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Effect of Modified Ketogenic Diets on Rats with induced Obesity

Eman S. Ibrahem*, Usama E. Mostafa**, Mostafa A. Ali**
Marwa N. Mohamed***

*Regional Center for Food and Feed, Agriculture Research Center, Giza, Egypt.
**Home Economics Department, Faculty of Specific Education, South Valley University, Qena, Egypt.
*******Home Economics Department, Faculty of Specific Education, Ain Shams University, Cairo, Egypt.

Abstract

The prevalence of obesity has been increased and has become a public health problem globally. Many strategies were done to treat obesity. This study was conducted to modify the ketogenic diet (KD) by replacing the animal fat by vegetable oils to reduce the bad effects of the traditional ketogenic diet. Seventy-two adult male albino rats were divided into two main groups, the first main group (A) (n=6) was fed on the basal diet and kept as negative control group (-ve), the second main obese group (B) rats (n=66) were divided into 11 subgroup 6 rats each. Subgroup (B1) was fed on high fat diet and served as positive control group (+ve). The obese subgroups from (B2-B6) were divided according to the first type of KD at (4:1), to subgroup (B2) was considered a positive control group for the KD at (4:1). While the other 4 subgroups (B3 to B6) were treated by a mixture of different oils including (olive, sesames, flaxseed). The other obese subgroups from (B7-B11) were divided according to the second type of KD at (6:3:1) to, subgroup (B7) was considered a positive control group for the KD at (6:3:1). While the other subgroups (B8 to B11) were treated by a mixture of different oils including the previous oils. At the end of the experiment (6 weeks), blood samples were collected to obtain Serum samples for biochemical assays. The obtained results showed that, after applying the different types of ketogenic diet (4:1) or (6:3:1) using different vegetable oils mixtures of (olive, flaxseed and sesame oils), obese rats had significant weight reduction (P<0.05), as well as improving lipid profile, blood glucose, liver and kidney functions as compared to control positive groups. The study recommends replacing the traditional ketogenic diet with the modified ketogenic diet (depends on mixture of vegetable oils), at the tested ratio in order to benefit from the nutritional value of these plant oils that have useful effect on the body function.

Key words: Ketogenic Diet (KD) – Obesity – Vegetable oils – Olive oil – Flaxseed oil - Sesame oil.

Introduction

The prevalence of obesity has reached epidemic proportions over the last few decades. In 2013, 36.9% of adult men (age ≥20 years) and 29.8% of adult women were considered overweight (body mass index [BMI] 25–29.9 kg m^2) or obese (BMI ≥30 kg m^2) ***(Ng et al., 2014),*** and recent trend analyses show that the number of subjects who are overweight or obese is continuing to rise worldwide ***(NCDRFC, 2016).***

According to the World Health Organization **(WHO),** Egypt ranks 18th among the highest prevalence of obesity worldwide ***(Global Obesity Levels, 2020).***According to "100 million health" survey, which was conducted in Egypt in 2019 and screened 49.7 million adult Egyptians (≥18 years old) were screened, 39.8% of them suffered from obesity (BMI ≥ 30 kg/m^2). Obesity was more prevalent in adult females 49.5% than adult males 29.5% ***(Aboulghate et al., 2021).***

Ketogenic diet (KD) contains very low carbohydrates (20-50 gram per day), high fat, and enough protein. Macronutrient intake from KD has 55- 60% fat, 30-35% protein, and 5-10% carbohydrate compositionKD is a term that shows dietary therapy with diet composition that results in ketogenic state in human metabolism ***(Oh and Uppaluri, 2019).***KD was originally used as therapy for epileptic patients both in children and adults. Then this diet develops its use for people with diabetes, cancer, cardiovascular disease, and may be used for weight loss. It is one of effective nonpharmacological measures for intractable epilepsy since 1920 ***(Meira et al., 2019).***

Diet of low carbohydrate causes a change in the body's metabolism thus initiating fatty acid oxidation. So, it also increases the life span of the person ***(Roberts et al., 2017).*** There are four different KDs available: the traditional 'classic' KD, the medium-chain triglyceride, ketogenic diet, the modified Atkins diet and the low glycemic index treatment***(Dhamija et al., 2013).***

The study was conducted to investigate the effect of a ketogenic diet on body weight status and proving the importance of replacing animal fat with plant oil mixture of (olive, sesame and flaxseed), on obese rats.

Materials and Methods

The biological experiment and the chemical analysis were carried out at the Post Graduated Lab, Faculty of specific education Economics, South Valley University, Qena.

Materials:

Oils and fats: Crude oils of (olive, flaxseed and sesame), corn oil and animal fats (beef tallow) were obtained from local markets, Qena, Egypt. **Chemicals:** Casein, cellulose, Vitamin mixtures and mineral mixtures were obtained from Al- Gomhuria Company, Cairo, Egypt. Corn starch was obtained from local market in Qena, Egypt.

Rats: Seventy-two adult male Albino rats weighing from 150-160 gm were purchased from the animal house in Food Technology Research Institute, Cairo, Egypt.

