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Research Article

Effects of Time-Restricted and Alternate- Day Intermittent Fasting on Liver Enzymes, Glycogen and Oral Glucose Tolerance Test in Streptozotocin-induced Diabetic Rats

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Abstract

Intermittent fasting (IF) has been reported to improve metabolic health in diabetes but the underlying mechanisms by which intermittent fasting promotes metabolic health in streptozotocin-induced diabetes have not been fully elucidated. This study investigated the effects of Time-Restricted (TR) and Alternate- Day (AD) Intermittent Fasting (IF) on body weight, liver enzymes, liver glycogen, blood glucose, and oral glucose tolerance test (OGTT) in streptozotocin-induced diabetic male Wistar rats. Sixty male Wistar rats (200-250g) were grouped into six groups (n=10). Group 1 (non-diabetic control) and Group 2 (non-diabetic +time-restricted intermittent fasting). Groups 3 - 6 received streptozotocin (50mg/kg) intraperitoneally (i.p.). After diabetes was confirmed, animals in groups 3, 5 and 6 were treated with Time-restricted intermittent fasting, metformin (200mg/kg) orally, and Alternate- day intermittent fasting protocols respectively, while group 4 animals were untreated (Diabetic control) for 28days. After 28 days, oral glucose tolerance test (OGTT), fasting blood glucose (FBG), liver function enzymes, Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), and Alkaline Phosphatase (ALP) were measured. The results showed that while there was significant decrease in body weight, there was significant increase in fasting blood glucose and concentrations of liver enzymes AST, ALT and ALP in group 4 compared to group 1. Time- restricted fasting, metformin treatment and Alternate day intermittent fasting caused significant decrease in body weight, fasting blood glucose and serum levels of AST, ALT and ALP in groups 3, 5 and 6 compared to group 4. Liver glycogen was significantly reduced in group 4 and increased in groups 3, 5 and 6 of diabetic rats. The study showed that Time-restricted (18: 6) and Alternate-Day intermittent fasting regimens ameliorated diabetes through improved glucose tolerance, liver glycogen synthesis and liver function enzymes.

Keywords

Diabetes, Streptozotocin, Time-Restricted Intermittent Fasting, Alternate-Day Intermittent Fasting, Metformin, Blood Glucose, Liver Enzymes, Liver Glycogen

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1. Introduction

Diabetes mellitus (DM) is a major global health problem affecting millions of people worldwide and causing serious problems in many organs and systems in the body. Diabetes is characterized by lack of complete control of blood glucose due to inadequate insulin secretion, insulin action or both. Impairment of insulin production causes insulin deficiency with consequent abnormalities in carbohydrates, fat and protein metabolism.

Fasting is deliberate abstinence from food but not water and can last from a few hours to several days or even weeks. Intermittent fasting [IF] has shown to be fruitful strategy in treating and managing illnesses such as obesity, diabetes, antioxidant stress and cardiometabolic disorders [1]. There are different patterns of intermittent fasting which include alternate day fasting (no calories consumption on fasting days), alternate day-modified fasting (consuming less than 25% of caloric requirements on fasting days), time restricted fasting (restricting food intake at specific times of the day), and periodic fasting (fasting on one to two days per week). The health benefits of IF have been reported in previous studies [2-4]. Clinical studies have shown that IF diets caused reduction in adult body mass index (BMI) and insulin resistance [5]. There are conflicting clinical reports on the effects of IF diets in patients with impaired glucose and lipid metabolism. The study of [6] reported that IF caused reduction in insulin resistance, body weight, waist circumference, and HbA1c and contributed to maintaining stable glucose levels after discontinued use of insulin. In contrast [7] found out that Ramadan IF for a month caused 0.11% increase in HbA1c in patients with metabolic syndrome.

