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RESEARCH

Pattern of dyslipidaemia in relation to statin use in patients with type 2 diabetes mellitus attending a tertiary care hospital

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Introduction: Atherosclerotic cardiovascular disease is a major contributor to morbidity and mortality in diabetic patients. Strict goal-directed lipid control in patients with diabetes is associated with better cardiovascular outcomes.
Aim: The main aim of this study is to describe the lipid profiles of a cohort of patients with type 2 diabetes mellitus in order to highlight the quality of lipid control by correlating the type and dose of lipid-modifying therapy used with lipid levels.
Method: A retrospective analysis was performed on 200 type 2 diabetic patients who attended the Charlotte Maxeke Johannesburg Academic Hospital diabetic clinic. Their lipid profiles and the type and dose of lipid-modifying therapy prescribed was assessed.
Results: Although the majority of participants (146 [73%]) were at the ideal level for total cholesterol, fewer (133 [66.5%]) were at the ideal level for triglycerides and 112 (56%) participants were at the ideal level for HDL cholesterol, only 53 (26.5%) participants were at target for LDL cholesterol, and very few, only 25 (12.5%), participants were at target for all four lipid parameters.
Conclusion: Higher doses of statins or the use of more potent statins with or without the addition of other lipid modifying drugs is recommended in order to achieve LDL cholesterol target in the majority of patients with type 2 diabetes.

Keywords: type 2 diabetes, dyslipidaemia, statin, lipid

Introduction

Type 2 diabetes mellitus is a metabolic disorder that results in persistently higher than normal serum glucose levels in untreated patients.[1] Long-term vascular complications are the cause of poor outcomes, such as death and disability,[2] with cardiovascular disease being the major cause.[3] Dyslipidaemia, which is an independent risk factor for cardiovascular disease, is present in the majority of patients with type 2 diabetes and affects all lipid fractions.[4]

Elevated total and LDL cholesterol (LDL-C) as well as elevated levels of triglycerides together with low levels of HDL cholesterol (HDL-C) are found in the majority of patients with type 2 diabetes.[4]

Reducing LDL-C levels confers significant protection against the higher risk of cardiovascular and cerebrovascular complications in dyslipidaemic patients.[4] A reduction in LDL-C by approximately 1 mmol/l decreases the five-year incidence of major coronary events by approximately 20%.[5]

HDL-C levels are also used as a marker of cardiovascular disease risk with low levels being associated with a greater risk of cardiovascular disease, independent of LDL-C levels.[6,7]

In addition, high triglyceride levels in both fasted and non-fasted patients are also associated with a greater cardiovascular risk.[8]

Treatment of diabetic dyslipidaemia with statins (or HMG CoA reductase inhibitors) has been shown to significantly reduce adverse cardiovascular events and these are therefore the drugs of choice in this setting.[2]

Several statins with differing potencies are currently in use. For example in the Collaborative Atorvastatin Diabetes Study (CARDS) study a low dose of atorvastatin (10 mg daily) decreased LDL-C by 40% and triglycerides by 19%.[9] The Euro Aspire studies revealed a reduction in total cholesterol levels greater than 4.5 mmol/l from 94.5% to 46.2% attributable to statin therapy.[10]

At maximal dose atorvastatin and rosuvastatin can potentially decrease LDL-C by as much as 60%.[5]

Another class of lipid-lowering therapy called fibrates (or peroxisome proliferator-activated receptor-α agonists), in the form of the drug ezetimibe, may be necessary to reduce LDL-C, especially in patients at high risk for cardiovascular disease.[11] The role of other treatment options for this purpose is still under investigation.

The combined use of a statin with a fibrate may be more beneficial than statin therapy alone in patients with type 2 diabetes and dyslipidaemia[12] but this has not been clearly demonstrated in cardiovascular outcome studies.[13]

Globally, poor control of diabetic dyslipidaemia remains a problem and an unacceptably low proportion of patients with diabetes attain the currently recommended lipid targets.[10]

Studies from countries such as Canada and the United States have demonstrated the difficulty of controlling dyslipidaemia, particularly LDL-C, in patients with diabetes.[14,15] One contributory factor has been the underutilisation of high-intensity statins or high doses of statins.[16]

The 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines for the management of type 2 diabetes mellitus have allowed for the goal-directed management of diabetic dyslipidaemia. These were the current guidelines when this study was conducted.

