

**THE ASSESSMENT OF LIPID LEVELS IN TYPE 2 DIABETIC PATIENTS IN
RELATION TO LIPID MODIFYING THERAPY AT THE CHARLOTTE MAXEKE
JOHANNESBURG ACADEMIC HOSPITAL (CMJAH) DIABETIC CLINIC**

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Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree
of Master of Medicine in Internal Medicine

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DECLARATION

I, Sagen Naidoo, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of MMed in Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



The 14th day of July, 2019

ABSTRACT

Introduction

Atherosclerotic cardiovascular disease is major contributor to morbidity and mortality in diabetic patients. Strict goal-directed lipid control 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 in March 2017. Their lipid profiles and the type and dose of lipid-modifying therapy prescribed to them were assessed.

Results

Although the majority of participants [146 (73%)] were at target for total cholesterol, fewer [133 (66.5%)] were at target for triglycerides, 112 (56%) participants were at target 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

The LDL-cholesterol levels of participants on statin therapy was significantly lower in statin-treated participants than in participants not treated with statins. However higher doses of statins or the use of more potent statins is recommended in order to achieve LDL-cholesterol target in the majority of diabetic patients.

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NOMENCLATURE

ACC: American College of Cardiology

AHA: American Heart Association

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

eGFR: Estimated glomerular filtration rate

HBA1C: Haemoglobin A1C or Glycated haemoglobin

HDL-C: High density lipoprotein cholesterol

LDL-C: Low density lipoprotein cholesterol

SEMDSA: Society for Endocrinology, Metabolism and Diabetes of South Africa

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CHAPTER ONE

1. INTRODUCTION

1.1 General Introduction

In 2012 the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) released guidelines for the management of type 2 diabetes mellitus. These guidelines have recently been revised. Included in these guidelines are target ranges for lipid levels and strategies for the use of lipid-modifying therapy in patients with dyslipidaemia including patients with diabetes mellitus. This has thus allowed for the goal-directed management of dyslipidaemia in patients with type 2 diabetes mellitus.

The diabetic clinic at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) has a patient base of more than 3 000. Patients with the added cardiovascular risk factor of dyslipidaemia are actively managed using lipid-modifying agents made available in accordance with the hospital's procurement policies. A study into the use of these drugs would formally highlight the standard of lipid control in diabetics at CMJAH. The SEMDSA lipid level targets will serve as a reference to assess this control.

Lipid profiles of these diabetic patients are done at least annually to detect abnormalities in lipid levels and to assess control in patients on lipid-modifying therapy. A retrospective statistical review of lipid profiles over a twelve month period would reveal the prevalence of dyslipidaemia. With a comprehensive database, associations between diabetic dyslipidaemia and other factors affecting lipid levels may become apparent.

Point-of-care glycated haemoglobin (HBA1C) levels are done as a measure of diabetic control on almost every visit at the diabetic clinic. The adequacy of diabetic treatment and control may have an influence on lipid control and therefore, indirectly on lipid-modifying therapy prescribed.

This study has the practical intention of influencing current practices at the diabetic clinic either by consolidating good practices or by identifying shortcomings which may be rectified in future.

1.2 Objectives

- To record all lipid levels [Total-cholesterol, triglyceride, HDL-Cholesterol (HDL-C) and LDL-Cholesterol (LDL-C)] and describe them in relation to the current lipid target levels for patients with type 2 diabetes mellitus attending the diabetic clinic at the Charlotte Maxeke Johannesburg Academic hospital (CMJAH) according to the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines.¹
- To describe the types and doses of lipid modifying therapy, predominantly statin therapy, prescribed and the association/correlation with the different lipid levels (Total-cholesterol, triglyceride, HDL-C and LDL-C) observed.
- To correlate glycaemic control as measured by HBA1c with lipid levels.

1.3 Literature Review

Type 2 Diabetes Mellitus is a metabolic disorder which results in persistently higher than normal serum glucose levels in untreated patients.² Long term vascular complications are the cause of poor outcomes, such as death and disability ³, with cardiovascular disease being the main cause.⁴ Dyslipidaemia is present in the majority of patients with type 2 diabetes and affects all lipid fractions.⁵ There is sufficient data associating dyslipidaemia with cardiovascular disease in both diabetic and non-diabetic patients with diabetic patients being at higher risk.⁶

Diabetic dyslipidaemia comprises a range of quantitative and qualitative abnormalities in lipids and lipoproteins. Elevated total-cholesterol and LDL-C as well as elevated levels of triglycerides together with low levels of HDL-C are found in the majority of patients with type 2 diabetes.⁵ On serum analysis high triglyceride, low HDL-C, and the presence of small dense LDL-Cs are commonly demonstrated.⁷ Statins should be started at a dose aimed at reaching a particular LDL-C goal.⁸

Dyslipidaemia and diabetes mellitus per se are risk factors for the development of cardiovascular disease.⁵ Reducing LDL-C levels confers significant protection against the higher risk of cardiovascular and cerebrovascular complications in dyslipidaemic patients.⁵ As such, lowering LDL-C has been the primary aim in reducing cardiovascular risk.⁹ A reduction in LDL-C by approximately 1 mmol/L decreases the five year incidence of major coronary events by approximately 20%.¹⁰ A proportion of patients who meet aggressive LDL-C targets will have low HDL-C levels.¹¹