Methods:

Classic Ketogenic diet (KD) has 55- 60% fat, 30-35% protein, and 5-10% carbohydrate composition ***(Oh and Uppaluri, 2019).*** Some modifications were carried out on KD by replacing the animal fat sources with different plant oil mixtures with two types including the first type of KD at (4:1), (Fats: (proteins and carbohydrate)), the second type of KD at (6:3:1), (Fats: Proteins: Carbohydrates).

Experimental design:

Seventy-two adult male albino rats were housed in well-ventilated cages, according to healthy specifications for about one week and fed on basal diet ***(Reeves et al., (1993))*** for adaptation, then they were assigned into two main groups.The first main group (**A**) (n=6) continued the basal diet for the whole experimental period and kept as negative control group (-ve).The second main group (**B**) (n=66) was fed on high fat diet for four weeks to induce obesity and was divided into 11 subgroups, six rats each.

-Subgroup (B1) was fed on high fat diet with beef tallow till the end of the experimental period and served as positive control group (+ve).

Other 5 obese subgroups from (B2:B6) were divided according to the first type of KD at (4:1) as follows:

-Subgroup (B2) fed on beef tallow and considered a positive control group for the KD at (4:1).

-Subgroup (B3) was fed on a Mixture of olive (65%), sesames (20%) and flaxseed (15%).

-Subgroup (B4) was fed on a Mixture of olive (60%), sesames (20%) and flaxseed (20%).

-Subgroup (B5) was fed on a Mixture of olive (55%), sesames (20%) and flaxseed (25%).

-Subgroup (B6) was fed on a Mixture of olive (20%), sesames (20%) and flaxseed (60%).

The other 5 obese subgroups from (B7:B11) were divided according to the second type of KD at (6:3:1) as follows:

-Subgroup (B7) fed on beef tallow and considered a positive control group for the KD at (6:3:1).

-Subgroup (B8) was fed on a Mixture of olive (65%), sesames (20%) and flaxseed (15%).

-Subgroup (B9) was fed on a Mixture of olive (60%), sesames (20%) and flaxseed (20%).

-Subgroup (B10) was fed on a Mixture of olive (55%), sesames (20%) and flaxseed (25%).

-Subgroup (B11) was fed on a Mixture of olive (20%), sesames (20%) and flaxseed (60%).

Thenutrient composition of basal diet and different types of ketogenic diet accordingto***(Nylen, et al., 2005 and Diana and Atmaka, 2020)***with some modifications illustrated in Table A.

At the end of the experiment (6 weeks), rats were fasted for 12 hours and then they were anesthetized with diethyl ether, then blood samples were collected to obtain serum samples that were stored at -20°C until biochemical assays.

Induction of obesity: Rats were fed on basal diet for four weeks according to **Reeves et al., (1993)** with some modification included (high fat diet) according to ***Min et al., (2004)*** containing: casein 14%, cellulose 5%, vitamin mixtures 1%, mineral mixtures 3.5%, sucrose 10%, (beef tallow 19% + corn oil 1%), l-cystine 0.18%, choline bitartrate 0.25 % and the remainder was starch to induce obesity.

Biological Evaluations:

The quantities of diet, which were consumed and/or wasted, were recorded every day while total feed intake (FI) of the experimental period (6 weeks) was calculated. In addition, rat's body weight (BW) was recorded weekly. Body weight gain percent (BWG%) and feed efficiency ratio (FER) were calculated according to ***Champman, et al., (1959)*** using the following equation:

$$\mathbf{BWG}\% = \frac{\text{Final body weight} - \text{Initial body weight}}{\text{Initial body weight}} \times 100$$

$$\mathbf{FER} = \frac{\text{weight Gain (g)}}{\text{Feed intake (g)}}$$

Chemical analysis:

Serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), triglyceride (TG) was determined according to the method of***Fossati and Principe, (1982)***, ***Albers et al., (1983)*** *and*

Jacobs and Vander, (1960), Respectively. Calculations of low-density lipoprotein cholesterol (LDL-c) and very low-density lipoprotein cholesterol (VLDL-c) by the equation of ***Fruchart (1982).*** Additionally, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured according to ***Reitman and Frankel (1957).***Serum urea ***(Kaplan, 1984)***and creatinine were measured according to ***(Murray, 1984).***

Statistical analysis: Results was presented as mean± standard Error (SE). Data were analyzed statistically by SPSS program, one-way ANOVA followed by post hoc multiple were used to make a comparison among different groups ***(Snedecor and Cochron, 1989).***

Table (A):

Nutrient composition of basal diet and different types of ketogenic diet according to***(Nylen, et al, 2005 and Diana and Atmaka, 2020)*** with some modifications:

Nutrients \ Diets		Basal diet (g/kg)	High fat diet (g/kg)	Ketogenic diet (g/kg)	Ketogenic diet (4:1) (g/kg)	Ketogenic diet (4:1) %	Ketogenic diet (6:3:1) (g/kg)	Ketogenic diet (6:3:1) %
Protein		140	140	250	140	16.04	130.85	30
L-Cystine		1.8	1.8	1.8	1.8		1.8	
Carbohydrate		725	560.7	50.7	34.15	3.94	78.85	10
Fat	Soy oil	40	10	30	-----	-----	-----	-----
	beef tallow	-----	190	570	-----	-----	-----	-----
	Mix oils	-----	-----	-----	707.8*	80	788.5*	60
Vitamin's mix.		10	10	10	10	1	10	1
Mineral's mix.		35	35	35	35	3.5	35	3.5
Fiber		50	50	50	50	5	50	5
Choline bitartrate		2.5	2.5	2.5	2.5	0.25	2.5	0.25

***Mix (B3&B8):** olive (65%), sesames (20%), flaxseed (15%). **Mix (B4&B9):** olive (60%), sesames (20%), flaxseed (20%). **Mix (B5&B10):** olive (55%), sesames (20%), flaxseed (25%). **Mix (B6&B11):** olive (20%), sesames (20%), flaxseed (60%).

