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ORIGINAL RESEARCH ARTICLE

Impact of Tofacitinib and Aspirin on Lipoprotein Levels in Type 2 diabetic Rats: Implications for Macrovascular Complications' Risk Mitigation

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ABSTRACT

Diabetes type 2 (T2D) related macrovascular complications are frequently linked to lipoprotein metabolism and the activation of inflammatory pathways. This study explores the impact of tofacitinib and aspirin on lipoprotein levels and inflammation in type 2 diabetic rats. Ten groups of eight rats each were treated with varying doses of tofacitinib and aspirin for nine weeks following induction of diabetes. Significant decreases in triglycerides, cholesterol, and LDL ($P<0.05$) were observed, along with increases in HDL levels, particularly at higher doses of tofacitinib 20 mg/kg and aspirin 200 mg/kg when compared with the diabetic control group. Additionally, treatment with both drugs at different doses significantly ($P<0.05$) reduced the artherogenic indices (CRI-I, CRI-II, AIP, AC), suggesting a decreased future risk of cardiovascular disease. A significant reduction ($P<0.05$) in TNF-α and IL-6 levels in all diabetic groups treated with tofacitinib and aspirin compared to the diabetic control group was observed. However, no significant reduction was observed in the groups treated with 20 mg/kg BW of tofacitinib and 200 mg/kg BW of aspirin for both TNF-α and IL-6, as well as in the group treated with 200 mg/kg BW of aspirin for TNF-α only. These results highlight the possibility of addressing inflammation to reduce cardiovascular risk and dyslipidemia in rats with type 2 diabetes.

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INTRODUCTION

The mortality rate associated with diabetes has become a global concern, with its prevalence not only limited to developed nations but also affecting developing countries. Recent statistics highlight a rapid increase in diabetes cases among both adults and children, with approximately 460 million people affected worldwide across all age groups and regions. (Vos et al., 2020). Another report by the International Diabetes Federation (IDF) indicates that people suffering from the disease worldwide between the ages of 20-76 are about 537 million, and the number is projected to rise to 643 million by 2030 and 783 million by 2045 (Sun et al., 2022), and around 1.3 billion by 2050 (Chan et al., 2021; Magliano et al., 2021). The estimated number of people with the disease in Africa was 24 million in 2021 and is predicted to increase by 129% to 55 million by 2045, even though this current statistic is not the actual population of people with the disease because more than half (54%) of people with diabetes in the African Region are undiagnosed (WHO, 2023). Although there are other forms of diabetes, type 1 and type 2 diabetes are more prominent. Over 90% of diabetes cases are type 2 diabetes, making it the most prevalent and common form of the disease (Chan et al., 2021). According to Wesolowska-Andersen et al. (2022), insulin resistance and beta cell dysfunction are the primary characteristics of type 2 diabetes, a multifactorial illness that can result in both macrovascular and microvascular complications (Cerf, 2013).

Insulin resistance affects lipoprotein metabolism through activation of hormone-sensitive lipase that results in lipolysis and increased generation and circulation of free fatty acids (Ormazabal et al., 2018). The fatty acids are transported to the liver, consequently generating a high level of VLDL, which is converted to LDL (Alves-Bezerra & Cohen, 2017). In addition, increased activation of ApoB mRNA translation in type 2 diabetes, leads to accumulation of apolipoprotein B (ApoB) required for more LDL synthesis. Furthermore, the production of advanced glycated end products (AGEs) as a result of blood glucose buildup, which causes covalent adducts formation with plasma proteins by a non-enzymatic process reaction known as glycation, is one of the major factors contributing to the high circulating LDL level in T2D (Singh et al., 2014). The LDL receptors are glycated by these AGEs, which alters their conformation and inhibits them from binding to liver receptors, thereby impeding their absorption and degradation. (Haas et al.,

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2013). Atherosclerosis, caused by increased circulation of low-density lipoproteins (LDLs), which promote cholesterol deposition in the arterial wall, the production of free radicals, and the activation of an inflammatory pathway that recruits macrophages and forms foam cells is the result of these dysregulations (Moore et al., 2013).

