



Research Article

Medium chain triglyceride-ketogenic diet elevates fasting blood glucose, lipid profile and liver enzymes but protects against high fat diet-induced changes

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Abstract

Obesity is associated with increased body mass index, abnormal glucose metabolism, liver injury, as well as alterations in lipid metabolism. Medium chain triglyceride-ketogenic diet (MCT-KD) is a diet with the potential of reverse obesity and its complications. This study was designed to evaluate body weight, fasting blood glucose, lipid profile and serum liver enzymes in male Wistar rats fed with a high-fat diet and MCT-KD. Twenty male Wistar rats were divided into four groups of five animals each. Group I animals were fed with normal diet feed (NDF). Group II was fed with MCT-KD only, Group III was fed with a high-fat diet only (HFD), while Group IV was fed with both HFD and MCT-KD on alternate days for 3 weeks. The results showed a significant increase in body weight and fasting blood glucose in the groups fed with MCT-KD only and HFD only when compared to the animals fed with the NDF group. There was a significant decrease in serum levels of total cholesterol, triglyceride and low-density lipoprotein in the group fed with MCT-KD and HFD on alternate days compared to the HFD and NDF groups. There was a decrease in the level of aspartate aminotransferase enzyme in all the groups compared to NDF. The alkaline phosphatase and alanine aminotransferase levels were higher in the MCT-KD and HFD only groups. These findings suggest that while MCT-KD holds the potential in counteracting diet-induced metabolic changes, its independent effects warrant careful consideration.

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Keywords

Obesity, ketogenic diet, body weight, blood glucose, lipid profile, liver enzymes.

1. Introduction

Obesity is a metabolic disease that has become a global concern because of its increasing prevalence and associated disabling complications [1, 2]. Although an individual's genetic predisposition for weight gain is considered a risk factor, dietary intake of excess calories has been reported to play a major

role [3, 4]. Thus, in obesity, there is a state of imbalance between calories ingested versus calories expended, leading to excessive deposition of fats in the adipose tissue [5]. Carbohydrates are the primary sources of energy in the body; however, when carbohydrate consumption exceeds the required amount, the excess

is then converted into fats [6]. Thus, the human body operates based on the first law of thermodynamics, according to which energy only changes form; it is neither created nor destroyed [7].

The ketogenic diet (KD), commonly called 'low-carbohydrate diet' is a diet containing low carbohydrates and high amounts of fats with moderate proteins [8]. The intake of low carbohydrates causes the body to switch to fat metabolism as the primary means of energy production, resulting in the production and use of ketone bodies (acetone, acetoacetate and β -hydroxybutyrate) [4, 9]. The medium chain triglyceride-ketogenic diet (MCT-KD) is a modification of the traditional ketogenic diet that allows for a higher carbohydrate intake while still maintaining a state of ketosis [10]. It was introduced in an attempt to improve the palatability of the ketogenic diet by incorporating MCT oils into the diet formulations, which were reported to have more ketogenic properties and are suitable for reducing excess calories [11, 12].

Obesity has been reported as the major underlying risk factor for type 2 diabetes mellitus, cardiovascular disorders and metabolic syndromes [13, 14]. It has been associated with alterations in lipid metabolism characterized by elevated serum triglyceride, low-density lipoprotein, and low high-density lipoprotein cholesterol levels [15]. Obesity also leads to the accumulation of excess fat in the liver, causing abnormal liver function with elevated liver enzymes [16]. Reduction in body weight has been the treatment target in obesity, with diet being considered a first-line approach [17]. Intake of fat supplements such as MCTs has been shown to increase energy expenditure and lead to greater loss of adipose tissues in humans [18]. Obese individuals who achieved weight loss were found to experience some improvement in obesity complications [19]. Kennedy et al. [20] reported that a ketogenic diet was able to reverse a high-fat diet-induced experimental obesity in mice. Another study reported that a reduction in fasting blood glucose levels was observed in Wistar rats fed with MCT-KD formulated with sunflower oil [21].