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.¹² The two main functions of HDL-C are reverse cholesterol transport and possible cardioprotection by means of anti-oxidative, anti-inflammatory and endothelium-dependent vasodilatory effects.⁷ In insulin-resistant people HDL-C has a critical function as an antioxidant and anti-inflammatory mediator.¹¹ An inversely proportional relationship exists between HDL-C levels and the prognosis of cardiovascular disease morbidity and mortality, independent of LDL-C levels.¹³ However studies with therapies that raise HDL-C have not demonstrated a reduction in cardiovascular events.¹²

High triglyceride levels in both men and women, and among fasted and non-fasted patients is also associated with a greater cardiovascular risk.¹⁴ An increase of 1 mmol/L in triglycerides has been associated with an increase in coronary heart disease of 32% in men and 76% in women.¹⁵ The combination of low HDL-C and elevated triglycerides has been shown to be a greater risk factor for major coronary events than an isolated high LDL-C level.¹⁶

High levels of triglycerides, high LDL-C, and low HDL-C are related to the formation of plaques in the inner lining of arteries i.e. atherogenesis.¹⁷ These plaques result in macrovascular complications namely, coronary artery disease, cerebrovascular disease, and peripheral vascular disease.¹⁸ The risk of having a myocardial infarction, which is due to underlying coronary artery disease, is considered to be the same in diabetics irrespective of a prior history of myocardial infarction.¹⁹ The American Diabetes Association has advocated statin use in the majority of type 2 diabetics as a

primary preventative measure for cardiovascular disease.¹⁹ Measures which have been shown to decrease the amount of hospital admissions for cardiac complications over a four year period are exercise, loss of weight, absence of smoking, and optimal drug therapy in particular lipid lowering therapy.¹⁵

Treatment of diabetic dyslipidaemia has been shown to reduce the risk of macrovascular complications. The class of drug called statins (or HMG CoA reductase inhibitors) are the first line in pharmacological treatment of dyslipidaemia in diabetic patients.³

Statins act mainly by increasing LDL-C receptor activity and reducing lipoprotein secretion by the liver.¹⁵ Treatment with statins has been shown to significantly reduce adverse cardiovascular events in dyslipidaemic patients and statins are therefore the drugs of choice in this setting.³ Statin monotherapy in diabetic patients has a positive effect in reducing lipid levels, even at high doses without significantly worsening their side effects.⁸ The significance of LDL-C reduction has been shown in large randomized studies which demonstrated a 21% reduction in the risk of major cardiovascular disease for every 1 mmol/L decrease in LDL-C.²⁰ Various statins with differing potencies are currently in use e.g. in the Collaborative Atorvastatin Diabetes Study (CARDS) a low dose of atorvastatin (10mg daily) decreased LDL-C by 40% and triglycerides by 19%.⁸ The Euro Aspire studies revealed a reduction in the number of patients with total cholesterol levels greater than 4.5 mmol/L from 94.5% to 46.2% - this was attributable to statin therapy.⁸ Doses of simvastatin between 20 and 40 milligrams per day (or intermediated dose statin), compared to a dose of ten milligrams per day (or low dose statin) are more effective in attaining LDL-C goals.¹¹ At maximal dose atorvastatin and rosuvastatin can potentially decrease LDL-C by as much as 60%.¹⁰ In addition to lowering LDL-C statins also reduce triglycerides and increase HDL-C modestly ¹⁰ but this effect is not as impressive and depends on dose of the statin.^{5,11} Statins also exhibit anti-inflammatory and anti-thrombotic effects and may serve to render atherosclerotic plaques stable.⁷ In patients with LDL-C levels less than 3 mmol/L simvastatin may reduce the risk of major coronary events in patients with or without coronary artery disease.²¹

In the landmark Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) treatment with atorvastatin in patients with type 2 diabetes showed a decrease in the risk of major cardiovascular events.²² Ten milligrams of atorvastatin has been associated with a significant reduction in cardiovascular disease, even without high LDL-C levels, and with a substantial reduction in LDL-C concentrations to well below recommended levels.²³ The risk of cerebrovascular disease may also be reduced by almost half with ten milligrams of atorvastatin.⁷ On average LDL-C levels may be reduced by 1.20 mmol/L when using atorvastatin at a dose of ten milligrams daily.²³ When compared to ten milligrams of atorvastatin daily, eighty milligrams of atorvastatin daily is more effective in reducing the risk of major cardiovascular events.¹¹

Patients at high risk for cardiovascular disease may need other types of agents, in addition to statins, to control dyslipidaemia.¹¹ The use of statins in diabetes has been recommended by the American Diabetes Association in patients with cardiovascular disease, regardless of lipid levels, or in patients over forty years with additional cardiovascular risk factors including albuminuria, dyslipidaemia, smoking, hypertension, and a family history of cardiovascular disease. In addition to this, diabetics under 40 years old with LDL-C greater than 2.6 mmol/L in spite of lifestyle modification, and who have multiple cardiovascular disease risk factors should receive statin therapy.⁷ The American College of Cardiology/ American Heart Association (ACC/AHA) guidelines advocate the use of statins in patients between 40 and 75 years of age with LDL-C greater than 1.8 mmol/L.²⁴

