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Correlation Between Lipid Profile and Diabetic Foot Complications in Patients with Uncontrolled Diabetes (HbA1c > 6.5%)

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Abstract: ***Background: Diabetic foot complications are a significant cause of morbidity in patients with uncontrolled diabetes. Lipid profile abnormalities, particularly low high-density lipoprotein cholesterol (HDL), have been suggested to contribute to the development of diabetic foot ulcers. This study aimed to investigate the correlation between lipid profile abnormalities, particularly HDL, and the presence of diabetic foot complications in patients with uncontrolled diabetes (HbA1c > 6.5%). Methods: This cross-sectional study included 99 participants, comprising 49 cases with diabetic foot complications and 50 controls without foot complications. Data were collected on demographic characteristics, HbA1c levels, and lipid profile parameters (total cholesterol, triglycerides, HDL, LDL, and VLDL). Statistical analyses included descriptive statistics, Wilcoxon rank-sum test, Fisher's exact test, Pearson's Chi-squared test, and logistic regression to assess associations between clinical and biochemical parameters and diabetic foot complications. Bayesian analyses were also performed for supplementary insights. Results: Cases had significantly higher HbA1c levels (median 8.80%) and lower HDL levels (median 23 mg/dL) compared to controls (HbA1c median 7.20%, HDL median 45 mg/dL). Logistic regression revealed that higher HbA1c (OR: 1.47) and lower HDL (OR: 0.38) were significantly associated with diabetic foot complications. Other lipid parameters (TCHOL, TG, LDL, and VLDL) showed no significant differences. A negative correlation was observed between HbA1c and HDL levels (Pearson's r = -0.281, p = 0.00489). Conclusion: Higher HbA1c and lower HDL cholesterol levels are significantly associated with diabetic foot complications in patients with uncontrolled diabetes. These findings highlight the importance of managing both glycaemic control and lipid profiles, particularly HDL, to prevent diabetic foot complications. Further longitudinal studies are needed to confirm these findings and explore potential therapeutic strategies targeting lipid metabolism in diabetic foot care.***

Keywords: Diabetes Mellitus, Type 2, Diabetic Foot Ulcer, Diabetic Foot Complications, High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), Dyslipidaemia, Glycated Haemoglobin A (HbA1c), Poor Glycaemic Control, Diabetes-Related Morbidity

1. Study Objectives

1) **Primary Objective**: To evaluate the correlation between lipid profile (specifically LDL and HDL cholesterol) and the incidence of diabetic foot ulcers in patients with uncontrolled diabetes (HbA1c > 6.5%).
2) **Secondary Objectives**:
   - To assess the association of lipid profile abnormalities (low HDL, high LDL) with the severity of diabetic foot ulcers.
   - To determine if controlling lipid levels can reduce the incidence or severity of diabetic foot ulcers in diabetic patients.

2. Justification for the Study

Diabetes mellitus (DM) refers to a group of metabolic disorders that lead to hyperglycemia due to either insulin resistance, inadequate insulin secretion, or both. In 2013, approximately 382 million individuals were diagnosed with diabetes, and it is projected that this number will rise to 592 million by 2035.

Chronic complications of diabetes are often classified as microvascular and macrovascular, based on the underlying pathophysiological mechanisms. Microvascular complications, which include retinopathy, nephropathy, and neuropathy, have significant impacts on the quality of life of diabetic patients. Specifically, diabetic foot, a common complication of neuropathy, is associated with vascular changes and poor wound healing.

Studies have shown that dyslipidaemia, characterized by high levels of LDL cholesterol and low levels of HDL cholesterol, can exacerbate diabetic complications, including diabetic foot ulcers. This study aims to explore the correlation between lipid profile (specifically LDL and HDL levels) and the incidence of diabetic foot ulcers in patients with uncontrolled diabetes (HbA1c > 6.5%).

Understanding this correlation is crucial, as it could potentially provide insights into preventive and therapeutic strategies for diabetic foot complications, which are a significant cause of morbidity and disability in diabetic patients.

Expected Outcomes:
This study is expected to reveal a significant correlation between the incidence and severity of diabetic foot ulcers and lipid profile abnormalities (particularly low HDL and high LDL levels) in patients with uncontrolled diabetes. The findings may contribute to developing targeted therapeutic strategies that focus not only on controlling blood glucose but

also on managing dyslipidaemias to prevent diabetic foot complications.

