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EFFECT OF MEDIUM CHAIN TRIGLYCERIDE-KETOGENIC DIET ON THE LUNGS OF TYPE 2 DIABETIC MALE NEW ZEALAND RABBITS

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ABSTRACT

Type 2 diabetes mellitus is a metabolic disorder that results in impairment of the lungs, associated with both structural and functional alterations. Ketogenic diet is a high-fat, moderate-protein and low-carbohydrate dietary regimen, with the potential of ameliorating diabetic lung complications. This study evaluated the effects of medium chain triglyceride-ketogenic diet (MCT-KD) on the lungs of type 2 diabetic male New Zealand rabbits. Type 2 diabetes was induced by feeding the rabbits formulated high fat diet for ten weeks. Twenty rabbits were divided into five groups of four rabbits each: Group I was a normoglycemic group fed with normal diet; Group II was a normoglycemic group fed with a MCT-KD; Group III was a diabetic group fed with normal diet; Group IV was a diabetic group fed with MCT-KD while Group V was a diabetic group fed with normal diet and oral administration of 4 mg/kg pioglitazone. There was a significant increase ($p < 0.05$) in cellular infiltration of total white blood cells, lymphocytes, neutrophils and macrophages into the bronchoalveolar lavage fluid of diabetic lungs. However, feeding with MCT-KD and administration of 4 mg/kg pioglitazone significantly decreased ($p < 0.05$) total white blood cells and the differential components in the diabetic lungs. The MCT-KD was observed to reduce the lung weight of the diabetic rabbits, however, no change was observed in the relative lung weight. Cellular infiltration, reduced alveolar spaces, distorted bronchial epithelium and oedema were observed in the lungs. These were observed to be alleviated after feeding with MCT-KD.

Keywords: Inflammation, Ketogenic diet, Lungs, Rabbits, Type 2 diabetes, White blood cells

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple aetiology, characterized by chronic hyperglycemia associated with impaired insulin signalling (WHO, 2024). Based on aetiopathogenesis, diabetes mellitus can be type 1 or type 2. The pathogenesis of type 2 diabetes varies between individuals and complicated by heterogeneity in the degree of insulin resistance and deficiency, genetic and environmental influences (ADA, 2009; Mayer-Davis *et al.,* 2018). Diabetes mellitus is associated with lung dysfunction, which involves series of complex mechanisms leading to impairment of lung structure and functions (Kolahian *et al.,* 2019; Machado *et al.,* 2021).

Chronic hyperglycemia leads to glycation of proteins producing Amadori products that undergo further modifications to form advanced glycation end products (Eidangbe, 2025). Cross-linking of collagen and elastin proteins of the lungs, contributes to both rigidity and loss of elasticity of pulmonary parenchyma and thickening of the pulmonary capillaries resulting in impaired pulmonary function (Nawale *et al.,* 2006; Almeida *et al.,* 2016). It also causes glycation of immunoglobulin and increases the chance of acute and chronic pulmonary infections that causes fibrosis of lung parenchyma and consequently reduces the lung mechanics (Ali, 2014). It has been reported that diabetic hyperglycemia damages the respiratory system due to the pulmonary interstitial injury caused by microangiopathy (Kaparianos *et al.,* 2008). The histological changes in diabetic lungs have been described by Kuziemsky *et al.* (2011), as thickening of walls of pulmonary alveoli caused by increased amounts of collagen and elastin; thickening of a basal membrane of alveoli, which leads to a decrease in pulmonary parenchymal elastic recoil ability; thickening of basal membrane of capillaries and endothelium causing increase in density of pulmonary micro vessels (Amal *et al.,* 2013). It has also been reported that a histological examination of a diabetic lung model, revealed that, the thickened basal membranes were fibrotic and were associated with an intense inflammatory reaction, characterized by massive inflammatory cell infiltration (Zheng *et al.,* 2017). Inflammation plays an important role in the pathogenesis of diabetic lung injury and is associated with the release of pro-inflammatory cytokines and oxygen free radicals from activated inflammatory cells such as neutrophils, eosinophils, monocytes and macrophages (Belvisi *et al.,* 2006; Dubo *et al.,* 2019). It has been reported that respiratory tract infections are responsible for a significant number of medical appointments by persons with diabetes compared to non-diabetic patients (Vishawakarma *et al.,* 2021). This is due to increased susceptibility to pulmonary infection, as a result of alteration in the chemotactic, phagocytic and bactericidal activity of polymorphonuclear leukocytes and impaired phagocytic function in diabetic patients (Casqueiro *et al.,* 2012; Bhargava & Lee, 2012).