The class of lipid-modifying therapy called fibrates (or peroxisome proliferator-activated receptor- α agonists) increase the breakdown and clearance of triglyceride-rich lipoproteins¹⁵ and consequently reduce cardiovascular risk in patients with dyslipidaemia associated with type 2 diabetes.¹¹ Bezafibrate may provide a clinical benefit in patients with triglyceride concentrations over 2.26 mmol/L by decreasing cardiovascular risk.²⁵ The combined use of a statin with a fibrate may be more beneficial than statin-therapy alone in patients with type 2 diabetes and dyslipidaemia¹⁵ but this has not been clearly demonstrated in cardiovascular outcome studies.²⁶

Globally, poor control of diabetic dyslipidaemia remains a problem and an unacceptably low proportion of patients attain currently recommended lipid targets.⁸ At the Charlotte Maxeke Johannesburg Academic Hospital diabetic clinic statin therapy is the first line in the treatment of diabetic dyslipidaemia. The initial drug of choice is simvastatin at a dose of 10mg or 20mg daily. The dosage is increased or a more potent statin is substituted depending on the response to the current statin. Other lipid-modifying agents, such as bezafibrate and ezetimibe, are added depending on the response to statin therapy and the lipid profile.

Although lipid-modifying therapy is the mainstay of lipid management other factors may impact on the control of lipid abnormalities. An important and sometimes overlooked reason for the difficulty in controlling dyslipidaemia is poor adherence to treatment which itself has various reasons, e.g. a patient's lack of understanding of the need for further treatment.¹⁹ Factors affecting the attainment of LDL-C targets are baseline LDL-C levels, positive smoking history, and age.¹⁹

Studies from countries such as Canada and the United States have demonstrated the difficulty of controlling dyslipidaemia, particularly LDL-C, in patients with diabetes.^{9,27} One contributory factor has been the underutilization of high intensity statins or high doses of statins.²⁸ Hwang et al.¹⁹ revealed a significant difference in physicians' perceptions and the recommended targets for hypercholesterolaemia in diabetics. A quarter of patients with diabetes and cardiovascular disease may need 3 or more lipid modifying agents to achieve a LDL-C of 70 mg/dL (1.8 mmol/L).¹⁹ Correct diet and increased physical activity have a positive impact on diabetic dyslipidaemia but in many patients lipid-modifying drugs will be needed to attain lipid targets.¹⁵ Despite the apparent risk of cardiovascular disease in patients with diabetic dyslipidaemia there remains a significant prevalence of suboptimal lipid control.¹¹

The cost of managing diabetes and its complications in the United States had doubled over a ten year period, while in Europe the cost of treating diabetes might be close to 100 billion US dollars by 2025.¹¹ Thus, there is a clear financial need to prevent

macrovascular and microvascular complications in patients at high risk, namely patients with uncontrolled diabetes, metabolic syndrome, and obesity.¹¹

The American Diabetes Association, European Society of Cardiology, and European Association for the Study of Diabetes recommend the following goals:

- Reduction of LDL-C to < 2.6 mmol/L in diabetics without added cardiovascular risks
- Reduction of LDL-C to < 1.8 mmol/L in diabetics with additional cardiovascular risk factor factors and in those with established cardiovascular disease
- If the above is not achievable then to aim for > 30% reduction of baseline LDL-C
- Patients over the age of 40 years should receive moderate to high intensity doses of statins.²⁹

The main priority in diabetics is still the attainment and maintenance of good glycaemic control to avoid worsening lipid abnormalities.²⁹

According to the SEMDSA, the current guidelines 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 < 2.5mmol/L in patients who do not meet all of the following criteria:
 - a. No cardiovascular disease and no chronic kidney disease
 - b. Less than 40 years old OR duration less than 10 years
 - c. No other cardiovascular risk factors

In accordance with international practices SEMDSA advocates the use of statins as first-line therapy in the treatment of diabetic dyslipidaemia.¹

The benefit of lipid control guidelines is that we're able to treat affected patients in a goal-directed manner, however local and International data have revealed an unexpected high prevalence of uncontrolled dyslipidaemia in diabetes. At the Charlotte Maxeke Johannesburg Academic Hospital Diabetic Clinic a study of the prevalence and control, based on lipid modifying therapy, of diabetic dyslipidaemia was considered necessary to determine if the current practices are adequate.

CHAPTER TWO

2. METHODS AND MATERIALS

2.1 Study Design

This was a retrospective observational study of patients with type 2 diabetes attending the diabetic clinic at the Charlotte Maxeke Johannesburg Academic Hospital.

2.2 Setting

The diabetic clinic, area 553, Charlotte Maxeke Johannesburg Academic Hospital.

2.3 Patient Selection

Inclusion criteria:

- All subjects with a clinical diagnosis of type 2 diabetes mellitus attending the Diabetic Clinic, CMJAH.

Exclusion criteria:

- New onset type 2 diabetes mellitus (< 3 months).
- Other types of diabetes mellitus (type 1 diabetes or secondary diabetes mellitus).
- Secondary causes of dyslipidaemia namely overt hypothyroidism, nephrotic syndrome, antiretroviral therapy for HIV infection, ethanol abuse, and oral steroid use.

