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The Effect of Different Ketogenic Diet Patterns on the Health Status of Obese Rats: A Comparative Study

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Abstract

This study investigates the effects of various ketogenic diets—Classic Ketogenic Diet, Modified Atkins Diet, Medium-Chain Triglyceride Diet, and Low-Glycemic Index Treatment—on weight loss, lipid profiles, liver and kidney function, as well as their impact on oxidative stress, inflammation, and certain hormones in obese rats. Thirty-six Sprague Dawley rats were divided into six groups, with one serving as a negative control that was fed a standard diet while the others were fed a high-fat diet for nine weeks to induce obesity. Afterwards, the obese rats were categorized into five groups: one continued on a standard diet as a positive control, while the others followed different ketogenic diets for six weeks, maintaining a standardized caloric intake. Results showed that rats on ketogenic diets had significant weight loss, improved lipid profiles, and enhanced liver and kidney functions compared to the positive control group. There were also reductions in the oxidative stress marker C-reactive protein (CRP) and thyroid-stimulating hormone (TSH), alongside increases in cortisol and triiodothyronine (T3) levels. These findings suggest that ketogenic diets provide several benefits for weight management and metabolic health. However, the increase in cortisol levels raises concerns about potential stress effects, highlighting the need for careful application in clinical settings. Further research is needed to assess long-term safety and relevance to human health.

Keywords: Hormonal Regulation, Liver, Ketogenic Diet, Kidney Function, Lipid Profile, Obesity, Oxidative Stress.

1. Introduction

Unwanted weight gain that results in obesity and overweight is now regarded as a chronic condition and is a major contributing factor to the global rise in chronic, non-communicable diseases. Those who suffer from overweight and obesity are also susceptible to low self-esteem, depression, and discrimination in their personal and professional lives due to the psychological and social stigmas associated with these disorders (Rubino *et al.*, 2020). Due to decreased worker productivity, higher disability, and early mortality, these physiological and psychological effects of obesity account for a significant portion of healthcare costs and also result in additional financial costs (Ramasamy *et al.*, 2019). obesity has a major role in the development of fatty liver, obstructive sleep apnea, hypertension, and diabetes mellitus. In Egypt, about 115 thousand fatalities a year are projected to be caused by obesity (19.08% of all estimated deaths in 2020). Obesity costs the Egyptian economy over 62 billion pounds annually, reflecting the expenses related to treating illnesses associated with adult obesity (Aboulghate *et al.*, 2021).

Controlling body weight and adiposity through a negative energy balance achieved through nutrition and physical activity is the key to treating and preventing obesity. However, the research on substitutes for the treatment of obesity, such as functional foods and bioactive substances, is becoming more and more important as a result of changes in people's lifestyles, including decreased physical activity and altered eating habits (Oladimeji and Adebo, 2024).

Effective solutions to tackle the rising obesity epidemic worldwide include a variety of options such as tailored diet plans, engaging behavioural lifestyle programs, dynamic exercise routines, and targeted medications like appetite suppressants and thermogenic agents. For individuals facing the most severe obesity, bariatric surgery presents a viable path to lasting change. Embracing these diverse strategies is crucial for achieving healthier lives and combating this urgent public health challenge (Sombra and Anastasopoulou, 2024). Most people who want to lose weight do it by cutting back on calories with a low fat or carbohydrate content. According to Kim (2020), there is no single best nutritional plan for managing one's diet and reducing energy intake. However, in some cases, an extremely low-calorie diet may be necessary for a short period. Diets based on specific macronutrient compositions, such as ketogenic or high-protein diets, can also be considered in certain situations. Numerous clinical trials have investigated the physiological effects of various diets on obesity treatment. These studies have

included research on low-calorie diets, and many more (Umphonsathien et al., 2019; Drabińska et al., 2021; Deshpande et al., 2023). The ketogenic diet (KD) is gaining popularity as a weight loss tool due to its successful usage as an adjunctive treatment for epilepsy (Corsello *et al*., 2023).

Ketogenic diet is defined as low calories, high levels of fat and protein, and very low levels of carbohydrates often less than 50 g/d (Zhu *et al*., 2022). Standard, cyclical, focused, and high-protein ketogenic diets are the four main varieties of the ketogenic eating plan (Malinowska and Żendzian-Piotrowska, 2024). Most research and recommendations centre on the normal ketogenic diet, which recommends a 70–20 fat-to-protein and carbs ratio. Ketone bodies, which are made when fats are broken down in the liver can replace glucose as an energy source, particularly for the brain and spinal cord, when carbohydrate consumption is reduced (Murakami and Tognini, 2022). According to recent studies, this diet shows promising results in helping obese people regulate their weight (Goldenberg *et al*., 2021; Luo *et al*., 2022). Low-carb diets alter the body's metabolism, which starts the process of fatty acid oxidation. Accordingly, it also prolongs a person's life (Pathak and Baar, 2023). The conventional or classic KD, the medium-chain triglyceride, the ketogenic diet, the modified Atkins diet, and the low glycemic index treatment are the four types of KDs that are now accessible (Barzegar *et al*., 2021).

Researchers employ diet-induced obesity animal models to examine the development of obesity and its risk factors. These models recreate human obesity more reliably than genetic models (de Moura e Dias *et al*., 2021). Research using animal models is usually conducted in controlled environments, which helps in understanding the results. This study aims to evaluate diet-induced obesity models in rats by comparing the effects of various ketogenic diets (specifically, the Classic Ketogenic Diet, Modified Atkins Diet, Medium-Chain Triglyceride Diet, and Low-Glycemic Index Treatment) on the health of rats with obesity.

