



Alpha lipoic acid improved blood glucose level and lipid profile in type-2 diabetic Wistar rats

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Abstract

Diabetes mellitus is one of the most common metabolic disorders that is associated with many complications such as dyslipidemia and cardiovascular disease. This study aimed to evaluate the effects of alpha lipoic acid (ALA) on blood glucose levels and lipid profile in type-2 diabetic male Wistar rats. Thirty (30) Wistar rats weighing between 200 – 250 grams were distributed into six groups of five each (n=5). Diabetes was induced using a high-fat diet for eight weeks with a single low dose of streptozotocin (40 mg/kg) intraperitoneally at the end of the sixth week. Group I served as normoglycemic control and received 1 ml/kg normal saline; groups II, III, IV, V, and VI were diabetic and received 1 ml/kg normal saline; glibenclamide 1 mg/kg; ALA 100 mg/kg, ALA 200 mg/kg and ALA 400 mg/kg; respectively. All administrations were done orally for a duration of 21 days. Blood glucose level was determined using the glucose oxidase method. Serum was collected for lipid profile determination. The results obtained from this study showed that ALA across all doses (100 mg/kg, 200 mg/kg, and 400 mg/kg) decreased significantly ($p < 0.05$) the fasting blood glucose level (10.02 ± 0.71 mmol/L, 8.78 ± 0.94 mmol/L and 8.6 ± 0.68 mmol/L, respectively) when compared to the diabetic control group (20.06 ± 0.70 mmol/L). Lipid profiles were improved with HDL- and LDL- cholesterols increasing and decreasing significantly (42.60 ± 1.66 mg/dL and 1.12 ± 3.68 mg/dL) in the 400 mg/kg ALA group compared to the diabetic untreated group (37.00 ± 2.55 mg/dL and 26.31 ± 2.95 mg/dL, respectively). Therefore, the study demonstrated that ALA has both antihyperglycemic and antilipidemic in type-2 diabetic Wistar rats.

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1.0 Introduction

Diabetes is a heterogeneous complex metabolic disorder characterized by elevated blood glucose concentration secondary to either resistance to the action of insulin, insufficient insulin secretion, or both (ADA, 2014). Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and other specific types. The other specific types are a collection of a few dozen individual causes (Polonsky, 2012). Diabetic patients are at higher risk of

developing other complications. The pattern of dyslipidemia usually presents with elevated triglycerides and small dense low-density lipoprotein cholesterol (LDL-C) and reduced levels of high-density lipoprotein cholesterol (HDL-C) (Petersen and Shulman, 2018). Increased LDL-C particle numbers from either elevated apolipoprotein B (ApoB) or low-density lipoprotein particles (LDL-P) are prominent features of dyslipidemia in diabetes (Warraich and Rana, 2017). Small dense LDL-P are more atherogenic

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and are associated with a higher rate of nephropathy. Individuals with diabetes have also been noted to have lower HDL levels (Dilworth *et al.*, 2021).

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), with a two to four-fold increase in cardiovascular disease risk compared with nondiabetic individuals (Garkuwa *et al.*, 2021; Vergès, 2015). Type 2 diabetes mellitus is associated with increased total plasma free fatty acids (FFAs) concentration and an elevated risk of CVD. The exact mechanisms by which the plasma FFAs profile of subjects with T2DM changes is unclear, but it is thought that dietary fats and changes to lipid metabolism are likely contributors (Sobczak *et al.*, 2019; Tijjani *et al.*, 2022). Altered blood glucose levels have important consequences for the body (Spiller *et al.*, 2018). They are directly or indirectly associated with many physiological processes including the control of glycogen and lipid metabolism, the control of food intake (satiety), maintenance of body weight and the regulation of inflammation, vasodilatation and basic cell growth and replication (Russell *et al.*, 2016; Sobczak *et al.*, 2019). Abnormalities of lipoprotein metabolism are one of the major factors contributing to cardiovascular risk in patients with type 2 diabetes, and diabetic dyslipidemia includes not only quantitative but also qualitative and kinetic lipoprotein abnormalities that are inherently atherogenic (Vergès, 2015).

