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Original Article

Prevalence of low HDL cholesterol and its associations among Sri Lankan patients with diabetes mellitus on statin therapy

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ABSTRACT

Aims: We aimed to study the prevalence and associations of suboptimal high density lipoproteins level, a characteristic feature in diabetic dyslipidemia among patients under statin therapy.
Materials and methods: From a database of 2416 patients, data on age, gender, duration of diabetes, body mass index (BMI) and waist circumference (WC), low density lipoproteins (LDL), triglyceride, high density lipoproteins (HDL) were obtained. Prevalence of suboptimal HDL (<40 mg/dL in males and <50 mg/dL in females) and its association with gender, age, duration of diabetes, BMI and WC were studied.
Results: The mean (SD) age of the sample (n = 2416) was 53 (10) years and 64.2% of them (n = 1550) were males. Prevalence of suboptimal HDL was 17.6%. Regression analysis revealed female gender, (OR 7.73, 95% CI 5.99–9.97) younger age (OR 0.98, 95% CI 0.97–0.99), higher BMI (OR1.05. 95% CI 1.00–1.2) and LDL level over 100 mg/dL (OR 1.004, 95% CI 1.00–1.007) had significant associations with suboptimal HDL.
Conclusions: Every sixth diabetic patient on statins has suboptimal HDL level. Females, younger and obese diabetic individuals should be more focused on achieving optimal HDL cholesterol levels.

1. Introduction

Cardiovascular disease (CVD) is the major cause of morbidity and mortality for patients with diabetes mellitus (T2DM) [1]. Patients with T2DM have a considerably higher risk of having cardiovascular disease (CVD) compared with age- and sex-matched patients without T2DM [2,3]. Even though, diabetes itself confers independent risk for future CVD, abnormalities in lipoproteins collectively named as diabetic dyslipidemia contribute to the higher risk of CVD among individuals with T2DM [2]. The typical pattern of dyslipidemia seen in patients with T2DM is elevated triglyceride (TG) and low high density lipoprotein (HDL-C) levels, although all lipoproteins have compositional abnormalities [4]. It is well documented that raised low density lipoproteins (LDL) and TG are associated with an increased risk of CVD [4,5]. Observational studies also suggest that low HDL-C is an independent risk factor for CVD [6].

Statin group of drugs substantially reduce elevated LDL cholesterol and triglycerides with favorable clinical outcomes, but they have a marginal effect on HDL level [7]. Search for more potent and safe pharmacotherapy to elevate suboptimal levels of HDL cholesterol individuals including those with diabetes has not yielded favorable results [8]. Thus, measures to elevate suboptimal levels of HDL cholesterol are currently limited to lifestyle modifications which are often faced with poor patient adherence. In the absence of a potent and safe pharmacological agent, patients with suboptimal levels of HDL cholesterol remain a category with a relatively higher CVD risk [9].

Practical and cost effective approaches to reduce cardiovascular morbidity and mortality among the rising population with diabetes require knowledge of prevalence, pattern and associations of major cardiovascular risk factors in a given community. In the absence of a potent pharmacological therapy to increase HDL cholesterol, recognition of characteristics of patients with diabetes having suboptimal levels of HDL is important. They would benefit from more intensive pharmacotherapy with statins and/or counseling on lifestyle modifications to optimize their HDL cholesterol level.

We carried out this cross sectional study in a sample of patients with diabetes under statin therapy presented to the regional

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diabetes center, Galle for annual screening. The objectives of our study were to estimate the prevalence of suboptimal HDL cholesterol level and to study the association of suboptimal HDL level with gender, indices of global and central obesity (body mass index and waist circumference), age at onset and duration of diabetes and glycemic control among individuals with diabetes under statin therapy.

2. Materials and methods

This cross-sectional study included patients with T2DM who underwent screening at a diabetes center in Southern Sri Lanka. All patients taking statin (atorvastatin, lovastatin or rosuvastatin) irrespective of the type and the dose for at least three months before the screening visit were included for the study. We excluded patients taking statins for a period of less than three months and patients taking statins with another lipid lowering drug such as fenofibrate and ezetimibe three months before the data collection. Patients with diabetic nephropathy and nephrotic range proteinuria and those taking long term steroids and thyroxin during the past three months were also excluded.

Data on gender, age at onset and duration of diabetes (to the nearest year), glycemic control (as percentage of glycosylated hemoglobin), body mass index (kg/m^2), waist circumference (cm) and lipid parameters including LDL, triglycerides, HDL (mg/dL) were obtained from the database. Total serum cholesterol was measured using a cholesterol oxidase enzymatic method and direct magnesium/dextran sulfate method was used to measure HDL cholesterol level. Friedewald equation was used to calculate LDL cholesterol.