Results and Discussions

Table (1):

Efficacy of different types of ketogenic diet on body weight of obese rats:

Groups	Parameters		IBW (g)	FBW(g)
G (A)	Control –ve		238.7±10.93 ^{A}	238.9±8.98 ^{BC}
G (B)	B1 : Control +ve		252.5±13.43 ^{A}	258.9±11.32 ^{A}
	B2 : Control +ve, for KD at (4: 1)		265.0±11.30 ^{A}	250.9±7.67 ^{AB}
	Mix Oil for KD at (4: 1)	(B3)	236.2±12.88 ^{A}	222.6±10.96 ^{DE}
		(B4)	261.8±18.61 ^{A}	213.2±5.76 ^{EF}
		(B5)	260.7±15.23 ^{A}	230.5±11.41 ^{CD}
		(B6)	244.0±14.44 ^{A}	205.8±2.67 ^{F}
	B7 : Control +ve, for KD at (6: 3:1)		258.7±19.41 ^{A}	211.2±4.95 ^{EF}
	Mix Oil for KD at (6:3:1)	(B8)	239.8±12.50 ^{A}	211.0±2.53 ^{EF}
		(B9)	242.0±19.09 ^{A}	206.4±8.74 ^{F}
		(B10)	248.3±13.12 ^{A}	220.8±15.43 ^{DE}
		(B11)	256.2±18.34 ^{A}	226.5±10.84 ^{CD}

***Mix (B3&B8):** olive (65%), sesames (20%), flaxseed (15%). **Mix (B4&B9):** olive (60%), sesames (20%), flaxseed (20%). **Mix (B5&B10):** olive (55%), sesames (20%), flaxseed (25%). **Mix (B6&B11):** olive (20%), sesames (20%), flaxseed (60%). Data are expressed as mean ± SE. Means with different superscript letters in the column are significantly differences at (P < 0.05).
IBW = Initial body weigh. **FBW**= Final body weigh

The results indicated that, there is no significant change on the initial body weight among all rats as shown in table (1). The high fat diet caused a significant (P<0.05) increase in FBW of rats as compared to the -ve control group (A). The FBW of the rats fed on KD at (4:1) group (B2) only was numerically decreased as compared to +ve control group (B1) that fed high fat diet, while all groups feeding the KD at (6:3:1) caused a significant (P<0.05) decrease of the FBW as compared +ve control group (B1).

A very low-calorie ketogenic diet was highly effective in terms of reducing body weight without inducing loss of lean mass***(Merra et al., 2016)*** and it is an effective way to lose weight, as they promote a non-atherogenic lipid profile and decreased insulin resistance ***(Abbasi, 2018).***

The current study results are consistent with the data obtained by ***(Manikam et al., 2018)***who observed that KD showed a better long-term effect for weight loss in obese patients than low-fat diet. Also ***Diana and Atmaka(2020)*** found decrease in body weight on applying the KD with carbohydrate intake up to 10% of total energy for 6 months that stimulate ketosis in body.While***, Omozee and Osamuyimen, (2018)*** showed no significant increase in weight of the experimental group that fed 65% fatty diet.

The rats fed on the two different KD modified diet with different mixture of plant oils had significant (P< 0.05) decrease in the FBW as compared to +ve group (B1). Also, the results showed a significant (P<0.05) decrease in FBW for all groups fed KD at (4:1) applied with different mixture of plant oil as compared to the +ve KD group.While no significant changes for the FBW were observed in groups treated with the type of KD (6:3:1) using the plant oil mixture (B8) or mixture (B9). Also, no change in FBW between the groups treated with KD at (6:3:1) with oil mixture (B10) or mixture (B11).

The highest body weight reduction was recorded at the subgroup fed on KD at (4:1) with oil mixture (B6) including olive (20%), sesames (20%), flaxseed (60%), followed by group treated with KD at (6:3:1) with oil mixture (B9) including olive (60%), sesames (20%), flaxseed (20%) then the group treated with KD at (4:1) with oil mixture (B4) including the same mix oil for group (B9).

The phenolic compounds of olive oil have antioxidant properties and have beneficial effects on obesity ***(Ambra et al., 2017).***

The obtained results were in line with the findings of ***(El-Aziz et al., 2020 and Tufail et al., 2020)***who found that sesame oil supplementation was significantly decreased the body weight. However, ***Raeisi-Dehkordi et al., (2018)*** reported that, sesame products consumption did not significantly affect body weight.