Ketogenic diet (KD), commonly called 'low-carbohydrate diet' is a diet containing low carbohydrates and high amount of fats with moderate proteins (Kossoff *et al.,* 2006; Li & Heber, 2020). 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) (Augustin *et al*., 2018; Hallberg *et al*., 2018). 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 (Liu & Wang, 2013). It was introduced in an attempt to improve the palatability of ketogenic diet by incorporating MCT rich oils like coconut oil, palm kernel oil and sunflower

oil into the diet formulations, which was reported to have more ketogenic properties and is suitable for reducing excess calories (Huttenlocher *et al*., 1971; Rego-Costa *et al*., 2012; Sanya *et al.*, 2016).

Diabetic complications are driven mainly by glucose metabolism; considering the fact that ketogenic diet reduces whole-body glucose metabolism, it can be hypothesized that a ketogenic diet, which increases blood levels of ketones and also decreases blood glucose levels, might prevent glucotoxity-associated diabetic complications particularly those in the lungs (Masood *et al.*, 2021). The aim of this study was to evaluate the effect of medium chain triglyceride-ketogenic diet on the lungs of type 2 diabetic male New Zealand rabbits.

MATERIALS AND METHODS

Equipment and Reagents

Digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany), Digital weighing machine (Danko Scale Co. Ltd., Jiangsu, China). Pioglitazone (CAS NO 111025-46-8) was obtained from Sigma Aldrich, St, Louis, MO, USA.Vital (Grower's) feed (Grand cereals Ltd, Jos, Plateau state, Nigeria). Simas Margarine (PT Salim Ivomas PratamaTbk, Indonesia), coconut oil (Texcoconut Oil, Niger State, Nigeria), coconut fruit, ground nut cake and oil (Samaru Market, Sabon Gari, Kaduna State, Nigeria), Vitamix (Vetindia Pharmaceuticals Ltd, India).

Experimental Animals

Twenty (20) apparently healthy male New Zealand rabbits, between five to six weeks, weighing approximately 500-700 g, were sourced and housed in the Animal house, Department of Pharmacology & Therapeutics, Faculty of Pharmaceutical Science, Ahmadu Bello University, Zaria. The rabbits were housed in cubicles and were allowed access to water *ad libitum*

The experimental protocol was reviewed and certified by the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC), with approval number ABUCAUC/2024/053.

Preparation of High Fat Diet and Medium Chain Triglyceride-Ketogenic Diet

High fat diet (HFD) was prepared according to the method of Okoduwa *et al.* (2017), as modified by Dubo *et al*. (2019); 10 g of normal animal diet feed (grower's feed) was mixed with 2.5 g Simas margarine, 2.5 g whole ground groundnut and 1 g of groundnut oil. The medium chain triglyceride ketogenic diet (MCT-KD) was prepared according to the method described by Kayode *et al.* (2020), with slight modification. Grower's feed (15%) was mixed with coconut fruit (50%), coconut oil (20%), vitamix (5%) and ground nut cake (10%). Coconut fruit and oil were to provide medium chain triglyceride, vitamix for vitamins and minerals while ground nut cake for proteins.

Induction of Type 2 Diabetes Mellitus

Type II diabetes mellitus was induced by feeding the rabbits with formulated high fat diet (HFD) for a period of ten (10) weeks. Diabetes was confirmed at the end of the ten weeks, and only rabbits with fasting blood glucose levels ≥ 8.3 mmol/L (150 mg/dl) were considered diabetic (Jimoh *et al.*, 2015).

