# DYSLIPIDAEMIA PATTERN AND PREVALENCE AMONG TYPE 2 DIABETES MELLITUS PATIENTS ON LIPID-LOWERING THERAPY AT A TERTIARY CENTRAL SOUTH AFRICAN HOSPITAL

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Submitted in compliance with the stipulations of Master of Philosophy degree in Endocrinology (MPhil Endocrinology) at the Faculty of Health Sciences, University of the Free State, Bloemfontein

17 September 2020

Supervisor: Prof TRP Mofokeng

Biostatistician: Ms R Nel

**DECLARATION (STUDENT)**

I, **Lebohang Pitso**, declare that the mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification Master of Philosophy in Endocrinology (MPhil in Endocrinology) at the University of the Free State, is my independent work and that I have not previously submitted it for a qualification at another institution of higher education.

**Date: 17 September 2020**

**Signature:**

**DECLARATION (SUPERVISOR)**

I, **Professor TRP Mofokeng**, the supervisor of this mini-dissertation in a publishable format entitled: “Dyslipidaemia pattern and prevalence among type 2 diabetes mellitus patients on lipid-lowering therapy at a tertiary central South African hospital”, hereby certify that the work in this project was done by Lebohang Pitso at the department of Internal Medicine, University of the Free State. I hereby approve the submission of this mini-dissertation and also affirm that it has not been submitted previously to this or any other institution for admission to a degree or any other qualification.

**Date: 17 September 2020**

**Signature:** 

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- Ms Riette Nel for her immense input in performing statistical analysis of the project and assisting with the interpretation of the data and analyses, and for displaying patience in this regard.

## DEDICATION

This project is dedicated to:

- My wife (Theola) and my two daughters (Reamohetse and Tshwanelo), for the family time they sacrificed. Your continuous support and encouragement are appreciated.
- My parents (Maleke and Mosela) for my upbringing and many sacrifices made to ensure I receive academic and social education.

*Keya leboha ho lona lohle* (“Thank you to all of you”).

**ABSTRACT**

Background

Atherosclerotic cardiovascular disease (ASCVD) is a major cause of death worldwide. A large number of deaths due to ASCVD occur among people with diabetes mellitus (DM). One of the important modifiable risk factors associated with ASCVD is dyslipidaemia and its prevalence is not known in central South Africa (SA). This study aimed to determine the pattern and prevalence of dyslipidaemia among type 2 diabetes mellitus (T2DM) patients on lipid-lowering therapy.

Methods

This descriptive, retrospective patient record study was conducted at Universitas Academic Hospital, Bloemfontein, in central SA. The study population included 143 consecutive T2DM patients of any age that attended the Diabetes Clinic from 1 January to 31 March 2019. The patients had to be on lipid-lowering therapy for a minimum duration of 3 months. Data was sourced from the clinic files and it included lipid profile, anthropometric and demographic data. Dyslipidaemia was defined using the 2018 SA dyslipidaemia guidelines.

Result

The median age of the study participants was 63 years (interquartile range 52-71 years). Majority of the participants (n=92; 64.3%) were female. The median duration of DM diagnosis was 18 years (interquartile range 13-23 years). The prevalence of dyslipidaemia was 86.7% that occurred in 124 out of the 143 subjects. Combined dyslipidaemia, namely triglycerides (TG) + low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) + TG or HDL + LDL, was the most common pattern (n=51; 42.5%) largely due to raised TG+LDL contributing 37.2% to this pattern. The second and third most common pattern was isolated (LDL, HDL or TG) and mixed dyslipidaemia (TG+HDL+LDL) at 40.8% and 16.7%, respectively. The most frequent abnormal lipid particle (n=84; 70%) was LDL cholesterol ≥ 1.8mmol/L. Of the 140 participants on statin therapy, only 5% were on high-intensity statin therapy.

Conclusion

There is a high prevalence of dyslipidaemia among DM patients despite the use of lipid-lowering therapy in this small retrospective study. The study highlights the need for better education of healthcare providers regarding the intensification of lipid-lowering therapy, along with improved strategies to address poor glycaemic control and other modifiable lifestyle factors.