2.4 Measurements

Levels of HBA1C, total cholesterol, HDL-C, triglycerides, and LDL-C were measured at the National Health Laboratory Services at CMJAH within the past 12 months.

2.4.1 Analysis of the lipid profile

The measurements used in this study were done between 07 March 2016 and 31 March 2017.

Prior to 20 August 2016 the ADVIA 1800 analyser manufactured by Siemens was used for the lipogram measurements. The LDL-C was not a direct measurement but calculated using the Friedewald equation: $[\text{LDL-C}] = [\text{Total chol}] - [\text{HDL-C}] - ([\text{TG}]/2.2)$. This gave a result in mmol/L.

From 20 August 2016 onwards lipograms were performed using the Roche/Hitachi cobas c 702 analyser which measured LDL-C directly, without using the Friedewald equation.

2.4.2 Measurement of HBA1C

The HBA1C was done as a “point of care” measurement i.e. it was done at the diabetic clinic. The machine used was the DCA Vantage Analyzer, manufactured by Siemens Healthcare Diagnostics Inc. This analyser calculates the values of HBA1C by measuring the HBA1C and dividing that by the total measured haemoglobin concentration: $\% \text{HBA1C} = (\text{HBA1C} / \text{Total Haemoglobin}) \times 100$. Each patient's blood was drawn up into a capillary cartridge which contained a reagent. The cartridge was thereafter inserted into the analyser which yielded a HBA1C result.

2.5 Sample Size, Statistical Methods and Data Analysis

Approximately 3000 patients with type 2 diabetes mellitus attend the Diabetic clinic at CMJAH. A sample size of 200 subjects was considered sufficient for this study. Patients were selected from all the patients who attended the Diabetic Clinic between 01 March 2017 and 31 May 2017. 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 ($\text{eGFR} < 30 \text{ ml/min/m}^2$), 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. The percentage of patients achieving SEMDSA lipid 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. The cohort of subjects with diabetic dyslipidaemia not on lipid-lowering therapy served as a comparison group.

2.6 Data Collection

The lists of patients for each diabetic clinic were obtained. Each patient file was retrieved and assessed for inclusion and exclusion into the study. Those subjects who met the inclusion criteria and did not meet the exclusion criteria were included in the study, their files were reviewed appropriately, and the necessary data was noted on the data collection sheet. Data comprised of HBA1C measurements, blood pressure, smoking history, weight, height, duration of diabetes, statin use, and demographic details. Blood results were obtained for the study period by using the patients' hospital numbers. Subjects whose blood samples were not taken within the study period were excluded from the study. Subjects who met the exclusion criteria were not included in the study. Blood results for total cholesterol, triglycerides, LDL-C, and HDL-C were retrieved from the National Health Laboratory Services online system at the following web page address: <https://trakcarelabwebview.nhls.ac.za/trakcarelab/csp/logon.csp?LANGID=1>. The HBA1C and lipograms were paired and used as data if they were done less than one month apart.

CHAPTER THREE

3. RESULTS

3.1 Characteristics of the Study Group

The characteristics of the study sample are shown in Table 3.1.

In this cohort of 200 participants the mean age was almost 60 years old. This is consistent with type 2 diabetes mellitus.

The sample population showed a predominance of females by 14 per cent. The female to male ratio was 1.3:1. There was no bias towards females, nor was there an obvious reason for this.

More than half of the participants were diagnosed with diabetes more than a decade ago, a significant time frame with regard to the development of cardiovascular complications.

The height measurements of all participants were not available therefore body mass index has not been calculated. Body weight measurements were available for all participants and a weight of more 100 kg was deemed to be unhealthy in this population. One in five participants weighed over 100 kg.

More than 80 per cent of participants had a known diagnosis of hypertension prior to the start of data collection. Of these participants almost 44 per cent were at target blood pressure.

Data on smoking was available for only 136 participants and of these almost 12 per cent were either currently in the habit of smoking or were ex-smokers.

One in eight participants had been diagnosed with cardiovascular complications from diabetes, and only 1 per cent of participants had chronic kidney disease.

Table 3.1 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 100kg	41 (20.5)
Pre-existent hypertension (SBP > 140mmHg, DBP > 80mmHg, or both)	162 (81)
Blood Pressure (mmHg)*	
Systolic	139.5 (20.56)
Diastolic	77.6 (12.30)
At target blood pressure (<140/80mmHg)	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 (eGFR < 30 mL/min/1.73m 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 which data were available).

Duration of diabetes, weight, eGFR (estimated glomerular filtration rate), systolic blood pressure, 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.