According to International Diabetes Federation (IDF), the global prevalence of diabetes among adults aged 20-79 years people was expected to be 10.5% (536.6 million) in 2021, rising to 12.2% (783.2 million) by 2045 [8]. This study examined whether Time-restricted or Alternate day intermittent fasting could improve insulin sensitivity and liver function enzymes in streptozotocin-induced diabetes in male Wistar rats. The liver plays an important role in metabolic homeostasis [9]. After feeding, the liver absorbs glucose and synthesize glycogen and triglycerides but releases glucose via glycogenolysis or gluconeogenesis, and initiates ketogenesis during fasting [10]. Different types of IF have been reported but not all can be applied to humans. Limited data is available on the effects of IF on liver function enzymes and liver glycogen in diabetes. The liver is one of the organs affected by diabetes and is important in glucose regulation [11]. The mechanisms by which IF promotes metabolic health in diabetes have not been fully studied. STZ selectively destroys pancreatic β-cells, causing hyperglycemia and is used in experimental diabetes models [12]. Therefore, this study investigated the effects of 28-day Time-restricted (18: 6) and Alternate- day intermittent fasting on body weight, liver glycogen, liver function enzymes, fasting blood glucose and oral glucose tolerance test (OGTT) in streptozotocin-induced diabetic male Wistar rats.

2. Materials and Methods

Forty-eight male Wistar rats weighing between (200-250g) were used for the study. For two weeks of acclimatization, animals were kept in transparent, clean plastic cages, floored with soft wood shavings in the animal house, Department of Physiology, University of Ibadan, Ibadan. They were kept under photoperiodic conditions (12 hr of light and 12 hr of darkness) and an ambient room temperature between 28 ℃-30 ℃ with unlimited access to standard rat chow and water. The experiment was carried out in accordance with the guidelines of the University of Ibadan, Animal Care and Use Research Ethics Committee (ACUREC) under strict compliance to the "Principle of Laboratory Animal Care". Food intake and body weight were measured daily and weekly respectively.

2.1. Preparation of Streptozotocin and Induction of Diabetes Mellitus

Prior to the induction of diabetes, streptozotocin (STZ) was dissolved in 50mM of sodium citrate buffer (0.1 M, pH 4.5), this is because STZ degrades within 15 to 20 minutes after dissolving in the citrate buffer, thus, STZ was prepared freshly and was injected within 5 minutes of dissolution. Diabetes was induced in experimental animals after an overnight fasting by injecting streptozotocin (STZ) 50mg/kg intraperitoneally and equal volume of citrate buffer (vehicle pH 4.5) was given intraperitoneally (i.p) to the control group animals. After administration of STZ 50mg/kg, animals in diabetic groups were given 10% of sucrose water (10g/100ml) during the night to prevent possible hypoglycemia and had access to normal food. After 72hr post diabetes induction, blood glucose was measured to confirm diabetes using the Accu Check glucometer. After overnight (16hr) fasting, blood was collected from caudal (tail) vein to estimate glucose level. Blood glucose greater than 200mg/dl was considered diabetic and used for the study. The diabetic rats were grouped into four (n=8) and used for the study.

2.2. Experimental Design and Treatment

Animals were randomly divided into six different groups (n=8) which are: Group 1 control non-diabetic ad libithum (CTRL), Group 2 non-diabetic + Time-Restricted intermittent fasting, 16: 8 (CTRL + IF), Group 3 Diabetic + Time- restricted fasting 16: 8; 16 hours of fasting with 8 hours eating window (DM+TRIF), Group 4 Diabetic control ad libithum (DM+CTRL), Group 5 Diabetic + metformin 200mg/kg (DM+MET) and Group 6 Diabetic + Alternate- Day fasting: food deprivation for 24 hr, followed by ad libithum access to food for another 24 hr (DM+ALDIF). Animals in groups 1, 4 and 5 had free access to food for 28 days.