According to the SEMDSA, the 2012 guidelines[17] for lipid control in diabetes are as follows:

- Total cholesterol < 4.5 mmol/l;
- LDL-C < 1.8 mmol/l;*
- HDL-C > 1.0 mmol/l (men) and > 1.2 mmol/l (women);
- Triglycerides < 1.7 mmol/l.

  * LDL-C goal is < 2.5 mmol/l in patients with diabetes who meet all of the following criteria:
    a. No cardiovascular disease and no chronic kidney disease;
    b. Less than 40 years old OR duration of diabetes less than 10 years;
    c. No other cardiovascular risk factors.

Lipid guidelines are of benefit as they provide recommendations on treatment and lipid treatment targets. However, both local and international data have revealed an unexpected high prevalence of uncontrolled dyslipidaemia in diabetes. At the Charlotte Maxeke Johannesburg Academic Hospital Diabetic Clinic the introduction of Simvastatin 20 mg once daily, then up-titrating the dose or changing the intensity of the statin based on subsequent lipid profiles, has been the statin-prescribing strategy of choice. A study of the prevalence and control of diabetic dyslipidaemia, based on lipid-modifying therapy, was considered necessary to determine whether the current practices are adequate.

Methods and materials

Ethics clearance was obtained from the Human Research Ethics Committee at the University of the Witwatersrand. A retrospective observational study of patients with type 2 diabetes attending the diabetic clinic at the Charlotte Maxeke Johannesburg Academic Hospital was conducted. The only inclusion criterion was type 2 diabetes mellitus while subjects were excluded if they had new onset type 2 diabetes mellitus (< 3 months duration), type 1 diabetes mellitus, secondary diabetes, or secondary causes of dyslipidaemia. Participants were selected between March 1, 2017 and May 31, 2017.

A sample size of 200 was deemed to be sufficient for the purposes of this study.

Demographic information including age, gender, weight, height, duration of diabetes, smoking, established cardiovascular disease, chronic kidney disease, diabetic treatment, lipid-modifying therapy, and blood results for point-of-care HBA1C and formal lipograms (total cholesterol, triglycerides, HDL-C and LDL-C) were collected. The HBA1C and lipograms were documented only if they were done within 1 month of each other and if both had been done within the preceding 12 months.

A descriptive analysis was conducted with summary measures such as mean and standard deviation (SD) for age, gender, weight, duration of diabetes, hypertension, smoking status, presence of cardiovascular disease, chronic kidney disease (eGFR < 30 ml/min/m^2), HBA1C and the different lipid parameters (total cholesterol, triglycerides, HDL-C and LDL-C). Frequency tables of patient use of medication for hyperglycaemia (oral hypoglycaemic agents/insulin), hypertension, and dyslipidaemia (no statin, low, moderate, and high-intensity statin therapy, dose, and other lipid-modifying therapy) were also produced. High-intensity statin therapy was considered to be daily doses of atorvastatin 40 mg, atorvastatin 60 mg, atorvastatin 80 mg, rosuvastatin 20 mg, or rosuvastatin 40 mg.

The percentage of patients achieving SEMDSA ideal lipid levels or targets was calculated according to the type and dose of lipid-modifying therapy used. Correlations between glycaemic control, lipid levels and intensity/dose of lipid modifying therapy were also assessed. A p-value of < 0.05 was considered significant.

Results

Characteristics of the study group

This cohort comprised 200 participants with a mean age of 58.9 years (SD ± 11.04) with 43% being male and 57% female. The duration of diabetes was more than 10 years in the majority (53%). Additional cardiovascular risk factors were common, namely hypertension (81%), excessive weight (20.5%) and smoking (12%). The lack of height measurements precluded calculating body mass index so a weight of more 100 kg was deemed to be overweight in this population. We acknowledge that an arbitrary weight of 100 kg is a limitation as a few participants may have had a normal body mass index. The demographics of the study cohort are shown in Table 1.

Description of the lipid profile

The lipid profiles are given in Table 2. Each lipid parameter had a wide range; however, the median for each, with the exception of LDL-C, reflected good control.

Three of the four lipid parameters were controlled for most participants; however, LDL-C was not at target and only a small percentage had all four lipid parameters controlled (Figure 1).

The median LDL-C was 2.21 mmol/l (IQR 1.13 mmol/l). Fifty-three participants had LDL-C at target. Participants requiring high-intensity statins had a median LDL-C of 2.34 mmol/l (IQR 1.37 mmol/l).