Insulin resistance is the primary mechanism leading to lipid derangements in individuals with diabetes. Free fatty acids (FFAs) released from adipose tissue are increased by an increase in peripheral resistance to insulin, and the released FFAs are taken up by the liver leading to more synthesis of triglycerides (Castillo-Núñez *et al.*, 2022). Triglyceride synthesis subsequently stimulates hepatic production of triglyceride-rich very low-density lipoprotein cholesterol (VLDL) and increased secretion of ApoB (Ormazabal *et al.*, 2018). Triglyceride-laden VLDL enriches LDL-C and HDL-C through the action of the cholesterol ester transfer proteins, making them more cholesterol-rich. These triglyceride-rich LDL molecules are then hydrolyzed by hepatic or lipoprotein lipase leading to the production of small dense LDL-C (Castillo-Núñez *et al.*, 2022). Therefore, the lipid derangements associated with diabetes are widespread, beyond just LDL elevation, making it challenging to rely on conventional means for cardiovascular risk reduction (Galicia-Garcia *et al.*, 2020; Giri *et al.*, 2018).

Alpha lipoic acid exhibits low toxicity at low doses. Treatment of male or female experimental animals with ALA did not cause any adverse effects. In addition, the long-term (two-year) administration of up to 60 mg/kg/day did not cause any adverse effects

(Cremer *et al.*, 2006). It has antioxidant properties hence, can effectively inhibit pathologies in which ROS have been implicated, such as diabetic neuropathy, ischemia-reperfusion injury, radiation injury, and diabetes-induced oral implant failure (Vallianou *et al.*, 2009; Serhiyenko *et al.*, 2018). In addition, ALA has many other biological functions including reducing inflammation, chelating the transitional metal ions, and modulating the signal transduction of nuclear factors (Tabrizi *et al.*, 2019). This study aimed to evaluate the effects of alpha lipoic acid (ALA) on blood glucose levels and lipid profile in type-2 diabetic male Wistar rats.

2.0 Materials and Methods

2.1 Drugs, Reagents, and Other Materials

All drugs and reagents were obtained commercially and were of analytical grades. The drugs, reagents, equipment, and other materials used for the study include alpha lipoic acid purchased from Puritan's Pride Inc. (Ronkonkoma, New York, USA). A digital glucometer was used for blood glucose determination (Accu-Check Advantage, Roche Diagnostic, Germany).

2.2 Animals, Induction of Diabetes, and Experimental Design

A total of thirty (30) male Wistar rats weighing 200 – 250 grams were used for the study. Animals were allowed for two weeks for acclimatization to the laboratory environment before the commencement of the experiments. The animals were handled by principles guiding the use and handling of experimental animals by the London Declaration of September 1977. Ethical approval was obtained from Bauchi State University Gadau Committee on Animal Use and Care (BASUG/FBMS/REC/VOL.2/23).

The rats were fasted for 12 – 16 hours before the commencement of the experiment but were allowed water *ad libitum* throughout the experiment. The normal groups were fed with standard rat feed only as described by De Magalhães *et al.* (2019) and with little modification, while the high-fat-diet groups were fed with a high-fat diet (HFD: 35% commercial feed, 25% groundnut, 25% fat, and 15% groundnut oil) for the induction of obesity and DM for six (6) weeks followed by a single dose of streptozotocin (STZ) 40 mg/kg intraperitoneally (IP) and high-fat diet for another 2 weeks. Rats fasted for 12 hours and fasting blood glucose levels were measured to confirm the establishment of diabetes (De Magalhães *et al.*, 2019). Rats with fasting blood glucose levels of 16 mmol/L were considered diabetic and selected for the study (De Magalhães *et al.*, 2019). The drug administration was done daily for 21 days, and estimation of fasting blood glucose level started before treatment (day 0) and continued on weekly bases, both were conducted between 0700 – 0900 hours. The rats were distributed

into six (6) groups of five (5) rats each ($n = 5$). All drug administrations were done orally for 21 days as follows. Group I served as normal control and received 1 ml/kg 0.9% normal saline; Group II, III, IV, V, and VI were all diabetic and received 1 ml/kg 0.9% normal saline, 1 mg/kg glibenclamide, 100 mg/kg ALA, 200 mg/kg ALA, 400 mg/kg ALA respectively.