2. Materials and Methods

2.1. Materials

Animals: thirty-six (36) *Sprague Dawley* strain male rats were purchased from the Faculty of Pharmacy Mansoura University, Egypt that were 12-14 weeks old with a body weight of 163±5 g. Guidelines for moral behaviour in the handling and use of animals in research were supplied by the Scientific Research Ethics Committee of Mansoura University (No: 311-9-8-2021)

Basal diet: According to Reeves et al. (1993), all diets were designed to satisfy rats' nutritional needs following the American Institute of Nutrition's (AIN-93G) guidelines.

Types and ratios of the used Ketogenic Diet :

The four ketogenic diets used in this work were formulated according to Kossoff and Hartman (2012) and are presented in Table (A)

Table 1. Composition of ketogenic diets used.

Ingredient	AIN-93G	HF	CKD	MCT	MA	LGIT
Cornstarch	397	315	0	0	0	0
Casein (>85% protein)	200	200	145	168	404	371
Dextrinized cornstarch	132	105	53	286	69	304
Sucrose	100	79	0	0	0	0
Corn Oil	70	10	0	0	0	0
Beef tallow	0	190	492	0	149	0
Olive oil	0	0	91	0	56	29
Flaxseed oil	0	0	119	0	73	38
Coconut oil	0	0	0	445	149	158
Fiber	50	50	50	50	50	50
Mineral mix (AIN-93G-MX)	35	35	35	35	35	35
Vitamin mix (AIN-93-VX)	10	10	10	10	10	10
L-Cystine	3	3	3	3	3	3
Choline bitartrate (41.1% choline)	3	3	3	3	3	3
tert-Butylhydroquinone (TBHQ) mg	14	14	14	14	14	14
Sum	1014	1014	1014	1014	1014	1014
Calories	3828	4476	7022	5722	5491	4501
Energy Density	3.8	4.4	6.9	5.6	5.4	4.4

Source: HF= High fat, CKD = Classic Ketogenic Diet, MCT= Medium-Chain Triglyceride, MA= Modified Atkins, LGIT= Low-Glycemic Index Treatment

2.2. Experimental Design:

2.2.1. Adaptation of Animals:

Thirty-six adult male albino rats were housed in well-ventilated cages. After being weighed upon arrival, the rats underwent a two-week acclimatization period. According to Reeves et al. (1993), they were provided with regular rat chow during this time and had unrestricted access to food and water. Following the acclimatization period, six rats were maintained on the basal diet and served as negative control (Group 1), while the remaining thirty were given a high-fat diet for nine weeks to promote obesity.

2.2.2. Induction of Obesity and Grouping of Animals

Male rats were fed a high-fat diet, as per Ibrahem et al. (2021), for nine weeks before the start of the experiment to induce obesity. The basal diet, which contained the necessary vitamins and minerals in powder form, was blended with fat until it achieved a uniform consistency similar to dough. After drying, the resulting chow

blocks were administered to the rats for nine weeks to induce obesity. Following this period, a ketogenic diet was introduced, which continued for an additional six weeks.

Following obesity induction, the 30 obese rats were divided into five groups (6 rats each), housed individually in cages, and classified as follows:

1. Group II: Obese rats were switched to a standard diet and served as the positive control group (+ve).
2. Group III (Traditional Ketogenic Diet - TKD Group): Obese rats were fed a traditional ketogenic diet (TKD) for 6 weeks
3. Group IV (Medium-Chain Triglycerides - MCT Group): Obese rats were fed a medium-chain triglycerides (MCT) diet for 6 weeks.
4. Group V (Modified Atkins - MA Group): Obese rats were fed a modified Atkins diet (MA) for 6 weeks.
5. Group VI (Low Glycemic Index Treatment - LGIT Group): Obese rats were fed a low glycemic index treatment (LGIT) diet for 6 weeks.

All groups received an identical caloric intake of 0.3 calories per gram of body weight per rat per day throughout the study. Weekly changes in body weight and feed intake were tracked for the duration of the 16 weeks. According to Chapman *et al.*, (1959), feed intake (gm) was determined every seven days. The body weight change percentage was calculated by using the following equations:

$$\text{Body weight change (\%)} = \frac{\text{Final weight (g)} - \text{weight after obesity (g)}}{\text{Weight after obseity}} \times 100$$

2.2.3. Blood Sampling

Rats were slaughtered at the end of the experiment, after an overnight fast, and each rat's blood was withdrawn from an ophthalmic vein. According to Drury and Wallington (1980), blood samples were placed into sterile, dry centrifuge tubes, allowed to clot at room temperature, and then spun for ten minutes at 5000 rpm to separate serum. The serum was kept in a deep freezer at -18°C before being utilized for biochemical investigations.
Biochemical analysis of serum:

Lipid profile

- Total cholesterol and triglycerides were determined according to Allain *et al.* (1974) and Fassati and Prencipe (1982), respectively using Bio-diagnostics kits, Egypt (Cat. No. CH 12 20 and Cat. No. TR 20), while HDL_{-C} was specified according to Lopes *et al. (*1977).
- LDL_{-C} and $VLDL_{-C}$ were calculated by using the method of (Friedewald *et al.*, 1972).
- LDLc = Total cholesterol - (HDL_C + $VLDL_C$)
  VLDLc = TG / 5

Liver function tests

- Serum alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured according to the method of Whitaker (1969) using Diamond diagnostics kits (CAT. NO. AL 10 31 for ALT, and CAT. NO. AS 10 61 for AST).

kidney function tests

- Serum uric acid was determined according to Fassati *et al.* (1980)
- Creatinine was determined according to the methods described by Young (2001).