3. Methods

Data were summarized using descriptive statistics. Continuous variables were reported as medians with interquartile ranges (IQR) due to non-normal distributions, while categorical variables were summarized as frequencies and percentages. Group comparisons for continuous variables were performed using the Wilcoxon rank-sum test, and categorical variables were compared using Fisher's exact test or Pearson's Chi-squared test, as appropriate. The primary outcome was the presence of diabetic foot complications (case group) compared to controls, and statistical significance was set at **$p < 0.05$**.

Associations between clinical and biochemical parameters and the presence of diabetic foot complications were evaluated using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). Pearson correlation coefficients were calculated to assess relationships between continuous variables, and their significance was tested. Effect sizes, including Hedges' **g** for continuous variables and odds ratios for categorical predictors, were computed to quantify differences between groups. Bayesian analyses were also conducted to complement traditional inferential methods, providing estimates and credible intervals for group differences and correlations. All statistical analyses were performed using **R version 4.2.2**.

4. Results

Participant Characteristics

A total of 99 participants were included in the study, comprising 49 cases (patients with diabetic foot complications) and 50 controls (patients without diabetic foot complications). The demographic and clinical characteristics of the participants are summarized in **Table 1**.

a) **Diagnosis**: Among the cases, 20% had Left Diabetic Foot-I, 8.2% had Left Diabetic Foot-II, 14% had Left Diabetic Foot-III, 24% had Right Diabetic Foot-I, 27% had Right Diabetic Foot-II, and 6.1% had Right Diabetic Foot-III. In contrast, all 50 controls were free of diabetic foot conditions (**$p < 0.001$**).
b) **Sex**: The distribution of sex did not differ significantly between the case and control groups (**$p = 0.7$**). 76% of cases and 72% of controls were male.
c) **Age**: The median age was similar across groups (**$p = 0.7$**), with a median of 60 years (IQR: 53–66) for cases and 60 years (IQR: 53–69) for controls.
d) **Duration of Diabetes Mellitus (DM)**: Cases had a significantly shorter duration of DM (**$p < 0.001$**) compared to controls. The median duration for cases was 0.0 years (IQR: 0.0–0.0), while for controls, it was 3.5 years (IQR: 0.8–10.0).

Biochemical Parameters

a) **HbA1c**: Cases had significantly higher HbA1c levels (**$p = 0.001$**). The median HbA1c for cases was 8.80% (IQR: 7.00–11.20), while for controls, it was 7.20% (IQR: 6.80–8.30). The odds of diabetic foot complications increased with higher HbA1c (OR: 1.47; 95% CI: 1.19–1.87; **$p < 0.001$**).
b) **Lipid Profile**:
   - **HDL**: Cases exhibited markedly lower HDL levels (**$p < 0.001$**), with a median of 23 mg/dL (IQR: 19–30) compared to controls with a median of 45 mg/dL (IQR: 42–49). Lower HDL was significantly associated with an increased likelihood of diabetic foot complications (OR: 0.38; 95% CI: 0.14–0.61; **$p = 0.007$**).
   - **Other Lipid Parameters** (Total Cholesterol [TCHOL], Triglycerides [TG], VLDL, and LDL) showed no significant differences between groups (**$p > 0.2$** for all).

Correlation and Effect Sizes

a) **HDL and HbA1c Correlation**: A significant negative correlation was observed between HDL levels and HbA1c (Pearson's r = -0.281; **$p = 0.00489$**), suggesting that poor glycaemic control is associated with lower HDL levels.
b) **Group Comparisons**:
   - Bayesian analyses revealed a significant difference in HDL between the groups, with an estimated difference of -23.1 mg/dL (95% CI: -26.7, -19.7; **$p < 0.001$**; Hedges' g = -2.61).
   - HbA1c levels were significantly higher in cases, with an estimated difference of 1.41% (95% CI: 0.61, 2.19; **$p < 0.001$**; Hedges' g = 0.75).