2.3. Measurement of Body Weight and Food Intake

The body weights of animals were measured before and after two weeks of acclimatization. After induction of diabetes, animals were weighed weekly during the twenty-eight-day experimental period using digital weighing scale. Food intake was measured daily in percentage. Total weight of feed provided per group was subtracted from the weight of daily feed remnants. Spilled food was allowed to dry fully to avoid measurement of wet weight added.

2.4. Oral Glucose Tolerance Test (OGTT)

OGTT was done on the 26th day of experimental period and after 12 hours of overnight fasting. Using a tail snip, blood was collected for glucose estimation using glucometer. Each animal was given a glucose solution of 2g/kg per body weight orally. Blood glucose was measured at 30 minutes intervals for (0 min, 30 min, 60 min 90 min, and 120 min).

2.5. Animal Sacrifice, Sample Collection and Biochemical Assays

Animals were sacrificed by cervical dislocation. Blood samples were collected via ocular puncture using heparinized capillary tube and transferred into plain sample bottles. The liver was collected and weighed immediately. Thereafter, 1g of fresh liver was removed from each animal and immersed in 30% potassium hydroxide for the determination of liver glycogen. Liver glycogen was estimated by modified anthrone reagent method as described by [13]. Liver function enzymes (Aspartate Aminotransferase (AST), Alanine Transaminase (ALT) and Alkaline Phosphatase (ALP) were measured using ELISA.

Statistical analysis

Data were analyzed using student's t-test and one-way analysis of variance (ANOVA) followed by post hoc test (Turkey positive test) for multiple comparisons. The significance level for all tests was $p<0.05$. All results were reported as mean plus standard error, Mean ± S. E. M.

3. Results

3.1. Effects of TRIF and ALDIF on Body Weight of STZ-Induced Diabetic Rats

STZ injection caused significant reduction in body weights of diabetic rats compared with control. Time restricted intermittent fasting caused significant decrease in body weights of nondiabetic rats compared with control. Time- restricted intermittent fasting, alternate- day intermittent fasting, and metformin treatment caused significant decrease in body weights of diabetic rats compared with diabetic control (Figure 1).

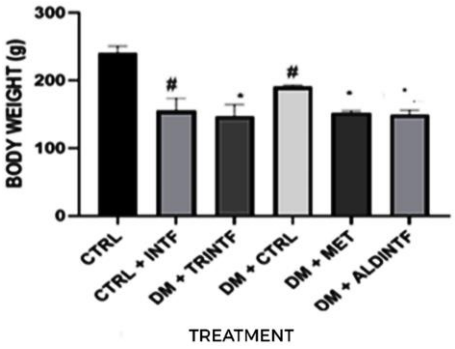

Figure 1. *Effects of time-restricted intermittent fasting, metformin treatment and alternate day intermittent fasting on body weight of streptozotocin-induced diabetes rats. *p<0.05 when compared with diabetic control group (DM+CTTRL), # p<0.05 when compared with non-diabetic control rats (CTRL).*

KEY:
CTRL: Non- Diabetic Control
CTRL + IF: Control + Time-Restricted Intermittent fasting
DM+ TRIF: Diabetic + Time Restricted Intermittent fasting
DM + CTRL: Diabetic Control
DM + MET: Diabetic + Metformin 200mg/kg
DM + ALDIF: Diabetic + Alternate day Intermittent fasting

3.2. Effects of TRIF, ALDIF and Metformin Treatment on Fasting Blood Glucose in STZ-Induced Diabetic Rats

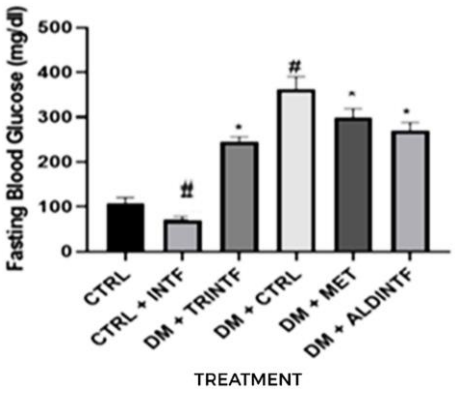

Figure 2. *Effects of time-restricted intermittent fasting, metformin treatment and alternate day intermittent fasting on fasting blood glucose of streptozotocin-induced diabetes rats. *p<0.05 when compared with diabetic control group (DM+CTTRL), # p<0.05 when compared with non-diabetic control rats (CTRL).*