Anti-inflammatory parameter:

- C-reactive protein: The CRP concentration in the serum was estimated according to Friedman and Young (2001).

Antioxidant parameters:

- Serum malondialdehyde (MDA) was measured calorimetrically according to the method of Satoh (1978).
- Total antioxidant capacity (TAC) was determined by the method of Koracevic *et al.* (2001).

Hormones:

- Serum cortisol was measured using the method outlined by Kytzia (2005).
- The assessment of thyroid stimulating hormone (TSH) was conducted by Uotila *et al.* (1981).
- Serum levels of thyroid hormone (Triiodothyronine) were assessed using Radioimmunoassay (RIA) as outlined by Patrono and Peskar (1987).
- Insulin was determined according to Burgi *et al.* (1988).
- Leptin was measured using Ultra-Sensitive Mouse Leptin ELISA kits (Morinaga Institute of Biological Science, Kanagawa, Japan) as mentioned by Abe (2022).

2.2.4. Statistical Analysis

The data was shown as means ± SD, and ANOVA was used for statistical analysis. According to Gomez and Gomez (1984), the computer program (Costate) was used to compare the means of the groups using a (LSD) statistic test at a significance level of 5%.

3. Results and Discussion

3.1. Effect of Different Ketogenic Diets on Body Weight Gain and Body Mass Index (BMI) of Obesity Rats:

The results in Table 1 indicate the effect of different ketogenic diets on body weight, weight gain, and BMI of rats in the normal control, positive control, and treated groups.

The results show that the initial weights of all the groups were similar, with no significant differences. Their weights ranged from 164.50± 5.20 to 167.50± 2.65 g. After six weeks of obesity induction, the rats were weighed

and then treated with the four keto diets. It was found that the weight of the obesity groups increased from 313.00±9.93 to 321.25±6.24 g which is significantly higher than the normal control (232.50±6.76 g).

It was observed that all ketogenic diets significantly reduced final body weight and the relative weight reduction percentage compared to the positive control.

The most effective diets were the traditional and modified Atkins, with no significant difference between them, although the modified Atkins demonstrated greater effectiveness.

According to Perticone *et al.* (2019), a ketogenic diet is an effective weight loss program, especially for those looking to decrease their fat mass while keeping their lean mass stable. In order to regulate overweight and obesity, it is not necessary to restrict specific nutrients, especially carbohydrates, or increase the consumption of food categories that have been associated with various diseases in excess (Corrêa *et al.* 2019; Goldberg *et al.* 2021).

Low-carb KD can cause hunger ketosis by simulating a state of starvation in the body. As a result, the body's glucose-based energy supply pattern was replaced by a ketone body energy supply mode, which depends on fat to encourage catabolism and decrease fat synthesis while increasing energy consumption due to gluconeogenesis. Acetoacetate, β-hydroxybutyric acid (soluble in water) and acetone (insoluble in water) are the ketone bodies that are created from the insoluble triglyceride. As a result, the energy-draining ketone body can be further eliminated through the excretion of urine (Urbain and Bertz, 2016). Furthermore, an increase in ketone bodies has been shown to reduce hunger (Nymo *et al.*, 2017). This could also explain why, even in the presence of excessive fat, KD can lower lipid metabolism indicators including total cholesterol, triglycerides, and low-density lipoprotein. It is thought to be the body's state of ketosis, which is seen in KD and extremely low-calorie diets and is linked to increased satiety and appetite suppression (Gibson *et al.*, 2015). By controlling hormones linked to appetite, ketone bodies may have a positive impact on hunger.

The current study's findings are in line with those of Manikam *et al.* (2018), who found that KD had a longer-lasting weight-loss effect on obese patients than low-fat diets. Additionally, Diana and Atmaka (2020) observed a drop in body weight after administering the KD, which stimulates the body's ketosis, with a carbohydrate intake of up to 10% of total energy for six months. However, Omozee and Osamuyimen (2018) found that the experimental group fed a 65% fatty diet did not significantly gain weight.

Sticking to a low-carbohydrate diet helps a lot of patients shed pounds. But these trendy eating plans can make hypercholesterolemia worse. Ketogenic diet (KD) results can be helpful for weight loss and changing body composition without major negative effects. The problem is that many studies have failed to include control diets and have instead used extremely low-calorie diets, which may make it harder to lose weight. In just six weeks, those on the low-carb diet lost three times as much weight as those on the ketogenic diet (Alharbi and Al-Sowayan 2020). Nasser *et al.* (2022) found that following a 10-week high-fat diet (HFD) with an 8-week ketogenic diet led to weight loss and reduction in fat mass.

The data in Table (1) revealed that the BMI was significantly increased in the obesity control group as compared to normal control where their values were 9.78 and 5.49, respectively.

Also, ketogenic diets recorded a significant reduction in BMI compared to the obesity control. All ketogenic diets had significant differences in comparison with the normal control, but their values were higher than the value of the normal control.

The most effective diets were TKD and MA where they reduced the BMI value with percentages of 21.09 and 20.78%, respectively. On the other hand, LGIT and MCT had a lower effect.

Ahmed et al. (2023) noted that obesity is often characterized by a high body fat percentage, which is commonly associated with an elevated body mass index (BMI). Significant changes were observed following a 10-week high-fat diet (HFD). Nasser *et al.* (2022) found that an eight-week ketogenic diet led to a similar reduction in fat mass and weight loss in rats. Perticone *et al.* (2019) reported that the ketogenic diet is effective for weight loss, especially when it decreases fat mass and keeps lean mass constant. According to Drabińska *et al.* (2022), the ketogenic diet is a great way to help people who are overweight, especially if they have tried other diets without success or if they need to lose weight quickly.