The development of metabolic syndrome was altered by flaxseed oil, because it has beneficial effects on lipids and glucose in addition to prevent the excess of body weight gain **(*Brant et al., 2012 and Tufail et al., 2020)*** and significantly decreased waist circumference of their patients **(*Akrami et al., 2018).*** Moreover, alpha linolic acid (ALA-rich Flaxseed oil induced decrease in adipocyte hypertrophy***(Baranowski et al., 2012),*** also protein levels of inflammatory markers in adipose tissue in obese rats. In addition to ***Kristensen et al., (2011)*** found that, flaxseed fibers baked into bread rolls significantly increased satiety in a dose dependent manner.

Ghasemi et al., (2021) reported that feeding flaxseed oil to the anti-diabetic effects and anti-oxidative properties improved the body mass index, serum glucose and insulin in rats.

Table (2):

Efficacy of different types of ketogenic diet on serum lipid profile of obese rats:

Groups \ Parameters			TC	TG	VLDL-c	LDL-c	HDL-c
			mg/dl				
G (A):	Control –ve		141.9±2.56 ^{F}	80.95±1.67 ^{E}	16.19±0.78 ^{C}	45.58±0.78 ^{E}	80.14±1.93 ^{C}
G (B):	B1: Control +ve		205.5±3.52 ^{C}	161.8±2.25 ^{B}	32.35±0.94 ^{A}	141.3±2.34 ^{C}	31.93±1.57 ^{G}
	B2: Control +ve, for KD at (4: 1)		247.6±3.11 ^{B}	173.1±1.78 ^{A}	34.61±0.73 ^{A}	177.1±2.68 ^{A}	35.98±1.37 ^{F}
	Mix Oil for KD at (4: 1)	(B3)	142.4±2.31 ^{F}	96.57±1.68 ^{D}	19.32±0.75 ^{B}	46.15±0.63 ^{E}	76.98±1.04 ^{CD}
		(B4)	137.9±1.77 ^{G}	81.40±1.85 ^{E}	16.28±0.56 ^{C}	50.10±0.51 ^{D}	71.57±1.52 ^{D}
		(B5)	144.0±2.54 ^{E}	103.6±1.50 ^{C}	20.73±0.91 ^{B}	43.88±0.24 ^{F}	79.37±1.71 ^{C}
		(B6)	141.1±1.38 ^{F}	94.69±1.47 ^{D}	18.94±0.62 ^{B}	50.15±0.42 ^{D}	72.04±1.49 ^{D}
	B7: Control +ve, for KD at (6:3:1)		261.6±3.44 ^{A}	170.4±1.66 ^{A}	34.08±0.51 ^{A}	170.8±0.37 ^{B}	56.79±1.45 ^{E}
	Mix Oil for KD at (6:3: 1)	(B8)	154.8±2.16 ^{D}	97.27±1.83 ^{CD}	19.45±0.27 ^{B}	47.78±0.84 ^{DE}	87.52±1.14 ^{A}
		(B9)	143.0±1.76 ^{F}	100.4±1.45 ^{CD}	20.09±0.37 ^{B}	45.25±0.71 ^{E}	77.71±1.25 ^{C}
		(B10)	144.4±1.36 ^{E}	99.37±1.41 ^{CD}	19.88±0.72 ^{B}	45.04±0.33 ^{E}	79.49±1.13 ^{C}
		(B11)	146.1±1.30 ^{E}	94.48±1.56 ^{D}	18.90±0.65 ^{B}	43.76±0.42 ^{F}	83.45±0.96 ^{B}

***Mix (B3&B8):** olive (65%), sesames (20%), flaxseed (15%). **Mix (B4&B9):** olive (60%), sesames (20%), flaxseed (20%). **Mix (B5&B10):** olive (55%), sesames (20%), flaxseed (25%). **Mix (B6&B11):** olive (20%), sesames (20%), flaxseed (60%). Data are expressed as mean ± SE. Means with different superscript letters in the same column are significantly different at ($P < 0.05$).

The high fat diet significantly (P<0.05) increased serum lipid profile for (B1) +ve control group when compared to (A) -ve control group. While serum TC, TG, LDL-c and HDL-c was significantly (P<0.05) increased in +ve control group fed different types of KD (B2,B7) as compared to +ve control group (B1) that fed high fat diet only. (Table 2)

Ng et al., (2014)reported that KD decreased plasma triglyceride levels and increased serum HDL-c in mice. The degree of obesity in diabetic mice was decreased according to ***(Rosenbaum et al., 2019; Abdurrachim et al., 2019; Guo et al., 2020 and Negm, 2020).*** Regardless of the method used to increase ketone delivery to the heart, a general favorable effect has been observed in cardiovascular disease ***(Yurista et al., 2021).*** Ketogenic diet can be safely used even in patients with pre-existing dyslipidemia ***(Unsal et al., 2021).***

Modified different types of KD with different oil mixture results in a significant (p<0.05) decrease in the mean level of serum TC, TG and LDL-c while serum HDL-c was significantly (P<0.05) increased as compared to both +ve control groups(B2,B7) fed on KD (4:1) or KD at (6:3:1). There were no changes in serum TC, TG and LDL-c for the rats fed KD at (4:1) with group (B3) or group (B6). Also, there are no significant changes in serum HDL-c for the groups (B3), (B4) or (B5). Moreover, the same trend was observed between the groups (B10) or (B11) fed KD at (6:3:1) with oil mixture for serum TC and TG and HDL-c. No statistical changes in serum LDL-c between the rats fed KD at (6:3:1) with oil mixture (B9) or (B10). Also, there are no statistical changes in serum TG among the groups fed KD at (6:3:1) with different oil mixture. Reduction in serum TC, TG was seen at the group (B2,B7) fed on KD at (4:1) or at (6:3:1) and oil mixture (B4 or B9) including olive (60%), sesames (20%), flaxseed (20%). While the highest increase in serum HDL-c was seen at the groups (B8 to B11) fed KD at (6:3:1) with oil mixture (B5,B3) respectively.

