ORIGINAL RESEARCH REPORT

The HDL Level in Diabetic Foot Ulcer Patients with and without Amputation at Dr. Soetomo General Academic Hospital Surabaya

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ABSTRACT

Background: Diabetic foot ulcers (DFU) are microvascular and macrovascular consequences of diabetes and are associated with neuropathy, vascular disease, and immunosuppression. Increased blood glucose levels may result in the glycosylation of proteins in the nerve cells of the foot, leading to ischemia and cellular disturbances that can damage muscular, sensory, and autonomic neurons. **Objective:** To compare the lipid profiles of amputated and non-amputated DFU patients. **Material and Method**: This was a cross-sectional, analytic, retrospective research using total sample approach to analyze the medical records of all diabetes patients admitted to Dr. Soetomo General Academic Hospital between February 2018 and December 2020, with or without amputation. **Result:** The average age of DFU patients at Dr. Soetomo General Academic Hospital was 55.6 9.4 years, and the majority of patients were female (57%). Diabetic foot ulcers were most prevalent in the age group ≥50 years old (74%), amputated DFU patients had larger mean total cholesterol, TG, LDL, and HDL than non-amputated DFU patients, although the difference was not statistically significant. While the mean LDL/HDL ratio was greater in non-amputated DFU patients, the difference was statistically insignificant. The HDL level was low in 84% of amputated DFU patients, whereas in non-amputated DFU patients it was 81%. **Conclusion:** This research showed no significant variation in total cholesterol, TG, LDL, HDL, or the LDL/HDL ratio between amputated and non-amputated DFU patients. Most DFU patients with and without amputations had low HDL values.

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Highlights

1. Diabetes mellitus is a category of metabolic disease characterized by uncontrolled hyperglycemia.
2. This study revealed no statistically significant differences in total cholesterol, TG, LDL, HDL, or LDL/HDL ratio between amputated and non-amputated DFU patients.

BACKGROUND

Diabetes mellitus is a group of metabolic illnesses defined by the presence of untreated hyperglycemia. The diverse etiopathology includes abnormalities in insulin production, insulin action, or both, and problems in carbohydrate, lipid, and protein metabolism (World Health Organization, 2019). Diabetes mellitus (DM) is a global issue whose incidence is rising globally. Morbidity and mortality of diabetes induced by microvascular and metabolic factors. Moreover, macrovascular problems are more prevalent (Romadhon., et al. 2019). Diabetes is a metabolic condition characterized by high levels of blood glucose. Uncontrolled hyperglycemia might result in complications such as diabetic foot (Dewi., et al. 2020). Diabetes foot ulcers are the most widespread and serious diabetes complications. These ulcers are linked to an increased risk of mortality, morbidity, and foot amputation (Jarl, et al., 2019).

DFU is one of the most frequent consequences of diabetes. Amputation is 10 to 20 times more prevalent among diabetics compared to non-diabetics, and it is estimated that a lower leg is amputated partially or entirely every 30 seconds worldwide (International Diabetes Federation, 2021).

Diabetes mellitus pathophysiology is characterized by neuropathy, vasculopathy, and immunosuppression. Increased blood glucose levels may result in the glycosylation of proteins in the nerve cells of the foot, leading to ischemia and cellular disturbances that can damage muscular, sensory, and autonomic neurons. As the sensory and motor function of the foot deteriorates, the risk of infection, skin ulcers, and gangrene increases. Immune changes in diabetic foot ulcers (DFU) will impede the healing process (Aumiller & Dollahite, 2015). Infections may increase the likelihood of amputations, disability, extended hospitalization, and mortality in diabetic patients (Bekele & Chelkeba, 2020).

Due to the high expense of treatment and care, DFU patients suffer stigma, job loss, social isolation, unhappiness with their body image, and a loss of productivity (Atosona & Larbie, 2019). To avoid these health and social issues, we must identify the risk factors for DFU as well as preventative measures against its sequelae. Age, male gender, lipid abnormalities, hypertension, neuropathy, nephropathy, poor glycemic control, white blood cell count, and ulcer size are risk factors for amputation in diabetic patients (Namgoong, et al., 2016).