**Keywords:** Atherosclerotic cardiovascular disease, diabetes mellitus, dyslipidaemia, South Africa, statin

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| | |
|---|---|
| ACR | Albumin creatinine ratio |
| ARV | Antiretroviral |
| ASCVD | Atherosclerotic cardiovascular disease |
| ATV/r | Atazanavir/ritonavir |
| AZT | Zidovudine |
| d4T | Stavudine |
| DTG | Dolutegravir |
| BB | Beta-blockers |
| BMI | Body mass index |
| DM | Diabetes mellitus |
| CAD | Coronary artery disease |
| CEPHEUS SA | CEntralised Pan-South African survey on tHE Undertreatment of hypercholeSterolaemia (CEPHEUS SA) |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| DYSIS | DYSlipidemia International Study |
| EFV | Efavirenz |
| eGFR | Estimated glomerular filtration rate |
| fT4 | Free thyroxine |
| IHD | Ischaemic heart disease |
| ALP | Atherogenic lipoprotein phenotype |
| TG | Triglyceride |

| | |
|---|---|
| HDL-C | High-density lipoprotein cholesterol |
| HDL | High-density lipoprotein |
| HbA1c | Glycated haemoglobin |
| LASSA | Lipid and Atherosclerosis Society of Southern Africa |
| LDL-C | Low-density lipoprotein cholesterol |
| LDL | Low-density lipoprotein |
| LPV/r | Lopinavir/ritonavir |
| MDRD | Modification of Diet in Renal Disease |
| PCR | Protein creatinine ratio |
| PVD | Peripheral vascular disease |
| RPV | Rilpivirine |
| SA Heart | South African Heart Association |
| SBP | Systolic blood pressure |
| sdLDL | Small dense low-density lipoprotein |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| TSH | Thyroid-stimulating hormone |
| VLDL | Very-low-density lipoprotein |
| apoB | Apolipoprotein B |
| CETP | Cholesteryl ester transfer protein |
| SA | South Africa |
| SEMDSA | Society for Endocrinology, Metabolism and Diabetes of South Africa |
| HIV | Human immunodeficiency virus |

| | |
|---|---|
| HT | Hypertension |

## LIST OF APPENDICES

## 1.1 Diabetes & cardiovascular disease

Diabetes mellitus (DM) is on the increase globally and most rapidly in the middle- and low-income countries.[1] An estimated 463 million global adult population were living with diabetes in 2019 and the global prevalence has doubled to 9.3% since 2000.[2] Of the 37.9 million deaths worldwide due to non-communicable diseases in 2012, atherosclerotic cardiovascular disease (ASCVD) made up almost half (17.5 million).[3] ASCVD resulted in the majority of the 5 million diabetes-related deaths in 2015, with Africa having one of the highest death rates from ASCVD due to DM.[3]

Dyslipidaemia association with increased cardiovascular (CV) events has been previously documented.[4,5] Elevated low-density lipoprotein cholesterol (LDL-C) as the cause of ASCVD is unequivocal.[6,7] People with DM have an increased risk of ASCVD and mortality compared to people without DM.[8,9] Coronary artery disease (CAD), ischaemic stroke and peripheral vascular disease (PVD) are all increased two- to four-fold in the DM population.[10,11] Heart failure risk is even greater with the risk reported as high as eight-fold in some studies.[10,12,13]

Statin therapies have been shown to improve CV outcomes.[14,15] Amongst the diabetes population, the CV benefits with the use of statins are seen for both primary and secondary prevention.[16,17] In people with type 2 diabetes mellitus (T2DM) statin therapy significantly reduces ASCVD events.[18] The 5-year incidence of major cardiovascular disease (CVD) events is reduced by 23% for every 1 mmol/L reduction in LDL-C.[18] As such, statin therapy is recommended as a first-line treatment for primary and secondary prevention of ASCVD by major society guidelines.[18,19] Ezetimibe, a non-statin therapy, has been proven to result in additional lowering of LDL-C levels when added to statin therapy.[20] In this study, the primary composite CV endpoint was significantly reduced in the statin-ezetimibe group compared to statin alone. Approximately 27% of the study population had the diagnosis of DM.[20]