To intensify the process, the apolipoprotein A-I (apoAI) in HDL also becomes glycated, modifying the particles by reducing their stability, promoting the dissociation of apoA-I from HDL, and impacting the structural cohesiveness of HDL particles. (Bonilha et al., 2021). It was reported that structural changes caused by apoA-I glycation reduced HDL binding to its liver receptor. This reduces HDL-reverse cholesterol transport and deteriorates HDL's ability to protect the heart. (Farbstein & Levy, 2012). All these processes set off a series of events that activate inflammatory pathways, produce proinflammatory cytokines, and recruit immune cells. The JAK-STAT and NF-KB signaling pathways are activated by the cytokines, which in turn increases the inflammatory response (Bako et al., 2019).

Inflammation plays a significant role in increasing insulin resistance and beta-cell secretion defects, both of which contribute to the development of type 2 diabetes. It also underlies the heightened risk of cardiovascular disease in individuals with diabetes and obesity. As a result, targeting inflammation could become a new therapeutic approach in the growing array of treatments for managing diabetes mellitus and its complications. By focusing on inflammation in diabetes, it may be possible to achieve better glycemic control and reduce both microvascular and macrovascular complications, including cardiovascular issues. Most treatments for type 2 diabetes mellitus (T2DM) currently focus on insulin resistance, but targeting inflammation could represent a paradigm shift in type 2 diabetes mitigation (Agrawal & Kant, 2014; Bako et al., 2019).

Moreover, several researches have reported the effect of targeting cytokines in the treatment of type 2 diabetes and complications through the use of anti-cytokine agents to inhibit the action of proinflammatory cytokines such as anti-IL-17 which plays a significant role in the inflammatory processes and development of T2D through activation of NF-KB signaling pathway responsible for upregulating the expression of other inflammatory cytokine genes such as IL-1β, IL-6, and TNF-α, IL-17, consequently contributing to macrovascular complications (Liu et al., 2023; Velikova et al., 2021).

Despite the advancement in the management of type 2 diabetes and complications through targeting inflammation via the use of anti-cytokines inhibitors, macrovascular complications remain a major challenge because the pathways responsible for the synthesis of these cytokines are still active and can synthesize other proinflammatory cytokines. Therefore, targeting these inflammatory pathways might be a novel approach to the mitigation of type 2 diabetes and complications. This study tends to investigate the novel approach of using tofacitinib and aspirin to modulate the JAK-STAT and NF-KB signaling pathways, which are the major pathways that synthesize cytokines, thereby potentially offering a new strategy to reduce cardiovascular risks in type 2 diabetes.

MATERIALS AND METHODS

Chemicals and Reagents

The following are some of the chemicals and reagents used during the research work: Citric acid, Sodium Hydroxide, Fructose, Methyl Cellulose, Metformin, Aspirin, lipid profile (HDL, CHO, TRIG) kits (Randox) were purchased from Royal Surgical Limited Kaduna State, Nigeria, Streptozotocin, Tofacitinib were purchased from Beijing Mesochem Technology China. Enzyme-linked immunosorbent assay (ELISA) reagent kits for Proinflammatory cytokines (IL-6 and TNF-α) were purchased from ELAB Science U.S.A.

Experimental animals

Wistar rats were procured from the Faculty of Veterinary Medicine, Ahmadu Bello University Zaria, Nigeria. The rats were maintained at room temperature and under 12 hours of light-dark cycle and were fed with commercial rat feed and drinking water *ad libitum*. The rats were maintained according to the standard established by the Animal Research Ethics Committee of Ahmadu Bello University Zaria (Ethical approval number: ABUCAUC/2019/24).

