. In 2012, diabetes was the direct cause of 1.5 million deaths globally [1]. The prevalence of obesity worldwide is estimated to mean that about 13% of adults (11% of men and 15% of women) were obese in 2016 [2]. Increased body mass index (BMI) represents a major risk factor for non-communicable diseases such as cardiovascular diseases, musculoskeletal disorders and diabetes [3].

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It is estimated that the risk of developing diabetes grows by 4.5% for every kilogram of body weight gain [3]. Obesity also represents a risk factor for SarS-Cov2 infection, progression [4, 5] and Oxidative stress [6, 7].

Diabetes cause severe chronic complications such as nephropathy, retinopathy, neuropathy, psychological disorders pregnancy, Breast feeding, renal failure (estimated glomerular filtration rate (eGFR) less than 60 ml/min); Cirrhosis; heart failure (NYHA III-IV); respiratory failure; and planned surgeries for unstable angina or arrhythmia. Recent stroke or myocardial infarction [8, 9]. Previous studies have demonstrated the beneficial effects of very low-calorie ketogenic diet (VLCKD) on weight loss in obese patients [10, 11]. However, there is still scarce evidence for the use

of VLCKD as a safe and effective tool for long-term management of T2DM. The use of VLCKD has also been associated with restoration of phase I insulin secretion and thus a significant reduction in the need for glucose-lowering agents including insulin [12]. Recently, the American Diabetes Association (ADA) has listed the use of VLCKD as a viable treatment option for the treatment of T2DM patients with obesity [13]. A 12-month VLCKD regimen for body weight and glycemic control in selected patients with T2DM and obesity [14, 15].

MATERIALS AND METHODS:

Subjects: Patients (women) included in this retrospective observational study were consecutively selected Among those who attended the Diabetes Unit at Dr. Farzat Ayoub hospital (Al-Hawash Private University Hospital) between June 2020 and February 2023 who followed the inclusion criteria and accepted commitment to the VLCKD nutrition program. It is important to note that patients were free to accept the VLCKD nutritional program after a careful explanation of the nutritional protocol. At admission, all patients signed an informed consent form in accordance with General Data Protection Regulation; Antidiabetic therapy (except metformin) was discontinued concurrently with the start of VLCKD diet.

Parameters were collected at the beginning of program (before starting program) and once every 3 months from the start of the diet. Thus the timing (T0) at the start of adherence was concealed. Then after 3, 6, 9, and 12 months, we obtained results corresponding to the timing (T0, T1, T2, T3, and T4) respectively. Inclusion criteria were: T2DM, defined as HbA1c > 6.5% (48 mmol/L) or fasting plasma glucose (FPG) level > 126 mg/dL (7 mmol/L) [2]. Moderately good metabolic control (HbA1c <8.5%) at the start of intervention allowing suspension of oral therapy (except metformin); BMI>27 kg/m^2 and lipid profile (TG, HDL, LDL). Antidiabetic medications could be adjusted throughout the study depending on HbA1c levels and plasma glucose monitoring.

Laboratory Assay and Anthropometric Parameters: Fasting blood sugar, HbA1C, and lipid level were measured [3, 16].

Anthropometric measurements were obtained from each patient 12 hours later overnight, Height (m) was measured using a stadiometer to the nearest 0.1 cm and BMI was calculated according to the Quetelet index (calculated by dividing body weight by the square of height (kg/m^2).

Nutritional Intervention: All patients who were willing to adhere a strict diet including nutritional supplements and meal replacement and did not present contraindications to VLCKD, underwent a multi-stage VLCKD protocol with the use of meal replacement (Therascience, New Penta SRL or Pronokal Group, each brand containing similar amounts of calories and a similar macronutrient composition) and was carefully followed by a dietitian at the Diabetes Center.

In the first phase (45 days) total daily energy intake was less than 800 calories with protein had Eaten daily between 1.2 and 1.5 grams per kg of ideal body weight to prevent loss of fat-free mass [10, 11].

During this first phase, patients ate four or five replacement meals per day according to their specific nutritional needs. In the second phase (45 days), one meal and then two replacement meals were replaced with conventional protein-containing foods (meat, fish, eggs, soybeans) at lunch and/or dinner [12, 13, 16].

During the first two phases, carbohydrate intake was severely restricted to induce ketosis and fat intake was very low and derived mostly from olive oil (20 g per day). The recommended amount of water is not less than 2.5 liters/day [17, 18, 19]. To avoid micronutrient deficiencies, mineral and vitamin supplements are also recommended [19, 20].