There was significant ($p< 0.05$) decrease in fasting blood glucose of non-diabetic rats treated with Time-restricted intermittent fasting regimens (18: 6) compared with control. STZ injection caused significant increase in fasting blood glucose levels of rats compared with non-diabetic control. However, Time-restricted intermittent fasting, Alternate- day intermittent fasting and metformin treatment caused significant de-

crease in blood glucose levels of diabetic rats compared to diabetic control DM +CTRL (Figure 2).

3.3. Effects of TRIF and ALDIF on Liver Glycogen of Streptozotocin-Induced Diabetic Rats

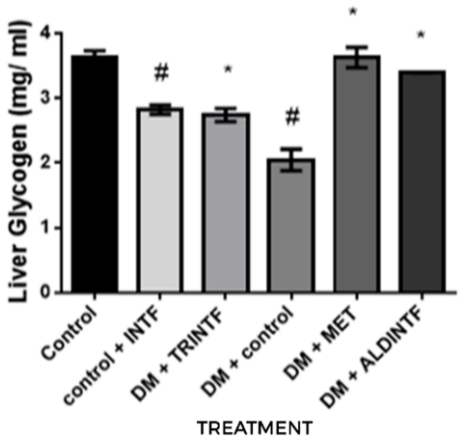

Figure 3. *Effects of time-restricted intermittent fasting, metformin treatment and alternate day intermittent fasting on liver glycogen of streptozotocin-induced diabetes rats. *p<0.05 when compared with diabetic control group (DM+CTTRL), # p<0.05 when compared with non-diabetic control rats (CTRL).*

Time-restricted intermittent fasting (TRIF) caused significant decrease in liver glycogen of non-diabetic rats compared with control. There was significant ($p < 0.05$) decrease in liver glycogen of diabetic (DM+control) rats compared with non-diabetic control group (CTRL+INTF). However, time-restricted intermittent fasting, alternate-day intermittent fasting and metformin treatment caused significant increase in glycogen levels of diabetic rats compared with diabetic control (Figure 3).

3.4. Effects of TRIF and ALDIF on Fasting Blood Glucose and OGTT in STZ-Induced Diabetic Rats

The fasting glucose level of diabetic rats was significantly higher compared with the non-diabetic control rats. The AUC also showed a significant increase in glucose level of diabetic rats after 120mins post glucose load. There was also an increase in the glucose level of the treated groups at 30 minutes post glucose load, but at 60 minutes, the blood glucose level started dropping. AUC showed a significant fall in all groups at 120 minutes except the diabetic control group (Figures 4 and 5).