### 1.2 Diabetic dyslipidaemia

Diabetic dyslipidaemia, also known as atherogenic lipoprotein phenotype (ALP) or atherogenic dyslipidaemia, manifests with elevated fasting and postprandial triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) and normal-to-mildly elevated low-density lipoprotein cholesterol (LDL-C) with the predominance of small dense low-density lipoprotein (sdLDL) particles.[18,21,22] The pathophysiology of this biochemical lipid abnormality is complex and still not fully understood. In patients with well-controlled type 1 diabetes mellitus (T1DM) on insulin, lipid abnormalities observed are few if any.[22] Diabetic dyslipidaemia typically manifest in patients with T2DM, obesity and metabolic syndrome as well as poorly controlled T1DM.[22]

Several factors are implicated in the development of diabetic dyslipidaemia pattern. One of the dominant and well-known mechanism is an overproduction of large, TG-rich very-low-density lipoprotein (VLDL) particles in the liver.[21,22] This in response to elevated levels of free fatty acids that are typical of T2DM.[21] The free fatty acids are released from the more metabolically active, centrally located adipocyte tissue in response to a lack of insulin action that ordinarily suppresses hormone-sensitive lipase and therefore lipolysis.[23] In addition to hepatic overproduction of TG-rich lipoproteins, there is decreased clearance of these lipoproteins.[21,22] The resulting elevation in TG-rich lipoproteins together with high TG intake, poor glycaemic control and certain medications in patients with T2DM all contribute to hypertriglyceridaemia.[21]

Reduced HDL-C is another feature of diabetic dyslipidaemia and is due to several mechanisms. Increased concentrations of TG-rich VLDL particles as found in DM promote and accelerate the exchange of TG from VLDL for cholesteryl esters in HDL.[21,23] Also, the TG-rich HDL is susceptible to increased catabolism leading to reduced measured HDL.[22,23] Glycation of apolipoproteins associated with DM further contributes to reduced HDL-C by promoting HDL catabolism.[23] These HDL-C abnormalities have led to the observation that reduced HDL is a precursor to the development of DM, rather than being a consequence of DM and insulin resistance.[23]

One of the important hallmarks of diabetic dyslipidaemia pattern is the production of sdLDL particles. Cholesteryl ester transfer protein (CETP) is an enzyme responsible for facilitating the transport of cholesteryl ester from HDL and LDL to VLDL.[23] In exchange, the transport of TG

from VLDL to HDL and LDL occurs in the opposite direction.[23] This exchange results in the production of smaller as well as denser LDL and HDL particles. This process is accelerated in both types of DM and results in the production of sdLDL.[23] In diabetes the LDL-C levels are commonly within a normal range, comparable to the non-diabetic population; however, the increased levels of sdLDL are atherogenic and associated with increased ASCVD.[21,23] The modification or glycation of the circulating LDL structure allows the apoB to bind the scavenger receptor on the macrophages in the arterial wall. The macrophages change into the foam cells that participate in the development of atherosclerosis associated with increased CVD.[23]

### 1.3 South African dyslipidaemia and type 2 diabetes mellitus guidelines

Dyslipidaemia is the quantitative and qualitative elevation of LDL-C, elevated TG or decrease in HDL-C. The 2018 South African (SA) dyslipidaemia guideline classifies DM as falling into high- and very high-risk categories. As such, the consensus statement recommends against using Framingham risk scoring in this group of patients for primary prevention of CV events to avoid underestimation of the CV risk.[24] Similarly, the 2017 SA type 2 diabetes mellitus guidelines discourage CV risk scoring as T2DM is considered to be a coronary risk equivalent and lipid-lowering therapy is indicated in almost all the patients.[25] A very high-risk category is any T2DM patient with one or more risk factors such as dyslipidaemia, smoking, hypertension (HT), or age >40 years. Their risk is equivalent to >30% on the Framingham CVD risk score, and the LDL-C therapeutic target is <1.8mmol/l.[24] Any T2DM patient aged <40 years without other CV risk factors is classified as high-risk with the Framingham CVD risk score equivalent to 15-30%. The LDL-C target with lipid-lowering therapy in this instance is <2.5mmol/l.[24] The LDL-C level is the preferred therapeutic target marker with every 1mmol/l reduction associated with a 20% reduction in CAD deaths, 15% reduction in stroke, 24% reduction in major coronary events and 10% reduction in all-cause mortality.[24,26] HDL-C of ≤1.2mmol/l in women and ≤1.0mmol/l in men and TG ≥1.7mmol/l are considered to confer higher CV risk and should be optimised in T2DM.[24,25] The SA dyslipidaemia guideline recommends further investigation for other risk factors such as T2DM whenever TG levels are ≥ 1.7mmol/l. Lipid-lowering treatment may be considered if TG >2.3mmol/l in patients at high- and very high-risk of ASCVD such as T2DM.[24] Statin is the preferred therapy for lowering TG. However, if TG >10mmol/l there is a high risk of