A total of 198 (99%) participants required a target LDL-C of 1.8 mmol/l and 2 participants (1%) required a target LDL-C of 2.5 mmol/l according to their individual risk factors.

Irrespective of a target level, 126 (63%) participants had a LDL-C of less than 2.5 mmol/l.

Lipid-modifying therapy

Among all participants, 83% were on lipid-modifying therapy while 17% were not. Only two types of statin, simvastatin and atorvastatin, were prescribed but at various dosages. In addition to statins a fibrate was prescribed in only 2% of patients (Supplementary table 1). Of those on statin therapy, the majority were on low-intensity statins (Table 3).

Table 1: Characteristics of the study group

Patient characteristics	(*n* = 200)
Age (years)*	58.9 (11.04)
Gender:	
Male	86 (43)
Female	114 (57)
Duration of diabetes:	
Less than and equal to 5 years	32 (16)
Between 5 and 10 years	62 (31)
More than 10 years	106 (53)
Weight more than or equal to 100 kg	41 (20.5)
Pre-existent hypertension (SBP > 140 mmHg, DBP > 80 mmHg, or both)	162 (81)
Blood pressure (mmHg): *	
SBP	139.5 (20.56)
DBP	77.6 (12.30)
At target blood pressure (< 140/80 mmHg)	71 (43.8) (*n* = 162)#
Smoking history:	*n* = 136#
Smoker	10 (7.4)
Ex-smoker	6 (4.4)
Established cardiovascular disease:	25 (12.5)
Coronary artery	17 (8.5)
Cerebrovascular	7 (3.5)
Peripheral artery	1 (0.5)
Chronic kidney disease (defines as eGFR < 30 ml/min/1.73 m^2)	2 (1)

Results expressed as *n* (%) except where indicated by an asterisk (*) where reported as mean (standard deviation).
Total number of participants (n) = 200, except where indicated by # (number of participants for whom data were available).
Duration of diabetes, weight, eGFR (estimated glomerular filtration rate), SBP = systolic blood pressure, DBP = diastolic blood pressure, age (years): calculated or measured relative to the subject's date of visit, percentages are calculated relative to the total number of subjects with data.

The mean total cholesterol in participants not on statin therapy was 4.45 mmol/l compared with a mean of 3.96 mmol/l in all participants on statin therapy indicating a significant difference ($p = 0.006$), most likely attributable to statin therapy. In this regard the mean was used as total cholesterol was distributed normally. Supplementary table 2 shows the means of each lipid parameter according to statin intensity.

Glycated haemoglobin (HBA1C) and the lipid profile

The range of HBA1C was from 5.0% to 17.3% with a median of 8.3% (IQR = 3.2%).

Table 4 shows how the HBA1C correlated with the lipid profile. The HBA1C showed a weak correlation with total cholesterol, LDL-C and HDL-C. It did, however, show a statistically significant positive correlation with triglycerides. Lower LDL-C levels were also associated with lower HBA1C levels ($p = 0.007$).

Table 2: Description of the lipid profile

Lipid fraction	Minimum (mmol/l)	Maximum (mmol/l)	Median and IQR (mmol/l)
Total cholesterol	1.98	7.20	3.99 (IQR 1.18)
Triglycerides	0.23	8.94	1.31 (IQR 1.1)
HDL-C	0.54	3.07	Men 1.06 (IQR 0.47) Women 1.24 (IQR 0.43)
LDL-C	0.69	5.87	2.21 (IQR 1.13)

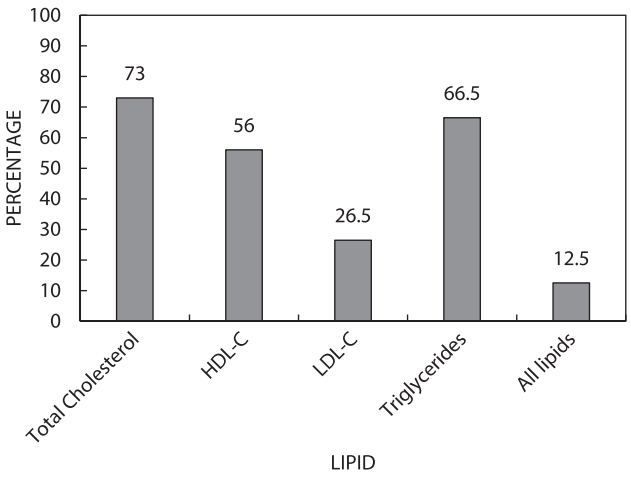

Figure 1: Lipids at target.