Optimal levels of glycemic control and lipids recommended by the American Diabetes Association were used as cutoff values [10]. These included glycosylated hemoglobin of 7.0% and LDL < 100 mg/dL, triglyceride <150 mg/dL, HDL > 40 mg/dL in males and >50 mg/dL in females.

2.1. Statistical analysis

All numerical data were expressed as means and standard deviations. Proportion with optimal glycemic control and each lipid parameter between males and females were expressed as percentages of total study sample. Logistic regression was carried out with suboptimal HDL (HDL < 40 mg/dL in males and <50 mg/dL in females) as the dependent variable and age at diagnosis and duration of diabetes, gender, BMI, WC as independent variables.

Table 1
Descriptive data of the patients with diabetes (n = 2416).

Factor	Mean (SD)
Duration of diabetes (years)	10 (5)
BMI (kg/m^2)	24.3 (3.4)
WC (cm)	90.4 (8.9)
HbA1C (%)	7.5 (0.7)
Total cholesterol(mg/dL)	200.9 (35.1)
HDL (mg/dL)	50.7 (7.8)
LDL (mg/dL)	125.8 (33.6)
TG (mg/dL)	117.6 (49.6)
Proportion of suboptimal HDL	17.4%
Proportion of suboptimal LDL	75.2%
Proportion of suboptimal TG	17.6%
Proportion of suboptimal HDL and LDL	96.7%
Proportion of suboptimal HDL and normal LDL	3.3%

3. Results

A total of 2416 eligible patients with diabetes mellitus were analyzed for this study. The mean age of the study sample was 53 ± 10 years (Table 1) and 64.2% were men. The mean LDL cholesterol for the cohort was 125.8 ± 33.6 mg/dl, with 75.2% of patients having LDL cholesterol ≥100 mg/dl (74.4% of men, 66.5% of women, $P < 0.001$). The mean HDL cholesterol level was 50.7 ± 7.8 mg/dl with males having higher HDL levels (51.5 ± 9.4) than females (48.9 ± 10.1, $P < 0.001$). Around 90% of study subjects had HDL cholesterol levels ≥40 mg/dl (90.7% of males and 93% of females).

Overall, the prevalence of dyslipidemia with at least one abnormal lipid parameter was seen in 89% of patients in the sample with higher prevalence observed in females (94%). Raised LDL-cholesterol was the commonest abnormality affecting 84%; however, raised triglyceride and low HDL-cholesterol were comparatively less common accounting for 19% and 17% respectively. Females had higher prevalence of unfavorable lipid abnormalities including raised LDL-cholesterol (91%) and low HDL-cholesterol (38%) (Fig. 1).

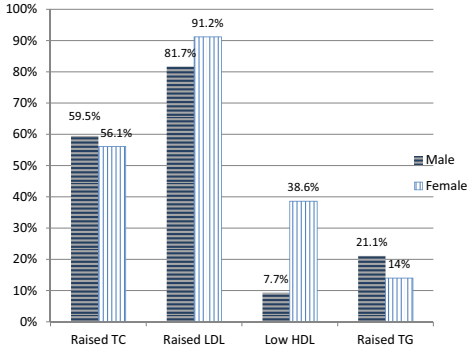
Nearly one in every five diabetic patients (17.4%) had suboptimal (low) HDL cholesterol (<40 mg/dl for men, <50 mg/dl for women). As shown in Fig. 1, the prevalence of suboptimal HDL was around five times higher in females than their male counterparts.

As shown in Table 2, patients with suboptimal HDL had a lower mean age when compared with the patients with normal HDL levels (P < 0.05). BMI, LDL and TG were significantly higher among patients with suboptimal HDL levels when compared with patients with normal HDL levels (P < 0.05). Duration of diabetes, waist circumference and glycemic control as indicted by mean HbA1C however, were not significantly different between patients with suboptimal and normal HDL levels.

Binomial logistic regression analysis revealed that younger age, female gender, higher BMI, raised LDL cholesterol and raised TG levels were significant associations of suboptimal HDL level in patients with diabetes under statin therapy (Table 3). The odds of having sub-therapeutic HDL among diabetic females under statin therapy were 7.73 times higher than males on statin therapy (95 % CI 5.99–9.97, P value <0.01).