Animal grouping and induction of type 2 diabetes

The animals were divided into ten groups, with each group consisting of 8 rats. The groups were designated as follows: Normal control (NC), Diabetic control (DC), Diabetic rats treated with tofacitinib at 10 mg/kg (DT10), Diabetic rats treated with tofacitinib at 20 mg/kg (DT20), Diabetic rats treated with aspirin at 100 mg/kg (DA100), Diabetic rats treated with aspirin at 200 mg/kg (DA200), Diabetic rats treated with aspirin at 100 mg/kg + tofacitinib at 10 mg/kg (DA1T1), Diabetic rats treated with aspirin at 200 mg/kg + tofacitinib at 20 mg/kg (DA2T2), Non-diabetic rats treated with aspirin at 200 mg/kg + tofacitinib at 20 mg/kg (A2T2NR), and Diabetic rats treated with metformin at 850 mg/kg (DMET).

The rats underwent an acclimatization period of one week and were then fasted overnight. Following this, they were provided with 10% fructose ad libitum for 14 days to induce insulin resistance, except for the NC and A2T2NR groups. Subsequently, the rats were injected

intraperitoneally with streptozotocin (STZ) at a dose of 40 mg/kg body weight, dissolved in citrate buffer (pH 4.5), to induce the chronic stage of type 2 diabetes through partial destruction of pancreatic β-cells.

Non-fasting blood glucose levels of all rats were measured using a glucometer one week after STZ induction by pricking the tail vein. Rats with non-fasting blood glucose levels greater than 300 mg/dL were considered diabetic, while those with levels below 300 mg/dL were excluded from the study. The drugs, dissolved in 0.5% methylcellulose, were administered daily for 9 weeks, with the NC group receiving the vehicle only.

Collection of blood

At the end of the experiment, blood samples were taken via cardiac puncture and quickly centrifuged at 3,000 rpm for 10 minutes to extract serum for analysis.

Analytical methods

Interleukin-6 TNF-α concentrations were measured at the end of the experimental period by an ELISA method using a rat ELISA kit for the respective parameters (Elab Science, USA) as described by the manufacturer. High-density lipoprotein (HDL), cholesterol (CHO), and triglycerides (TAG) levels were measured using their respective kits as described by the manufacturer, and the following formulas were used to calculate the low-density lipoprotein (LDL) and artherogenic indices:

LDL-Cholesterol (mg/dl) = Total Cholesterol- [HDL-(TG/5)]

Atherogenic Index of Plasma (AIP) =Log (Triglycerides/HDL-C)

Castelli Risk Index I=Total Cholesterol/ HDL-C

Castelli Risk Index II=LDL-C/HDL-C

Atherogenic Coefficient (AC) =Total Cholesterol−HDL-C/HDL-C

Statistical analysis

Data were presented as means ± standard error. Differences between the means of test and control groups were determined by multivariate analysis of variance (MANOVA) using Tukey's HSD multiple range post-hoc test. The relationships between the parameters were analyzed using Pearson correlation in Statistical Package for Social Sciences (SPSS) software version 22.0 (IBM Corporation, NY, USA). All experiments were conducted independently three times (n=3) at a 95% confidence interval. Values were considered significantly different at $P<0.05$."

RESULTS

The study evaluated the impact of standard anti-inflammatory drugs (tofacitinib and aspirin) on the level of proinflammatory cytokines (IL-6 and TNF-α) and lipid profile parameters (triglycerides (TRIG), cholesterol (CHO), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)) in rats with type 2 diabetes. Multivariate analysis of variance (MANOVA) was performed to analyse the interaction between drugs at different dosages on proinflammatory cytokines and lipid profile parameters. Table 1 illustrates a significant reduction ($P<0.05$) in TNF-α and IL-6 levels in all diabetic groups treated with tofacitinib and aspirin compared to the diabetic control group. However, no significant reduction was observed in the groups treated with 20 mg/kg BW of tofacitinib and 200 mg/kg BW of aspirin for both TNF-α and IL-6, as well as in the group treated with 200 mg/kg BW of aspirin for TNF-α only. Also significant ($P<0.05$) reduction in LDL, CHO, and TRIG levels when compared to the diabetic control group in groups treated with 200 mg/kg of aspirin and 20 mg/kg was observed.

