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FASTING LIPID PROFILE AND ITS ASSOCIATION WITH THE RISK OF DIABETIC FOOT ULCERS IN TYPE 2 DIABETES MELLITUS.

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ABSTRACT

BACKGROUND: Diabetic foot ulcer is the leading micrcirculatory complication of type 2 diabetes mellitus (T2DM) and is considered a significant factor leading to lower limb amputation.

Objective: To evaluate the fasting lipid profile and its association with the risk of diabetic foot ulcers in individuals with T2DM. **METHODS:** A comparative cross-sectional study was carried out at Baqai Medical University from June 2023 to 2024. A total of 138 participants were grouped into healthy controls, T2DM, and foot ulcer in diabetic patients, enrolled via convenience sampling. The median values of three groups were analyzed using one-way ANOVA technique and the Kruskal-Wallis test for parameters that were not normally distributed. Post hoc analysis was performed with Dunnett's T3 test for variables with significant ($p<0.05$) differences, and risk assessment was conducted based on 95% confidence intervals and odds ratio. SPSS version 23 was used for gathering and evaluating the data. **RESULTS:** The median fasting lipid profiles differed significantly among the three groups ($p<0.01$). Low-density lipoproteins (LDL), triglycerides (TG), and very low-density lipoproteins (VLDL) did not show significant differences ($p>0.05$) among the all three groups, according to Dunnett's T3 test for multiple comparisons. However, significant association ($p<0.05$) existed between cholesterol and HDL levels. Among these parameters TG, HDL, and VLDL were significantly associated with risk in T2DM, and serum cholesterol, TG, HDL, LDL, and VLDL showed significant risk association for DFUs with $p<0.05$ by using Multinomial Logistic Regression. **CONCLUSION:** The results of this research showed a significant association of fasting lipid profile components (TG, HDL, VLDL) with T2DM, and plasma fat, TG, HDL, LDL, and VLDL with DFUs.

KEY WORDS: T2DM, DFU, lipid, triglyceride, low-density lipoprotein, very low-density lipoproteins.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease that impairs the pancreas's ability to produce insulin and/or its effectiveness on tissue cells. It is characterized by hyperglycemia, which significantly contributes to global illness and death. Persistent high blood sugar levels are a major driver of vascular complications, including both microvascular and macrovascular

damage[1]. T2DM currently affects 537 million people aged 20 to 79. By 2030, this number is projected to rise to 643 million, affecting one in ten individuals. Every ten seconds, more than three new cases of type 2 diabetes are diagnosed. The global count is expected to surpass 783 million by 2045. The International Diabetes Federation (IDF) estimates that 30.8% of Pakistani adults aged 20 to 79 have diabetes, and by 2025, that figure is expected to reach 11.5 million cases. Diabetic foot ulcers (DFUs) will occur in about 15% of the 150 million people with diabetes worldwide[2]. DFUs severely impact quality of life, increase health risks, and impose heavy financial burdens on families, individuals, and healthcare systems. Amputation is a serious complication of T2DM[3]. The risk of lower limb amputation is 10–30 times higher in patients with T2DM patients than those without the disease. Every 30 seconds, a lower limb is lost globally due to diabetes-related complications. People with type 2 diabetes account for nearly 80% of non-traumatic lower limb amputations. The foot ulcers are a common devastating complication that often leads to increased morbidity and longer hospital stays. About 1–4% of diabetic patients develop gangrene, possibly requiring amputation. Risk factors for DFUs include peripheral arterial disease (PAD), ischemia, angiopathy (micro- or macrovascular), and peripheral neuropathy[4]. The American Heart Association defines dyslipidemia as triglyceride (TG) levels over 150 mg/dL, high-density lipoprotein (HDL) in males below 40 mg/dL and in females below 50 mg/dL, and total cholesterol above 200 mg/dL. Dyslipidemia damages blood vessel linings, promoting atherosclerosis and diabetic foot problems. In diabetics, dyslipidemia often results from both quantity and quality abnormalities in lipoproteins. Common patterns include high triglycerides and total cholesterol, with low HDL cholesterol. These imbalances foster atherogenic processes that can lead to foot ulcers, infections, tissue damage, gangrene, and ultimately, amputation. Atherosclerosis is main cause of death among diabetics, often presenting as cerebrovascular disease, coronary heart disease, or peripheral vascular disease[5]. T2DM interferes with lipid metabolism, causing abnormal levels of cholesterol, triglycerides, HDL, and LDL. Patients with diabetic foot ulcers (DFUs) often show reduced HDL levels alongside elevated LDL, triglycerides, and total cholesterol. These abnormalities contribute to blood vessel damage and an increased risk of cardiovascular disease[4]. Cell membranes depend on lipids, such as cholesterol and triglycerides, which are also essential for inflammation control and wound healing. Elevated TG, LDL, and total cholesterol are independently associated with diabetic foot ulcers. These lipids can promote atherosclerosis, obstructing flow of blood to the lower extremity and increasing the risk for ulcer formation. An additional critical factor in managing diabetic foot ulcers is wound healing, which can be hindered by dyslipidemia. Dyslipidemia can disrupt angiogenesis—the formation of new blood vessels essential for repairing damaged tissue[6]. Currently, the relationship between fasting lipid profiles and the occurrence of diabetic foot ulcers in T2DM has not been thoroughly studied. This observation study aims to evaluate this relationship and determine whether lipid profiles in patients with T2DM can serve as risk factors for DFUs.