2.3 Determination of Fasting Blood Glucose Level

The blood samples were obtained from the rat tail vein on days 0 (pre-treatment) and 21 (post-treatment). A digital glucometer was used to measure the blood glucose levels using the glucose oxidase principle (Beach and Turner, 1958) using the digital glucometer (Accu-Check Advantage, Roche Diagnostic, Germany), and results were expressed in mmol/L.

2.4 Termination of Experiment and Sample Collection

On day 21, all rats were subjected to light anesthesia by exposing them to chloroform soaked in cotton wool and placed in an aesthetic box. Blood samples of about 5 ml were collected from the heart of each rat from all groups by cardiac puncture. The samples were collected in Eppendorf tubes and allowed to clot. Thereafter, serum was separated by centrifugation at 3000 g for 10 minutes. The serum was used for the lipid profile assay.

2.5 Serum lipid profiles assay

This was determined colorimetrically, using colorimetric assay kits (Randox, Northern Ireland) according to the manufacturer's instruction, and values were expressed in mmol/L. Serum Low-Density Lipoprotein (LDL) Level was estimated using the Friedewald formula and the values were expressed in mmol/L. Lipid components assayed include TC, TG, and HDL-C and components calculated include

LDL-C, atherogenic index (AI), coronary artery index (CAI), and cardiac index (CI).

$LDL-C = TC - (TGL/5 + HDL-C)$ (Friedewald *et al.*, 1972).

$AI = (TC - HDL-C)/HDL-C$
(Lamarche *et al.*, 1996).

$CI = TC/HDL-C$ (Kang *et al.*, 2004)

$CAI = LDL-C/HDL-C$ (Kang *et al.*, 2004)

2.6 Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22 was used to analyze the data. Data obtained were presented as mean \pm standard error of the mean (SEM). Analysis of variance (ANOVA) was employed to compare the level of significance between experimental groups. Significance was considered at $p < 0.05$.

3.0 Results

3.1. Blood Glucose Levels of Alpha Lipoic Acid Treated Diabetic Wistar Rats

To determine the effect of ALA on fasting blood glucose level (Table 1), diabetic animals were given different doses of ALA (100 mg/kg, 200 mg/kg, and 400 mg/kg) daily for 21 days and blood glucose level was checked at the beginning (day 0) and continued on weekly bases. We observed a significant ($p < 0.05$) decrease in the fasting blood glucose level across the three doses after 21 days especially in the 400 mg/kg (8.60 ± 0.68 mmol/L) administered group compared to the first day of administration (20.44 ± 1.01 mmol/L). Also, the 400 mg/kg ALA groups showed significant [$F(5, 30) = 55.51, p < 0.0001$] reduction (Group VI: 8.60 ± 0.68 mmol/L) in fasting blood glucose level compared to the diabetic control group (Group II: 20.06 ± 0.70 mmol/L).