Furthermore, there was a significant ($P<0.05$) rise in HDL levels in these groups, indicating that both aspirin and tofacitinib have a positive effect on modulating the lipid profile parameters. To obtain the relationship between inflammation and lipid profile parameters, Pearson correlation was conducted and shown in Table 2. There was a negative correlation between HDL and the proinflammatory cytokines, while a positive correlation was observed between TRIG, CHO, LDL, and the proinflammatory cytokines.

In order to evaluate the risk of cardiovascular disease linked to the treatment, atherogenic indices were also computed and shown in Table 3. In comparison to the diabetic control group, the groups treated with tofacitinib at both 10 mg/kg and 20 mg/kg, aspirin at both 100 mg/kg and 200 mg/kg, and the group receiving a combined dose of aspirin at 100 mg/kg and tofacitinib at 10 mg/kg, showed a significant ($P<0.05$) decrease in the levels of atherogenic indices, including atherogenic index of plasma (AIP), Castelli's Risk Index I (CRI-1), Castelli's Risk Index II (CRI-II), and atherogenic coefficient (AC).

DISCUSSION

Altered lipoprotein metabolism, characterized by decreased HDL and increased levels of triglycerides (TRIG), cholesterol (CHO), and LDL, is a major contributor to macrovascular complications in type 2 diabetes (T2D). In this study, we examined the anti-inflammatory effects of tofacitinib and aspirin on lipid profile parameters in rats with T2D. Remarkably, reducing inflammation by blocking the NF-ϰB and JAK-STAT signaling pathways with varying dosages of tofacitinib and aspirin, as evidenced by the reduction in proinflammatory cytokine levels, led to a significant rise in

HDL levels and a corresponding decrease in CHO, TRIG, and LDL levels. The negative correlation between HDL and both proinflammatory cytokines and CHO, TRIG, and LDL suggests that targeting inflammation with these medications may be effective in reducing the dyslipidemia associated with T2D, thereby lowering the risk of cardiovascular complications. Mechanistically, the ability of aspirin and tofacitinib to reduce inflammation may be linked to a decrease in insulin resistance, as reported by Bako et al. (2019). This reduction in insulin resistance could upregulate the expression of APO-A1, a crucial element needed for HDL synthesis, and APO B-100, essential for LDL synthesis. Additionally, it may enhance the expression of LDL receptors in the liver, facilitating the uptake and degradation of LDL by lysosomes. These mechanisms might explain the observed rise in HDL levels and the drop in LDL levels following treatment (Jaichander et al., 2008; Kluck et al., 2020) (Deng et al., 2022; Sundaram & Yao, 2010)

Additionally, both drugs may promote cholesterol efflux from peripheral cells to HDL by upregulating ABCA1 transport protein or lecithin cholesterol acyl transferase (LCAT), which converts cholesterol into cholesteryl esters for transport to the liver by HDL, thereby reducing the level of cholesterol. Increased LCAT activity is generally believed to be anti-atherogenic by promoting reverse cholesterol transport (Deng et al., 2022; Wolk et al., 2017). Scavenger receptor class B type 1 (SR-B1), which binds to HDL and promotes the transfer of cholesterol esters from HDL into the liver, may also be more highly expressed in response to tofacitinib and aspirin (McInnes et al., 2014; Pérez-Baos et al., 2017; Viñals et al., 2005). The drugs' capacity to decrease homone-sensitive lipase expression in adipose tissues and de novo cholesterol synthesis by inhibiting HMG CoA reductase in the liver, as well as to increase lipoprotein lipase expression, may account for the reduction in TRIG levels (Althaher, 2022; McInnes et al., 2014; Zhang et al., 2022).