acute pancreatitis and in this instance, fibrate therapy is preferred along with insulin, dietary and lifestyle modifications.[24] Despite the association of low HDL-C with increased CVD risk, there is no strong CV benefit to support the use of therapy aimed specifically at the HDL-C target.[24]

### 1.4 Under-treatment of dyslipidaemia

Despite the higher risk of ASCVD associated with an abnormal lipid profile, dyslipidaemia is undertreated. In one multi-centre study of over 7 000 participants in Europe, prevalence and treatment of atherogenic dyslipidaemia was assessed. Only 45% of the participants with atherogenic dyslipidaemia were on lipid-lowering therapy.[27] In another South African study that evaluated achievement of LDL-C targets in patients on lipid-lowering therapy in clinical practice, only 41.4% of patients achieved their LDL-C target.[28] In the Europe study approximately 27%, and in the South African study 64% of the participants had T2DM.[27,28] In another tertiary centre in Gauteng province, Daya et al[29] reported a high (93.5%) prevalence of dyslipidaemia despite statin use among 200 T2DM patients. Up to 80% of the participants in this study had elevated LDL-C of >1.8mmol/l as the most prevalent lipid abnormality.[29]

### 1.5 Rationale of the study

A previous report assessing lipid goal attainment in patients on lipid-lowering therapy in central South Africa was done in the private sector.[30] Additionally, in the CEPHEUS SA study, both patients with and without DM were included.[30] In our setting, there is a lack of data regarding the prevalence and pattern of dyslipidaemia among T2DM patients on lipid-lowering therapy in the public sector setting. Additionally, data regarding the attainability of lipid targets using lipid-lowering therapy in T2DM patients is not known. The rationale of this study was based on the observation of local and global literature indicating the presence of residual diabetic dyslipidaemia due to the failure of T2DM patients to achieve recommended lipid level targets. Available data also highlights the excess CV risk associated with residual diabetic dyslipidaemia. The scale of dyslipidaemia despite lipid-lowering treatment associated with T2DM in our setting is not known.

### 1.6 Study hypothesis

Based on the pathophysiology of T2DM and insulin resistance as well as literature review, we hypothesised that the prominent pattern of dyslipidaemia would be the combined pattern namely elevated TG and low HDL-C. Given the available prevalence studies, we hypothesised that the prevalence of dyslipidaemia in this study among T2DM would be high despite the use of lipid-lowering therapy and that a large number of T2DM patients would not be achieving the desired LDL-C targets.

### 1.7 Objectives

The study aimed to determine the pattern and prevalence of dyslipidaemia among T2DM patients on lipid-lowering therapy attending a public-sector tertiary diabetes clinic in the Free State province of South Africa. Also, the attainability of the LDL-C treatment target amongst other lipid level targets was investigated.

## 1.8 References


1. World Health Organization. *Global Report on Diabetes*. Geneva; 2016. http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf?sequence=1. Accessed January 4, 2019.

2. International Diabetes Federation. *IDF Diabetes Atlas Ninth Edition 2019*.; 2019. http://www.idf.org/about-diabetes/facts-figures. Accessed March 21, 2021.