Table 1: Effects of Alpha Lipoic Acid on Fasting Blood Glucose Levels of Type-2 Diabetic Wistar Rats

GROUPS	Day 0 (mmol/L)	Day 7 (mmol/L)	Day 14 (mmol/L)	Day 21 (mmol/L)
Normal + NS (1 ml/kg)	4.88 ± 0.50	4.60 ± 0.47	4.68 ± 0.29	4.84 ± 0.25^b
DM + NS (1 ml/kg)	19.96 ± 1.20^a	21.70 ± 1.39^a	20.00 ± 1.12^a	20.06 ± 0.70^a
DM + Glib (1 mg/kg)	19.76 ± 1.02^a	$18.26 \pm 0.65^{a,b}$	$12.92 \pm 0.84^{a,b,c,d}$	$7.02 \pm 0.79^{a,b,c,d}$
DM + ALA (100 mg/kg)	20.86 ± 1.40^a	$16.74 \pm 1.48^{a,b}$	$11.64 \pm 0.87^{a,b,c,d}$	$10.02 \pm 0.71^{a,b,c,d}$
DM + ALA (200 mg/kg)	21.44 ± 1.14^a	$18.70 \pm 0.78^{a,b}$	$13.18 \pm 0.79^{a,b,c,d}$	$8.78 \pm 0.94^{a,b,c,d}$
DM + ALA (400 mg/kg)	20.44 ± 1.01^a	$18.18 \pm 1.01^{a,b}$	$12.18 \pm 1.05^{a,b,c,d}$	$8.60 \pm 0.68^{a,b,c,d}$

Values having superscript letters a, b, and c are statistically significant ($p < 0.05$) compared with the normal control group (Normal + NS), diabetic control group (DM + NS), and days 0 and 7 respectively. **NS:** Normal saline; **DM:** Diabetes mellitus; **Glib:** Glibenclamide; **ALA:** alpha lipoic acid.

a, b – values with column were significantly different ($p < 0.05$) compared with normal (normal + NS) and diabetic control (DM + NS) groups respectively.

c, d – values within rows were significantly different ($p < 0.05$) compared with day 0 and day 7 respectively

3.2 Serum Lipid Profiles in Alpha Lipoic Acid Treated Type-2 Diabetic Wistar Rats

To determine the effect of ALA on serum lipid profile level (Table 2), diabetic animals were given different doses of ALA (100 mg/kg, 200 mg/kg, and 400 mg/kg) daily for 21 days and lipid profiles were assessed after the last administration. We observed a significant decrease in the total cholesterol [F(5, 30) = 9.27, $p < 0.0001$], triglycerides [F(5, 30) = 73.23, $p < 0.0001$] and low-density lipoprotein cholesterol [F(5, 30) = 6.81, $p < 0.0001$] in the 200 mg/kg administered

group (group V) with values of 57.49 ± 4.16 mg/dL, 44.98 ± 5.25 mg/dL and 8.49 ± 5.10 mg/dL compared to the diabetic control group (group II) with values of 78.55 ± 5.08 mg/dL, 76.22 ± 3.78 mg/dL and 26.31 ± 2.95 mg/dL respectively. However, there was no significant [F(5, 30) = 0.80, $p > 0.05$] increase in the high-density lipoprotein cholesterol level in the ALA 400 mg/kg bw group (group VI: 42.60 ± 1.66 mg/dL) compared to the diabetic control group (group II: 37.00 ± 2.55 mg/dL).

Table 2: Changes in Serum Lipid Profile (Total Cholesterol, Triglycerides, and High-Density Lipoprotein Cholesterol) in Alpha Lipoic Acid Treated of Type-2 Diabetic Wistar Rats

Groups	TC (mg/dL)	Trig (mg/dL)	HDL-chole (mg/dL)
Normal + NS (1 ml/kg)	46.40 ± 2.06	18.40 ± 1.86	38.00 ± 1.58
DM + NS (1 ml/kg)	78.55 ± 5.08^b	76.22 ± 3.78^b	37.00 ± 2.55^b
DM + Glib (1 mg/kg)	60.35 ± 5.21	9.97 ± 0.67^a	39.00 ± 2.45
DM + ALA (100 mg/kg)	64.75 ± 3.51	39.34 ± 2.16^a	38.40 ± 2.93
DM + ALA (200 mg/kg)	57.49 ± 4.16^a	44.98 ± 5.25^a	40.00 ± 1.58
DM + ALA (400 mg/kg)	46.82 ± 2.67^a	15.50 ± 0.52^a	42.60 ± 1.66^a

Values having a,b superscript are statistically significant ($p < 0.05$) compared with the diabetic control group (DM + NS). NS: Normal saline; DM: Diabetes mellitus; Glib: Glibenclamide; ALA: alpha lipoic acid; TC: total cholesterol; Trig: triglycerides; HDL-chole: high-density lipoprotein cholesterol.