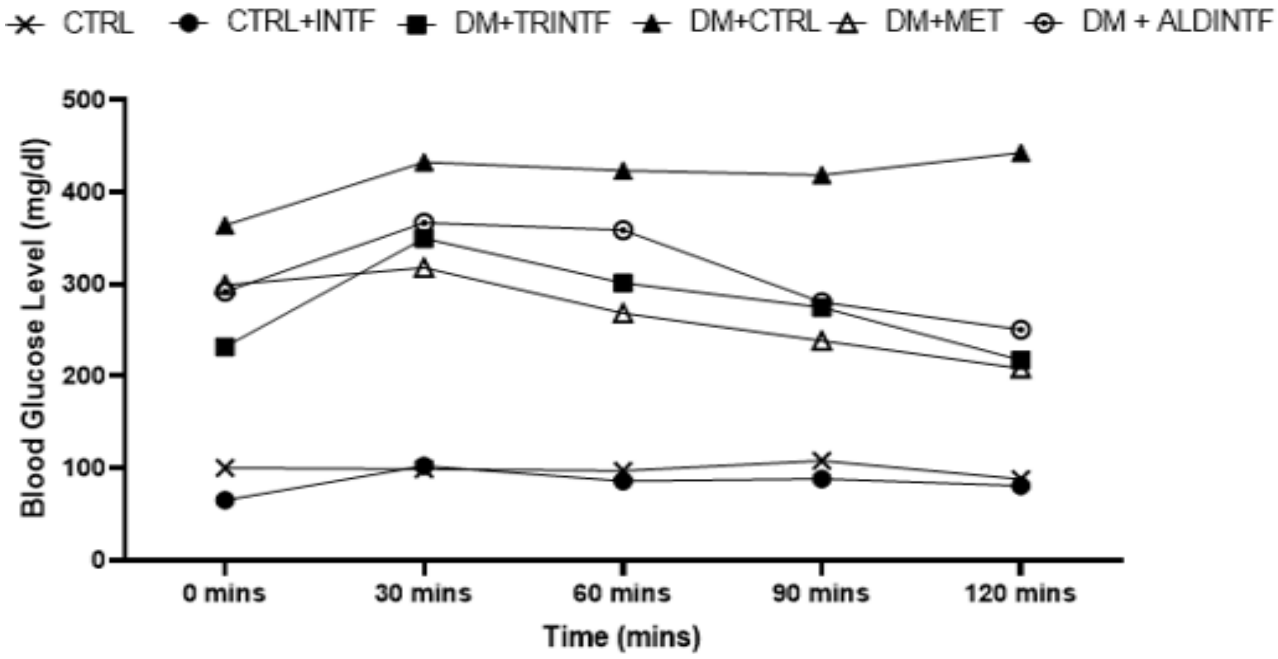

Figure 4. *Effects of time-restricted, metformin treatment and alternate day intermittent fasting on fasting blood glucose and Oral Glucose Tolerance Test of streptozotocin-induced diabetic rats. *p<0.05 when compared with DM + CTTRL, # p<0.05 when compared with the non-diabetic control.*

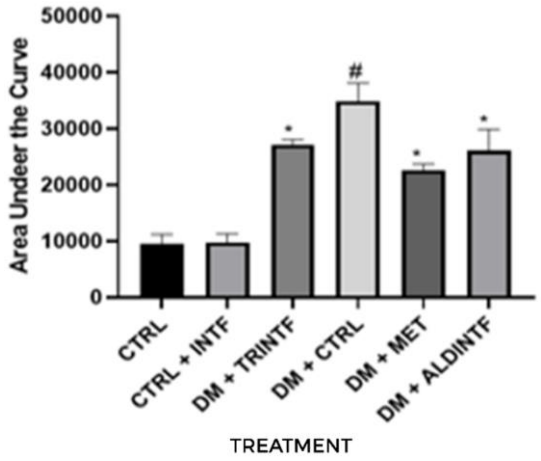

Figure 5. *Area under the curve (AUC) showing glucose tolerance test on the effects of time-restricted, metformin treatment and alternate day intermittent fasting on fasting blood glucose in streptozotocin-induced diabetic rats. *p<0.05 when compared with DM + CTTRL, # p<0.05 when compared with the non-diabetic control. Area under the curve is (mg/dl×min).*

3.5. Effects of TRIF and ALDIF on Liver Function Enzymes (AST, ALT, and ALP Levels) in STZ-induced Diabetic Rats

In this study, there was significant increase ($p < 0.05$) in serum levels of AST (57.0 ± 2.6), ALT (95.9 ± 3.6) and ALP (46.4 ± 1.9) respectively of diabetic control (DM + CTRL) compared to the non-diabetic CTRL group for AST (50.6 ± 0.6), ALT (77.7 ± 1.0), ALP (30.7 ± 0.6) respectively. Serum level of ALP was significantly increased in DM+ CTRL group (46.4 ± 1.9) compared to control (30.7 ± 0.6). However, TRIF and ALDIF caused significant decrease ($p < 0.05$) in serum level of ALP (37.3 ± 2.6, 34.4 ± 1.2) respectively compared to DM+CTRL (46.4 ± 1.2) (Figure 6).