Poor diabetic control therefore had a minor influence on lipid levels.

Tables 5 and 6 describe the HBA1C in more detail according to gender and body weight.

HBA1C < 7% and the lipid profile

Figure 2 shows the correlation between HBA1C < 7% and the lipid profile.

HBA1C levels of less than 7% did not influence total cholesterol, LDL-C and HDL-C. However, good glycaemic control to an HBA1C of less than 7% was associated with lower triglyceride levels. With regard to having all four lipid parameters at target, an HBA1C of less than 7% showed no correlation.

Discussion

Overall, the results of this study reveal a disappointingly high prevalence of poorly treated diabetic dyslipidaemia in type 2 diabetics. The long-term cerebrovascular, cardiovascular and peripheral vascular complications in this population are potentially

Table 3: Statin therapy according to intensity

Statin intensity	Number on treatment	Percentage
No statin	34	17
Low intensity[1]	96	48
Moderate intensity[2]	56	28
High intensity[3]	15	7.5

[1]Low intensity (simvastatin 10 mg, simvastatin 20 mg, atorvastatin 10 mg).
[2]Moderate intensity (simvastatin 40 mg, simvastatin 60 mg, atorvastatin 20 mg).
[3]High intensity (atorvastatin 40 mg, atorvastatin 60 mg, atorvastatin 80 mg, rosuvastatin 20 mg, rosuvastatin 40 mg).

Table 4: Correlation of HBA1C and lipid profile.

Lipid fraction	Correlation coefficient (r)	*p*-value
Total cholesterol	0.20	<0.01
Triglycerides	0.15	0.03
HDL-C	0.02	0.83
LDL-C	0.19	0.01

Table 5: Breakdown of HBA1C

Category	Median (%)	IQR (%)
Males	8.3	3.3
Females	8.2	3.3
Total cholesterol < 4.5 mmol/l	7.9	2.9
Triglycerides < 1.7 mmol/l	8.1	3.1
HDL-C > 1.0 (men), > 1.2 (women)	8.3	3.4
LDL-C at target	7.7	2.7
Weight ≥ 100 kg	8.2	3.5

preventable with adequate lipid control. The study is a reflection of the global prevalence of uncontrolled diabetic dyslipidaemia. A study in China demonstrated that 54.9%, 43.7% and 37.4% of participants were not at goal (according to local practice guidelines) for LDL-C, triglycerides and HDL-C respectively.[18] Similar rates of prevalence have been reported in the Canadian[14] and German[19] arms of the DYSlipidemia International Study.

In the South African context, the prevalence of uncontrolled dyslipidaemia is reflected in studies done in the private sector only,[20] and in both the public and private sectors.[21,22] In these studies, the prevalence of uncontrolled LDL-C ranged from 47.7% to 58.6%.

In this cohort, according to the SEMDSA guidelines, total cholesterol, triglycerides and HDL-C were controlled in more than half the population. However, only about a quarter of the participants had LDL-C at target. Of note, only one in eight patients have all lipid parameters controlled. Ideally, all four parameters should be at target or the ideal level to minimise the risk of vascular complications.[4] The strategy by which statin therapy was used in this study therefore did not result in optimal control of diabetic dyslipidaemia.

Participants on low-intensity statins have lipid profiles closest to the guidelines. However, this may have been the result of the initiation of low-intensity statin therapy because of only mild hyperlipidaemia in these subjects. The participants not on a statin have lipid profiles similar to the patients on medium- and high-intensity statins. All levels of statin intensity failed to adequately control levels of LDL-C. Participants in whom high-intensity statin therapy was prescribed were more likely those with severe dyslipidaemia. These participants were, however, not at goal for their lipid targets and were not receiving supplementary lipid-lowering therapy, revealing a need for additional lipid-lowering therapy such as ezetimibe.

On average, participants not on statin therapy did not have significantly different triglyceride levels compared with those on statin therapy. However, this finding does not take into consideration the state of glycaemic control in these participants.