Animal Grouping

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

Group I: Normoglycemic rabbits fed with normal diet feed for 4 weeks.

Group II: Normoglycemic rabbits fed with formulated MCT-KD for 4 weeks.

Group III: Diabetic rabbits fed with normal diet feed for 4 weeks.

Group IV: Diabetic rabbits fed with formulated MCT-KD for 4 weeks

Group V: Diabetic rabbits fed normal diet feed and administered 4 mg/kg pioglitazone for 4 weeks (Liu *et al.*, 2017).

Determination of Body Weight and Relative Lung Weight

The body weights of the New Zealand rabbits were measured with a digital weighing scale every week until the end of the treatment. The relative lung weight was calculated using the right lung as follows:

$$Relative\ lung\ weight = \frac{Right\ lung\ weight\ (g)}{Body\ weight\ (g)}\ \text{x}\ 100\%$$

Collection of Broncho Alveolar Fluid (BALF)

At the end of the experiment, the animals were euthanized by cervical dislocation. Broncho Alveolar lavage procedure was performed surgically in New Zealand rabbits. The collected fluid (Called BALF) was placed in plain sample containers and then centrifuged at 3000 x *g* for 10 minutes. The subnatant was used for differential white blood cell count (Chaudhari *et al.*, 2011).

Haematological Analysis

Total and differential white blood cell count was carried out in the collected as described by Cheesbrough (1999).

Histology of the Lung Tissues

The right lungs were used for the histology, using H & E staining technique as described by Bancroft and Stevens (1990).

Statistical Analysis

All results are expressed as mean + Standard Error of Mean (SEM). Data collected were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test for multiple comparison between groups. In all cases, values of $p < 0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS) version 25.0 was used for the analysis.

RESULTS AND DISCUSSION

Effect of Medium Chain Triglyceride-Ketogenic Diet on Body Weight and Relative Lung Weight of type II Diabetic Male New Zealand Rabbits

Table 1 shows the body weight and relative lung weight of type II diabetic male New Zealand rabbits fed with MCT-KD. There was a significant increase ($p < 0.05$) in the lung weight 10.61±0.30 g) and body weight (1876.25±37.79 g) of diabetic rabbits fed with normal diet feed when compared with the lung weight (6.50±0.33 g) and body weight (1153.75±43.58 g) of normoglycemic rabbits fed with normal diet feed respectively. However, there was no significant change in the relative lung weight ($p > 0.05$) when the diabetic and the normoglycemic fed with normal diet feed were compared. The diabetic and the normoglycemic rabbits fed with MCT-KD had a significantly higher ($p < 0.05$) relative lung weight when compared with the other groups. The diabetic group administered 4 mg/kg pioglitazone had no significant change in the values of relative lung weight but the lung weight was significantly lowered ($p < 0.05$) compared diabetic fed with normal diet.

Effect of MCT-KD on Total and Differential White Blood Cell Count in Bronchoalveolar Fluid of Type II Diabetic Male New Zealand Rabbits

In Table 2, there was a significant increase ($p < 0.05$) in the total WBC count in the diabetic rabbits fed with normal diet (5.66±0.10 x 10^3 µL) compared with normoglycemic rabbits fed with normal diet (4.39±0.09 x 10^3 µL) and with MCT-KD (4.67±0.05 x 10^3 µL). However, there was a significant decrease ($p < 0.05$) in total WBC count in the diabetic group fed with MCT-KD (4.44±0.09 x 10^3 µL) and the one administered 4 mg/kg pioglitazone (4.45±0.05 x 10^3 µL). The percentage of lymphocytes, neutrophil and macrophages counts were significantly increased ($p < 0.05$) in the diabetic rabbits fed normal diet feed as compared to the normoglycemic rabbits fed normal diet feed. The diabetic rabbits fed with MCT-KD had a significantly decreased percentage counts of lymphocyte and macrophages but not neutrophils ($p > 0.05$). There was however, no significant change ($p > 0.05$) in the percentage counts of eosinophils and basophils when all the groups were compared with each other.