Guasch-Ferre et al., (2015) mentioned that olive oil lowered the risk of Type 2 diabetes mellitus 40% in patients with a high CVD risk. Also, ***Tsartsou et al., (2019)*** showed that olive oil consumption can improve blood glucose and lipid profile ***(Negm, 2020)***in diabetic patients

Quasem et al., (2009) showed that when they administered sesame oil it caused adequate reduction in lipid hydroperoxides. ***Jillian, (2010)*** stated that sesame seed oil contains phytoestrogen and could increase total antioxidant capacity as estrogen lessened the TG and LDL-C and enhancing antioxidant status. ***El-Baz et al., (2015)***found lipid reduction in hypercholesterolemic rat models on administrating 5 and 10% sesame seed oil due to the increase in sesame lignin contents. The results were supported ***Hoan and Anh (2016)*** who found lower concentration of lipids in rabbits supplemented with 5 % sesame seed oil.

Tufail et al., (2020); Aslam, et al., (2020)and ***Ali and Al-Janabi (2021)*** showed that treatment with sesame oil caused a significant decrease in the concentrations of LDL-c and increased the concentration of HDL-c, due to the presence of sesamin, in sesame seeds that prevents the absorption of cholesterol from the intestine ***(Kashyapa et al 2018 and Khatun et al., 2021).***

Flaxseed chutney supplemented diet could lower the serum cholesterol and as a potential source of antioxidants, it could exert protection against hepatotoxic damage induced by carbon tetrachloride in rats***(Faseehuddin and Madhusudhan, 2007)*** who attributed it due to not only to polyunsaturated fatty acids PUFAs, mainly linolenic acid, but also to fiber and lignans - enriched flaxseed that may also provide beneficial results on weight reduction***(Paulina et al., 2018),*** fat accumulation, and improving the lipid profiles ***(Tufail et al., 2020).*** Phenolic compounds in olive oil have also been related to increased levels of HDL-c ***(Servili et al., 2013).***

Table (3):
Efficacy of different types of ketogenic diet on liver functions of obese rats:

Groups \ Parameters			AST (μ/L)	ALT (μ/L)
G (A):	Control –ve		90.24±2.49 F	43.76±1.98 G
G (B):	B1: Control +ve		131.68±1.29 B	66.70±1.32 B
	B2: Control +ve, for KD at (4: 1)		130.50±2.28 B	64.59±2.17 B
	Mix Oil for KD at (4: 1)	(B3)	101.75±3.25 E	56.19±1.04 C
		(B4)	97.56±2.67 EF	53.61±1.36 D
		(B5)	102.75±3.25 E	50.58±1.73 E
		(B6)	99.97± 3.26 E	49.41±1.96 E
	B7: Control +ve, for KD at (6:3: 1)		137.83±5.45 A	70.63±1.72 A
	Mix Oil for KD at (6:3: 1)	(B8)	113.49±3.21 C	56.48±1.85 C
		(B9)	115.65±2.89 C	49.48±1.24 E
		(B10)	106.44±3.92 D	47.26±1.43 F
		(B11)	94.69±4.51 F	51.56±1.48 DE

***Mix (B3&B8):** olive (65%), sesames (20%), flaxseed (15%). **Mix (B4&B9):** olive (60%), sesames (20%), flaxseed (20%). **Mix (B5&B10):** olive (55%), sesames (20%), flaxseed (25%). **Mix (B6&B11):** olive (20%), sesames (20%), flaxseed (60%). Data are expressed as mean ± SE. Means with different superscript letters in the same column are significantly different at (P < 0.05).

The rats fed on different types of ketogenic diet had significant (P<0.05) increase in (aspartate aminotransferase) AST and (alanine aminotransferase) ALT compared to the -ve control group as shown in table (3). Also, the rats fed on ketogenic diet at (6:3:1) had significant (P<0.05) increase in liver functions compared to the +ve control group fed on ketogenic diet at (4:1).

Vilar-Gomez et al., (2019) demonstrated that one year of the low-carbohydrate, high-fat (LCHF) was effective in improving liver enzymes, where mean ALT, was reduced by 29% on diabetic patient. On the other hand, no significant changes in ALT were recorded by (**Watanabe et al., 2020**). From baseline to week 12,***Jian et al., (2021)*** observed that the plasma AST of KD group was significantly lowered than that in control group (p < 0.05), suggesting the superiorityof KD than conventional treatment in improving liver function.