MATERAIL AND METHODS

With permission from BASR and the Ethics Committee, this comparative cross-sectional study was conducted at Baqai Medical University in Karachi over one year, from June 2023 to June 2024. The sample size was determined using the Open EPI sample size calculator version 3.01, resulting in a total of 138 samples. These samples were divided into three groups: 48 individuals with T2DM, 48

Individuals with DFUs, and 48 healthy controls. The inclusion criteria for the study included type 2 diabetic patients of either gender diagnosed for more than five years, individuals with diabetic foot ulcers—regardless of whether they were ischemic or neuropathic—and healthy controls evaluated through fasting blood glucose and hemoglobin A1C (HbA1C) tests. Exclusion criteria included type 1 diabetes mellitus, history of gestational diabetes mellitus, a history of deep venous thrombosis (DVT), or foot ulcers resulting from trauma, as well as patients on medication for dyslipidemia and those unwilling to participate. After obtaining a brief medical history and conducting a clinical examination, informed written consent was secured in accordance with the Helsinki Declaration, and 5 ml of fasting blood samples were collected. Calibration Process: Following the application protocol established by Briogene for lipid profiles, the Indiko Thermoscientific system self-calibrates using a calibrator and quality control materials[10]. Testing Procedure: Spin the sample tube in a centrifuge at 4000 rpm for fifteen minutes. Carefully pour the serum into the sample cup. Select the appropriate test, then add both the control and test calibrator. Start the test and obtain precise control results before proceeding with the samples. After confirming the control findings, place the sample rack into the rotor. Place the sample cup in the rack and select the test again. Start the test and monitor for the results. Record the outcome. For parameters that did not follow a normal distribution, we used the Kruskal-Wallis test and one-way ANOVA to compare median values among the healthy group, individuals with T2DM, and those with DFUs. Dunnett's T3 test was conducted for post hoc analysis to examine variables that showed significant differences ($p < 0.05$), and risk assessment was performed based on 95% confidence intervals and odds ratios (OR). SPSS version 23 was used for gathering and evaluating the data.

RESULTS

Table-1 (A & B) reports the relationship of fasting serum lipid profiles: In the control group, the median (interquartile range, IQR) for cholesterol was 175 (41), for triglycerides 104.5 (69), for HDL-cholesterol 45 (14), for LDL-cholesterol 106 (43), and for VLDL-cholesterol 167.5 (57). In the diabetic group, median (IQR) values were 167.5 (57) for cholesterol, 151 (91) for triglycerides, 42.5 (10) for HDL-cholesterol, 108 (60) for LDL-cholesterol, and 30.2 (18.2) for VLDL-cholesterol. In the ulcer group, median (IQR) values were 142.5 (58.5) for cholesterol, 142.5 (86.5) for triglycerides, 122 (12.5) for HDL-cholesterol, 82 (38) for LDL-cholesterol, and 24.4 (17.3) for VLDL-cholesterol. The Kruskal-Wallis test indicated significant differences among all three groups regarding cholesterol, TG, HDL, LDL, and VLDL levels ($p < 0.01$) see Table 1 (A). However, Dunnett's T3 test revealed no significant differences between the DFUs and T2DM groups in triglyceride levels ($p = 0.82$), LDL levels ($p = 0.99$), or VLDL levels ($p = 0.82$). In contrast, all other group comparisons demonstrated statistical significance ($p < 0.05$) see Table 1 (B).