Effect of Medium Chain Triglyceride-Ketogenic Diet on the Histology of Lungs of Type II diabetic Male New Zealand Rabbits

Plates I-V show the histology of the lungs of normoglycemic rabbits fed with normal diet feed, normoglycemic rabbits fed with MCT-KD, diabetic rabbits fed with normal diet feed, diabetic rabbits fed with MCT-KD and diabetic rabbits administered 4 mg/kg pioglitazone respectively. The lung of normoglycemic rabbits fed with normal diet feed shows normal alveolar spaces and epithelial cells with no cellular infiltration of inflammatory and obvious oedema. The histology of normoglycemic rabbits fed with MCT-KD also shows normal alveolar spaces with no obvious alterations. However, the lung histology of diabetic rabbits fed with normal diet feed is characterized by marked cellular infiltration of inflammatory cells, reduced alveolar spaces, thickened epithelial cells. The lungs of diabetic rabbits fed with MCT-KD show normal alveolar spaces with mild cellar infiltration and no obvious histopathological changes. The diabetic rabbits administered 4 mg/kg pioglitazone, had their lungs with mild cellular infiltration but normal alveolar spaces

Table 1: Effect of Medium Chain Triglyceride-Ketogenic Diet on Body Weight and Relative Lung Weight of type II Diabetic Male New Zealand Rabbits

GROUPS	Right Lung weight (g)	Body Weight (g)	Relative Lung Weight (%)
NG+NDF	6.50±0.33^{a}	1153.75±43.58^{a}	0.57±0.03^{a}
NG+MCT-KD	7.18±0.56^{ab}	990.25±14.72^{b}	0.73±0.06^{b}
DB+NDF	10.61±0.30^{c}	1876.25±37.79^{c}	0.57±0.01^{a}
DB+MCT-KD	9.02±0.13^{cd}	1441.75±37.97^{d}	0.63±0.02^{ab}
DB+PGTZ	8.45±0.37^{bd}	1547.25±17.43^{d}	0.55±0.03^{a}

Results are presented as mean ± standard error of mean of four (4) rabbits. Values with different superscripts (a, b, c, d) down the columns indicate statistically significant difference ($p<0.05$) between groups.
NG=normoglycemic; NDF=normal diet feed; MCT-KD= medium chain triglyceride-ketogenic diet; DB= diabetes; PGTZ= 4 mg/kg pioglitazone

Table 2: Effect of Medium Chain Triglyceride-Ketogenic Diet on Total and Differential White Blood Cell Count in Bronchoalveolar Fluid of type II Diabetic Male New Zealand Rabbits

GROUPS	WBC (X10^3 µL)	L (%)	N (%)	M (%)	E (%)	B (%)
NG+NDF	4.39±0.09^{a}	45.58±1.18^{ad}	39.40±1.27^{ab}	8.50±0.27^{a}	3.23±0.30	0.43±0.25
NG+MCT-KD	4.67±0.05^{a}	47.00±1.15^{ab}	37.05±1.95^{a}	8.65±0.45^{a}	3.15±2.62	0.56±0.26
DB+NDF	5.66±0.10^{b}	56.30±1.44^{b}	46.78±1.08^{b}	11.10±0.66^{b}	3.43±0.46	0.79±0.08
DB+MCT-KD	4.44±0.09^{a}	32.85±2.20^{c}	44.40±1.94^{ab}	7.00±0.21^{a}	3.33±0.40	0..69±0.24
DB+PGTZ	4.45±0.05^{a}	26.65±4.05^{cd}	45.33±2.76^{b}	7.85±0.55^{a}	2.95±0.11	0.55±0.21

Results are presented as mean ± standard error of mean of four (4) rabbits. Values with different superscripts (a, b, c, d) down the columns indicate statistically significant difference ($p<0.05$) between groups.
NG=normoglycemic; NDF=normal diet feed; MCT-KD= medium chain triglyceride-ketogenic diet; DB= diabetes; PGTZ= 4 mg/kg pioglitazone; L=lymphocytes; N=Neutrophils; M= macrophages; Eosinophils; B=Basophils