Table 3: Changes in Serum Lipid Profile (Low-Density Lipoprotein Cholesterol, Cardiac, Coronary Artery, and Atherogenic Indices) in Alpha Lipoic Acid Treated Type-2 Diabetic Wistar Rats

Groups	LDL-chole (mg/dL)	CI	CAI	AI
Normal + NS (1 ml/kg)	4.72 ± 1.46	1.22 ± 0.03	0.12 ± 0.04	0.22 ± 0.03
DM + NS (1 ml/kg)	26.31 ± 2.95^b	2.14 ± 0.11^b	0.72 ± 0.08^b	1.14 ± 0.11^b
DM + Glib (1 mg/kg)	19.35 ± 4.61	1.55 ± 0.11	0.50 ± 0.11^a	0.55 ± 0.11
DM + ALA (100 mg/kg)	18.49 ± 3.34^a	1.71 ± 0.11	0.50 ± 0.10^a	0.71 ± 0.11
DM + ALA (200 mg/kg)	8.49 ± 5.10^a	1.45 ± 0.13^a	0.22 ± 0.13^a	0.45 ± 0.13^a
DM + ALA (400 mg/kg)	1.12 ± 3.86^a	1.11 ± 0.09^a	0.04 ± 0.08^a	0.11 ± 0.09^a

Values having a,b superscript are statistically significant ($p < 0.05$) compared with the diabetic control group (DM + NS). NS: Normal saline; DM: Diabetes mellitus; Glib: Glibenclamide; ALA: alpha lipoic acid; LDL-chole: low-density lipoprotein cholesterol; CI: cardiac index; CAI: Coronary artery index; AI: Atherogenic index

4.0 Discussion

Alpha lipoic acid (ALA) has been used for some years now as an antioxidant with antihyperglycaemic and anti-inflammatory effects and to treat many ailments because of its wide spectrum of pharmacological activities (Duch, 1999; Mendoza-núñez *et al.*, 2019). In this study, we observed that all three doses of alpha lipoic acid (100, 200 and 400 mg/kg) significantly ($p < 0.05$) decreased the fasting blood glucose level when compared to the control group. The decrease in the fasting blood glucose level observed in the present study indicates that daily administration of ALA has improved the hyperglycemic condition induced by a high-fat diet/streptozotocin in experimental animals. This suggests that ALA has a strong antihyperglycemic effect. Although the decrease observed in the 400 mg/kg group is lower, it was not significant when compared to the other ALA groups. The hypoglycemic effect of ALA showed almost similar effects to that of the standard drug used (glibenclamide). Also, both the glibenclamide and ALA treatment groups (all three doses) and the normoglycemic control group showed no significant ($p > 0.05$) difference, suggesting that ALA might have led to the recovery of insulin resistance and aided in the transport of glucose into tissues. The findings of the present study agreed with that of Ansar *et al.* (2011) who also demonstrated that ALA improved insulin resistance and diabetic condition in type-2 diabetic patients (Ansar *et al.*, 2011). Similarly, Elbadawy *et al.* (2021) also reported an ameliorative effect of ALA on peripheral neuropathy, glycated hemoglobin, and lipid profiles in diabetic patients (Elbadawy *et al.*, 2021).