Supplementation with all different oil mixtures significantly (P<0.05) decreased serum ALT and AST as compared to both control groups fed different types of KD. The improvement of liver functions was observed at the group of rats fed on KD at (4:1) with oil mixture “B6” including olive (20%), sesames (20%), flaxseed (60%). On the other hand, group “B11” that included same mix oil, provide the best improvement in serum AST and group (B10) that contains the following oil mixture (olive (55%), sesames (20%), flaxseed (25%) for serum ALT for the rats fed KD at (6:3:1) when compared to other groups.

Supplementation with olive oil improved liver functions and reduced the severity of liver injury***(Hassanen and Ahmed, 2015).*** These may be attributed to the presence of omega-3 fatty acids that have significant beneficial effects on liver regeneration. Addition of virgin olive oil to the KD improved both kidney and liver functions which was supported by ***Santangelo et al., (2016)*** who demonstrated that extra virgin olive oil consumption preserved hepatic and renal tissue from damages. ***Lama et al., 2017; Rezaei et al., 2019 and Negm, (2020)*** showed that olive oil improved liver function.

Regrading to sesame oil,***Hassanzade-Taheri et al., (2019)*** revealed that sesame oil significantly increased the liver weight in rats. The fat diet which contains the combination of flaxseeds and sesame seeds, or their oils improved the health status of rats suffering from non-alcoholic fatty liver disease (**El-Aziz et al., 2020**). Bacterial glycolytic activity increased in the distal intestine by flaxseeds and led to decrease hepatic fat "especially triglyceride accumulation" ***(Paulina et al., 2018).***

Table (4):
Efficacy of different types of ketogenic diet on serum kidney functions of obese rats:

Groups \ Parameters			Urea	Creatinine
			mg/dl	
G (1):	Control –ve		35.77±1.45 ^{C}	0.72±0.02 ^{E}
G (B):	B1: Control +ve		54.29±0.96 ^{A}	1.20±0.03 ^{A}
	B2 :Control +ve, for KD at (4: 1)		46.90±0.87 ^{B}	0.98±0.01 ^{B}
	Mix Oil for KD at (4: 1)	(B3)	27.97±0.37 ^{F}	0.77±0.04 ^{D}
		(B4)	31.31±1.25 ^{E}	0.72±0.06 ^{E}
		(B5)	32.31±0.88 ^{D}	0.74±0.07 ^{E}
		(B6)	33.27±0.94 ^{D}	0.75±0.02 ^{D}
	B7: Control +ve, KD at (6:3: 1)		48.82±0.64 ^{B}	0.94±0.04 ^{C}
	Mix Oil for KD at (6:3: 1)	(B8)	31.11±0.75 ^{E}	0.75±0.03 ^{D}
		(B9)	30.17±0.64 ^{E}	0.75±0.01 ^{D}
		(B10)	35.20±0.84 ^{C}	0.76±0.04 ^{D}
		(B11)	33.65±0.92 ^{D}	0.74±0.02 ^{E}

***Mix (B3&B8):** olive (65%), sesames (20%), flaxseed (15%). **Mix (B4&B9):** olive (60%), sesames (20%), flaxseed (20%). **Mix (B5&B10):** olive (55%), sesames (20%), flaxseed (25%). **Mix (B6&B11):** olive (20%), sesames (20%), flaxseed (60%). Data are expressed as mean ± SE. Means with different superscript letters in the same column are significantly different at ($P < 0.05$).

It was noticed that serum urea and creatinine were significantly ($P<0.05$) increased for the +ve control group (B1) which were fed on high fat diet compared with the -ve control group (A) as shown in table (4). The rats fed on KD at (4:1) or at (6:3:1) groups (B2 to B11) had significant ($P<0.05$) decrease in the mean level of serum urea and creatinine as compared to +ve control group (B1).

The findings of ***(Omozee and Osamuyimen, 2018)*** have shown that the intake of high fat ketogenic diet is not harmful to the heart, however the increase in serum creatinine in the experimental group may be due to their effects on the kidney or muscle wastage which might be responsible for maintenance of their body weight.

In this study the modified KD at (4:1) or at (6:3:1) with plant oils at different mixtures produced a significant ($P<0.05$) decrease in serum urea and creatinine compared to +ve control group (B2,B7) that fed on KD only. For the groups fed on KD at (4:1) with plant oils, there was no significant changes in kidney functions between group (B5) or group (B6) for serum urea and between group (B4) or group (B5) for serum creatinine.

The groups fed on KD at (6:3:1), there was no change in serum urea between the group (B8) or group (B9). Moreover, there was no significant change in serum creatinine among the groups (B8, B9 or B10). The improvement in kidney functions was observed at the groups fed on KD at (4:1) with oil mixture (B4), containing olive (60%), sesames (20%), flaxseed (20%), followed by groups fed on KD at (6:3:1) with oil mixture (B11) containing olive (20%), sesames (20%), flaxseed (60%).