Moreover, the groups' atherogenic indices decreased as a result of the hypolipidemic effects of both aspirin and tofacitinib, indicating a decreased risk of cardiovascular disease in the future (Liu et al., 2023; Xie et al., 2019). Research has indicated that AIP is a predictor of vascular events, diabetes, and high blood pressure. Even in cases where the absolute values of the individual components of the fasting lipid profile appear normal, AIP and other lipid indices, such as Castelli's Risk Index I & II and atherogenic coefficient (AC), have been demonstrated to significantly contribute to the estimation of the risk of coronary heart disease (CAD). Comparing these lipid ratios to individual lipid parameters is thought to be a more accurate indicators of CAD. (Kim et al., 2022; Namitha et al., 2022). Clinically, these findings suggest that dual inhibition of JAK-STAT and NF-ϰB pathways could offer a therapeutic advantage in managing dyslipidemia and reducing cardiovascular risks in type 2 diabetes.

Table 1: Effect of tofacitinib and aspirin on lipid profile parameters and proinflammatory cytokines of type 2 diabetic rats

	TNF-α (pg/mL)	IL-6 (pg/mL)	HDL-CHO (mg/dl)	TRIG (mg/dl)	CHO (mg/dl)	LDL-CHO (mg/dl)
NC	261.78±58.94^{a}	26.23±5.25^{a}	561.32±35.00^{a}	30.11±2.14^{a}	54.41±15.70^{a}	499.11±46.05^{a}
DC	1302.95±84.33^{b}	150.87±9.54^{b}	28.95±5.70^{b}	171.65±16.50^{b}	289.45±19.25^{b}	1294.83±17.07^{b}
DT10	584.34±55.20^{ac}	44.69±10.20^{a}	369.08±31.11^{c}	134.73±9.46^{bc}	129.81±7.00^{cd}	787.68±31.03^{c}
DT20	1239.33±211.52^{bc}	118.78±12.90^{bc}	357.73±42.95^{c}	79.97±5.80^{c}	115.30±9.19^{ad}	773.55±45.65^{c}
DA100	794.22±70.35^{c}	92.41±10.38^{ce}	211.84±26.52^{d}	82.41±2.77^{c}	225.56±24.14^{be}	1030.20±32.61^{d}
DA200	1036.5±87.88^{bc}	102.22±7.29^{ce}	215.04±28.15^{d}	81.98±4.88^{c}	177.56±14.87^{ce}	978.92±25.19^{d}
DA1T1	414.43±65.45^{ac}	38.63±5.94^{a}	182.12±21.74^{d}	146.70±9.48^{b}	194.20±8.42^{ce}	1041.42±21.28^{d}
DA2T2	471.45±54.09^{ac}	47.36±8.01^{ae}	201.69±24.01^{d}	136.80±9.37^{b}	270.08±12.92^{b}	1095.75±34.21^{d}
DA2T2NR	330.19±47.02^{a}	37.92±6.42^{a}	531..73±42.02^{a}	53.74±11.90^{c}	60.95±5.50^{a}	539.97±38.98^{a}
DMET	532.39±106.26^{ac}	66.05±9.41^{ae}	200.26±23..36^{d}	126.21±10.76^{b}	211.61±19.04^{e}	1036.59±20.09^{d}

NC= normal control DC= diabetic control DT10=diabetic rats treated with 10 mg/kg bw of tofacitinib DT20=diabetic rats treated with 20 mg/kg bw of tofacitinib DA100= diabetic rats treated with 200 mg/kg bw of aspirin; DA200= diabetic rats treated with 200 mg/kg bw DA1T1= diabetic rats treated with combination of 100 mg/kg bw aspirin/ 10 mg/kg bw tofacitinib DA2T2= diabetic rats treated with combination of 200 mg/kg bw aspirin/ 20 mg/kg bw tofacitinib A2T2NR= normal rats treated with combination of 200 mg/kg bw aspirin/ 20 mg/kg bw tofacitinib; DMET= diabetic rats treated with 850 mg/kg bw of metformin. The results are expressed as the mean ± SE. Different alphabets indicate significant differences (Tukey's-HSD multiple range *post hoc* test, P<0.05).