Table- 1 (A) Relationship of fasting serum lipid profile in study participants.

Parameters	Healthy (n=46)		T2DM (n=46)		DFUs (n=46)	p-value
Cholesterol	175	(153-194)	167.5	(147-204)	142.5 (116-174.5)	<0.01*
TG	104.5	(82-151)	151	(117-208)	122(99.5-186)	<0.01*
HDL-cholesterol	45	(42-56)	42.5	(37-47)	32(28-40.5)	<0.01*
LDL	106	(89-132)	108	(78-138)	82(67-105)	<0.01*
VLDL	21.7	(16.4-32)	30.2	(23.4-41.6)	24.4(19.9-37.2)	<0.01*

* Statistical significant< 0.05 p-value, *p-value <0.05 in post hoc analysis.

Table- 1 (B)- POST HOCK ANALYSIS OF FASTING SERUM LIPID PROFILE IN STUDY PARTICIPANTS

Dependent Variable	(I)Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% C I Lower Bound	Upper Bound
Cholesterol	Healthy	Diabetic	4.93478	9.51504	.862	-17.6182	27.4877
	Healthy	Ulcer	20.83498	9.62256	.081	-1.9728	43.6428
	Diabetic	Ulcer	15.90020	9.62256	.228	-6.9076	38.7080
TG	Healthy	Diabetic	-56.84783*	17.48258	.004	-98.2858	-15.4099
	Healthy	Ulcer	-46.25692*	17.68013	.027	-88.1631	-4.3507
	Diabetic	Ulcer	10.59091	17.68013	.821	-31.3153	52.4971
HDL	Healthy	Diabetic	4.93478*	1.94450	.033	.3258	9.5437
	Healthy	Ulcer	13.64032*	1.96648	.000	8.9793	18.3013
	Diabetic	Ulcer	8.70553*	1.96648	.000	4.0445	13.3666
LDL	Healthy	Diabetic	-.86957	7.95283	.993	-19.7197	17.9806
	Healthy	Ulcer	22.28162*	8.04270	.017	3.2185	41.3448
	Diabetic	Ulcer	23.15119*	8.04270	.013	4.0880	42.2143
VLDL	Healthy	Diabetic	-10.43043*	3.50579	.010	-18.7400	-2.1209
	Healthy	Ulcer	-8.31225	3.54541	.053	-16.7157	.0912
	Diabetic	Ulcer	2.11818	3.54541	.822	-6.2853	10.5217

Statistical significant< 0.05 p-value, Post hoc analysis using Tukey's HSD test.

Table-2 reports the findings of Risk Assessment using Multinomial Logistic Regression with fasting serum lipid profile in study participants, showing that a higher level of plasma fat was associated with a lower likelihood of developing Type 2 Diabetes Mellitus (T2DM) (Odds Ratio OR = 0.99, Confidence Interval CI: 0.98-1.00. In contrast, there was a higher likelihood of elevated triglycerides in individuals with T2DM (OR = 1.00), {C.I.: 1.00-1.01} and a lower likelihood of high-density lipoprotein levels (OR = 0.94), {C.I.: 0.90-0.99}. There was also a higher likelihood of low-density lipoprotein levels (OR = 1.00), {C.I.: 0.99-1.01} and very-low-density lipoprotein levels (OR = 1.05), {C.I.: 1.01-1.09}. Similarly, the data indicated a decrease in the likelihood of DFUs (OR = 0.98), {C.I: 0.97-0.99}, an increase in triglycerides (OR = 1.01), {C.I: 1.00-1.01}, a decrease in high density lipoprotein levels (OR = 0.84), {C.I: 0.78-0.89}, a reduction in low density lipoproteins levels (OR = 0.98), {C.I: 0.97-0.99}, and an increase in very low density lipoprotein levels (OR = 1.04), {C.I: 1.01-1.08}. Among these variables TG, HDL, VLDL were significant likelihood variables for T2DM and with plasma cholesterol, TG, HDL, LDL, and VLDL were found to be significant likelihood variables for DFUs with $p<0.05$ by using Multinomial Logistic Regression.

Table 2 Risk Assessment Using Multinomial Logistic Regression with fasting serum lipid profile in study participants.