Previous studies targeted the ameliorative action of ketogenic diets on already-induced obesity in experimental animals. This study, however, looked at

the possibility of ketogenic diet in preventing the development of diet-induced obesity when administered together with a high-fat diet on alternate days to experimental animals. Therefore, this study aimed at evaluating the protective effect of formulated MCT-KD on obesity-induced alterations in body weight, fasting blood glucose level, lipid profile and serum liver enzymes in male Wistar rats.

2. Materials and methods

2.1. Materials

Digital glucometer (Accu-Chek, Roche Diagnostics GmbH, Mannheim, Germany), digital weighing scales, normal diet feed (vital feed, Grand Cereals Ltd, Jos, Plateau State, Nigeria), Simas Margarine (PT Salim Ivomas Pratama Tbk, Indonesia), coconut oil (Orange market, Mararraba Nasarawa State, Nigeria), groundnut oil and groundnut powder (Samaru market, Zaria, Kaduna State, Nigeria), 50 mg/kg ketamine hydrochloride and 5 mg/kg diazepam (Putney, Inc., Portland).

2.2. Experimental animals

Twenty (20) male Wistar rats of about 10-12 weeks and weighing 120g-140g were purchased from the animal house of the Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Medical Sciences Ahmadu Bello University, Zaria. The animals were kept in well-aerated laboratory cages in the animal house of the Department of Human Physiology and were allowed to acclimatize to the laboratory environment for two weeks before the commencement of the experiment.

2.3. Formulation of high-fat diet

The formulation of high-fat diet (HFD) was done according to the method described by Dubo et al. [22] with some modifications. The HFD was prepared by mixing 54% of normal diet feed (vital feed), with 14% of Simas margarine, 27% groundnut powder and 5% (v/w) groundnut oil.

2.4. Formulation of medium chain triglyceride-ketogenic diet (MCT-KD)

The MCT-KD was formulated by mixing 30% normal diet feed (vital feed), 30% groundnut powder and 15% Simas margarine with 25% (v/w) coconut oil to provide the MCT oil, according to the method described by [21] with some modifications.

2.5. Proximate analysis

Quantification of nutritional compositions of normal diet feed and formulated high-fat diet and MCT-KD was conducted at the Institute for Agricultural Research (IAR), Ahmadu Bello University, Zaria, Nigeria.

2.6. Animal grouping

The animals were divided into 4 groups of 5 animals each as follows:

Group I: Rats were fed with a normal diet for 3 weeks.

Group II: Rats were fed with a formulated high-fat diet for 3 weeks.

Group III: Rats were fed with formulated MCT-KD for 3 weeks.

Group IV: Rats were fed with formulated high fat and MCT-KD on alternate days (24-hour alternation) for 3 weeks.

2.7. Determination of body weight

The body weights of the rats were weighed with a digital weighing scale every week until the 3rd week of the study, and measurement was taken for each rat in grams (g).

2.8. Determination of fasting blood glucose

The fasting blood glucose level was measured weekly using the Accu-Chek Active Diabetes Monitoring Kit (Roche Diagnostics GmbH, Mannheim, Germany) in overnight fasted Wistar rats, based on the glucose oxidase method [23]. The blood was obtained from the tail vein and the reading was recorded in mg/dl.

2.9 Collection of blood sample

At the end of the three (3) weeks feeding period, the animals were anaesthetized with 50 mg/kg ketamine hydrochloride and 5 mg/kg diazepam [24]. Blood samples were collected and centrifuged at 3000×g for 10 minutes. The serum was used for the determination of lipid profile and liver enzymes.

2.10. Estimation of lipid profile

2.10.1. Determination of serum total cholesterol (TC)

The serum level of total cholesterol was quantified after enzymatic hydrolysis and oxidation of the sample as described by the method of Stein [25]. Briefly, 1000 µl of the reagent will be added to each of the samples and standard. This was incubated for 10 minutes at 20-25 °C after mixing, and the absorbance of the sample (A_{sample}) and standard (A_{standard}) was

measured against the reagent blank within 30 minutes at 546 nm.