Cardiovascular disease (CVD) accompanied by dyslipidemia and atherogenic disorders is common in individuals with type 2 diabetes. Dyslipidemia is one of the most common risk factors for DFU (Shankarprasad, et al., 2015). High total cholesterol (T Chol), high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and elevated levels of tiny dense LDL particles are characteristic of diabetes individuals with lipid abnormalities, often known as "diabetic dyslipidemia." Additionally, low-density lipoprotein cholesterol (LDL-C) levels may rise or remain constant (Bhowmik, et al., 2018).

According to Pei et al. (2014), low HDL cholesterol levels are associated with diabetes foot, thus, efforts should be made to increase HDL cholesterol levels to avoid diabetic foot. According to Ikura et al. (2015), in patients with DFU, decreased HDL cholesterol levels may be an independent predictor of lower extremity amputation (LEA) and wound-related mortality. A high amount of TG is the most prevalent blood lipid anomaly in diabetes populations, according to another research. Increased TG levels are caused by hyperinsulinemia, not hyperglycemia, which is offset by insulin resistance (Hirano, 2018). While, according to Robbins (2017), dyslipidemia, mainly high LDL and HDL, is considered to have a role in atherogenesis, which may lead to ischemia and ultimately n ecrosis in DFU.

Numerous studies have related lipid profiles to the risk of diabetes mellitus. However, there is less evidence tying the lipid profile of a diabetic foot ulcer to the risk of amputation in the most current literature. Furthermore, not all of those studies are comparable in terms of lipid profiles in diabetics. Knowing the difference between the lipid profiles of amputated and non-amputated diabetic foot ulcer patients is of clinical and public health significance, and such information could form the basis for prevention programs and prognoses for diabetic foot ulcer patients and patients at high risk for amputation in Indonesia.

OBJECTIVE

This study was conducted to compare the difference in the lipid profiles of amputated and non-amputated diabetic foot ulcer patients at the Dr. Soetomo General Academic Hospital in Surabaya.

MATERIAL AND METHOD

This was a cross-sectional, observational, analytic research using the total sampling approach. This study included T2DM patients admitted to inpatient wards at Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, for patients with diabetic foot ulcers with or without amputation hospitalized in the Internal Medicine and Thoracic and Cardiovascular Departments from January 2019 to December 2020. Consideration was given to maintaining the confidentiality of patient-identifiable information.

All DFU patients hospitalized between January 2019 and December 2020 who met the inclusion criteria had full medical records, comprehensive lipid profiles, and patient administration. The exclusion criteria were inadequate or ambiguous information. From the medical record, the age, gender, and lipid profile (total cholesterol, TG, LDL, HDL, and the LDL/HDL ratio) were extracted. The lipid profile utilized in this study was the most recent lipid profile found in the medical records of patients admitted to Dr. Soetomo General Hospital Surabaya. Data collected were compiled and presented as mean ± standard deviation analyzed using Mann Whitney test with $p<0.05$ considered statistically significant using SPSS.

RESULT

The criteria were met by 202 of the 465 DFU patients admitted between January 2019 and December 2020. Sixty-nine patients (34.2%) of them were amputated, and the other was non-amputated (Table 1). The patients generally came in with a mean age of 55.61±9.48 years old. The youngest patient was 32 years old and the oldest patient was 83 years old, and there were slightly more female patients (57%) than male DFU patients. Patients aged 50 and up were the most common demographic (Table 1).

The mean values of total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein were higher in amputated DFU patients than in the non-amputated group, although they were not statistically significant. However, there was no difference in HDL levels between the two groups. Sixty-six percent of males and 76% of females with amputations had low HDL levels, compared to 85% of males and 78% of females with DFU who did not have amputations (Figure 3).