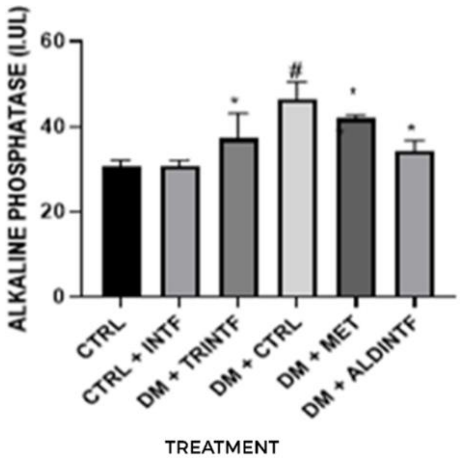

Figure 6. *Effects time-restricted intermittent fasting, metformin treatment and alternate day intermittent fasting on Alkaline phosphatase (ALP) of streptozotocin-induced diabetes rats. *p<0.05 when compared with DM + CTRL, # p<0.05 when compared with CTRL (non-diabetic control).*

There was significant increase in ALT of DM+ CTRL group (95.9 ± 3.6) compared with CTRL group (77.7 ± 1.0). Treatments with time-restricted and Alternate day intermittent fasting regimens caused significant decrease in serum level of ALT in diabetic rats (88.4 ± 4.2, 77.4 ± 2.0 respectively) compared to DM+ CTRL (95.9 ± 3.6), (Figure 7).

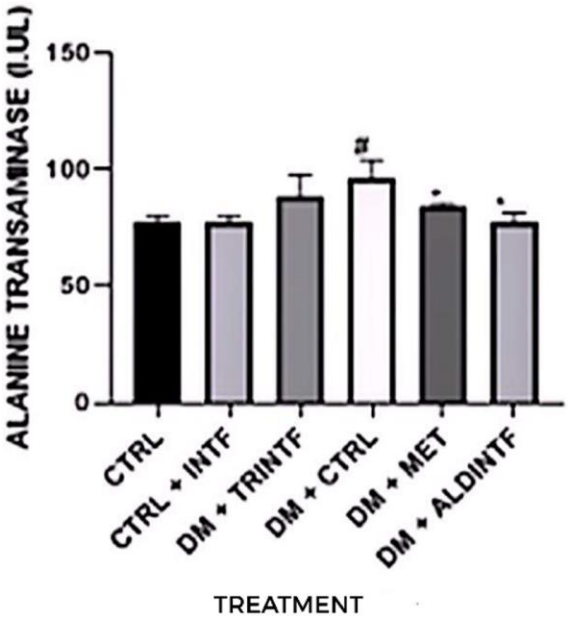

Figure 7. *Effects time-restricted intermittent fasting, metformin treatment and alternate day intermittent fasting on Alanine Transaminase (ALT) of streptozotocin-induced diabetes rats. *p<0.05 when compared with DM + CTTRL group, # p<0.05 when compared with the CTRL control.*