Santangelo et al., 2016 and Alazawi and Almahdawi, (2018)reported that extra-virgin olive oil consumption preserved hepatic and renal tissue from damages in diabetic rats.They found that using olive oil reduces the level of urea and maintains its normal level against changes in the body.Also, ***(Negm, 2020)*** reported that supplementation with olive oil improved liver and kidney functions**.**

The speculated renal protective agent in flaxseed oil was due to the antioxidant compounds in flaxseed oil***(Omar, 2018)*** and the anti-inflammatory ability of ALA in flaxseed oil***(Kheira et al., 2019).*** Overall, feeding flaxseed oil could protect the changes of biochemical parameters***(Tang et al., 2021).***

Table (5):
Efficacy of different types of ketogenic diet on the random blood sugar of obese rats:

<table>
<tr><th colspan="3">Parameters
Groups</th><th>Glucose
(mg/dl)</th></tr>
<tr><td>G (A):</td><td colspan="2">Control -ve</td><td>82.10±3.5 D</td></tr>
<tr><td rowspan="11">G (B):</td><td colspan="2">B1: Control +ve</td><td>154.15±2.6 C</td></tr>
<tr><td colspan="2">B2: Control +ve, KD at (4 : 1)</td><td>177.80±2.7 A</td></tr>
<tr><td rowspan="4">Mix Oil for KD at (4: 1)</td><td>Mix oil (B3)</td><td>76.45±2.3 E</td></tr>
<tr><td>Mix oil (B4)</td><td>68.95±3.1 F</td></tr>
<tr><td>Mix oil (B5)</td><td>71.45±1.6 F</td></tr>
<tr><td>Mix oil (B6)</td><td>76.25±2.4 E</td></tr>
<tr><td colspan="2">B7 Control +ve, KD at (6:3: 1)</td><td>159.50±3.5 B</td></tr>
<tr><td rowspan="4">Mix Oil for KD at (6:3: 1)</td><td>Mix oil (B8)</td><td>79.85±1.6 D</td></tr>
<tr><td>Mix oil (B9)</td><td>81.20±1.2 D</td></tr>
<tr><td>Mix oil (B10)</td><td>64.25±1.1 G</td></tr>
<tr><td>Mix oil (B11)</td><td>65.15±0.9 G</td></tr>
</table>

***Mix (B3&B8):** olive (65%), sesames (20%), flaxseed (15%). **Mix (B4&B9):** olive (60%), sesames (20%), flaxseed (20%). **Mix (B5&B10):** olive (55%), sesames (20%), flaxseed (25%). **Mix (B6&B11):** olive (20%), sesames (20%), flaxseed (60%). Data are expressed as mean ± SE. Means with different superscript letters in the same column are significantly different at ($P < 0.05$).

Different types of ketogenic diet on random blood sugar of obese rats were illustrated at table (5). The results illustrated that group (B1) fed on high fat diet significantly ($P<0.05$) increased blood glucose as compared to -ve negative control group (A) fed on basal diet. Moreover, feeding on different types of KD at (4:1) or at (6:3:1) "from groups B3 to B11" significantly ($P<0.05$) increased the mean level of blood glucose as compared with the +ve control group (B1) fed on high fat diet only.

Ramesh et al., (2005) reported that, diabetic rats fed on a diet supplemented with sesame oil (6%) decreased the levels of blood glucose of diabetic rats due to high amount of monounsaturated fatty acid of this oil. Moreover, high monounsaturated fat diet improves glycemic control by exerting protective effect against β-cell death and augmenting insulin sensitivity ***(Brehm et al., 2009).***

Serum glucose increased in obese rats, while after the administration of KD supplemented with different oils, the blood glucose was reduced which may be due to the protection of ß-cells in pancreas to produce insulin that enhance glycogen synthase ***(Choudhury et al., 2017). Abdurrachim et al., (2019)*** showed that KD caused an improvement in blood levels of glucose and insulin concentrations in diabetic rats. ***Luukkonen et al., (2020)***supported this study by having ketogenic diet for 6 day markedly decreased hepatic insulin resistance, associated with decreased endogenous glucose production and serum insulin concentrations.

Different types of KD modified with different oil mixture significantly ($P<0.05$) decreased the level of blood glucose when compared to both +ve control fed on KD at (4:1) group (B2) or at (6:3:1) group (B7). It was noticed that there was no significant changes in blood glucose between the groups fed on KD at (4:1) with oil mixture (B3 or B6) as well as between oil mixture (B4 or B5). On the other hand, there was no significant changes in blood glucose among the groups fed on KD at (6:3:1) with oil mixture (B8 or B9) as well as oil mixture (B10 or B11). The blood glucose reduction was recorded at the groups fed KD at (6:3:1) with oil mixture (B10) containing (olive (55%), sesames (20%), flaxseed (25%) followed by oil mixture (B11) including olive (20%), sesames (20%), flaxseed (60%).