Total cholesterol concentration = $A_{\text{sample}} / A_{\text{standard}} \times 196.86$ mg/dL.

2.10.2. Determination of serum triglyceride (TG)

The serum triglyceride level was determined after enzymatic hydrolysis of the sample with lipases as described by Tietz [26]. Briefly, 1000 µl of the reagent was added to each sample and standard. This was incubated for 10 minutes at 20-25 °C after mixing, and the absorbance of the sample (A_{sample}) and standard (A_{standard}) was measured against the reagent blank within 30 minutes at 546 nm.

Triglyceride concentration = $A_{\text{sample}} / A_{\text{standard}} \times 194.0$ mg/dL.

2.10.3. Determination of serum high density lipoprotein cholesterol (HDL-c)

The serum level of high-density lipoprotein cholesterol (HDL-C) was measured using the method of Wacnic and Albers [27]. Low-density lipoproteins (LDL and VLDL) and chylomicron fractions in the sample was precipitated quantitatively by the addition of phosphotungstic acid in the presence of magnesium ions. The mixture was allowed to stand for 10 minutes at 20-25 °C and centrifuged for 10 minutes at 4000 g. The supernatant represented the HDL-C fraction. The cholesterol concentration in the HDL fraction, which remained in the supernatant, was determined.

2.10.4. Determination of serum high density lipoprotein cholesterol (LDL-c)

The serum level of LDL-C was measured according to the protocol of Friedewald et al. [28] using the equation below.

$LDL-C = TC - (TG/5 + HDL-C)$. The value is expressed in mg/dL

2.11. Determination of liver enzymes

The measurements of the activities of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase enzymes were carried out by spectrophotometric determination of their absorbance using analytical grade reagent kits (Randox Laboratories Limited, Crumlin, and County Antrim, United Kingdom) as described by Bessey et al. [29].

2.12. Statistical analysis

Data collected on weekly body weight and fasting blood glucose were analyzed using mixed-design analysis of variance (ANOVA), while data on serum levels of lipid profiles and liver enzymes were analyzed using one-way ANOVA. In each case, Tukey's *post hoc* test was used for multiple comparisons. Results are presented as mean ± standard error of the mean (SEM). Values of $p < 0.05$ were considered statistically significant. Statistical Package for the Social Sciences (SPSS) version 25.0 was used for the analysis.

3. Results

3.1. Result of proximate analysis of the diet formulations

The proximate analysis result for normal diet feed (NDF), medium chain triglyceride-ketogenic diet (MCT-KD) and high-fat diet (HFD) as shown in Table 1, shows the approximate nutrient compositions of the diets; NDF contained fats 17%, protein 26%, carbohydrates 57%, formulated HFD contained fat 54%, protein 19% Carbohydrates 27%, while MCT-KD contained fats 71%, protein 18%, carbohydrates 11%.

Table 1. Result of proximate analysis of the diet formulations

Diets	Lipid (%)	Protein (%)	CHO (%)
NDF	17.0	25.6	57.4
HFD	53.8	19.0	27.2
MCT-KD	70.8	18.0	11.2

NDF: Normal diet feed, MCT-KD: Medium chain triglyceride-ketogenic diet, HFD: High-fat diet, CHO: Carbohydrate

3.2. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on body weight in male Wistar rats

The result in Fig. 1 shows the effect of MCT-KD and HFD on body weight taken weekly for three weeks. One week after the commencement of the feeding, there was a significant increase ($p < 0.05$) in the body weight of Wistar rats fed with only MCT-KD when compared with NDF group. On weeks 2 and 3, the rats fed with HFD only and MCT-KD only had increase in body weight compared to the NDF group. However, the rats fed with both HFD and MCT-KD on alternate days while on week 3 showed a significant reduction in body weight ($p < 0.05$) compared to the MCT-KD only group on week 2 of the feeding. The rats in each feeding group showed a linear increase in body

weight across the weeks; however, the rats fed with both HFD and MCT-KD had body weights less than the other groups at the end of the 3 weeks.