Dyslipidemia is positively linked to hypertension and hypertension is a significant risk factor for impaired cognitive performance (Ariyanti, 2019; Bamidele *et al.*, 2022). In this study, a significant decrease in total cholesterol, triglycerides, and LDL-c were observed in all the ALA-treated groups compared to the diabetic control group. This is an indication that ALA, especially at 200 mg/kg and 400 mg/kg caused an improved lipid profile. In the same vein, increased HDL-c was observed in the 400 mg/kg ALA group in this study. However, type-2 diabetes mellitus has been associated with decreased HDL-C in previous studies. The increase in HDL-c observed in this study is an indication that ALA at 400 mg/kg has improved dyslipidemia by increasing the level of good cholesterol (HDL-C) and reducing the level of bad cholesterol (LDL-C). Further, ALA has significantly decrease the level of CI, CAI and AI. This is important because the integrity of blood vessels and blood transport is important to ensure constant tissue perfusion. Atherogenic agents are known to take part in the genesis and progression of arteriosclerosis. This

result agrees with the findings of Amom *et al.* (2008) who reported lipid-lowering, anti-atherosclerotic, low plasma TC and LDL levels and reduction in atherosclerosis formation in hypercholesterolemic-induced rabbits treated with ALA (Amom *et al.*, 2008). However, our results contradict that of Sun *et al.* (2012) who reported that ALA does not affect serum lipids in patients with age-related macular degeneration (Sun *et al.*, 2012).

5.0 Conclusion

The present study demonstrated that ALA has an antihyperglycemic effects and Type-2 DM causes dyslipidemia which was significantly improved after 21 days of administration of ALA.

Declarations

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Ethics approval and consent to participate

Ethical approval was obtained from Bauchi State University Gadau Committee on Animal Use and Care (BASUG/FBMS/REC/VOL.2/23). The animals were handled by principles guiding the use and handling of experimental animals in Bauchi state university Gadau and by the London Declaration of September 1977.

Consent for publication

All authors have read and consented to the submission of the manuscript.

Availability of data and material

Not Applicable.

Competing interests

All authors declare no competing interests.

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Authors' contributions

UAG conceptualized the design of the study. MIAS, AA, and MUK supervised the study and prepared the first draft of the manuscript. UAG, MIAS, and AA helped in the data collection and analysis. UAG and MUK did the interpretation of the results. All authors read and approved the final manuscript.

References

Amom, Z., Zakaria, Z., Mohamed, J., Azlan, A., Bahari, H., Baharuldin, M. T. H., Moklas, M. A., Osman, K., Asmawi, Z., and Hassan, M. K. N. (2008). Lowering Effect of Antioxidant Alpha Lipoic Acid in Experimental Atherosclerosis. *Journal of Clinical Biochemistry and Nutrition*,