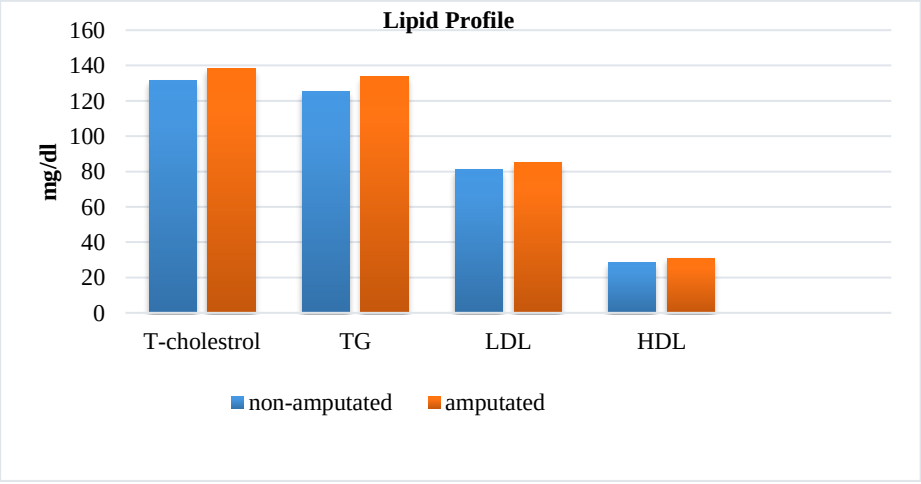

Figure 1. Mean values of lipid profile in non-amputated and amputated DFU patients

The total cholesterol levels of all non-amputated DFU patients were within normal limits while in amputated DFU patients 90% were in normal range (Figure 2). The mean LDL/HDL ratio in non-amputated DFU patients was 3.6, while in patients with amputation it was 3.52 (Figure 2).

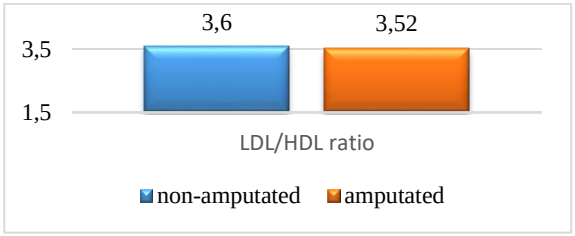

Figure 2. Mean value of LDL/HDL ratio in non-amputated and amputated DFU patients

Table 1. Demographic variables among non-amputated and amputated DFU patients

Variables	Group	Non-amputated frequency	%	Amputated frequency %	%
Gender	Male	60	45%	27	39.4 %
	Female	73	55%	42	60.2 %
Age	< 50 years old	36	27%	16	23 %
	≥ 50 years old	97	73%	53	77 %
Total		133		69	

Triglyceride levels differed between DFU patients with amputated limbs and those without. Twelve percent of non-amputated DFU patients had elevated TG levels, compared to 18% of amputated patients (Figure 3). Figure 3 shows that 58% of DFU patients with and without amputation have an ideal LDL/HDL ratio, whereas 42% of same patients have an elevated LDL/HDL ratio.

Table 2. The range of lipid profile in amputated and non-amputated DFU

Parameters	DFU status	
	133	69
	Non-amputated	Amputated
Total cholesterol (mg/dl)		
Normal range <200	133 (100%)	63 (90%)
Borderline 200-239	0	3(5%)
High ≥ 240	0	3 (5%)
TG (mg/dl)		
Normal range <150	94 (70%)	45 (64%)
Borderline 150-199	25 (18%)	12 (18%)
High ≥ 200	14 (12%)	12 (18%)
LDL (mg/dl)		
Optimal <100	89 (67%)	49 (71%)
Borderline 100-160	44 (33%)	17 (24%)
High ≥ 160	0	3 (5%)
HDL (mg/dl)		
Low <40	108 (81%)	58 (84%)
Borderline 40-59	23 (17%)	5 (7%)
High ≥60	2 (2%)	6 (9%)
LDL/HDL ratio		
Optimal <3.5	78 (58.6%)	40 (58%)
High ≥3.5	55 (41.4%)	29 (42%)