Table 2: Relationship between proinflammatory and lipid profile parameters

Control Variables			TRIG	CHO	HDL	LDL	TNF_ALPHA	IL_6
GROUPS	TRIG	Correlation	1	0.649	-0.682	0.717	0.225	0.204
		SG (2-tailed)	.	0	0	0	0.116	0.156
		df	0	48	48	48	48	48
	CHO	Correlation	0.649	1	-0.828	0.919	0.354	0.482
		SG (2-tailed)	0	.	0	0	0.012	0
		df	48	0	48	48	48	48
	HDL	Correlation	-0.682	-0.828	1	-0.982	-0.456	-0.595
		SG (2-tailed)	0	0	.	0	0.001	0
		df	48	48	0	48	48	48
	LDL	Correlation	0.717	0.919	-0.982	1	0.437	0.573
		SG (2-tailed)	0	0	0	.	0.002	0
		df	48	48	48	0	48	48
	TNF_ALPHA	Correlation	0.225	0.354	-0.456	0.437	1	0.786
		SG (2-tailed)	0.116	0.012	0.001	0.002	.	0
		df	48	48	48	48	0	48
	IL_6	Correlation	0.204	0.482	-0.595	0.573	0.786	1
		SG (2-tailed)	0.156	0	0	0	0	.
		df	48	48	48	48	48	0

SG = Significance

Table 3: Effect of tofacitinib and aspirin on artherogenic indices of type 2 diabetic rats.

	AIP	CRI-I	CRI-II	AC
NC	3.73±0.05^{a}	0.10±0.03^{a}	0.91±0.13^{a}	53.41±15.70^{a}
DC	5.80±0.06^{b}	12.09±3.19^{b}	53.93±12.81^{b}	288.45±19.25^{b}
DT10	4.56±0.51^{cd}	0.36±0.03^{a}	2.22±0.29^{a}	128.81±6.95^{c}
DT20	4.36±0.07^{c}	0.35±0.058^{a}	2.42±0.45^{a}	114.29±9.19^{c}
DA100	4.58±0.05^{cd}	1.11±0.12^{a}	5.02±0.59^{a}	228.40±9.61^{d}
DA200	4.63±0.08^{cd}	0.87±0.14^{a}	5.43±1.23^{a}	162.36±5.39^{ce}
DA1T1	4.87±0.06^{d}	1.10±0.10^{a}	5.56±0..69^{a}	198.64±8.50^{de}
DA2T2	4.88.±0.08^{d}	1.60±0.25^{a}	6.38±1.09^{a}	281.25±5.61^{b}
DA2T2NR	3.95±0.11^{e}	0.12±0.01^{a}	1.08±0.17^{a}	59.95±5.50^{a}
DMET	4.80±0.06^{d}	1.07±0.11^{a}	5.30±0.38^{a}	210.61±19.04^{de}

NC= normal control DC= diabetic control DT10=diabetic rats treated with 10 mg/kg bw of tofacitinib DT20=diabetic rats treated with 20 mg/kg bw of tofacitinib DA100= diabetic rats treated with 200 mg/kg bw of aspirin; DA200= diabetic rats treated with 200 mg/kg bw DA1T1= diabetic rats treated with combination of 100 mg/kg bw aspirin/ 10 mg/kg bw tofacitinib DA2T2= diabetic rats treated with combination of 200 mg/kg bw aspirin/ 20 mg/kg bw tofacitinib A2T2NR= normal rats treated with combination of 200 mg/kg bw aspirin/ 20 mg/kg bw tofacitinib; DMET= diabetic rats treated with 850 mg/kg bw of metformin. The results are expressed as the mean ± SE. Different alphabets indicate significant differences (Tukey's-HSD multiple range *post hoc* test, P<0.05)

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CONFLICT OF INTEREST

There is no conflict of interest

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