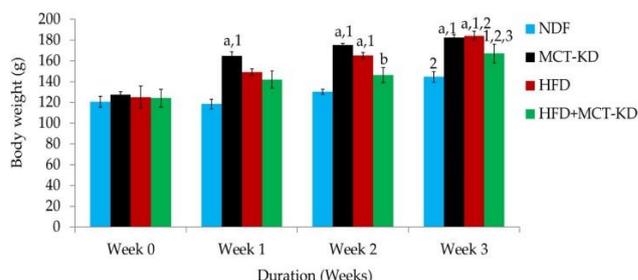


Figure 1. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on body weight in male Wistar rats (Results are presented as mean ± SEM. Each bar represents a mean of five rats analyzed using mixed-design ANOVA and Tukey's *post hoc* test. Superscripts a, b = Significant difference ($p < 0.05$) compared to NDF and MCT-KD groups respectively. Superscripts 1, 2, 3 = Significant difference ($p < 0.05$) compared to week 0, week 1 and week 2 respectively. NDF: Normal diet feed, MCT-KD: Medium chain triglyceride-ketogenic diet, HFD: High-fat diet).

3.3. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on fasting blood glucose level in male Wistar rats

There was a significant increase ($p < 0.05$) in fasting blood glucose level in the HFD only group when compared with the MCT-KD only group and the group fed with both HFD and MCT-KD on alternate days during the first week of the feeding, as shown in Fig. 2.

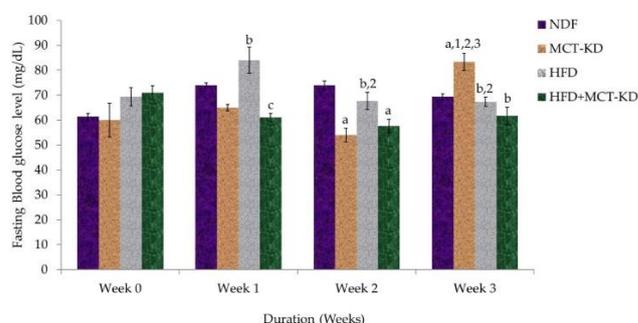


Figure 2. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on fasting blood glucose level in male Wistar rats

(Results are presented as mean ± SEM. Each bar represents a mean of five rats analyzed using mixed-design ANOVA and Tukey's *post hoc* test. Superscripts a, b = Significant difference ($p < 0.05$) compared to NDF and MCT-KD groups respectively. Superscripts 1, 2, 3 = Significant difference ($p < 0.05$) compared to week 0, week 1 and week 2 respectively. NDF: Normal diet feed, MCT-KD: Medium chain triglyceride-ketogenic diet, HFD: High-fat diet).

Table 2. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on lipid profile in male Wistar rats

Groups	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
NDF	42.36±8.19	36.98±6.14	5.02±0.30	29.88±8.32
MCT-KD	25.82±6.20	18.76±2.90 ^a	8.52±2.30	12.76±5.00 ^a
HFD	32.40±8.10	10.86±1.34 ^a	7.68±1.30	22.66±7.50
HFD+MCT-KD	15.34±2.20 ^{a,c}	8.22±1.70 ^a	8.52±2.10	5.18±2.04 ^{a,c}

Results are presented as mean ± SEM. Each bar represents a mean of five rats analyzed using one-way ANOVA, followed by Tukey's *post-hoc* test. Superscripts a, c = Significant difference ($p < 0.05$) compared to NDF and HFD groups respectively. NDF: Normal diet feed, MCT-KD: Medium chain triglyceride-Ketogenic diet, HFD: High-fat diet. TC: Total Cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein.

On week 2, the fasting blood glucose level in the MCT-KD group was significantly lower ($p < 0.05$) compared to NDF and HFD groups, while the NDF group had a significantly higher fasting blood glucose compared to the MCT-KD and HFD groups.