Table 3. The characteristics of lipid profile in amputated and non-amputated DFU

Parameters	Group	N	Mean ± SD	Range	P
Total cholesterol (mg/dl)	Non-amputated	133	131.52 ± 36.23	43-193	0.922
	Amputated	69	138.5 ± 52.4	69-391	
TG (mg/dl)	Non-amputated	133	125.2 ± 64.32	14-543	0.461
	Amputated	69	134 ± 71.1	30-333	
LDL (mg/dl)	Non-amputated	133	81.14 ± 28	14-148	0.899
	Amputated	69	85.2 ± 43.8	14-297	
HDL (mg/dl)	Non-amputated	133	28.6 ± 15	3-106	0.621
	Amputated	69	31 ± 19	6-100	
LDL/HDL ratio (mg/dl)	Non-amputated	133	3.60 ± 2.46	0.54-21.33	0.837
	Amputated	69	3.52 ± 2.27	0.62-11.29	

The mean LDL for DFU patients with amputation was 85.3 mg/dl, which was higher than the mean LDL for DFU patients without amputation (81.1 mg/dl) but statistically insignificant (Table 3). Most of the DFU patients with amputated legs had below-the-knee amputations, 36% above-the-knee amputations, and 5% had toe amputations.

DISCUSSION

According to the findings, there were more female than male DFU patients. This differed from prior research, such as an Egyptian study in which 67.3% of DFU patients at high risk for amputation were male, whereas 50% of DFU patients at low risk were male (Soliman, et al., 2022).

In our study, the mean age of amputated DFU patients was 56.89±9.1 years old, and the mean age of non-amputated DFU patients was 54.9±9.6 years old. Similar to a research conducted in the United Arab Emirates, diabetics with foot ulcers are more prevalent among those aged 50 to 59 (Manda, et al., 2012), which is similar to our study. In contrast, neither age nor gender were significant predictors of amputation in a Japanese research (Ikura, et al., 2015).

In our study in Indonesia, the total cholesterol, triglyceride, LDL, and HDL differences between the amputated and non-amputated DFU groups were not statistically significant. These findings were consistent with those from other studies. A study in Saudi Arabia detected no relation between the risk for amputation and LDL, triglycerides, or total cholesterol (Musa, et al., 2018). According to a Japanese study, neither triglyceride levels nor LDL cholesterol levels were indicators of the risk of amputation in the future (Ikura, et al., 2015). Moreover, there was no difference in the levels of triglycerides, LDL, or total cholesterol between diabetics with and without ulcers, but only the DFU patients had low HDL levels (Manda, et al., 2012). According to a research conducted in Turkey, TG, total cholesterol, LDL cholesterol, and ox-LDL did not vary significantly between amputated and non-amputated DFU patients (Muhtaroğlu, et al., 2016). There was no significant correlation between diabetic foot and LDL-cholesterol, TC, or TG levels, according to a meta-analysis of case-control studies. This outcome did not match the American Diabetes Association's recommendations (American Diabetes Association, 2012). However, decreased HDL cholesterol was associated with increased risk of developing DFU (Pei, et al., 2014).

According to a study, determining insulin resistance can be done with high accuracy using the low-density lipoprotein/high-density lipoprotein cholesterol ratio (LDL/HDL ratio) (Zhang, et al., 2015). Another study found that the risk of prediabetes is positively connected with an elevated LDL/HDL ratio (Kuang, et al., 2022). All of these results suggested that the LDL:HDL ratio might be a reliable indicator of blood glucose metabolism. However, it is not yet apparent how the LDL/HDL ratio relates to diabetes. Other studies are required to determine the level of the LDL/HDL ratio in amputated and non-amputated DFU patients to determine whether this ratio can be used to predict ulcers in diabetes patients.