5. Summary of Key Findings

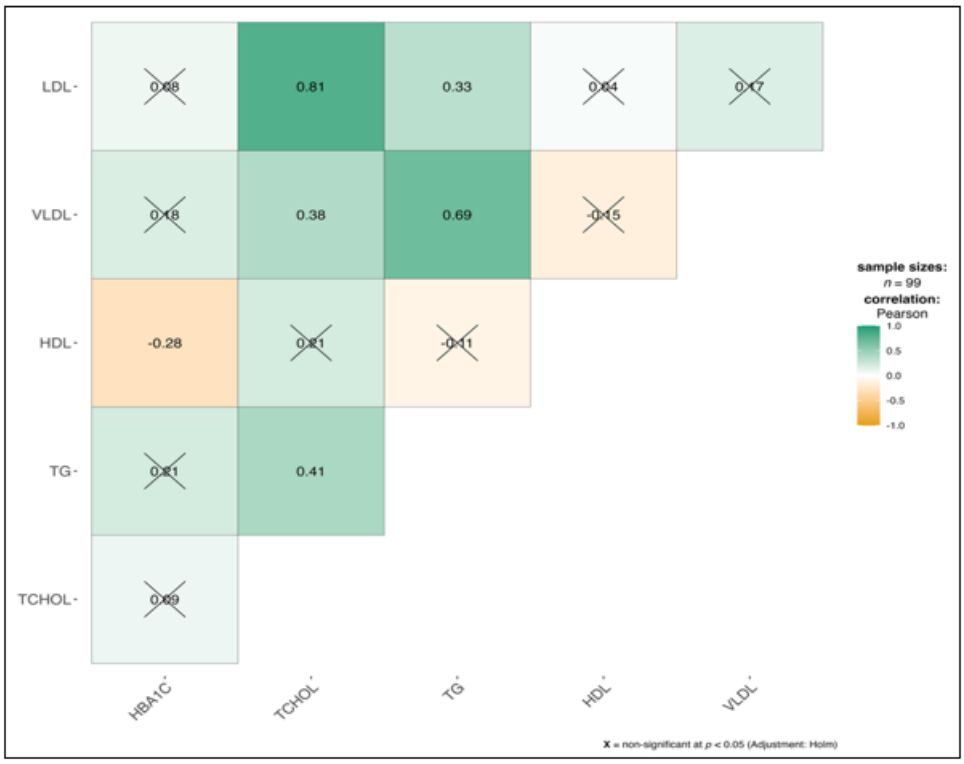
- Higher HbA1c levels and lower HDL levels were significantly associated with the presence of diabetic foot complications.
- Age, sex, and other lipid profile components (TCHOL, TG, VLDL, LDL) were not significant predictors of diabetic foot complications.