3.2 Description of the Lipid Profile

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

Table 3.2 Lipids at target

	Number (%)
Total cholesterol	146 (73)
Triglycerides	133 (66.5)
HDL-C	112 (56)
LDL-C	53 (26.5)
All four of the above parameters	25 (12.5)

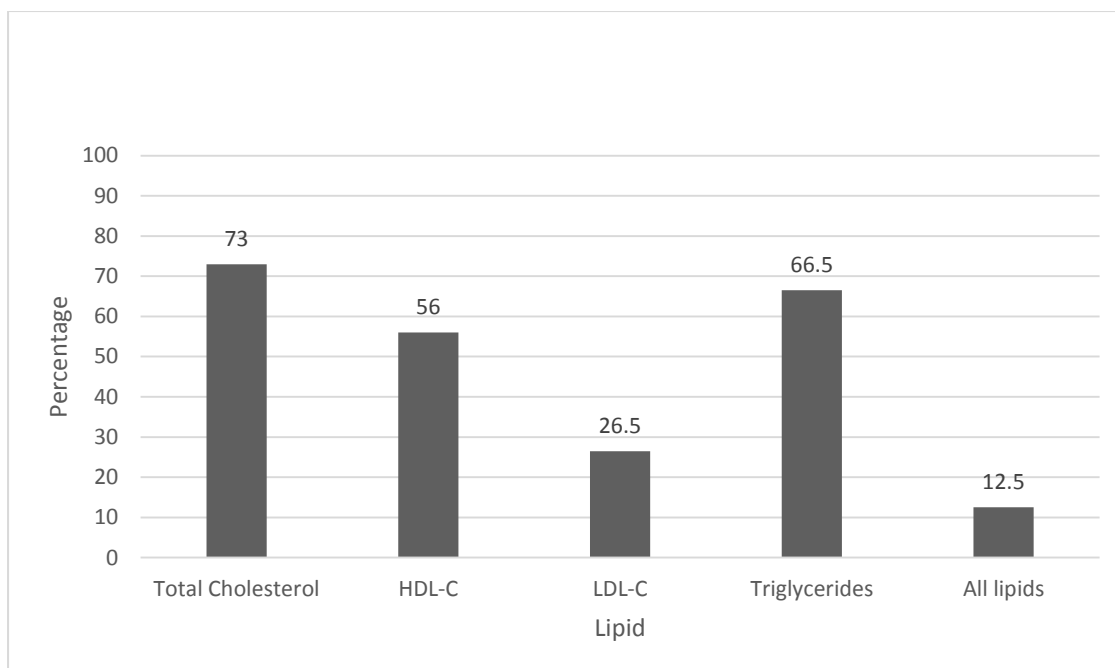


Figure 3.1 Lipids at target

Each lipid parameter ranges widely from being well within a target reference limit to being far out of this limit. However, the average of the measurements for each parameter reflect good control of all parameters except LDL-C.

Table 3.3 Description of the lipid profile

Lipid fraction	Minimum (mmol/L)	Maximum (mmol/L)	Average (mmol/L)
Total cholesterol	1.98	7.20	4.05
Triglycerides	0.23	8.94	1.65
HDL-C	0.54	3.07	Men 1.11 Women 1.29
LDL-C	0.69	5.87	2.33

3.3 Lipid-modifying Therapy

168 (84%) participants were on lipid-modifying therapy, while 32 (16%) were not.

Only 2 types of statins were prescribed but at various dosages. In addition to statins a fibrate had been prescribed to 2 per cent of patients.

Table 3.4 Distribution of patients according to type of lipid-modifying therapy

Treatment	Number on treatment	Percentage
Simvastatin 10 mg	18	9
Simvastatin 20 mg	74	37
Simvastatin 40 mg	24	12
Simvastatin 60 mg	1	0.5
Simvastatin 80 mg	0	0
Atorvastatin 10 mg	4	2
Atorvastatin 20 mg	31	15.5
Atorvastatin 40 mg	14	7
Atorvastatin 60 mg	1	0.5
Atorvastatin 80 mg	0	0
Bezafibrate	4	2
Statin and Fibrate	3	1.5
Fibrate only	1	0.5
Other	0	0

17 per cent of participants were not on statin therapy and of the remaining 83 per cent more than half were on low intensity statins.

Table 3.5 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)

Participants who were not on statin therapy had acceptable lipid levels and statin therapy was therefore not indicated.

The mean total cholesterol in participants not on statin therapy was 4.45 mmol/L compared to 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.

The use of low intensity statin therapy for mild diabetic dyslipidaemia had led to lipid levels within the target ranges. The lipid levels in patients on low intensity statin therapy was significantly better than the levels in patients not on statins.

Participants on moderate intensity statin therapy had their lipid levels at target.

Participants in whom high intensity statin therapy was prescribed were 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 to attain lipid targets.

Table 3.6 Statin intensity and lipid levels

Statin intensity	Mean total cholesterol (mmol/L)	Mean triglycerides (mmol/L)	Mean HDL-C (mmol/L)	Mean LDL-C (mmol/L)
No statin	4.45	1.53	1.30	2.69
Low intensity	3.75	1.36	1.21	2.11
Moderate intensity	4.19	1.89	1.20	2.44
High intensity	4.52	2.86	1.09	2.62

3.4 Glycated Haemoglobin (HBA1C) and the Lipid Profile

The range of HBA1C was 5.0% to 17.3% with a mean of 8.7% (SD = 2.34%).

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.

3.5 HBA1C and LDL-C

A statistically significant (p-value of 0.007) positive linear relationship between HBA1C and LDL was obtained from the correlation test.