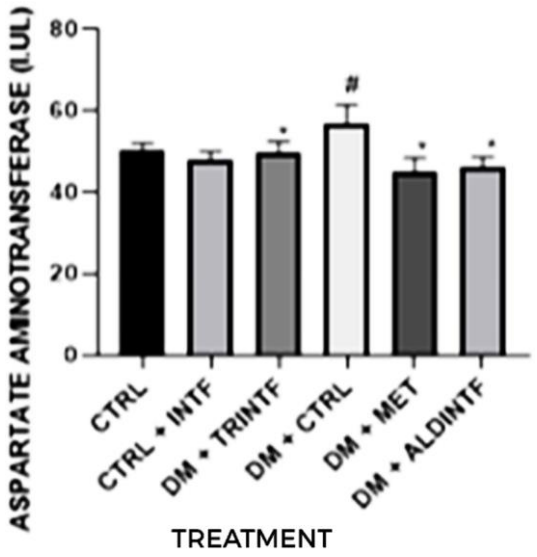

Figure 8. *Effects time-restricted intermittent fasting, metformin treatment and alternate day intermittent fasting on Aspartate Aminotransferase (AST) of streptozotocin-induced diabetes rats. *p<0.05 when compared with DM + CTTRL group, # p<0.05 when compared with (CTRL) non-diabetic control.*

4. Discussion

The study investigated the effects of time- restricted and alternate- day intermittent fasting regimes and meltformin treatment on body weight, liver function enzymes, liver glycogen and oral glucose tolerance test in streptozotocin-induced diabetes in male Wistar rats. Streptozotocin (STZ) is a diabetogenic chemical used in animal models to induce diabetes and is cytotoxic to pancreatic β-cells [12].

The findings of this study demonstrated a decrease in fasting blood glucose and body weight of diabetic rats treated with Time-restricted and Alternate-day intermittent fasting regimens compared with diabetic control. This is consistent with the studies of [6, 14-16]. The observed decrease in body weight and fasting blood glucose in the present study may be due to activation of AMPK (adenosine-monophosphate activated protein kinase) and may explain how TRIF and ALDIF lower blood glucose and promotes weight loss. Intermittent fasting has been reported to cause an increase in AMP-activated protein kinase (AMPK) levels and upregulation of AMPK pathway. Activation of AMPK improves insulin sensitivity and promotes expression and activity of GLUT4 thereby increasing glucose uptake. This enables the body to utilize and manage blood glucose [15, 17, 18]. AMPK also activates lipases causing release of fatty acids and promotes beta-oxidation.

In the present study, the observed decrease in fasting blood glucose and body weight of diabetic rats treated with TRIF and ALDIF may also be due to a metabolic switch. After hours of fasting, there is a shift from utilization of glucose to fatty acids and ketones as energy substrates. Intermittent fasting has been reported to help with weight control and improve glucose metabolism thereby preventing the development of diabetes [5]. Previous studies have also reported significant reduction in body weight, and visceral fat of patients treated with IF [19, 20]. The results of the present study in which Time-restricted and Alternate-day intermittent fasting caused a decrease in fasting blood glucose in both normal and diabetic groups compared with the controls contrast the studies of [21, 22] which reported that IF had no effect on blood glucose and that, IF caused an increase in fasting blood glucose [23].

Metformin treated group also showed reduction in body weight and fasting blood glucose compared with diabetic control. This might be due to its effect on hypothalamic appetite-regulation centers including leptin sensitivity [18]. Metformin has been shown to inhibit gluconeogenesis and activates AMPK thereby enhances insulin sensitivity, promotes translocation and expression of GLUT4 [18].

In this study, time-restricted intermittent fasting caused a decrease in liver glycogen and fasting blood glucose levels of non-diabetic rats, this may explain partly the mechanism by which intermittent fasting maintains metabolic health. During fasting, maintenance of blood glucose depends on glycogen store in the liver and muscle. The liver supplies energy to the body under physiological conditions. It has been reported that 12-24hr of fasting depletes hepatic glycogen, and a switch to a metabolic mode that utilizes fat-derived ketone bodies, free fatty acids and non-hepatic glucose as energy sources [24, 25]. In the present study, time-restricted fasting (18: 6) caused a decrease in liver glycogen and fasting blood glucose level of non-diabetic rats compared with the control.