- 43(September), 88–94.
- Ansar, H., Mazloom, Z., Kazemi, F., and Hejazi, N. (2011). *Effect of alpha-lipoic acid on blood glucose, insulin resistance, and glutathione peroxidase of type 2 diabetic patients*. 98(711), 584–588.
- Ariyanti, R. (2019). *Dyslipidemia Associated with Hypertension Increases the Risks for Coronary Heart Disease: A Case-Control Study in Harapan Kita Hospital, National Cardiovascular Center, Jakarta*. 2019. <https://doi.org/10.1155/2019/2517013>
- Bamidele, O., Ayebatonyo, M., and Davies, C. (2022). *Obesity and Dyslipidemia as Risk Factors of Vascular Cognitive Impairment in Adult Hypertensive Nigerian*. 34(23), 334–342. <https://doi.org/10.9734/JAMMR/2022/v34i234869>
- Beach, E. F., and Turner, J. J. (1958). An enzymatic method for glucose determination in body fluids. *Clinical Chemistry*, 4(6), 462–475.
- Castillo-Núñez, Y., Morales-Villegas, E., and Aguilar-Salinas, C. A. (2022). Triglyceride-Rich Lipoproteins: Their Role in Atherosclerosis. *Revista de Investigacion Clinica; Organo Del Hospital de Enfermedades de La Nutricion*, 74(2), 061–070. <https://doi.org/10.24875/RIC.21000416>
- Cremer, D. R., Rabeler, R., Roberts, A., and Lynch, B. (2006). *Long-term safety of -lipoic acid (ALA) consumption: A 2-year study*. 46, 193–201. <https://doi.org/10.1016/j.yrtph.2006.06.003>
- De Magalhães, D. A., Kume, W. T., Correia, F. S., Queiroz, T. S., Allebrandt Neto, E. W., Dos Santos, M. P., Kawashita, N. H., and De Franca, S. A. (2019). High-fat diet and streptozotocin in the induction of type 2 diabetes mellitus: A new proposal. *Anais Da Academia Brasileira de Ciencias*, 91(1), 1–14. <https://doi.org/10.1590/0001-3765201920180314>
- Dilworth, L., Facey, A., and Omoruyi, F. (2021). Diabetes mellitus and its metabolic complications: The role of adipose tissues. In *International Journal of Molecular Sciences* (Vol. 22, Issue 14). <https://doi.org/10.3390/ijms22147644>
- Duch, D. E. (1999). Resin transfer molded high temperature composites. *International SAMPE Symposium and Exhibition (Proceedings)*, 44(10), 1149–1160. <https://doi.org/10.1016/j.bbagen.2009.07.026>. Alpha-lipoic
- Elbadawy, A. M., Elmoniem, R. O. A., and Elsayed, A. M. (2021). Alpha lipoic acid and diabetes mellitus: potential effects on peripheral neuropathy and different metabolic parameters. *Alexandria Journal of Medicine*, 57(1), 113–120. <https://doi.org/10.1080/20905068.2021.1907961>
- Friedewald, W. T., Levy, R. I., and Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*, 18(6), 499–502.
- Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., and Martín, C. (2020). Pathophysiology of type 2 diabetes mellitus. In *International Journal of Molecular Sciences* (Vol. 21, Issue 17, pp. 1–34). MDPI AG. <https://doi.org/10.3390/ijms21176275>
- Garkuwa, U. A., Alhassan, A., Tanko, Y., Ibrahim, B., Yakubu, A. B., and Garkuwa, A. H. (2021). Curcumin Improves Serum Electrolytes and Lipid Profiles of Diabetic Wistar Rats. *Dutse Journal of Pure and Applied Sciences (DUJOPAS)*, 7(1), 242–249.
- Giri, B., Dey, S., Das, T., Sarkar, M., Banerjee, J., and Dash, S. K. (2018). Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity. *Biomedicine and Pharmacotherapy*, 107, 306–328. <https://doi.org/https://doi.org/10.1016/j.biopha.2018.07.157>
- Kang, M. J., Lee, E. K., and Lee, S. S. (2004). Effects of two P/S ratios with same peroxidizability index value and antioxidants supplementation on serum lipid concentration and hepatic enzyme activities of rats. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, 350(1–2), 79–87. <https://doi.org/10.1016/j.cccn.2004.07.005>
- Lamarque, B., Moorjani, S., Lupien, P. J., Cantin, B., Bernard, P. M., Dagenais, G. R., and Després, J. P. (1996). Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec cardiovascular study. *Circulation*, 94(3), 273–278. <https://doi.org/10.1161/01.cir.94.3.273>
- Mendoza-núñez, V. M., García-martínez, B. I., Rosado-pérez, J., Santiago-osorio, E., and Pedraza-chaverri, J. (2019). *The Effect of 600 mg Alpha-lipoic Acid Supplementation on Oxidative Stress, Inflammation, and RAGE in Older Adults with Type 2 Diabetes Mellitus*. 2019. <https://doi.org/10.1155/2019/3276958>
- Ormazabal, V., Nair, S., Elfeky, O., Aguayo, C., Salomon, C., and Zuñiga, F. A. (2018). Association between insulin resistance and the