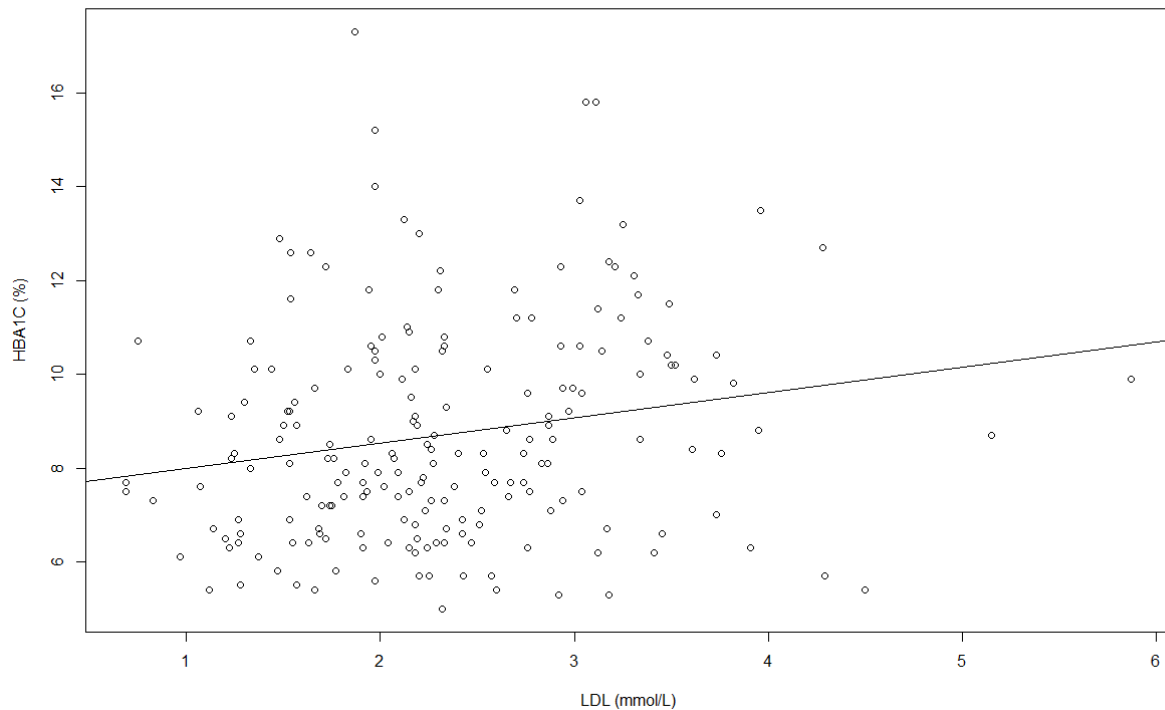


Figure 3.2 Relationship between HBA1C and LDL-C

3.6 HBA1C < 7% and the Lipid Profile

HBA1C levels less than 7% did not influence total cholesterol, LDL-C, and HDL-C. It did correlate with a lower triglyceride level. Good glycaemic control to a HBA1C of less than 7% improved triglyceride levels but did not improve other lipid parameters. With respect to having all four lipid parameters at target, the HBA1C of less than 7% showed no correlation.

3.7 Blood Pressure

There is no significant correlation between systolic or diastolic blood pressure and weight more than 100 kg or with lipid levels.

CHAPTER FOUR

4. DISCUSSION

4.1 Summary of the Results

Using the SEMDSA guidelines lipid targets as lipid-control goals, the majority of participants have their total cholesterol, triglycerides, and HDL-C at target but do not have their LDL-C at target. In addition, the vast majority of patients do not have all four lipid parameters at target.

Most of the participants are on lipid-modifying therapy with simvastatin being the most commonly used agent.

Among the participants who have controlled diabetes i.e. a HBA1C of less than or equal to seven per cent, only the level of triglycerides appears to be positively affected by this. There was no association between diabetic control and the other lipids levels, namely total cholesterol, HDL-C, and LDL-C.

With regard to other cardiovascular risk factors: a fifth of the participants have a weight of at least 100 kilograms, just over 80 per cent of participants are hypertensive, only two out of every five hypertensive participants have blood pressures at target, and the average HBA1C of this sample is 8.7 per cent, which by definition is uncontrolled diabetes. However neither blood pressure nor weight correlated significantly with any of the lipid levels.

4.2 Limitations of the Study

The lipid analysers were changed on 20 August 2016 therefore all the lipid readings were not done by one analyser. This may or may not have an impact on the results.

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 may have been slightly different had they been done on the same day.

4.3 Discussion of the Results

In this cohort the low percentage of participants meeting all lipid targets allows us to conclude that the prevalence of diabetic dyslipidaemia is significant. The strategy in which statin therapy is used has not resulted in optimal control of diabetic dyslipidaemia. This is a global problem as evidenced by numerous studies. In a Chinese study 54.9%, 43.7%, and 37.4% of participants were not at goal (according to local practice guidelines) for LDL-C, TG, and HDL-C respectively.³⁰ Similar rates of prevalence have been reported in the Canadian ⁹ and German ²⁰ arms of the DYSlipidemia International Study.