3. International Diabetes Federation. *Diabetes and Cardiovascular Disease*. Brussels: International Diabetes Federation; 2016. doi:10.1017/CBO9781139939577.002

4. Pol T, Held C, Westerbergh J, et al. Dyslipidemia and risk of cardiovascular events in patients with atrial fibrillation treated with oral anticoagulation therapy: Insights from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *J Am Heart Assoc*. 2018;7(3). doi:10.1161/JAHA.117.007444

5. Rygiel K. Hypertriglyceridemia - common causes, prevention and treatment strategies On the crossroads of high TG and CV risk - a safe passage for our patients. *Curr Cardiol Rev*. 2018;14(1):67. doi:10.2174/1573403x14666180123165542

6. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

7. Michos ED, McEvoy JW, Blumenthal RS. Lipid Management for the Prevention of Atherosclerotic Cardiovascular Disease. Jarcho JA, ed. *N Engl J Med*. 2019;381(16):1557-1567. doi:10.1056/NEJMra1806939

8. Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. *Diabetol Metab Syndr*. 2017;9(1):25. doi:10.1186/s13098-017-0225-1

9. Katsiki N, Banach M, Mikhailidis DP. Is type 2 diabetes mellitus a coronary heart disease

equivalent or not? Do not just enjoy the debate and forget the patient! *Arch Med Sci*. 2019;15(6):1357-1364. doi:10.5114/aoms.2019.89449

10. Martín-Timón I. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes*. 2014;5(4):444. doi:10.4239/wjd.v5.i4.444

11. Kamil S, Sehested TSG, Carlson N, et al. Diabetes and risk of peripheral artery disease in patients undergoing first-time coronary angiography between 2000 and 2012 - A nationwide study. *BMC Cardiovasc Disord*. 2019;19(1):234. doi:10.1186/s12872-019-1213-1

12. Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 Diabetes Mellitus and Heart Failure, A Scientific Statement From the American Heart Association and Heart Failure Society of America. *J Card Fail*. 2019;25(8):584-619. doi:10.1016/j.cardfail.2019.05.007

13. Kenny HC, Abel ED. Heart Failure in Type 2 Diabetes Mellitus: Impact of Glucose-Lowering Agents, Heart Failure Therapies, and Novel Therapeutic Strategies. *Circ Res*. 2019;124(1):121-141. doi:10.1161/CIRCRESAHA.118.311371

14. Koskinas KC, Siontis GCM, Piccolo R, et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. *Eur Heart J*. 2018;39(14):1172-1180. doi:10.1093/eurheartj/ehx566

15. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532-2561. doi:10.1016/S0140-6736(16)31357-5

16. Naeem F, McKay G, Fisher M. Cardiovascular outcomes trials with statins in diabetes. *Br J Diabetes*. 2018;18(1):7-13. doi:10.15277/bjd.2018.161

17. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: Evidence report and systematic review for the US preventive services task force. *JAMA - J Am Med Assoc*. 2016;316(19):2008-2024. doi:10.1001/jama.2015.15629

18. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455

19. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678

20. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489

21. Blom DJ. Dyslipidaemia in Type 2 Diabetes. *S Afr J Diabetes Vasc Dis*. 2013;10(2):48-50. https://0-journals.co.za.wagtail.ufs.ac.za/docserver/fulltext/sajdvd/10/2/sajdvd_v10_n2_a2.pdf?expires=1538597176&id=id&accname=57783&checksum=B9DF8F8B6E090721DE5BAE1B2DE75E14. Accessed October 3, 2018.

22. Athyros VG, Doumas M, Imprialos KP, et al. Diabetes and lipid metabolism. *Hormones*. 2018;17(1):61-67. doi:10.1007/s42000-018-0014-8

23. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes Dyslipidemia. *Diabetes Ther*. 2016;7(2):203-219. doi:10.1007/s13300-016-0167-x

24. Kluq E, Raal F, Marais D, et al. South African dyslipidaemia guideline consensus statement: 2018 update A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA). *South African Med J*. 2018;108 (Part 2):973-1000. doi:DOI:10.7196/SAMJ.2018.v108i11.13383

25. Amod A (Ed.). SEMDSA 2017 Guidelines for the Management of Type 2 diabetes mellitus. *JEMDSA*. 2017;22(1 (Supplement 1)):S1-S196. https://www.semdsa.org.za/images/647-4385-1-pb.pdf. Accessed March 4, 2019.