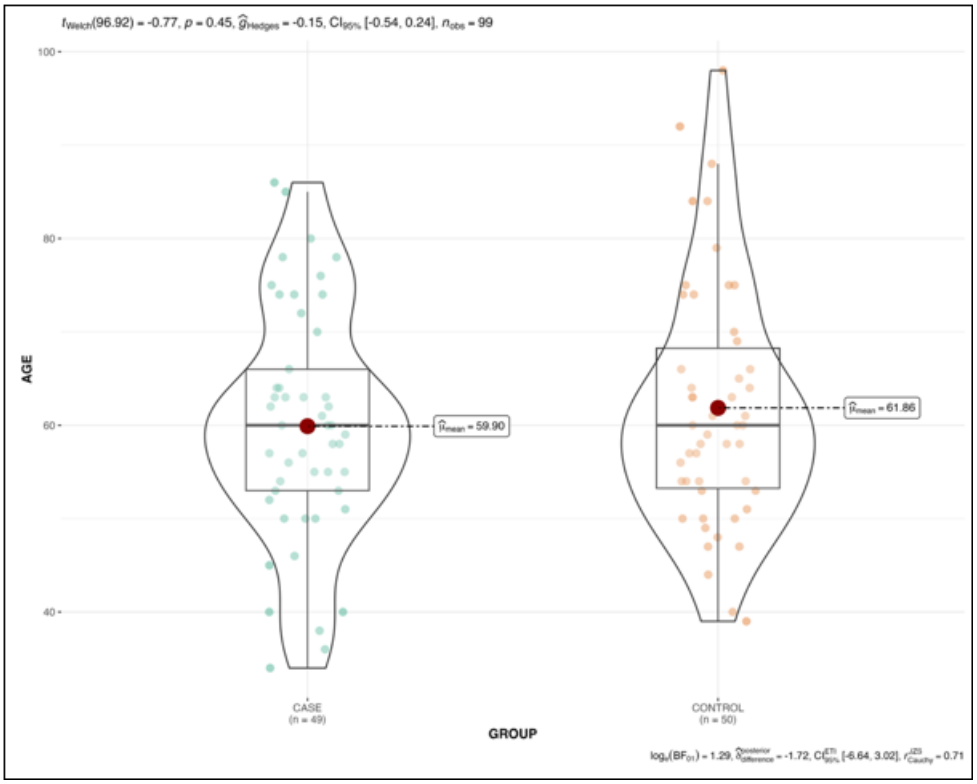
Table 1: Descriptive Statistics

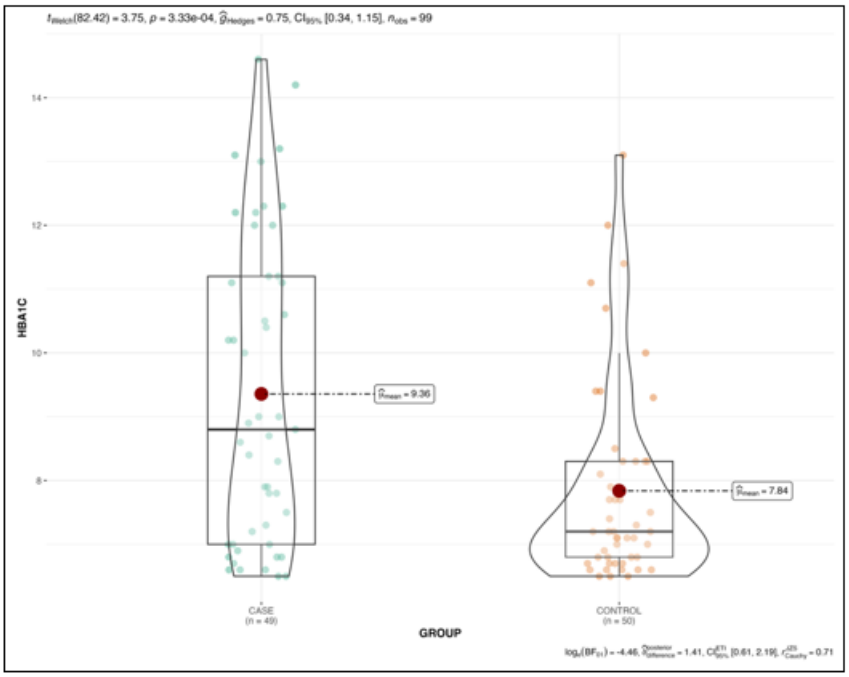
Characteristic	Overall (N = 99)	Case (N = 49)	Control (N = 50)	p-value
Diagnosis				<0.001
Control	50 (51%)	0 (0%)	50 (100%)	
LT Diabetic Foot - I	10 (10%)	10 (20%)	0 (0%)	
LT Diabetic Foot - II	4 (4%)	4 (8.2%)	0 (0%)	
LT Diabetic Foot - III	7 (7.1%)	7 (14%)	0 (0%)	
RT Diabetic Foot - I	12 (12%)	12 (24%)	0 (0%)	
RT Diabetic Foot - II	13 (13%)	13 (27%)	0 (0%)	
RT Diabetic Foot - III	3 (3%)	3 (6.1%)	0 (0%)	
Sex				**0.7**
Female	26 (26%)	12 (24%)	14 (28%)	