This study reveals that, according to the SEMDSA guidelines, total cholesterol, triglycerides, and HDL-C are generally at target. While there's no literature defining an acceptable level of dyslipidaemic prevalence in diabetics, this study shows the most well controlled lipid fraction is triglycerides with two thirds of the cohort having triglycerides at target. Along with a level of HDL-C control of just over half the sample population and a low level of LDL-C control of approximately a quarter, the level of triglycerides control may also not be optimal. Of note, only one in eight patients has all lipid parameters controlled. Ideally, all four parameters should be at target to minimize the risk of vascular complications.⁵

Despite having well-defined treatment goal guidelines the clinical practice of pharmacologically controlling diabetic dyslipidaemia remains poor. Possible underlying reasons need to be sought, such as suboptimal treatment strategies and undertreatment.⁸

Individual factors or a combination of factors may have contributed to the high prevalence of dyslipidaemia.

Clinician lack of exposure to treatment guidelines leading to a gap in knowledge in this area may be a factor. Reasons for this possible lack of exposure need to be explored

however the poor dissemination of guidelines or an absence of boldly displaying the current guidelines in the clinic setting could be possible reasons.

The suboptimal selection of lipid-lowering therapy may be another impediment in the control of diabetic dyslipidaemia. The ability to choose and successfully titrate therapy may be influenced by 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.⁹

Patient factors such as the adoption of a more westernized diet and following a more sedentary lifestyle are obstacles to good glycaemic and lipid control. Poor adherence to therapy is a pervasive problem. This study has not explored treatment compliance but in clinical practice this is certainly a factor in suboptimal lipid control.

Resource limitations in the public sector is another consideration when attempting to explain the poor control of diabetic dyslipidaemia. Simvastatin is the only statin readily dispensed on a routine prescription. Despite its time-honoured and proven efficacy, when maximal doses are reached and fail to provide adequate lipid control the need for more potent statins, such as atorvastatin, is invoked. Herein lies a possible reason for suboptimal statin use; the dispensing of more potent statins often requires special motivation and stock levels are sometimes depleted. The required motivation stems from a need to regulate the use of these expensive drugs. These statins are usually maintained at lower stock levels compared to simvastatin resulting in the risk of depletion, which often occurs.

Staff shortage at fully booked clinics impairs the quality of consultations. The emphasis unwittingly shifts towards seeing patients at a faster rate which results in the optimization of lipid-lowering measures being overlooked. Optimizing drug therapy, counselling on treatment adherence and lifestyle modification, and referring to dieticians generally falls away when faced with greater patient loads.

HBA1C more than 7%, which may be considered to be uncontrolled diabetes mellitus, is associated with worse dyslipidaemia compared with HBA1C less than 7%. This association is was also demonstrated in a study directed specifically toward the

relationship between glycaemic control and the serum lipid profile in type 2 diabetic patients,¹⁷ and in a large scale Malaysian study of more than 28,000 participants.⁶ These findings highlight the point that good glycaemic control is an important contributor to optimizing lipid levels. One may even consider a six month period of trying to optimize glycaemic control before initiating lipid-lowering therapy.

The only lipid abnormality which consistently correlates with obesity is a high triglyceride level.³¹

Although no relationship was demonstrated between blood pressure and lipid levels other studies did show a significant relationship between hypertension and high LDL-C levels in type 2 diabetics.³² This may need to be explored further. A possible reason for this statistical difference might be the difference in participant demographic.

A positive relationship exists between overweight or obesity and high blood pressure with obese individuals having up to a two-fold higher prevalence of hypertension as compared to the non-obese.³³ In this study body mass indices of participants could not be ascertained so a weight of more than 100 kg was used as a representation of overweight, and possibly obesity. No significant relationship could be drawn between blood pressure and weight more than 100 kg.

Lipid-modifying therapy was prescribed for 84 per cent of the participants with statins being the most prescribed agent. Of the statins only simvastatin and atorvastatin are prescribed and at various intensities.

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 fail to exhibit control of LDL-C. This implies that in addition to high intensity statins other agents such as ezetimibe are required to lower LDL-C to target.

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

Participants who are not on statin therapy have comparable levels of HDL-C to those who are on statin therapy.

The benefit of statin therapy is reflected in the significantly lower LDL-C levels in statin-treated participants compared to participants not treated with statins. Despite the suboptimal prevalence of controlled LDL-C, statin therapy would have a positive impact in preventing cardiovascular complications by reducing LDL-C.²³

Lower LDL-C levels are associated with lower HBA1C levels. Measures to lower and thus improve LDL-C will also improve HBA1C and reduce the risk of cardiovascular complications.

Higher total cholesterol, triglyceride, and LDL-C levels are associated with higher HBA1C levels. Optimal control of diabetes (a HBA1C level of less than or equal to 7.0 per cent) will help significantly lower lipid levels in statin-treated patients. This may obviate the need for escalating to more potent statins or adding other classes of lipid-lowering therapy; a benefit which would be appreciated in a resource-constrained setting.

Glycaemic control has not been shown to have an influence on HDL-C. The optimal control of HDL-C may therefore be a desired effect of statin-therapy independent of HBA1C level.

An obvious conclusion which can be drawn from the above findings is that glycaemic control does not influence having all four lipid parameters (total cholesterol, triglycerides, LDL-C, and HDL-C) at target, with target being the ideal lipid control goal for all diabetics.

Participants with all lipids at target had the best average systolic and diastolic blood pressures.