Table 1. Effect of different ketogenic diets on body weight and BMI of obese rats:

Parameters / Groups		Weight change					BMI
		Weight at the beginning (g)	Weight after obesity (g)	Final weight (g)	Weight reduction (g)	Weight reduction percentage	
Control (-V)		165.25^{a}±2.50	232.50^{b}±6.76	185.75^{d}±7.93	46.75^{bc}±12.74	20.58^{bc}±5.64	5.49^{d}±1.33
Control (+V)		166.00^{a}±3.92	313.00^{a}±9.93	294.50^{a}±7.85	18.50^{a}±11.03	5.59^{a}±3.34	9.78^{a}±1.67
TKD	Mean ± SD	164.50^{a}±5.20	318.75^{a}±2.99	264.25^{c}±3.77	54.50^{c}±5.69	16.67^{c}±1.88	7.72^{c}±3.93
MCT	Mean ± SD	167.50^{a}±2.65	313.50^{a}±8.96	277.75^{b}±8.62	35.75^{b}±14.22	10.83^{ab}±4.36	8.72^{b}±3.67
MA	Mean ± SD	165.25^{a}±4.43	320.75^{a}±11.09	258.50^{c}±7.00	62.25^{c}±13.60	18.60^{c}±4.08	7.75^{c}±3.60
LGIT	Mean ± SD	165.75^{a}±2.99	321.25^{a}±6.24	275.50^{b}±3.11	45.75^{bc}±7.59	13.75^{bc}±2.28	8.11^{c}±3.08

Source: Results are presented as means ±SD & (n=6 for each group).
The mean values in each column with different superscript letters are significantly different at $p < 0.05$
TKD: traditional ketogenic diet
MCT: medium chain triglyceride
MA: modified Atkins
LGIT: low glycemic index treatment.

3.2. Effect of Different Ketogenic Diets on Lipid Profile of Obese Rats

Table 2 compares the mean values of the lipid profile of obese rats treated with ketogenic diets with that of the normal and positive controls.

There was a significant increase in lipid profile parameters, including total cholesterol, triglycerides, LDL-c, and VLDL-c levels, in the positive obesity control group compared to the normal control group, while the serum HDL level decreased ($P<0.05$).

The lipid profile was affected by the different ketogenic diets in obese rats' groups. Total cholesterol, triglycerides, LDL-c and VLDL-c were decreased under the effect of all ketogenic diets, which recorded the lowest values with LGIT and TKD without any significant difference between them, followed by MCT and MA compared to the positive control. The rate of the reduction in LGIT and TKD ketogenic diets groups was 36.00 and 31.53% for total cholesterol, 45.39 and 42.20% for both triglycerides and VLDL--c and 79.08 and 81.80% for LDL-c, respectively.

However, after six weeks after administration of ketogenic diets, the level of HDL -c increased in the treated groups compared to the positive group. In the TKD diet, the highest level of HDL was noticed followed by MCT, MA and LGIT ketogenic diets. The increase in their HDL levels were 36.6, 30.77, 23.08 and 22.38%, respectively.

People who are overweight or obese, particularly those who have diabetes, and who follow a low-fat diet tend to have worse metabolic parameters related to weight, glycemic management, and lipid profiles than those who follow a ketogenic diet, which improved these parameters (Choi *et al.*, 2020). According to Lee and Lee (2021), this strategy has the potential to reduce metabolic dysfunction-related mortality and sickness in certain patient populations. While athletes with elevated total cholesterol levels should be closely monitored before starting a ketogenic diet, research has shown that ketones can reduce body fat percentage as stated by Drabińska *et al.* (2021).

In this study, rats fed various ketogenic diets exhibited significantly lower levels of total cholesterol, triglycerides, LDL-c and VLDL-c and an increase in HDL-c level compared to the positive control group. These findings are consistent with those of Paoli et al. (2013), which indicated that an increase in HDL levels is associated with a reduced risk of coronary heart disease. Mouse studies have shown that KD increases serum HDL-c and decreases plasma triglyceride levels (Ng *et al.*, 2014). In obese people, the cholesterol, triglycerides, and LDL cholesterol decreased after just two weeks of a low-calorie ketogenic diet (Choi et al., 2018). A study by Guo et al. (2020) and Negm (2020) showed that diabetic mice had a lower incidence of obesity. The ketogenic diet is safe for everyone, including those who already have dyslipidemia **(Yılmaz et al., 2021)**.

Table 2. Effect of different ketogenic diets on the lipid profile of obese rats.