At the end of the three weeks, the fasting blood glucose level in the MCT-KD only group was significantly higher ($p < 0.05$) when compared to the other feeding groups. The fasting blood glucose in MCT-KD only group decreased in weeks 1 and 2 but increased on week 3, while HFD only group increased on week 1 then decreased in the last week. The groups fed with both HFD and MCT-KD on alternate days and NDF showed no significant change ($p > 0.05$) in fasting blood glucose levels across the weeks.

3.4. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on lipid profile in male Wistar rats

The result in Table 2 shows that total cholesterol was significantly increased ($p < 0.05$) in the group fed with both HFD and MCT-KD when compared to HFD only and NDF groups. The level of triglyceride was lower in all the feeding groups compared to NDF, while low density lipoprotein was significantly lower ($p < 0.05$) in the group fed with both HFD and MCT-KD when compared to HFD. However, there was no change in the level of high-density lipoprotein cholesterol in all the feeding groups ($p > 0.05$).

3.5 Effect of medium chain triglyceride ketogenic diet and high-fat diet on liver enzymes in male Wistar rats

The level of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) was significantly higher ($p < 0.05$) in the group fed with MCT-KD only, compared to the other feeding groups, as shown in Fig. 3a. The ALP level of the group fed HFD only was also significantly higher compared to the group fed with

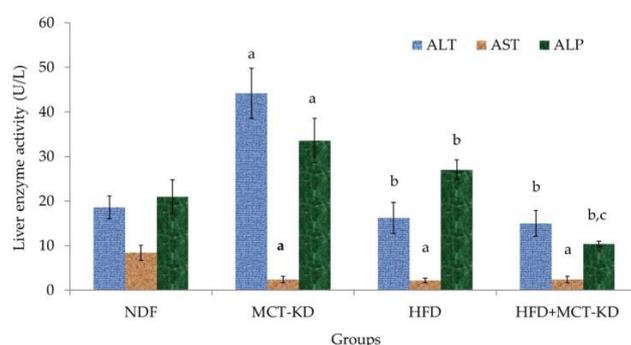


Figure 3a. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on liver enzymes in male Wistar rats (Results are presented as mean ± SEM. Each bar represents a mean of five rats analyzed using one-way ANOVA, followed by Tukey's *post-hoc* test. Superscripts a, b, c = Significant difference ($p < 0.05$) compared to NDF, MCT-KD and HFD groups respectively. NDF: Normal diet feed, MCT-KD: Medium chain triglyceride-ketogenic diet, HFD: High-fat diet. ALT= alanine transaminase; AST= Aspartate transaminase; ALP= Alkaline phosphatase).

both HFD and MCT-KD. Aspartate aminotransferase (AST) level in the NDF group was significantly higher than in the other groups. In Fig. 3b, ALT/AST was significantly higher ($p < 0.05$) in the MCT-KD only group when compared to the other groups. The HFD only group and the group fed with both HFD and MCT-KD had higher ($p < 0.05$) ALT/AST ratios compared to the NDF group.

4. Discussion

An unhealthy lifestyle characterized by excessive consumption of diets high in carbohydrates and lack of physical exercise has been reported as a major underlying cause of metabolic disorders such as obesity [30]. In this study, obesity was modelled in Wistar rats by administering a high-fat, high-carbohydrate diet commonly called a 'high-fat diet'. A medium chain triglyceride-ketogenic diet (MCT-KD) was formulated with coconut oil to provide the MCT

oil, having high fat and low carbohydrate content. The

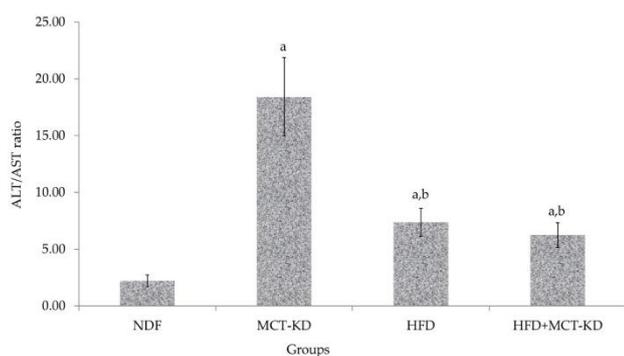


Figure 3b. Effect of medium chain triglyceride-ketogenic diet and high-fat diet on ALT/AST ratio in male Wistar rats (Results are presented as mean± SEM. Each bar represents a mean of five rats analyzed using one-way ANOVA, followed by Tukey's *post-hoc* test. Superscripts a, b = Significant difference ($p < 0.05$) compared to NDF and MCT-KD groups respectively. NDF: Normal diet feed, MCT-KD: Medium chain triglyceride-ketogenic diet, HFD: High-fat diet).