Santangelo et al., (2016) demonstrated that extravirgin olive oil consumption significantly reduced fasting plasma glucose in diabetic rats. Virgin olive oil improved blood glucose levels in streptozotocin -induced diabetic rats which agree with the results of the present study. This is due to the ability of phenolic compounds and monounsaturated fatty acids such as oleic acid to decrease the concentration of blood sugar by raising insulin sensitivity in cells ***(Alkhatib et al., 2018).*** Also, ***Schwingshack et al., (2017) and Tsartsou et al., (2019)*** demonstrated that olive oil consumption can improve blood glucose and lipid profile in diabetic patients.***El-Aziz et al., (2020)*** reported that, supplemented bakery with flaxseed or flaxseed oil for 12 weeks decreased blood glucose and improved lipid profile in type 2 diabetics

Virgin Olive oil is a functional food with a high content of mono-unsaturated fatty acids (MUFA), plus 1% omega-3 PUFA, 73.3% oleic acid (MUFA), 7.9% omega-6 PUFA, and 13.5% saturated fatty acids (SFA) ***(Psaltopoulou et al., 2011).*** It also includes other minor biologically active elements, such as polyphenols ***(Covas et al., 2006).***The phenolic compounds are essential in stimulating the blood insulin secretion, and this is due to the oleuropein found in olive oil and its role in triggering and releasing insulin and increasing cell glucose intake ***(Gonzalez, 2007).***

Yu et al. (2017) reported that feeding medium dosage of flaxseed oil could effectively inhibit the metabolic activation of adipose tissue macrophages, and thus improved tissue insulin signaling.***Tufail et al., (2020)***suggested that there is strong evidence for sesame oil on regulation of blood glucose level and lipid peroxidation in diabetic rats.On the other hand, flaxseed oil could significantly reduce the concentrations of fasting blood glucose, blood lipid in contrast with the control ***(Zhu et al., 2020).***

Conclusion

Improved ketogenic diets with modified different plant oils, may be of benefits in fighting the human obesity and its complications. It is suggested to perform this study on humans in clinical trials.

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تأثير الأنظمة الغذائية الكيتونية المعدلة علي صحة فئران التجارب المصابة بالسمنة

إيمان سامى إبراهيم* أسامة السيد مصطفى**
مصطفى أحمد على* مروة ناصر محمد*****

***المركز الإقليمي للأغذية والأعلاف ـ مركز البحوث الزراعية ، الجيزة، مصر**
**** قسم الاقتصاد المنزلى، كلية التربية النوعية ، جامعة عين شمس، القاهرة، مصر**
***** قسم الاقتصاد المنزلى، كلية التربية النوعية، جامعة جنوب الوادى ، قنا، مصر**

الملخص العربى

لقد ازداد انتشار السمنة وأصبحت مشكلة صحية عامة على مستوى العالم. ويوجد العديد من الاستراتيجيات لعلاج السمنة. أجريت هذه الدراسة لتحسين وتعديل النظام الغذائي الكيتوني إلي استبدال الدهون الحيوانية بالزيوت النباتية للحد من الآثار السيئة للنظام الغذائي الكيتوني التقليدي. تم تقسيم اثنان وسبعون من ذكور الفئران إلى مجموعتين رئيسيتين ، المجموعة الرئيسية الأولى (أ) (ن = 6) تم تغذيتها على النظام الغذائي الأساسي وتم الاحتفاظ بها كمجموعة ضابطة سالبة ، المجموعة الرئيسية الثانية / الفئران البدينة (ب) (ن = 66) تم تقسيمها إلى 11 مجموعة فرعية 6 فئران لكل منهما. تم تغذية المجموعة الفرعية (ب1) على نظام غذائي عالي الدهون واستخدمت كمجموعة ضابطة موجبة. تم تقسيم هذه المجموعات الفرعية من (ب2:ب6) حسب النوع الأول منالغذاء الكيتوني بنسبة (4:1) ، المجموعة الفرعية (ب2) تم استخدامها كمجموعة ضابطة موجبة للنوع الغذاء الكيتوني (4: 1). بينما تمت تغذية المجموعات الفرعية الأربعة الأخرى علي الغذاء الكيتوني المدعم بخليط من الزيوت النباتية المختلفة بما في ذلك (زيتون ، سمسم ، بذور الكتان). تم تقسيم المجموعات البدينة الفرعية الأخرى (ب7:ب11) وفقًا للنوع الثاني منالغذاء الكيتوني بنسبة (6: 3: 1) ، واعتبرت المجموعة الفرعية (ب7) مجموعة ضابطة موجبة للنوع الغذاء الكيتوني (6: 3: 1) . بينما تمت تغذية المجموعات الفرعية الأخرى علي الغذاء الكيتوني بمزيج من الزيوت المختلفة مثل الزيوت النباتية السابقة. في نهاية التجربة (6 أسابيع) تم جمع عينات الدم للحصول على عينات السيرم لإستخدامه في تقدير القياسات البيوكيميائية. أظهرت النتائج المتحصل عليها أنه بعد التغذية علي الأنواع المختلفة من الغذاء الكيتوني (4: 1) أو (6: 3: 1) باستخدام خليط زيوت نباتية مختلفة من (زيت الزيتون ، بذور الكتان وزيت السمسم) ، أدت الي حدوث إنخفاض معنوي في وزن الجسم (P <0.05) في الفئران البدينة، وكذلك تحسن في مستوى الدهون ، وظائف الكبد والكلى ونسبة الجلوكوز في الدم مقارنة بالمجموعات الضابطة الموجبة. لذلك يوصي باستبدال النظام الغذائي الكيتوني التقليدي بالنظام الغذائي الكيتوني المعدل (المعتمد على خليط من الزيوت النباتية) بالنسب التي تم إستخدامها، وذلك للإستفادة من القيمة الغذائية لهذه الزيوت التي لها تأثير مفيد على وظائف الجسم.