Parameters / Groups		Lipid profile				
		CH (mg/dl)	**TG (mg/dl)**	**HDL (mg/dl)**	**VLDL-c**	**LDL-c**
Control (-V)		$56.25^{d}\pm3.40$	$70.50^{d}\pm4.80$	$38.25^{bc}\pm4.11$	$14.10^{d}\pm0.96$	$3.90^{d}\pm0.35$
Control (+V)		$106.25^{a}\pm5.12$	$141.00^{a}\pm10.58$	$35.75^{c}\pm5.50$	$28.20^{a}\pm2.12$	$42.30^{a}\pm4.63$
% of change (**)		88.89	100.00	-6.54	100.00	984.62
TKD	Mean ± SD	$72.75^{c}\pm6.94$	$81.50^{cd}\pm8.66$	$48.75^{a}\pm6.95$	$16.30^{cd}\pm1.73$	$7.70^{d}\pm4.31$
	% of change (*)	-31.53	-42.20	36.36	-42.20	-81.80
MCT	Mean ± SD	$83.50^{b}\pm4.20$	$90.25^{c}\pm10.05$	$46.75^{a}\pm4.03$	$18.05^{c}\pm2.01$	$18.70^{c}\pm4.01$
	% of change (*)	-21.41	-35.99	30.77	-35.99	-55.79
MA	Mean ± SD	$99.25^{a}\pm7.63$	$125.00^{b}\pm11.63$	$44.00^{ab}\pm4.40$	$25.00^{b}\pm2.33$	$30.25^{b}\pm5.48$
	% of change (*)	-6.59	-11.35	23.08	-11.35	-28.49
LGIT	Mean ± SD	$68.00^{c}\pm10.10$	$77.00^{cd}\pm7.70$	$43.75^{ab}\pm5.50$	$15.40^{cd}\pm1.54$	$8.85^{d}\pm5.58$
	% of change (*)	-36.00	-45.39	22.38	-45.39	-79.08

Source: Results are presented as means ±SD - (n=6 for each group).
(**) % of change relative to the negative control (-V).
(*) % of change relative to the positive control (+V).
The mean values in each column with different superscript letters are significantly different at $p<0.05$
TKD: traditional ketogenic diet
MCT: medium chain triglyceride
MA: modified Atkins.
LGIT: low glycemic index treatment

3.3. Effect of Different Ketogenic Diets on Liver and Kidney Function Parameters in Obese Rats

Liver function parameters, namely ALT and AST, and kidney function parameters, namely creatinine and uric acid, for normal control and obese rats, are presented in Table 3. Serum ALT and AST levels were elevated in the positive control group compared to the normal control, without a significant difference between them. However, a significant reduction in serum ALT and AST levels was observed in all the treated groups on the various ketogenic diets.

After six weeks of ketogenic diets in obesity groups, significant reductions in liver function parameters, specifically ALT and AST, were observed. MA diet was the best in this respect, followed by LGIT diet without a significant difference between them. The reductions recorded with MA diet were 52.91 % for ALT and 59.22% for AST, while their reductions with LGIT diet were 43.82% for ALT and 54.41 % for AST compared to the positive control group.

The obesity rats that were treated with the TKD ketogenic diet exhibited a significant decrease in enzyme levels, with a reduction of 36.13% for ALT and 43.09% for AST compared to the positive control group. In contrast, the MCT diet showed the lowest reduction percentages, with a decrease of 24.48% for ALT and 23.31% for AST compared to the positive control.

On the other hand, the tested kidney function parameters (creatinine and uric acid) elevated significantly in the positive control group compared to the normal control in percentages of 69.05 and 47.81%, respectively.

The use of ketogenic diets in groups with obesity led to a reduction in two kidney function parameters compared to the positive control group. The MCT diet resulted in the most significant reductions, with a decrease of 30.94% in creatinine levels and 25.22% in uric acid levels. The LGIT diet also showed notable reductions, with a 29.58% decrease in serum creatinine and a 27.89% decrease in uric acid compared to the positive control.

The TKD and MA ketogenic diets resulted in smaller reductions, with serum creatinine decreasing by 12.68% and 7.04%, respectively. Serum uric acid levels also declined, with decreases of 3.86% and 7.42% for the TKD and MA diets, respectively, compared to the positive control group.

Accumulation of lipids in the liver is a direct result of obesity, which can cause liver dysfunction (Vernon *et al.*, 2011). Patients with diabetes showed an improvement in liver ALT enzymes, with a percentage of 29% after following a low-carb, high-fat (LCHF) diet for one year (Vilar-Gomez *et al.*, 2019). Based on the findings of Li *et al.* (2021), a notable distinction in human plasma AST levels was observed between the KD consisting of approximately 5%–10% of energy from carbohydrates (≤50 g/day), 18%–27% from protein, and 70%–75% from fat and control groups beginning in week 12, suggesting that KD outperforms more traditional approaches to improving liver function.

Drabińska et al. (2022) found that adult rats, which had become obese as adolescents due to their diet, were placed on a restrictive diet that included a 20% caloric reduction compared to a standard diet (consisting of 8% soy oil as a fat source and 8% cellulose). They concluded that a ketogenic diet (KD) is a safe treatment for juvenile obesity, as it does not worsen renal function.

While uric acid is associated with insulin resistance, diabetes, and poor cardiovascular health, it is also important to recognize that it can serve as a marker for metabolic syndrome. Uric acid can contribute to insulin resistance, dyslipidemia, and abdominal obesity (Mazidi et al., 2018). In our study, one positive effect of the KD was that the uric acid levels were lower and closer to those of the normal control group.

Additionally, the low protein content (7%) in the targeted ketogenic diet (TKD) explains the reduced urea levels observed in the rats on the KD, as proteins are the primary source of urea in the blood.

Table 3. Effect of different ketogenic diets on liver and kidney function of obese rats.