The maximum duration of the first two phases (ketosis stages) was 3 months (T1), The length of these phases was customized according to the weight loss goal [12].

In the later stages, daily calories were increased gradually and incrementally Carbohydrate reintroduction was performed starting with low-GI carbohydrates.

At the end of six months, all patients had restarted eating all types of carbohydrates (Fruits, dairy products, legumes, breads and cereals). From

months 6 to 12, patients followed a balanced diet, with a daily caloric intake ranging from 1,500 to 2,000 calories according to the patient's metabolic needs [21, 22].

During the diet protocol it was necessary to promote the gradual and personalized introduction of physical activity and a healthy lifestyle. The entire dietary protocol was continued for at least 12 months (T2) [23]. Daily sodium intake was less than 5g, The nutritional plan consists of five daily meals according to the Mediterranean dietary approach [30, 31]. The source of protein is mainly legumes, eggs and fish. While whole grains, fresh fruits and vegetables are the main source of carbohydrates [24, 25].

Statistical Analysis: Twenty three consecutive patients who satisfied inclusion and exclusion criteria for VLCKD in the planned period were included in this retrospective observational study. All data considered for statistical analysis were retrieved from existing clinical records. Results are presented as mean standard deviation (SD), Normality was assessed with the Kolmogorov–Smirnov test, Independent Samples t Tests were calculated for each variable with a normal distribution to compare metabolic and anthropometric values in patients following VLCKD.

Within each diet group, paired t tests were used to test whether the changes from baseline to 3 and 6 and 9 and 12months were significantly different from zero. Mean values of anthropometric and biochemical parameters at baseline, T1 and T2 and T3 and T4 groups were compared using t-paired test in Comparisons, Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software (version 24, IBM).

RESULTS: In results of our study on T1, T2,T3 and T4 of VLCKD each of weight, BMI, fasting plasma Glucose, HBA1c, Total Cholesterol, LDL and TriG were statistically significant And no significant decreasing in HDL and Creatintine **Table 1.**

TABLE 1: ANTHROPOMETRIC AND BIOCHEMICAL PARAMETERS (SD) AT BASELINE T1 AND T2 AND T3 AND T4 GROUPS

Parameters	VLCKD T0	VLCKD T1	*p* T0-T1	VLCKD T2	*p* T0-T2	VLCKD T3	*p* T0-T3	VLCKD T4	*p* T0-T4
Weight (kg)	113.6 ± 19.1	101.1± 16.1	0.000	88.6 ± 10.4	0.000	78±9.2	0.000	80.1±8.8	0.000
BMI (kg/m2)	39.4 ± 6.0	36.9 ± 2.3	0.004	30.8 ± 4.3	0.000	27.5±3.5	0.000	27.1±2.8	0.000
FPGlu (mg/dL)	120.2 ± 12.8	103.0 ±15.0	0.000	105. ± 7.1	0.000	101.2±3.5	0.000	102.22±4.4	0.000
HbA1c (%)	6.7 ± 0.84	5.7 ± 0.70	0.000	6.0 ± 0.65	0.000	5.7±0.4	0.000	5.7±0.34	0.000
Tot Chol (mg/dL)	210.7 ± 25.1	198.5 ±24.7	0.000	160.1± 33.1	0.000	158.2±10.21	0.000	164.66±10.11	0.000
HDL (mg/dL)	45.3 ± 10.2	45.8 ± 12.22	0.248	41.0 ±8.4	0.000	44.2±6.1	0.211	45.1±5.5	0.840
LDL (mg/dL)	128.8 ± 29.1	115.5 ± 23.3	0.000	88 ±28.5	0.000	80.1±12.0	0.000	82.12±7.6	0.000
TriG (mg/dL)	168.2 ± 26.4	169.8 ± 20.7	0.192	155.1±12.2	0.000	145.2±7.13	0.000	150.2±4.3	0.001
Creatinine (mg/dL)	0.88 ± 0.22	0.84 ± 0.15	0.015	0.78± 0.5	0.112	0.62±0.6	0.005	0.68±0.71	0.091

BMI: Body Mass Index; Tot Chol: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; VLCKD, Very-low-calorie ketogenic diet. Statistically significant changes in weight and metabolic control at 3 months (T1) and 6 months (T2) and 9 months (T3) and 12 months (T4) versus baseline were assessed with t-paired test. The level of significant difference was set to $p < 0.05$, corresponding to a 5% first type error. All values are presented as mean SD. Significant p values are highlighted in bold.