The observed reduction in liver glycogen of diabetic rats in the present study may be due to decrease in the activity of glycogen synthase caused by STZ injection [26]. However, Time-restricted and Alternate-day intermittent fasting caused liver glycogen of diabetic rats to greatly increase compared with diabetic control. This may be due to improved insulin sensitivity and activity of glycogen synthase. Intermittent fasting has been reported to improve activity of glycogen synthase and reduced glycogen phosphorylase activity in diabetic rats [26]. This implies that Time-restricted and Alternate-Day intermittent fasting regimes are effective in ameliorating diabetes through improved insulin sensitivity and liver glycogen synthesis and may explain partly the mechanism by which intermittent fasting improves metabolic health in diabetes. A recent study reported an impairment in the liver to synthesis glycogen due to decreased activity of glycogen synthase because of insulin deficiency which in turn caused hyperglycemia [27]. The findings of this study contrast the observation of [18] which reported higher glycogen levels in prediabetic rats compared with IF group.

In this present study, the blood glucose of diabetic rats remained elevated after administration of glucose load during OGTT [28, 29]. Time-restricted and Alternate day fasting regimens caused the blood glucose levels to fall to fasting levels between 1hr and 2hrs after glucose load at OGTT in diabetic rats while in untreated diabetic rats, the blood glucose levels remained high 1hr and 2hrs after glucose load at OGTT. Intermittent fasting has been reported to lower glucose absorption from the intestine and improve insulin sensitivity [17, 30]. In the present study, the observed decrease in body weight of rats treated with intermittent fasting may also contribute to improved glucose tolerance.

The findings of this study showed that STZ-induced hyperglycemia contributed to liver damage which resulted in increased serum levels of liver enzymes AST, ALT and ALP [11]. Liver enzymes ALT, AST and ALP are biomarkers of liver function, used to evaluate hepatic functions and are increased in liver diseases [1]. The results of this study in which time-restricted and alternate- day intermittent fasting regimens significantly reduced concentrations of liver enzymes AST, ALT and ALP in diabetic rats are consistent with previous studies [1, 31, 32]. The reduction in level of liver enzymes suggests an improvement in liver function [1, 33]. The significant reduction in body weight of animals may explain how time-restricted and alternate-day intermittent fasting improves liver function and metabolic health in diabetes [1]. The liver is one of the organs that is affected in diabetes and plays a key role in glucose regulation. Liver damage contributes to pro-

gression of diabetes and other systemic complications associated with the disease [34]. In diabetes, liver dysfunction is linked to some pathological processes including insulin resistance [11]. The results of this study revealed that Time-restricted and Alternate- day intermittent fasting regimens enhanced liver function in diabetes by lowering markers of liver damage. This may explain partly how IF improves metabolic health in diabetes. The findings of the present study helped us better understand the physiological and biochemical changes that occur during Intermittent fasting in both normal and diabetic rats.

5. Conclusion

The findings of this study reveal that STZ-induced diabetes caused an increase in liver function enzymes which may be due to liver damage. The study also shows that time-restricted (18: 6) and alternate- day intermittent fasting regimens can be an effective approach to improve metabolic health and prevent lifestyle disease such as diabetes through improvement in glucose tolerance, liver glycogen synthesis and liver function enzymes.

Abbreviations

DM	Diabetes Mellitus
IF	Intermittent Fasting
TRIF	Time-Restricted Intermittent Fasting
ADIF	Alternate-Day Intermittent Fasting
OGTT	Oral Glucose Tolerance Test
FBG	Fasting Blood Glucose
AST	Aspartate Aminotransferase
ALT	Alanine Transaminase
ALP	Alanine Phosphatase
BMI	Body Mass Index
STZ	Streptozotocin
AMPK	Adenosine Monophosphate Kinase

Author Contributions

Isehunwa Grace Olufunmilayo: Conceptualization, Data curation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing

Akanji Omolola Nafisat: Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft

Shittu Shehu-Tijani Toyin: Data curation, Formal Analysis, Methodology, Software, Visualization

Shittu Seyyid Alli: Data curation, Formal Analysis, Methodology, Visualization

Conflicts of Interest

The authors declare no conflicts of interest.

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