Parameters / Groups		Liver function tests		Kidney function tests	
		ALT (U/L)	**AST (U/L)**	**Creatinine (mg/dl)**	**Uric acid (mg/dl)**
Control (-V)		$97.00^{ab}\pm10.03$	$376.00^{a}\pm24.81$	$0.42^{c}\pm0.05$	$2.28^{b}\pm0.24$
Control (+V)		$107.25^{a}\pm14.10$	$410.75^{a}\pm34.81$	$0.71^{a}\pm0.05$	$3.37^{a}\pm0.18$
% of change (-V)		10.57	9.24	69.05	47.81
TKD	Mean ± SD	$68.50^{cd}\pm11.82$	$233.75^{c}\pm35.06$	$0.62^{b}\pm0.06$	$3.24^{a}\pm0.19$
	% of change (+V)	-36.13	-43.09	-12.68	-3.86
MCT	Mean ± SD	$81.00^{bc}\pm13.04$	$315.00^{b}\pm28.41$	$0.49^{c}\pm0.08$	$2.52^{b}\pm0.24$
	% of change (+V)	-24.48	-23.31	-30.99	-25.22
MA	Mean ± SD	$50.50^{d}\pm11.45$	$167.50^{d}\pm17.56$	$0.66^{ab}\pm0.05$	$3.12^{a}\pm0.23$
	% of change (+V)	-52.91	-59.22	-7.04	-7.42
LGIT	Mean ± SD	$60.25^{d}\pm13.52$	$187.25^{d}\pm24.69$	$0.50^{c}\pm0.06$	$2.43^{b}\pm0.19$
	% of change (+V)	-43.82	-54.41	-29.58	-27.89

Source: Results are presented as means ±SD and % of change from (+V).
(n=6 for each group).
The mean values in each column with different superscript letters are significantly different at $p < 0.05$
TKD: traditional ketogenic diet
MCT: medium chain triglyceride
MA: modified Atkins
LGIT: low glycemic index treatment.

According to research by Ibrahem *et al.* (2021), obese rats that followed various ketogenic diet regimens (4 fat:1 protein and carb) or (6 fat:3 protien:1 carb) utilizing different vegetable oil mixtures (olive, flaxseed, and sesame oils) experienced significant improvements in their liver, and kidney functions when compared to positive control groups.

3.4. Effect of Different Ketogenic Diets on Oxidative Stress and Anti-Inflammatory Activity in Obese Rats

Serum levels of malondialdehyde (MDA) and total antioxidant capacity (TAC) were measured to evaluate antioxidant activity, while serum C-reactive protein (CRP) was measured to assess anti-inflammatory activity in rat groups treated with ketogenic diets as shown in Table 4. There were no significant differences in MDA, TAC, and CRP values between the normal and the positive control groups. On the other hand, the serum levels of MDA and CRP decreased, while the TAC level increased significantly in the treated obese rats with different ketogenic diets compared to the positive control. The most effective system was the TKD ketogenic diet, which showed a decrease of 54.43% in MDA and 42.33% in CRP, along with an increase of 88.98% in TAC compared to the positive control group, followed by LGIT, MA, and then MCT diets.

Permanently elevated oxidative stress and persistent low-grade inflammation are both linked to obesity (Marseglia *et al.*, 2014). Diseases associated with obesity arise as a result of cellular damage caused by persistent oxidative stress. One typical indicator for oxidative status measurement is the measurement of enzymatic antioxidant activity, which represents the level of antioxidant protection (Finaud and Filaire, 2006). Increased ROS production may result from the increased complexity of fat metabolism, which includes reduction, oxidation, hydroxylation, and conjugation (Garbow *et al.*, 2011). The impact of KD on oxidative stress has not been definitively addressed in prior research. In contrast, taekwondo practitioners who adhered to a KD for three weeks were safeguarded against exercise-induced oxidative stress. (Rhyu *et al.*, 2014). Although the antioxidant enzymes were unaffected by KD for 2 weeks, healthy women's total oxidative status improved (Nazarewicz *et al.*, 2007). An animal study indicated that KD reduced oxidative stress following traumatic brain injury (Greco *et al.*, 2016). Patients with obesity who underwent very-low-calorie KD did not experience any improvement in oxidative stress (Valenzano *et al.*, 2019). Malondialdehyde, a prominent indicator of oxidative stress, is formed when polyunsaturated fatty acid peroxidation products degrade, therefore a study by Ho *et al.* (2013) found that KD lowers oxidative stress by decreasing the trend for malondialdehyde.

Table 4. Effect of different ketogenic diets on oxidative stress and anti-inflammatory activity in obese rats.

Parameters / Groups		Oxidative stress		Anti-inflammatory
		MDA (nmol/ml)	TAC (mM/L)	CRP
Control (-V)		$16.43^{a}\pm1.33$	$0.71^{bc}\pm0.14$	$2.85^{a}\pm0.29$
Control (+V)		$17.14^{a}\pm1.67$	$0.63^{c}\pm0.09$	$3.00^{a}\pm0.32$
	% of change (-V)	4.32	-11.27	5.26
TKD	Mean ± SD	$7.81^{b}\pm3.93$	$1.19^{a}\pm0.30$	$1.73^{b}\pm0.46$
	% of change (+V)	-54.43	88.89	-42.33
MCT	Mean ± SD	$10.28^{b}\pm3.67$	$1.00^{ab}\pm0.10$	$2.03^{b}\pm0.40$
	% of change (+V)	-40.02	58.73	-32.33
MA	Mean ± SD	$9.22^{b}\pm3.60$	$1.05^{a}\pm0.22$	$1.93^{b}\pm0.40$
	% of change (+V)	-46.21	66.67	-35.67
LGIT	Mean ± SD	$9.01^{b}\pm3.08$	$1.11^{a}\pm0.24$	$1.80^{b}\pm0.42$
	% of change (+V)	-47.43	76.19	-40.00

LGIT: low glycemic index treatment.