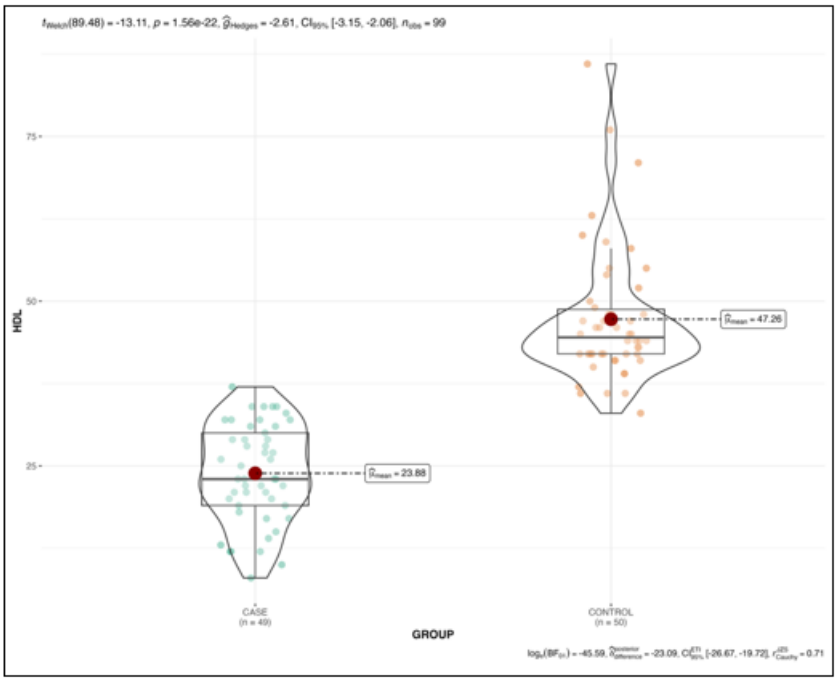
Male	73 (74%)	37 (76%)	36 (72%)	
Age (median, IQR)	60 (53–69)	60 (53–66)	60 (53–69)	**0.7**
Duration of DM (median, IQR)	0.1 (0.0–4.0)	0.0 (0.0–0.0)	3.5 (0.8–10.0)	**<0.001**
HbA1c (median, IQR)	7.80% (6.80–10.20%)	8.80% (7.00–11.20%)	7.20% (6.80–8.30%)	**0.001**
TCHOL (median, IQR)	126 (102–159)	126 (101–147)	126 (112–178)	**0.2**
TG (median, IQR)	103 (81–166)	103 (82–163)	115 (76–166)	**0.8**
HDL (median, IQR)	36 (23–45)	23 (19–30)	45 (42–49)	**<0.001**
VLDL (median, IQR)	24 (18–39)	27 (18–40)	24 (18–34)	**0.4**
LDL (median, IQR)	69 (42–90)	75 (49–89)	64 (39–96)	**0.5**

Values presented as number (%); Median (Q1, Q3). Statistical significance was determined using Fisher's exact test, Pearson's Chi-squared test, and Wilcoxon rank-sum test, as appropriate.






HBA1C
14
12
10
8
9.36
7.84
CASE
(n = 49)
CONTROL
(n = 50)
GROUP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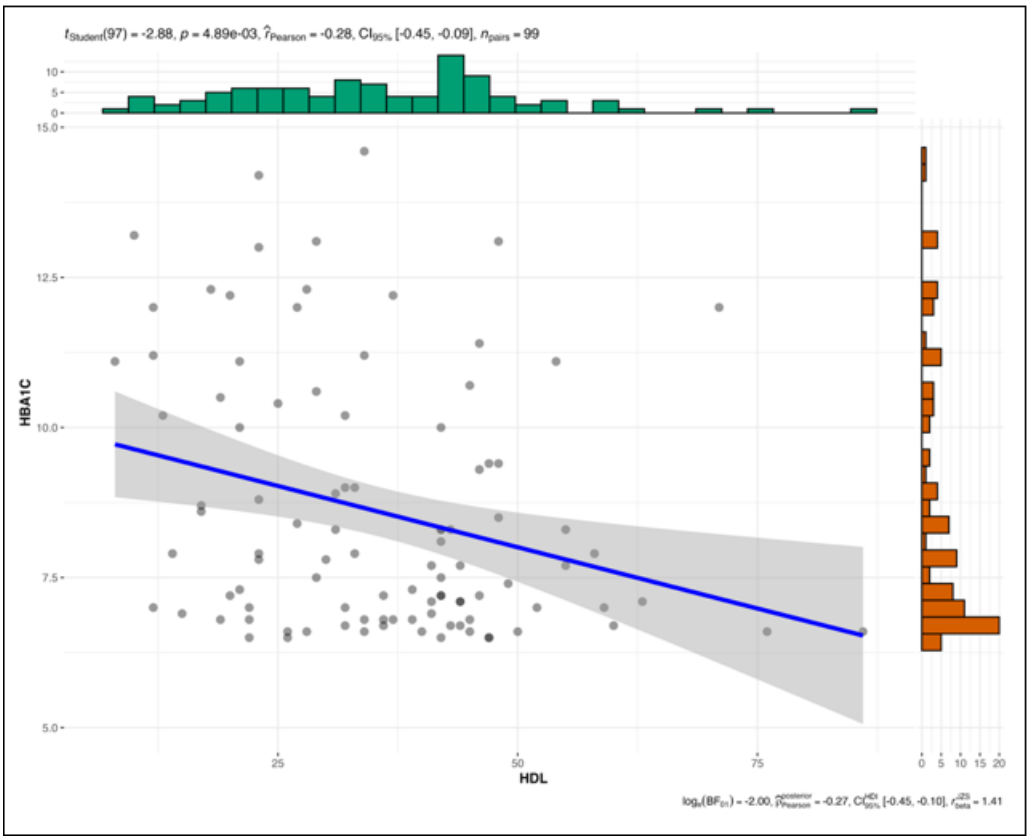
50
25
47.26
23.88
CASE
(n = 49)
CONTROL
(n = 50)
GROUP