Although in our study there was no difference in HDL levels between amputated and non-amputated DFU patients, our study revealed that the HDL level was low in both groups. Low HDL levels were

seen in 96% of males and 76% of females who were amputated patients, while among the non-amputated patients, 85% of males and 78% of females had a low HDL level. Other studies have indicated a substantial association between low HDL cholesterol levels and the prevalence of minor and major extremities amputations and ulcer-related mortality (Ikura, et al., 2015). Nevertheless, a growing body of evidence shows that a lowered blood HDL level is a significant risk factor for the onset of DFU. In particular, other studies in Egypt report that a low HDL level is a predictor for limb amputation in DFU (Soliman, et al., 2022).

The dysfunction of HDL is ultimately caused by a substantial reduction in structural integrity, which has been commonly reported in both malignant and cardiometabolic illnesses (Vekic, et al., 2022). Consequently, HDL functioning and composition should be monitored and evaluated in a wider sense as indications of metabolic alterations associated with a range of clinical illnesses, particularly in DFU patients. HDL stimulates cholesterol outflow from foam cells, hence reducing cholesterol accumulation in atherosclerotic lesions (Zeljkovic, et al., 2021). Glycation and oxidation of apoA-I are increased by prolonged hyperglycemia, and the accumulation of acute phase proteins in HDL is stimulated by a pro-inflammatory state that is often present in diabetic patients (McEneny, et al., 2015). The absence of a significant difference in the lipid profile in amputated and non-amputated DFU patients may be due to earlier treatment for DFUs and good compliance. Most diabetic patients with foot ulcers have one or more of the following risk factors: neuropathy, vascular disease, foot deformity, or peripheral neuropathy. Microvascular disease and inadequate glycemic control are the main factors. Socio-demographic factors appear to be critical in the emergence of diabetic foot ulcers (Khan, et al., 2020). Treatment also plays a big role in reducing the risk of the lipid profile, especially after the patient's diagnosis with DFU. These drugs may include statins, bile acid sequestrants, or fibrates (International Diabetes Federation, 2020). Dyslipidemia is not the only risk factor for amputation. Many factors must be considered in foot amputation, including hypertension, diabetes, chronic renal disease, and smoking (Firnhaber & Powell, 2019), and the main cause of amputation in diabetic individuals is a delay in wound healing. Hyperglycemia, ongoing inflammation, micro- and macrovascular dysfunction, and neuropathy all contribute to the delayed healing of DFU (Baltzis, et al., 2014; Husakova, et al., 2022).

Foot ulcers and amputation are common complications of diabetes mellitus. Patients with improper glucose control with PAD presence and hypertension are a risk factor for amputation (Pemayun, et al., 2015). While we did not investigate the association between diabetes duration and foot ulcers in our study, a longer duration of diabetes was likely associated with more diabetic complications, such as micro- and macrovascular complications, which were likely to play crucial roles in the skin breach and persistence of the ulcer. The risk of neuropathy may be reduced by avoiding risk factors such as inadequate blood glucose management. Neuropathy sufferers must improve their glycemic control, practice proper foot care, and educate the general public in order to reduce their risk of foot ulceration and amputation. To provide complete treatment for people with diabetes, a multidisciplinary healthcare team is required.

Strength and limitations

The physicians will be able to make a prognosis about the health status of DFU patients according to their lipid profile, the population of DFU patients with amputation, and the clinical significance of HDL levels in DFU. Our study also had some limitations, such as the fact that the confounding factors and the full description of the foot ulcer were not given priority in this study. During the follow-up period, we did not notice any time-dependent changes in serum lipid profiles, and we did not evaluate apolipoproteins and proinflammatory cytokines such as interleukin-6 and tumor necrosis factor (TNF).

CONCLUSION

There was no difference in total cholesterol, triglycerides, LDL, HDL, or the LDL/HDL ratio between amputated and non-amputated DFU patients. However, this study found that the majority of DFU patients had low HDL cholesterol levels.

Acknowledgment
None

Conflict of Interest
All authors have no conflict of interest.

Ethic Consideration
The research protocol was approved by the Committee on Medical Research Ethics in the Faculty of Medicine, Universitas Airlangga (0753/LOE/301.4.2/I/2022).

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Author Contribution
All authors have contributed to all processes in this research, including preparation, data gathering, analysis, drafting, and approval for publication of this manuscript.

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