high-fat diet (HFD) and MCT-KD were administered on alternate days to investigate the possible potentials of MCT-KD in preventing high-fat diet-induced-obesity and its related complications on blood glucose and lipid metabolism as well as liver enzymes.

In the present study, it was observed that three weeks feeding of Wistar rats with HFD resulted in increased body weight. This could be due to the deposition of excess fats in the adipose tissue, consequently leading to an increase in body mass index, indicating obesity [17]. However, HFD administered on alternate days with MCT-KD did not show a change in body weight, which suggests that MCT-KD was able to prevent an increase in body weight induced by HFD. Although the MCT-KD administered alone showed an increase in body weight, it was not significant compared to HFD-fed rats. Mobbs et al. [31] reported that reduction in body weight might be an essential component of the mechanism of action of the ketogenic diet in the treatment of obesity. This explained why previous studies that investigated the ketogenic diet's ability to improve symptoms of obesity observed a reduction in body weight [32]. However, there are inconsistent findings on the pattern of weight changes after ketogenic diet usage both in humans and in animal studies. A study by Sanya et al. [21] for example, revealed no change in body weight between the ketogenic diet group and the normal diet group. This is contrary to the initial claim but agrees with the

findings of this study. Medium chain triglycerides have been shown to increase energy expenditure because they are rapidly absorbed into the bloodstream providing instant energy, due to their quick absorption and oxidation [18, 33]. The HFD co-administered with MCT-KD might have provided a synergistic action by increasing the fat content, consequently leading to increased ketogenic properties that prevented the elevation of body weight observed in this study when HFD and MCT-KD were given separately.

The fasting blood glucose level followed the same pattern as the body weight on the third week of the feeding. Although previous studies reported that the ketogenic diet improves glycemic control, it was observed in this study that the ketogenic diet alone increased blood glucose level, however, when MCT-KD was administered concurrently with a high-fat diet, no significant change was observed. This suggests that MCT-KD prevented the elevation of blood glucose levels caused by HFD as reported by previous research [20, 34]. Based on this result, it means that the ketogenic diet's ability to decrease blood glucose levels may be dependent on the existence of obesity-causing factors. Atkinson [35] reported that body weight is correlated with blood glucose level in obesity; as such, weight loss may be responsible for decreased hepatic output observed after ketogenic diet intervention. This assertion could be true for this study; as changes in body weight due to the effects of MCT-KD directly reflect the fasting blood glucose level.

In this study, it was observed that consumption of HFD together with MCT-KD led to a decrease in serum total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-c) but no change was observed in the concentration of serum high-density lipoprotein cholesterol (HDL-c). A similar observation was made by Kenney et al. [20] where the levels of TC, TG and LDL-c were decreased while HDL-c increased when the ketogenic diet was administered. However, the ketogenic diet was given after the induction of obesity, showing its ability to reverse dyslipidemia of obesity. Our study showed that ketogenic diet could also prevent a rise in plasma levels of the lipid profile when administered concurrently with HFD. A study by Noain et al. [36]