Variables	T2DM OR (95% C.I)	DFUs OR (95% C.I)
Cholesterol	0.99 (0.98-1.00)	0.98* (0.97-0.99)
TG	1.0* 1(1.00-1.01)	1.01* (1.00-1.01)
High density lipoprotein	0.94* (0.90-0.99)	0.84* (0.78-0.89)
LDL	1.00 (0.99-1.01)	0.98* (0.97-0.99)
VLDL	1.05* (1.01-1.09)	1.04* (1.01-1.08)

* Statistical significant< 0.05 p-value.

DISCUSSION

The study aimed to assess the fasting lipid profile and its association with the development of foot ulcers in people with T2DM. The T2DMS is a chronic metabolic disorder caused by endocrine dysfunction, which presents multiple challenges worldwide. One of its common side effects is microangiopathy, which includes both microvascular and macrovascular issues. The DFUs are a severe microvascular complication significantly impacting patients' health and quality of life, leading to recurrent hospital stays, high costs, and psychological stress for patients and their families. Compared to individuals without diabetes, those with diabetes are twice as likely to develop lower limb conditions such as foot ulcers, neuropathy, and amputations—affecting 30% of those over 40 years old[10]. There is growing awareness of the links among diabetic foot ulcers, neuropathy, dyslipidemia, and atherosclerosis, which extend beyond just cardiovascular problems. Atherosclerosis, peripheral neuropathy, and DFUs share similar risk factors and mechanisms of action[11]. Dyslipidemia contributes to the overlapping onset and progression of these microvascular and macrovascular complications in diabetic patients. More research is needed on this parameter, as, despite extensive studies on this association, information remains limited regarding the significance of the lipid profile in DFUs. The diabetic dyslipidemia is characterized by a triad of increased TG, elevated LDL, and decreased HDL-C levels—common lipoprotein metabolism disorders associated with T2DM[12]. The levels of VLDL, LDL, triglycerides, and others did not show significant ($p > 0.05$) differences among healthy individuals, T2DM patients, and those with DFUs in this study Table 1-A. These findings contrast with existing literature that often reports alterations in lipid profiles, including triglycerides, LDL, and VLDL, in diabetes and its complications[13]. Similar to our findings, other studies also found no Significant associations ($p > 0.05$) between lipid levels across diabetic foot ulcer patients[15,16]. However, total cholesterol levels showed a significant ($p<0.05$) difference among healthy, T2DM, and DFU groups. Consistent with our results, several studies reported a significant association ($p<0.05$) of cholesterol values among these groups[17,18]. This study also found significant associations ($p<0.05$) between cholesterol and HDL-cholesterol across participants, which has important implications for managing lipid-related disorders in diabetes and DFUs. The association between cholesterol and HDL may be influenced by factors such as insulin resistance, hyperglycemia, and inflammation, all of which impact lipid metabolism. This highlights the complex relationship between cholesterol and HDL as a cardiovascular risk factor and the importance of developing tailored treatment plans for individuals with T2DM and DFU[19,20,21]. Using Multinomial Logistic Regression, triglycerides (TG), HDL, and VLDL were significantly associated with the risk of developing T2DM ($p<0.05$) (Table 2). Similar observations were expressed by Hernández et al. for TG, Zhao et al. for HDL, and Skeie et al. for VLDL (20, 21, 22). These lipid parameters—TG, HDL, and VLDL—are closely associated with pathogenesis to the development of T2DM, mainly through insulin resistance and metabolic syndrome. Additionally, Multinomial Logistic Regression showed that serum cholesterol, triglycerides, HDL, LDL, and VLDL had a significant association with the risk of DFUs ($p<0.05$), emphasizing the critical role of dyslipidemia in the etiology and progression of DFUs. This supports the broader understanding that metabolic dysfunction significantly contributes to DFU development. A study by Zhang et al. (2014) found that diabetic patients with DFUs had significantly higher levels of

LDL, total cholesterol, and triglycerides compared to those without ulcers[22]. Jiang et al. (2022) identified triglycerides and HDL-C as key risk factors in DFU pathogenesis[23].

CONCLUSION

This research highlights a profound association of abnormal lipid profile with T2DM and DFUs, particularly elevated LDL and triglycerides, and decreased HDL. The early assessment of diabetes risk through metabolic and family history, targeted lifestyle changes, and regular lipid monitoring can significantly prevent complications, and paving the way for targeted therapeutic strategies for preventing the complications in healthy, T2DM, and in DFU patients.

ETHICS APPROVAL: The ERC gave ethical review approval. **BMU-EC/01-202323/02/2023**

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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AUTHORS' CONTRIBUTIONS:

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

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