Changing in of anthropometric and biochemical parameters (SD) at baseline, T1 and T2 and T3 and T4 groups explained in **Fig. 1, 2, 3, 4, 5, 6, 7, 8, 9 .**

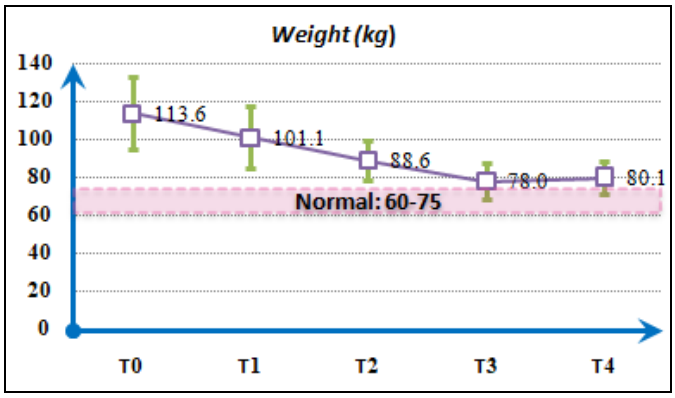

FIG. 1: EFFECT OF VLCKD AFTER 3,6,9, 12 MONNTHES IN WHEIGT

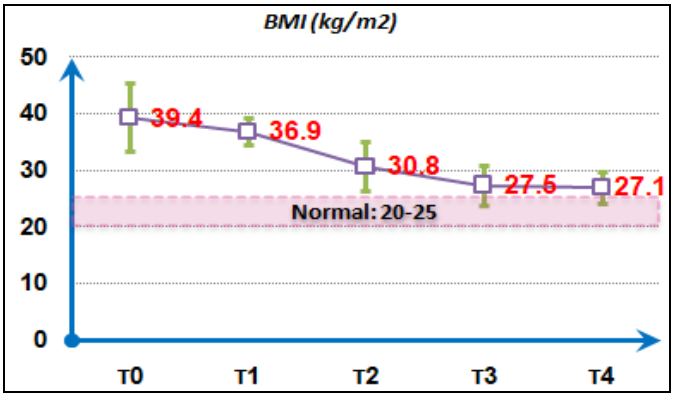

FIG. 2: EFFECT OF VLCKD AFTER 3,6,9, 12 MONNTHES IN BMI

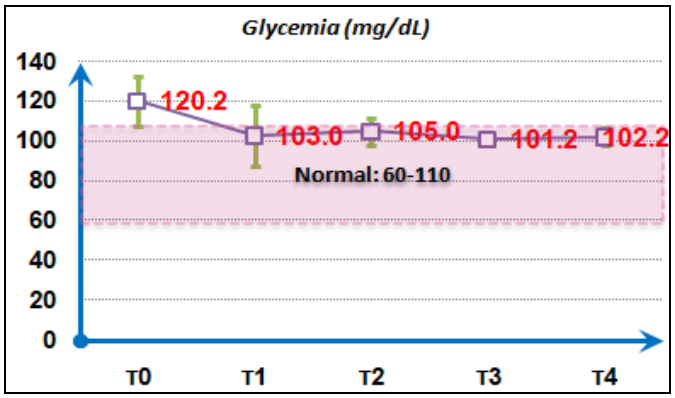

FIG. 3: EFFECT OF VLCKD AFTER 3, 6,9,12 MONNTHES IN FASTING PLASMA GLUCOSE

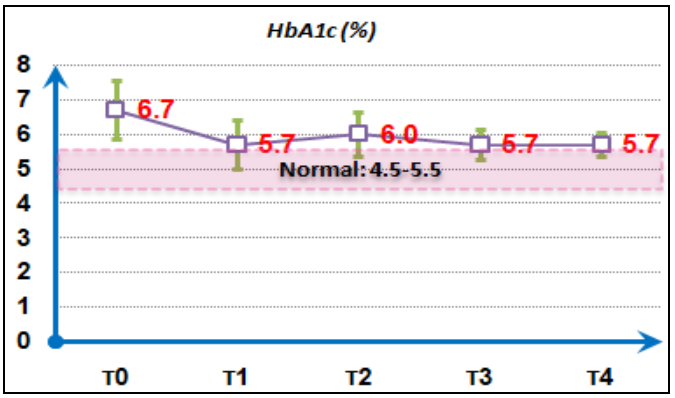

FIG. 4: EFFECT OF VLCKD AFTER 3, 6,9,12 MONNTHES IN GLYCLATED HMOGLOBINE HBA1C%

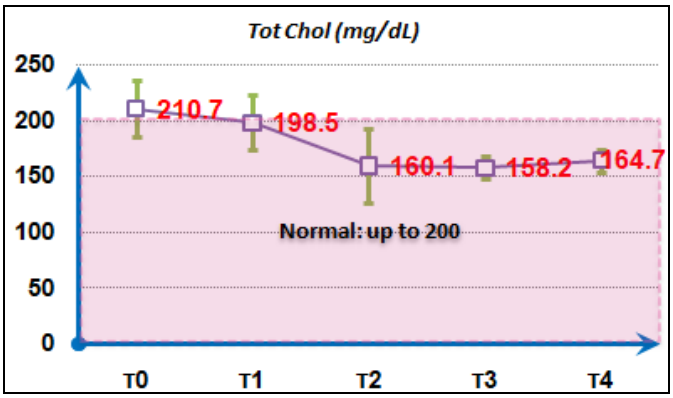

FIG. 5: EFFECT OF VLCKD AFTER 3, 6,9,12 MONNTHES IN TOTAL CHOLESTEROL

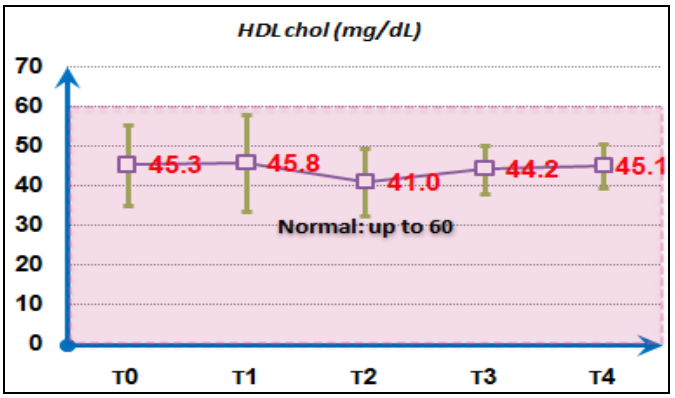

FIG. 6: EFFECT OF VLCKD AFTER 3, 6,9,12 MONNTHES IN HIGH DENSITY LIPOPROTEIN

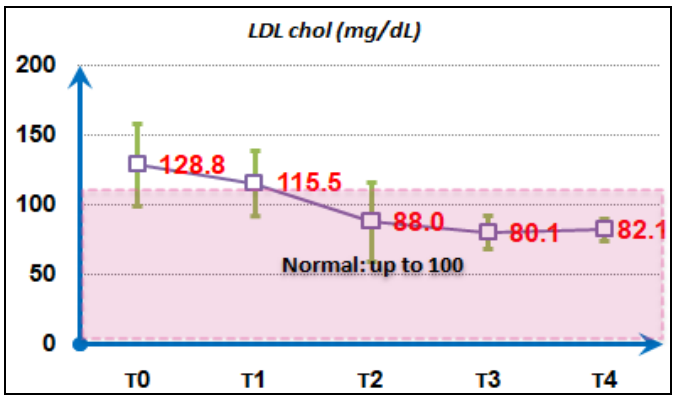

FIG. 7: EFFECT OF VLCKD AFTER 3, 6,9,12 MONNTHES IN LOW DENSITY LIPOPROTEIN

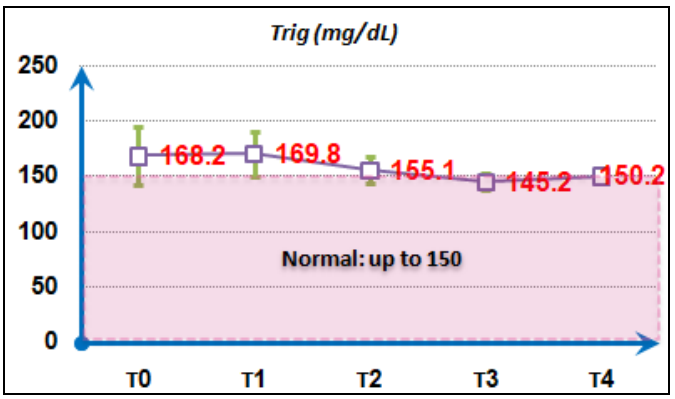

FIG. 8: EFFECT OF VLCKD AFTER 3, 6,9,12 MONNTHES IN TRI ACYL GLYCEROL

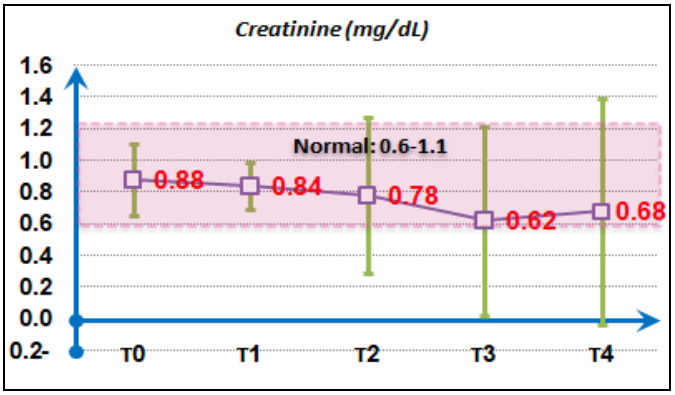

FIG. 9: EFFECT OF VLCKD AFTER 3, 6,9,12 MONNTHES IN CREATININE