reported that the ketogenic diet caused an increase in serum concentrations of TC and LDL-c, relating it to rapid weight loss due to the mobilization of adipose tissue cholesterol as the fat cells shrink. Thus, the effects of the ketogenic diet on total cholesterol and low-density lipoprotein cholesterol are less predictable despite the improvement of dyslipidemia [37]. Buren et al. [38] also reported an increase in LDL-c after 4 weeks of feeding with a ketogenic diet in healthy young women. Although the MCT-KD administered alone in this study increased body weight and fasting blood glucose level, we did not observe a significant change in its effect on lipid profile. The result also showed that MCT-KD consumption led to no change in HDL concentration. This is similar to the findings of Swift et al. [39], who observed no change in serum level concentration of HDL during 6 days of maintenance feeding with MCT and mixed-chain triglycerides. A high HDL-c level is related to a lower risk of cardiovascular diseases [40], thus, HDL-c is termed "good cholesterol" [41]. Despite the lack of significance on the serum level of HDL-c in this study, the fact that HFD could not decrease the level of HDL-c when fed together with MCT-KD, means MCT-KD has some protective effects that may require further investigation.

Serum liver enzymes alanine aminotransferase (ALT) and alkaline phosphatase (ALP) determined in this study were observed to be increased in the MCT-KD only group despite their decrease in the group fed with both HFD and MCT-KD, while aspartate aminotransferase (AST) level was low in the formulated diet groups compared to NDF. Because of the increase in the level of ALT, the ALT/AST ratio was also higher in the MCT-KD-only group. Previous studies reported that obese individuals are at high risk of developing non-alcoholic fatty liver disease (NAFLD) characterized by an elevated level of liver enzymes [2, 42]. Elevated ALT level is more specific to liver injury than elevated AST, as it is primarily found in abundance in the cytoplasm of the hepatocytes [43]. When expressed as ALT/AST ratio, it provides information on the aetiology of liver injury, aspartate aminotransferase (AST) usually rises in conjugation with alanine aminotransferase (ALT) to indicate hepatocellular injury [44]. Thus, the ALT/AST ratio increases with the degree of fatty infiltration,

implying that the leakage of enzymes from the hepatocyte is largely from the cytoplasmic compartment and that the leakage increases with progressive fatty infiltration [45].

The result on the liver enzyme is supported by Haghghatdoost et al. [46] who reported that a low carbohydrate diet decreased intrahepatic fat content but not liver enzymes levels. Another study by Anekwe et al. [47] observed that the ketogenic diet increases LDL-C, TC and liver enzymes, consequently leading to the development of non-alcoholic fatty liver disease. Although our study revealed that MCT-KD decreased the level of liver enzymes and ALT/AST ratio when given together with HFD, it, however, increased the liver enzymes and ALT/AST ratio when it was administered alone. Gaysteyger et al. [48] stated that the positive effect of weight loss may improve liver diseases, but despite that, liver enzymes may transiently increase immediately after a diet induced weight loss.

5. Conclusions

This study demonstrates that medium chain triglyceride-ketogenic can effectively mitigate high-fat diet-induced metabolic disturbances, such as elevated body weight, fasting blood glucose, and altered lipid profiles, when used in combination with high-fat diet. However, when administered alone, MCT-KD leads to significant increase in these parameters. These findings suggest that while MCT-KD holds the potential in counteracting diet-induced metabolic changes, its independent effects warrant careful consideration. Future studies should explore long-term impacts and underlying mechanisms to better understand the therapeutic potential and risks associated with MCT-KD.

Ethical Consent

The experimental protocol was reviewed and certified by the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC), with approval number (ABUCAUC/2021/007). Strict adherence to the Ethical Committee's directives was observed.

Authors' contributions

Conceptualization, B.D.A.; Methodology, A.I.S., H.D., S.E.O.; Validation, C.E.E., U.F.; Software,

N.T.J., S.C.; Formal analysis, B.D.A., A.S.; Investigation, B.D.A., A.S.; Resources, H.D., S. E.O.; Data curation, A.I.S., A.S.; writing—original draft preparation, B.D.A. H.D., A.I.S.; Visualization, C.E.E., N.T.J.; Writing- review & editing, B.D.A., Supervision, B.D.A., U.F.; Project administration, B.D.A., A.S.; Funding acquisition, S.C., U.F.

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Availability of data and materials

All relevant data are within the paper and its supporting information files. Additional data will be made available on request according to the journal policy.

Conflicts of interest

The authors declare no conflict of interest

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