4. Discussion

In this study, we present detailed dyslipidemia prevalence in a large cohort of diabetic patients under statin therapy and the factors influence the sub-therapeutic HDL in these patients. Our



TC- total cholesterol, LDL- low density lipoprotein, HDL- low high density lipoprotein, TG-triglycerides.

Fig. 1. Prevalence of abnormal lipid parameters according to gender. TC – total cholesterol, LDL – low density lipoprotein, HDL – low high density lipoprotein, TG-triglycerides.

Table 2
Comparison of clinical characteristics between patients with suboptimal HDL and normal HDL.

Variable	Suboptimal HDL	Normal HDL	P value
Number (%)	420 (17.4%)	1947 (80.6%)	
Age (years)	52 (11)	53 (10)	0.04[a]
Proportion of males	117 (7.7%)	1404 (93.7%)	<0.01[b]
Duration of diabetes (years)	9.3 (5.2)	9.7 (5.9)	0.2[a]
BMI (kg/m^2)	24.8 (3.6)	24.2 (3.4)	<0.01[a]
WC (cm)	90.2 (9.3)	90.4 (8.8)	0.58[a]
HbA1C (%)	7.4 (0.6)	7.4 (0.7)	0.94[a]
Total Cholesterol(mg/dL)	199.4 (36.5)	201.2 (34.8)	0.34[a]
LDL (mg/dL)	130.8 (35.4)	124.6 (33.1)	<0.01[a]
TG (mg/dL)	124.5 (49.4)	116.1 (49.5)	<0.01[a]
Proportion of suboptimal LDL	97 (23%)	327 (17%)	<0.01[b]
Proportion of suboptimal TG	338 (81%)	1472 (76%)	<0.01[b]

[a] Students *t* test.
[b] Chi-square test.

Table 3
Association between clinical risk factors and suboptimal HDL level.

Clinical risk factor	Odds ratio (95% CI)	P value
Age	0.98 (0.97–0.99)	<0.01
Gender (female)	7.73 (5.99–9.97)	<0.01
Duration of diabetes	1.00 (0.98–1.02)	0.93
LDL Cholesterol	1.01 (1.00–1.02)	0.04
Triglycerides	1.01 (1.00–1.02)	<0.01
HbA1C	1.02 (0.86–1.22)	0.81
Body mass index	1.05 (1.00–1.2)	0.04
Waist circumference	0.99 (0.97–1.01)	0.26

study revealed that the prevalence of suboptimal levels of HDL among patients with diabetic dyslipidemia on statin therapy was17.6%. Females were seven times more likely to have suboptimal HDL level than male patients. Younger age, LDL > 100 mg/dL, and higher BMI were significantly associated with suboptimal HDL level. Furthermore, three out of four patients taking statins have their LDL cholesterol above the recommended level of 100 mg/dL and the proportion with suboptimal HDL among those with suboptimal LDL(>100 mg/dL) was higher than those in the category with optimal LDL(<100 mg/d L).

Analysis of diabetic dyslipidemia across different ethnicities have revealed that Indian Asians with diabetes had the highest prevalence (62.4%) of suboptimal HDL levels and the corresponding figures for Central Europeans, Northern Europeans and Japanese patients with diabetes were 23%, 37% and 25% respectively [11]. In the Framingham study, suboptimal HDL cholesterol level was found in 21% and 25% among males and females with diabetes as opposed to 12% and 15% participants without diabetes [12]. Analysis of lipid profiles of newly diagnosed subjects recruited to the United kingdom prospective diabetes study (UKPDS) revealed significantly lower levels of mean HDL cholesterol (39 vs 43 mg/dL in males and 43 vs 55 mg/dL in females) compared to aged matched non diabetic controls [13].

Prevalence of suboptimal HDL in 17.4% of statin treated patients in our study is lower than the previously reported figures of HDL cholesterol level among individuals with diabetes from the Asian and other ethnicities. When considering the observed difference in our study and previously reported levels, it is important to note that the prevalence rates reported by the UKPDS and Framingham studies represent the HDL levels at the time of diagnosis of diabetes before commencing any therapy. Severe hyperglycemia present in patients at the time of diagnosis of diabetes can reduce the level of HDL cholesterol[14]. Lower proportion of patients with suboptimal levels of HDL in our study could also be due to the HDL raising effects of statins and other lifestyle modifications patients were following after having diagnosed with T2DM. Mean HbA1c of 7.5% in our study indicates a satisfactory glycemic control and it might had a positive influence on the prevalence of HDL.