In the results of our study on T3 (9 months in VLCKD) each of weight, so BMI, fasting plasma Glucose, so HBA1c, Total Cholesterol, LDL and TriG were statistically significant decreased in comparing with T0 **Table 2**.

On T4 (12 months in VLCKD) each of weight, so BMI, fasting plasma Glucose, so HBA1c, Total Cholesterol, LDL and TriG were statistically significant decreased in comparing with T0 **Table 2**.

TABLE 2: ANTHROPOMETRIC AND BIOCHEMICAL PARAMETERS (SD) AT T3 /T0 GROUPS

Parametres	Δ T0-T3 (Mean ± SD)	p T0-T3
Weight (kg)	35.6 ± 9.9	0.000
BMI (kg/m2)	11.9 ± 2.5	0.000
Glycemia (mg/dL)	19 ± 9.31	0.000
HbA1c (%)	1 ± 0.43	0.000
Tot Chol (mg/dL)	52.5 ± 14.89	0.000
HDL chol (mg/dL)	1.1 ± 4.09	0.211
LDL chol (mg/dL)	48.7 ± 17.1	0.000
Trig (mg/dL)	22.99 ± 19.27	0.000
Creatinine (mg/dL)	0.26 ± 0.39	0.005

TABLE 3: ANTHROPOMETRIC AND BIOCHEMICAL PARAMETERS (SD) AT T4 /T0 GROUPS

Parametres	Δ T0-T4 (Mean ± SD)	p T0-T4
Weight (kg)	33.5 ± 10.3	0.000
BMI (kg/m2)	12.3 ± 2.2	0.000
Glycemia (mg/dL)	18 ± 8.41	0.000
HbA1c (%)	1 ± 0.5	0.000
Tot Chol (mg/dL)	46 ± 15	0.000
HDL chol (mg/dL)	0.2 ± 4.7	0.840
LDL chol (mg/dL)	46.7 ± 21.5	0.000
Trig (mg/dL)	18 ± 22.1	0.001
Creatinine (mg/dL)	0.20 ± 0.55	0.091

CONCLUSIONS: The present work is a retrospective observational study, which was evaluated in hospital clinical practice to determine the effectiveness of VLCKD diet for diabetes management.

The study confirms that VLCKD represents a safe and effective tool in the management of obesity and T2DM, also in accordance with the recommendations of the American Diabetes Association [26]. Due to its beneficial metabolic effects, VLCKD should be considered as a safe and effective strategy for lifestyle intervention and metabolic rehabilitation in properly selected and motivated patients with obesity and T2DM [12, 27], which may lead to a reduction or even suspension of drug therapy and was primarily due to the amelioration of β cell function, whereas no contribution of insulin sensitivity was shown [28, 29].

These findings indicate that calorie restriction has an important regulatory effect on the metabolism of obese patients with NIDDM that is independent of weight loss [29]. In result, the long-term of VLCKD restriction produced substantial decreases in fasting plasma glucose, HbA1c %, Weight loss, BMI,

TriG, Total Cholesterol, unsignificated decreasing in HDL and Creatinine in comparing after 9 months with Parameters before starting Regime, And these Biological Parameters remained statically constant.

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CONFLICTS OF INTEREST: Nil

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