- development of cardiovascular disease. In *Cardiovascular Diabetology* (Vol. 17, Issue 1, pp. 1–14). BioMed Central. <https://doi.org/10.1186/s12933-018-0762-4>
- Petersen, M. C., and Shulman, G. I. (2018). Mechanisms of insulin action and insulin resistance. In *Physiological Reviews* (Vol. 98, Issue 4, pp. 2133–2223). <https://doi.org/10.1152/physrev.00063.2017>
- Polonsky, K. S. (2012). The Past 200 Years in Diabetes. *New England Journal of Medicine*, 367(14), 1332–1340. <https://doi.org/10.1056/nejmra1110560>
- Russell, W. R., Baka, A., Björck, I., Delzenne, N., Gao, D., Griffiths, H. R., Hadjilucas, E., Juvonen, K., Lahtinen, S., Lansink, M., Loon, L. Van, Mykkänen, H., Östman, E., Riccardi, G., Vinoy, S., and Weickert, M. O. (2016). Impact of Diet Composition on Blood Glucose Regulation. *Critical Reviews in Food Science and Nutrition*, 56(4), 541–590. <https://doi.org/10.1080/10408398.2013.792772>
- Serhiyenko, V., Serhiyenko, L., Suslik, G., and Serhiyenko, A. (2018). *Alpha-lipoic acid: mechanisms of action and beneficial effects in the prevention and treatment of diabetic complications*. 7(4), 174–178. <https://doi.org/10.15406/mojph.2018.07.00224>
- Sobczak, A. I. S., Blindauer, C. A., and Stewart, A. J. (2019). Changes in plasma free fatty acids associated with type-2 diabetes. In *Nutrients* (Vol. 11, Issue 9, pp. 1–42). <https://doi.org/10.3390/nu11092022>
- Spiller, S., Blüher, M., and Hoffmann, R. (2018). Plasma levels of free fatty acids correlate with type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*, 20(11), 2661–2669. <https://doi.org/https://doi.org/10.1111/dom.13449>
- Sun, Y., Dong, Y., Fan, R., Zhai, L., and Bai, Y. (2012). *Effect of (R) - α -Lipoic Acid Supplementation on Serum Lipids and Antioxidative Ability in Patients with Age-Related Macular Degeneration*. 293–297. <https://doi.org/10.1159/000338444>
- Tabrizi, R., Borhani-Haghighi, A., Mirhosseini, N., Lankarani, K. B., Naghibzadeh-Tahami, A., Akbari, M., Heydari, S. T., Sangari, M., Kolahdooz, F., Raygan, F., and Asemi, Z. (2019). The effects of alpha-lipoic acid supplementation on fasting glucose and lipid profiles among patients with stroke: a systematic review and meta-analysis of randomized controlled trials. In *Journal of Diabetes and Metabolic Disorders* (Vol. 18, Issue 2, pp. 585–595). *Journal of Diabetes and Metabolic Disorders*. <https://doi.org/10.1007/s40200-019-00423-0>
- Tijjani, H., Danyaro, A. M., Olatunde, A., and Kura, A. U. (2022). Antihyperglycemic activity of verbenone and L-arginine in nicotinamide-streptozotocin-induced diabetic mice: in vitro and in vivo studies. *Beni-Suef University Journal of Basic and Applied Sciences*, 11(1). <https://doi.org/10.1186/s43088-022-00271-7>
- Vallianou, N., Evangelopoulos, A., and Koutalas, P. (2009). Alpha-lipoic acid and diabetic neuropathy. In *Review of Diabetic Studies* (Vol. 6, Issue 4, pp. 230–236). <https://doi.org/10.1900/RDS.2009.6.230>
- Vergès, B. (2015). Pathophysiology of diabetic dyslipidaemia: where are we? In *Diabetologia* (Vol. 58, Issue 5, pp. 886–899). <https://doi.org/10.1007/s00125-015-3525-8>
- Warraich, H. J., and Rana, J. S. (2017). Dyslipidemia in diabetes mellitus and cardiovascular disease. In *Cardiovascular Endocrinology* (Vol. 6, Issue 1, pp. 27–32). <https://doi.org/10.1097/XCE.0000000000000120>