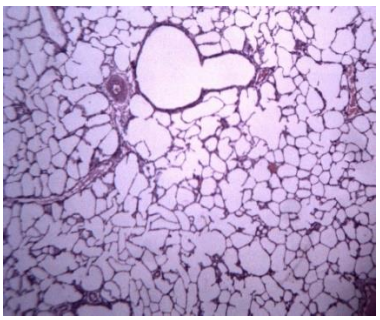
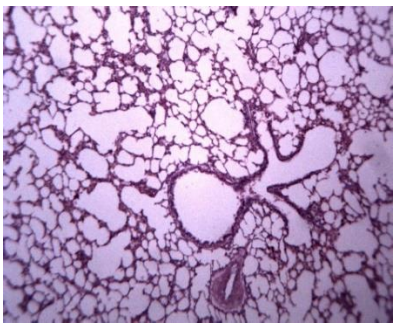


Plate 1



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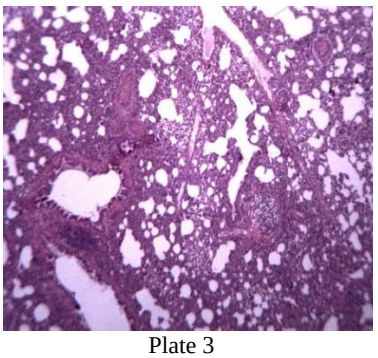

Plate 3

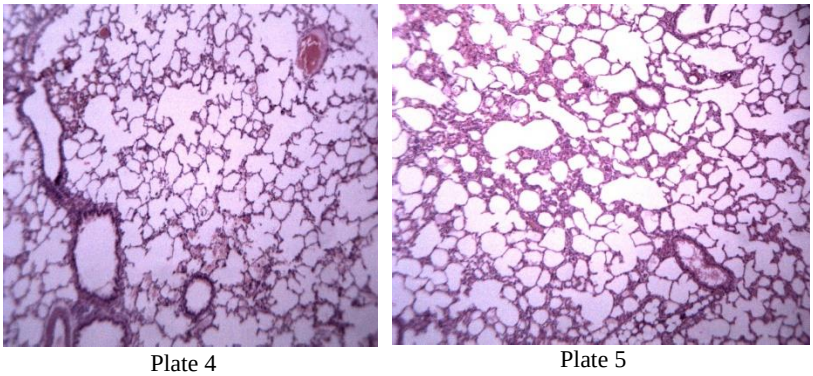

Plate 4 Plate 5

Figure 1: Effect of Medium Chain Triglyceride-Ketogenic Diet on the Histology of Lungs of Type II diabetic Male New Zealand Rabbits

Photomicrographs of lungs of Normoglycemic rabbits fed NDF (Plate I), Normoglycemic rabbits fed MCT-KD (Plate II), Diabetic rabbits fed NDF (Plate III), Diabetic rabbits fed MCT-KD (Plate IV) and Diabetic rabbits fed normal diet feed and administered 4 mg/kg Pioglitazone (Plate V). H&E, Magnification X100