Source: Results are presented as means ±SD and % of change from (+V).
(n=6 for each group).
The mean values in each column with different superscript letters are significantly different at $p < 0.05$
TKD: traditional ketogenic diet
MCT: medium chain triglyceride
MA: modified Atkins

3.5. Effect of Different Ketogenic Diets on Some Hormones of Obese Rats

The results in Table 5 indicate the effect of different ketogenic diets on hormones cortisol, T3 and TSH in normal and obese rats.

Cortisol level in positive control was lower than the normal control with no significant difference between them. After 6 weeks of different ketogenic diets, the levels of cortisol elevated significantly in all the treated groups compared to the positive control without statistically significant difference between them. However, the most effective one was TKD which raised the cortisol level by 84.21% followed by LGIT and MA with an increase percentage of 68.42% for both, then MCT by increasing 57.89% compared to the positive control.

Restricting calories can be stressful and cause an increase in cortisol production, which is only a natural result of the hormone's physiological function in energy expenditure (Tomiyama *et al.*, 2010). Furthermore, Purnell et al. (2009) speculate that following successful diet-induced weight loss, elevated HPA activity may promote visceral fat accumulation. It has been shown that after 24 weeks of dieting, metabolic clearance, cortisol production rate, and free cortisol levels in males with obesity do not significantly change from baseline; however, in this same group, cortisol production increased with further weight loss. Researchers discovered that individuals whose diets were very low in carbohydrates exhibited higher levels of the stress hormone cortisol in their urine compared to those whose diets were lower in fat or glycaemic index. (Gasior *et al.*, 2006; Ebbeling *et al.*, 2012). Plasma cortisol levels were shown to be higher in patient populations who were given KDs as potential treatments, according to multiple research. For instance, Fraser *et al.* (2003) found that all people with epilepsy had higher cortisol levels in plasma collected before and after KD medication. The same study found that KD raised plasma cortisol levels in RA patients (Fraser *et al.*, 2000).

The results in Table 4 revealed a state of hypothyroidism (high TSH and low T3) in the positive control group compared to the normal control group.

Serum T3 levels were reduced in the positive group, showing a statistically significant difference compared to the normal group. In contrast, ketogenic diets resulted in a substantial increase in T3 levels, with a significant difference compared to the positive group. Serum TSH level increased significantly in the positive group (0.24±0.035 uIU/ml) compared to the normal group (0.05±0.013 uIU/ml); however, it was markedly lower in the ketogenic diet groups compared to the positive control.

The results revealed that the groups that received the ketogenic diets of TKD, MCT and LGIT exhibited significant increases in T3 hormone. In contrast, the diet of MA had no significant effect on the T3 hormone compared to the positive control. The best diet for raising the T3 level was LGIT followed by TKD and MCT with increased percentages of 119.28, 95.24 and 76.19%, respectively. The decreased percentage in serum TSH level was 66.67% for LGIT group and 50% in both TKD and MCT groups compared to the positive control. These results indicate that the LGIT diet is perfect for obese people to lose weight and improve thyroid function.

A shift in thyroid function is one potential "metabolic advantage" of ketogenic diets. It is well established that thyroid hormones influence critical metabolic pathways involved in energy balance (energy expenditure and storage) as well as lipid and carbohydrate metabolism, and the complex interactions among the various pathways involving thyroid hormones remain not fully understood. Metabolic rate and adaptive thermogenesis are two processes influenced by thyroid hormones, and these processes, in turn, impact body mass. Several factors can affect thyroid function, including changes in the expression of thyroid hormone transporters, the relative expression of thyroid hormone receptor isoforms, local ligand activation and inactivation, and the activity of receptor corepressors and coactivators (Mullur *et al.*, 2014). Previous studies have shown that dietary carbohydrate restriction reduces T3 levels (Phinney *et al.*, 1983). Another study found that three weeks of sustained ketosis (KD) dramatically reduced T3 level (Iacovides *et al.*, 2022). After two weeks of a ketogenic diet, endurance-trained cyclists had lower T3 levels than those in the control group who ate a healthy, balanced diet (Phinney *et al.*, 1983), an adaptation that conserves muscle glycogen may be responsible for the fall in T3. Carbohydrate restriction, also known as nutritional ketosis, appears to alter the ratio of circulating thyroid hormones. Brdar *et al.* (2021) discovered that a high intake of protein or foods heavy in saturated fatty acids had a negative correlation with FT3 and FT4 concentrations, whereas a high intake of high GI foods like fruit juices and refined bread, pasta, and rice had a positive correlation with TSH concentration and a negative correlation with FT4 and FT3 concentrations.

The results presented in Table 5 show a significant decrease in insulin levels in the positive control group compared to the normal control group, with a reduction of 41.55%. In contrast, the group treated with the MA diet experienced a considerable increase in serum insulin levels. However, the other three groups did not show any significant changes compared to the positive control. Notably, the normal diet, which focused solely on reducing caloric intake, was the most effective in maintaining insulin levels and achieving normoglycemia.

The results indicate that the most effective ketogenic diet for raising serum insulin levels in obese rats was the modified Atkins diet.

KD may lessen blood glucose fluctuations, lower blood glucose, and lessen the absorption of intestinal monosaccharides. According to a study by Myette-Côté *et al.* (2018), KD can significantly and quickly help patients control their blood sugar levels. This can reduce the amount of feedback fasting insulin that the patients produce, stabilize blood sugar levels, and lessen blood sugar fluctuations in diabetic patients.