Females with diabetes in our study were seven times more likely to have suboptimal HDL. This could be partly due to the higher cut-off value used to define optimal HDL in females compared to males (>50 mg/dL for females' vs >40 mg/dL for males). Gender differences in the control of cardiovascular risk factors among those with and without diabetes have been reported worldwide [15]. Due to a number of reasons including fertility issues and contraindication of statins during pregnancy and breast feeding, women are undertreated with statins than males. Our findings also highlight the gender discrepancies in the delivery of care focused on the modifiable CVD risk factors in women. These findings emphasizes the need for intensification of strategies to elevate HDL cholesterol by wider use of statins and advising on lifestyle modifications such as increasing physical activity for females with diabetic dyslipidemia.

Studies revealed that individuals with South Asian ethnicity develop diabetes at a younger age and carry worse CVD risk profile than their counterparts in other ethnicities [16]. We too found a similar trend in our study with younger age in patients with diabetic dyslipidemia having a significant association with lower HDL levels, a strong risk factor for CVD. These findings should strengthen the need to intensify HDL raising strategies in younger patients with diabetic dyslipidemia.

Three out of four subjects (75.2%) in our study have not attained LDL cholesterol goal. This is a higher percentage than the reported figures of suboptimal LDL among the statin treated patients with diabetic dyslipidemia which vary from 54 to 57% in previous studies in Europe and United States [17,18]. There are no previous data published from our country on the attainment of LDL goals among patients with diabetes taking statins. Hence, finding a higher proportion of patients with diabetes with suboptimal LDL should be a catalyst for further research on this area. Several factors such as therapeutic inertia by the treating physicians or use of less potent statins and poor compliance by the younger patients with diabetes could be responsible for the observed higher prevalence of patients with suboptimal LDL among the statin treated patients. As LDL levels over 100 mg/dL is significantly associated with suboptimal HDL among patients in our study, measures to optimize the elevated LDL with the use of more potent statin could address both lipid abnormalities in diabetic dyslipidemia.

Low levels of serum HDL along with high serum triglycerides is considered as a surrogate marker of insulin resistance [19]. Waist circumference and body mass index are the two widely used anthropometric indices of obesity indicating insulin resistance. In this study, we only found a significant association of suboptimal HDL level only with BMI and not with WC. This finding too need to be given due consideration in the light of rising incidence of obesity in South Asian region and its association with adverse CVD risk profile.

Findings of this study have several implications. We found a lower prevalence of suboptimal HDL among statin treated patients with diabetes than the previously reported figures in the region. Finding of suboptimal LDL among three fourths of patients taking statins should be taken seriously and should call for urgent action to intensify statin therapy with use of increased dose or a potent statin in patients with diabetic dyslipidemia. As the proportion with suboptimal HDL was higher in the category with LDL over 100 mg/dL above mentioned measure will have a positive impact on achieving not only optimal LDL level but the HDL level as well.

The main strength of our study is the inclusion of large number and diabetic patients with different durations, age at onset of diabetes with a relatively optimal glycemic control (mean HbA1c

7.55). Those helped us to study the association of low HDL level with several clinical parameters.

Non availability of information on the type of statin which prevented us from analyzing the agent and dose related effects on HDL cholesterol level is a limitation of this study. We verified the compliance with prescribed statin from clinical notes and direct questioning from the study participants which may have left some room to include patients with poor adherence to statin therapy.

This is the first study to report on the prevalence of sub optimal HDL level in patients with diabetic dyslipidemia on statin therapy in our country. Although our findings which originate from a regional center catering to a group of middle class patients may not represent the countrywide statistics on the subject, we found several significant gaps in the lipid lowering therapy with statins in patients with diabetic dyslipidemia.

5. Conclusions

Every sixth patient (17%) on statin therapy for diabetic dyslipidemia has HDL cholesterol lower than the recommended level. Females with diabetic dyslipidemia on statin therapy are seven times more likely to have suboptimal levels of HDL. Body mass index, younger age and LDL cholesterol level above 100 mg/dL have significant associations with suboptimal HDL level among patients with diabetes under statin therapy.

Conflicts of interest

Authors declare that there are no conflicts of interest regarding the publication of this paper.

Patient consent

Informed written consent was obtained from all patients.

Ethical approval

Ethical approval for this study was obtained from the institutional research committee, Faculty of Medicine, University of Ruhuna. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee of Faculty of Medicine, University of Ruhuna and with the 1964 Helsinki declaration.

Authors contributions

TPW designed and wrote the study plan and involved in data collection, analysis and writing the manuscript. HMMH designed and wrote the study plan and involved in data collection,analysis and writing the manuscript. GL contributed by analysing data, and writing the manuscript.

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