Overall, the results reveal a disappointingly high prevalence of diabetic dyslipidaemia in type 2 diabetics. The long-term cerebrovascular, cardiovascular, and peripheral vascular complications in this population are potentially preventable with adequate lipid control. The level of diabetic dyslipidaemia revealed in this cohort of patients, which may well be a true reflection of all type 2 diabetics is unacceptable. All possible reasons for this should be sought, prioritised and remedied.

CHAPTER FIVE

5. CONCLUSION AND RECOMMENDATIONS

Diabetic dyslipidaemia has long since established itself as a serious entity with disastrous cardiovascular complications. Researchers and clinicians have acknowledged the resulting, and potentially preventable, consequences.

An ever-growing database of studies has highlighted the global difficulty in controlling diabetic dyslipidaemia, and this study reiterates the challenge. A variety of causes for suboptimal control have been identified and many of these are complex problems. Despite the many challenges, those responsible for the provision of healthcare, both clinicians and non-clinicians, should endeavor to find solutions or at least mitigate the consequences.

Poorly treated diabetic dyslipidaemia invites more difficulties. As an example, the financial expenses associated with an untreated ailing diabetic population may be significant. But, above all else, the disservice to patients by not optimizing our management of diabetic dyslipidaemia is inexcusable.

In short, improved and consistent measures are required to ensure all lipid parameters in diabetic patients are at target.

At the conclusion of this study the following recommendations are made:

- Doctors working at the diabetic clinic should be updated regularly with the SEMDSA guidelines. They should also be advised on which lipid-modifying agents are available and the intensities of these agents. A suggested strategy for prescribing lipid-modifying therapy may need to be provided.
- Consulting rooms should have the latest SEMDSA guidelines displayed in plain sight as a reminder and reference aid to serve clinicians.
- Hospital administrators should consider the dyslipidaemic burden and allow for easier access to the more potent statins.

- Procurement policies need to be revised to prevent stock depletion of the already difficult-to-obtain higher potency statins.
- Greater awareness needs to be created to highlight the dreadful consequences of diabetic dyslipidaemia in an attempt to attract much needed resources.

CHAPTER SIX

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APPENDICES

APPENDIX A

DATA COLLECTION SHEET

Study number	
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Age					
Gender	Male			Female	
Race	Black	White	Indian	Coloured	Other:
Weight					
Height					
BMI					
Duration of DM					
Hypertension	Yes			No	
	Treated	Untreated			
	Latest BP:				
Smoking	Yes		No		Ex
Established Cardiovascular Disease	Yes			No	
	Coronary artery disease	Cerebro-vascular disease	Periph. artery disease		
CKD (eGFR<30mL/min/1.73m ²)	Yes			No	
Diabetic treatment	Oral Agents			Insulin	
	Metformin	Sulfonyl urea	Other	Yes	No

SERUM LEVELS (Must be within previous 12 months)					
Date					
HbA1c					
Total Cholesterol					
Triglyceride					
HDL-Cholesterol					
LDL-Cholesterol					

LIPID MODIFYING THERAPY			
On treatment	Yes		No
	Duration:		
Current lipid lowering therapy (at time of lipid profile)			
Simvastatin	10mg OD	20mg OD	
	40mg OD	Other	
Atorvastatin	10mg OD	20mg OD	
	40mg OD	Other	
Other statin + dose			
Ezetimibe + dose			
Fibrate + dose			
Other			
Other			

Other	
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CONCOMITANT MEDICATION	
Drug and Dose	
Drug and Dose	
Drug and Dose	
Drug and Dose	
Drug and Dose	
Drug and Dose	
Drug and Dose	
Drug and Dose	
Drug and Dose	
Drug and Dose	



R14/49 Dr Sagen Naidoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170146

NAME: Dr Sagen Naidoo
(Principal Investigator)
DEPARTMENT: Internal Medicine
Division of Endocrinology and Metabolism
Charlotte Maxeke Johannesburg Academic Hospital

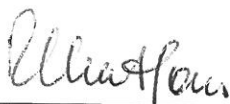
PROJECT TITLE: The Assessment of Lipid Levels in Type 2 Diabetic Patients in Relation to Lipid Modifying Therapy at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Diabetic Clinic

DATE CONSIDERED: 27/01/2017

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Frederick Raal

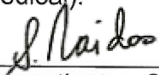
APPROVED BY: 
Professor P. Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 22/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in January and will therefore be due in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

01 March 2017
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES



12 April 2017

Dr Sagen Naidoo

Department of Internal Medicine

Charlotte Maxeke Johannesburg Academic Hospital

Sent by email to: sagen_aidoo@yahoo.com

Dear Dr Naidoo

Re: Protocol Ref no: M170146

Protocol Title: The Assessment of Lipid Levels in Type 2 Diabetic Patients in Relation to Lipid Modifying Therapy at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Diabetic Clinic

Principal Investigator: Dr Sagen Naidoo

Protocol Amendments

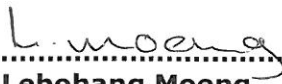
This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the protocol amendments for the abovementioned protocol, as detailed in your letter dated 23 March 2017.

The following documents were received:

- Cover Letter dated 23 March 2017.
- Study Proposal.
- HREC (Medical) Clearance Certificate.

Thank you for keeping us informed and updated.

Yours Sincerely,


.....
Mr Lebohang Moeng
Administrative Assistant
Human Research Ethics Committee (Medical)