Gomez-Arbelaez *et al.* (2017) stated that a very low-calorie ketogenic diet successfully lowered body weight without causing a loss of lean mass. It is also a useful weight-loss strategy since it lowers insulin resistance and promotes a non-atherogenic lipid profile (Abbasi, 2018). Researchers found that ketogenic diets, as compared to low-fat diets, improved metabolic parameters associated with weight, glycemic control, and lipid profiles in obese and overweight individuals, especially those with a history of diabetes (Choi *et al.* 2020). In some patient groups, this measure may lessen the severity of illness and death caused by metabolic dysfunction (Lee and Lee, 2021).

Table 5 also shows the effect of different ketogenic diets on the leptin hormone level in obese rats. There was a significant ($P<0.05$) increase in the leptin level of positive control compared to the normal control group.

Table 5. Effect of different ketogenic diets on some hormones in obese rats.

Parameters / Groups		Hormones				
		Cortisol (µg/dl)	**T3 (ng/ml)**	**TSH (µIU/ml)**	**Insulin (pg/ml)**	**Leptin (ng/ml)**
Control (-V)		$0.21^{bc}\pm0.024$	$0.52^{a}\pm0.036$	$0.05^{c}\pm0.013$	$257.50^{a}\pm13.92$	$2.89^{d}\pm0.27$
Control (+V)		$0.19^{c}\pm0.022$	$0.21^{d}\pm0.030$	$0.24^{a}\pm0.035$	$150.50^{c}\pm26.03$	$4.09^{a}\pm0.15$
% of change (-V)		-9.52	-59.62	380.00	-41.55	41.52
TKD	Mean ± SD	$0.35^{a}\pm0.079$	$0.41^{bc}\pm0.072$	$0.12^{b}\pm0.034$	$165.50^{bc}\pm21.89$	$3.21^{cd}\pm0.30$
	% of change (+V)	84.21	95.24	-50.00	9.97	-21.52
MCT	Mean ± SD	$0.30^{ab}\pm0.057$	$0.37^{c}\pm0.053$	$0.12^{b}\pm0.028$	$175.00^{bc}\pm19.17$	$3.74^{ab}\pm0.22$
	% of change (+V)	57.89	76.19	-50.00	16.28	-8.56
MA	Mean ± SD	$0.32^{a}\pm0.061$	$0.26^{d}\pm0.033$	$0.21^{a}\pm0.029$	$182.75^{b}\pm13.30$	$3.23^{cd}\pm0.26$
	% of change (+V)	68.42	23.81	-12.50	21.43	-21.03
LGIT	Mean ± SD	$0.32^{a}\pm0.067$	$0.46^{ab}\pm0.039$	$0.08^{bc}\pm0.036$	$160.75^{bc}\pm24.62$	$3.52^{bc}\pm0.26$
	% of change (+V)	68.42	119.28	-66.67	6.81	-13.94

Source: Results are presented as means ±SD and % of change from (+V).
(n=6 for each group).
The mean values in each column with different superscript letters are significantly different at $p<0.05$
TKD: traditional ketogenic diet
MCT: medium chain triglyceride
MA: modified Atkins
LGIT: low glycemic index treatment.

Leptin levels were reduced in the obese groups following a ketogenic diet, with the most affected group being those on a targeted ketogenic diet (TKD), closely followed by those on a modified Atkins (MA) diet, with no significant difference between the two. This was followed by low glycaemic index treatment (LGIT) and medium-chain triglycerides (MCT) compared to the positive control. The decrease in leptin levels was 21.52%, 21.03%, 13.94%, and 8.56% for the TKD, MA, LGIT, and MCT ketogenic diets, respectively.

Consistent with the findings from body composition analysis, leptin is believed to indicate an increase in fat mass (Kinzig et al., 2010). The hypothalamus regulates food intake and body weight by controlling leptin levels (Schwartz et al., 2000). In studies, the appetite-suppressing effect of leptin was diminished in rats that became obese due to a high-fat or non-ketogenic diet (Fam et al., 2007). Kinzig et al. (2010) found that, unlike rats on high-fat diets, rats on ketogenic diets did not lose their leptin sensitivity, despite having a higher fat mass percentage. It was also found that the level of triglycerides affected the peripheral leptin level (Banks *et al.*, 2004). Triglycerides play an indirect role in leptin resistance by preventing the hormone from crossing the blood-brain barrier. Some have hypothesized that ketogenic diets can help people with obesity maintain the weight loss benefits of leptin, which include reduced appetite and more feelings of fullness after eating less. Nevertheless, the results of the experiments must confirm this. Kinzig *et al.* (2010) noted that triglycerides did not increase following a ketogenic diet. According to Drabińska *et al.*, (2022), the groups who followed a high-fat diet initially had somewhat greater plasma leptin concentrations compared to the conventional diet group in the beginning. The levels of this hormone were found to be significantly greater in the ketogenic diet group following the restrictive diet, compared to the conventional diet group with 20% calorie restriction, which had the lowest concentration. After 4 weeks of growth, the leptin level in the group that followed the normal diet increased fivefold.

4. Conclusion

It can be concluded that all ketogenic diets significantly reduced body weight compared to the positive control group, with the Modified Atkins (MA) and Traditional Ketogenic Diet (TKD) being the most effective. These diets also decreased levels of total cholesterol, triglycerides, LDL cholesterol (LDL-c), and VLDL cholesterol (VLDL-c). The lowest cholesterol levels were observed in the Low Glycemic Index Treatment (LGIT) and TKD groups. Additionally, HDL cholesterol (HDL-c) levels increased notably after six weeks, particularly in the TKD group. Various ketogenic diets under investigation may be beneficial in combating human obesity and its associated problems particularly on liver and kidney function, as well as lipid profile. It is recommended to conduct this study on humans in clinical trials.

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