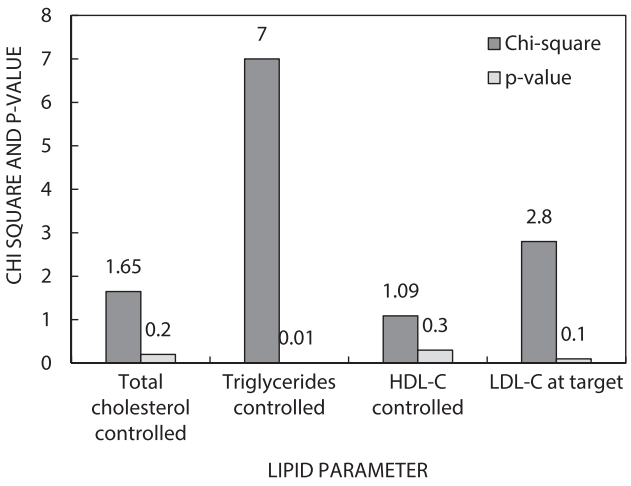

Figure 2: Correlation of controlled/at-target lipids for participants with HBA1C < 7%.

Participants who were not on statin therapy have comparable levels of HDL-C to those on statin therapy. The benefit of statin therapy is reflected in the significantly lower LDL-C levels in statin-treated participants compared with participants not treated with statins. Despite the suboptimal prevalence of controlled LDL-C, statin therapy should have a positive impact in preventing cardiovascular complications by reducing LDL-C.[9]

In this study an HBA1C of more than 7%, which may be considered to be poorly controlled diabetes mellitus, was associated with worse triglyceride levels, as the only difference when compared with an HBA1C of less than 7%. This association was also reported in a study directed specifically towards the relationship between glycaemic control and the serum lipid profile in type 2 diabetic patients,[23] and in a large scale Malaysian study of more than 28 000 participants.[24] These findings highlight the point that good glycaemic control is an important contributor to optimising lipid levels. This may obviate the need for escalating to more potent statins or adding other classes of lipid-lowering therapy, a benefit that would be appreciated in a resource-constrained setting. One may even consider a six-month trial period to optimise glycaemic control before modifying or up-titrating lipid-lowering therapy.

A limitation of the study was the timing of serum analysis. Not all participants had their lipograms and HBA1C done on the same day. Some participants had their lipograms done before their diabetic clinic appointments. Lipograms and HBA1C were paired only if they were done within 30 days of each other. It is possible that either or both of the lipid and HBA1C readings might have been slightly different had they been done on the same day.

However, in this study the selection of lipid-lowering therapy was suboptimal and compounded by a lack of appropriate

Table 6: Weight ≥ 100kg, lipid profile and HBA1C

	Median total cholesterol (mmol/l) (IQR)		Median triglycerides (mmol/l) (IQR)		Median HDL-C (mmol/l) (IQR)		Median LDL-C (mmol/l) (IQR)		Median HBA1C % (IQR)	
Gender	< 100 kg	≥ 100 kg	< 100 kg	≥ 100 kg	< 100 kg	≥ 100 kg	< 100 kg	≥ 100 kg	< 100 kg	≥ 100 kg
Male	3.62 (0.90)	4.11 (1.12)	1.24 (0.95)	1.65 (1.74)	1.07 (0.49)	0.98 (0.40)	2.1 (0.81)	2.21 (1.17)	8.3 (3.3)	8.7 (3.2)
Female	4.22 (1.29)	3.89 (0.93)	1.35 (1.03)	1.29 (1.08)	1.26 (0.42)	1.08 (0.42)	2.42 (1.13)	2.15 (0.86)	8.3 (3.3)	8.0 (3.2)

dose titration. Various correctable factors may be postulated for the poor control of diabetic dyslipidaemia so that effective practical solutions can be enforced. The ability to choose and successfully titrate therapy may be influenced by the clinician's knowledge of a statin's potency, maximal dosage, need to escalate to a more potent agent or add another agent, and the experience of the clinician in this regard.[14] Trends towards Westernised diets and sedentary lifestyles present obstacles to good glycaemic and lipid control. Concerns for safety, toxicity and side effects, as well as ethnicity and lower socio-economic status, have been cited as patient factors for poor statin adherence.[20–22] In the public sector the lack of drug availability, due to formulary restrictions and at times stock shortage, is a common problem while staff shortage in large diabetic clinics impairs the holistic management of diabetic dyslipidaemia.

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