6. Discussion

This study aimed to evaluate the correlation between lipid profile abnormalities and the presence of diabetic foot complications in patients with uncontrolled diabetes. The primary findings of this study suggest that high HbA1c levels and low HDL cholesterol are significantly associated with the development of diabetic foot complications, while other lipid parameters (LDL, TCHOL, TG, and VLDL) were not significant predictors.

HbA1c and Diabetic Foot Complications

Our findings show that higher HbA1c levels were strongly associated with an increased risk of diabetic foot complications. The median HbA1c for cases was significantly higher than for controls, and the odds ratio for the occurrence of diabetic foot complications increased with higher HbA1c levels. This is consistent with previous studies which have highlighted the importance of good glycaemic control in preventing complications, including diabetic foot ulcers. Poor glycaemic control is known to contribute to neuropathy, impaired wound healing, and microvascular damage, all of which are critical factors in the development of diabetic foot complications. Our results support the need for tighter glycaemic control in diabetic patients, as recommended by clinical guidelines for the prevention of diabetic complications.

Lipid Profile and Diabetic Foot Complications

A key finding of this study was the significant association between lower HDL cholesterol levels and the presence of diabetic foot complications. Cases had markedly lower HDL levels compared to controls, and this finding was statistically significant. Lower HDL levels have been associated with increased cardiovascular risk, and more recently, studies have shown that low HDL can impair wound healing and promote inflammation, both of which are crucial in the pathogenesis of diabetic foot ulcers.

In contrast, other lipid parameters, including total cholesterol (TCHOL), triglycerides (TG), VLDL, and LDL, showed no significant differences between the groups. This finding suggests that HDL may play a more central role in the development of diabetic foot complications than other components of the lipid profile, at least in the context of uncontrolled diabetes. The negative correlation between HDL levels and HbA1c observed in our study further reinforces the link between poor glycemic control and altered lipid metabolism, specifically low HDL levels.

7. Strengths and Limitations

The strengths of this study include its well-defined patient population, the use of comprehensive biochemical analysis, and the statistical methods employed, such as Bayesian analyses and logistic regression, to evaluate associations between variables. These methods provided robust results and strengthened the conclusions drawn.

However, there are several limitations. The study design was cross-sectional, meaning that causal relationships between lipid profile abnormalities and diabetic foot complications cannot be definitively established. Additionally, while we focused on the lipid profile as a potential factor, other unmeasured factors, such as inflammatory markers or genetic predispositions, could also contribute to the development of diabetic foot complications. Future studies with longitudinal designs are needed to confirm the temporal relationship and causality.

8. Implications for Practice

The findings of this study suggest that managing both blood glucose levels and lipid profiles, particularly HDL levels, could be crucial in preventing diabetic foot complications. Clinicians should consider monitoring lipid profiles alongside glycaemic control in diabetic patients, particularly those at risk for foot complications. Interventions aimed at raising HDL levels, such as lifestyle modifications and pharmacologic therapies, may be beneficial in reducing the incidence and severity of diabetic foot ulcers. However, further research is needed to explore the potential for targeted therapies aimed at improving lipid metabolism in this patient population.

9. Conclusion

In conclusion, this study demonstrates a significant association between high HbA1c levels and low HDL cholesterol with the presence of diabetic foot complications in patients with uncontrolled diabetes. These findings highlight the importance of managing both glycaemic control and lipid abnormalities in preventing diabetic foot ulcers. Given the lack of significant associations with other lipid parameters, future research should focus on the specific role of HDL in the pathogenesis of diabetic foot complications and explore potential therapeutic strategies targeting lipid metabolism. This study provides a foundation for future investigations into the complex interplay between glycaemic control, lipid metabolism, and diabetic complications, with the ultimate goal of improving patient outcomes in those with diabetes.

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