NDF=normal diet feed; MCT-KD= medium chain triglyceride-ketogenic diet

Discussion

In this study, there was increased presence of white blood cells in the bronchoalveolar lavage fluid (BALF) of the diabetic rabbits. This is an indication of recruitment and infiltration of inflammatory cells into the lungs in diabetes. This result is in agreement with the outcome of a study by Dubo *et al.* (2019), who also reported increased counts of total white blood cells and their differential components in diabetic lungs as consequences of systemic inflammation associated with increased total white blood cell count in the blood. Pulmonary alveolar macrophages (PAMs) are component of innate immunity in the pulmonary system that play an important role in defence of the lungs against invading pathogens. According to Kloc *et al.* (2020), high glucose levels, modifies macrophage metabolism causing failures in the innate immune and inflammatory processes, indicating immune response dysfunction in diabetic patients leading to a higher risk of lung infections. Another study reported that a wide range of neutrophil and macrophage functions, including chemotaxis, adherence, phagocytosis, ability to kill phagocytosed microorganisms with free radicals and respiratory burst are impaired in diabetes (Kolahian *et al.,* 2019). Loose junctions between airway epithelial cells, which increase the transepithelial glucose gradient along with increase in the glucose concentrations in the airways and lungs due to hyperglycemia and insulin resistance, may impair the defense against infection, resulting in lung bacterial overgrowth in type II diabetes (*Fernández-Real et al., 2010;* Baker & Baines, 2018). No changes were observed in the differential counts of eosinophils and basophils in this study; although, these cells were reported to be mostly altered in allergic airway diseases such as asthma (Dawud *et al.,*2016; Hussain & Liu, 2024).

Ketogenic diet was observed to decrease white blood cell count and its differential components in diabetic rabbits. A study by De Nucci *et al.* (2023), reported that ketogenic diet caused a reduction in low-grade inflammation in obese and overweight subjects, as demonstrated by a significant decrease in white blood cell counts. In another study, ketogenic diet was said to reduced inflammation in epilepsy by decreasing total white blood cell and neutrophil count (Schreck *et al.,* 2017). Lima *et al.* (2017) also reported that ketogenic diet consumption decreased white blood cell and lymphocyte count in damaged muscles after intense exercise. In this study, the normoglycemic animals fed with ketogenic diet did not show a change in total white blood cell count or any of the differential components. This implies that ketogenic diet's ability to decrease total and differential white blood cell count in the diabetic lungs may be dependent on the existence of lung inflammation. Although, it was reported that pioglitazone, an antidiabetic drug acting through PPAR-γ decreased lung vascular permeability, neutrophil influx, pro-inflammatory cytokine production and pulmonary leukostasis (Standiford *et al.,* 2005). This could also be another mechanism by which ketogenic diet was able to decrease infiltration of leukocytes into the lungs.

The histology of the lung tissues of diabetic rabbits showed collapse and dilated alveolar with damage walls, thickened interstitium with cellular infiltration of inflammatory cells, bronchial epithelial cells hypertrophy, and mild oedema was also observed. This result is consistent with the findings of Mahmood *et al.* (2024), who in addition to what was observed in this study, reported thickening of smooth muscles around the bronchioles which are indicative of bronchoconstriction in a viable lung. The mechanisms of structural alterations in the diabetic lungs have been explained in previous studies to be related hyperglycemia-induced activation of various inflammatory pathways in the lung (Dubo *et al.,* 2019). Another mechanism involved in diabetic lung injury is the non-enzymatic glycosylation of the proteins of the lungs, causing impaired cross linkage of collagen and elastin, decreasing their strength and elasticity (Suarez *et al.,* 2016). Loose junctions between epithelial cells, increase the transepithelial glucose gradient along with increase in the glucose concentrations in the lungs, exacerbate the glycosylation process (Baker & Baines, 2018). The weights of the lungs of the diabetic rabbits were observed to be more than the normoglycemic and diabetic that were treated with ketogenic diet and pioglitazone. This increase in lung weight could be explained by the increased transepithelial glucose transport into the lung tissues in diabetes which may have added to the weight of the lungs as described by Baker and Baines (2018). Although, the relative lung weight in the diabetic animals fed with normal diet was not significantly different when compared with the normoglycemic and diabetic treated with ketogenic diet and pioglitazone. This may be due to the corresponding increase in the body weight observed in the diabetic animals fed with normal diet. Ketogenic diet was able to decrease the structural changes in the diabetic lungs and the infiltration of inflammatory cells into the lungs.

CONCLUSION

Medium chain triglyceride-ketogenic diet decreases the infiltration of inflammatory cells as well the structural alterations in the lungs of type II diabetic rabbits. Thus, it can be concluded that, has anti-inflammatory properties that were effective in alleviating diabetic complications in the lungs.

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