26. Soran H, Dent R, Durrington P. Evidence-based goals in LDL-C reduction. *Clin Res*

*Cardiol*. 2017;106(4):237-248. doi:10.1007/s00392-016-1069-7

27. Halcox JP, Banegas JR, Roy C, et al. Prevalence and treatment of atherogenic dyslipidemia in the primary prevention of cardiovascular disease in Europe: EURIKA, a cross-sectional observational study. *BMC Cardiovasc Disord*. 2017;17(1):160. doi:10.1186/s12872-017-0591-5

28. Blom DJ, Raal F, Amod A, Naidoo P, Lai Y. Management of low-density lipoprotein cholesterol levels in South Africa: the International ChoLesterol management Practice Study (ICLPS). *Cardiovasc J AFRICA* •. 2019;30(1):15-23. doi:10.5830/CVJA-2018-054

29. Daya R, Bayat Z, Raal F. Prevalence and pattern of dyslipidaemia in type 2 diabetes mellitus patients at a tertiary care hospital. *J Endocrinol Metab Diabetes South Africa*. 2017;22(3):31-35. doi:10.1080/16089677.2017.1360064

30. Raal F, Schamroth C, Blom D, et al. CEPHEUS SA : a South African survey on the undertreatment of hypercholesterolaemia : cardiovascular topics. *Cardiovasc J Afr*. 2011;22(5):234-240. doi:10.5830/CVJA-2011-044

## CHAPTER 2 – PUBLISHABLE MANUSCRIPT

### Title

Dyslipidaemia pattern and prevalence among type 2 diabetes mellitus patients on lipid-lowering therapy at a tertiary central South African hospital


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**Abstract**

Background

Atherosclerotic cardiovascular disease (ASCVD) is a major cause of death worldwide. A large number of deaths due to ASCVD occur among people with diabetes mellitus (DM). One of the important modifiable risk factors associated with ASCVD is dyslipidaemia and its prevalence is not known in central South Africa (SA). This study aimed to determine the pattern and prevalence of dyslipidaemia among type 2 diabetes mellitus (T2DM) patients on lipid-lowering therapy.

Methods

This descriptive, retrospective patient record study was conducted at Universitas Academic Hospital, Bloemfontein, in central SA. The study population included 143 consecutive T2DM patients of any age that attended the Diabetes Clinic from 1 January to 31 March 2019. The patients had to be on lipid-lowering therapy for a minimum duration of 3 months. Data was sourced from the clinic files and it included lipid profile, anthropometric and demographic data. Dyslipidaemia was defined using the 2018 SA dyslipidaemia guidelines.

Result

The median age of the study participants was 63 years (interquartile range 52-71 years). Majority of the participants (n=92; 64.3%) were female. The median duration of DM diagnosis was 18 years (interquartile range 13-23 years). The prevalence of dyslipidaemia was 86.7% that occurred in 124 out of the 143 subjects. Combined dyslipidaemia, namely triglycerides (TG) + low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) + TG or

HDL + LDL, was the most common pattern (n=51; 42.5%) largely due to raised TG+LDL contributing 37.2% to this pattern. The second and third most common pattern was isolated (LDL, HDL or TG) and mixed dyslipidaemia (TG+HDL+LDL) at 40.8% and 16.7%, respectively. The most frequent abnormal lipid particle (n=84; 70%) was LDL cholesterol ≥ 1.8mmol/L. Of the 140 participants on statin therapy, only 5% were on high-intensity statin therapy.

Conclusion

There is a high prevalence of dyslipidaemia among DM patients despite the use of lipid-lowering therapy in this small retrospective study. The study highlights the need for better education of healthcare providers regarding the intensification of lipid-lowering therapy, along with improved strategies to address poor glycaemic control and other modifiable lifestyle factors.

**Keywords:** Atherosclerotic cardiovascular disease, diabetes mellitus, dyslipidaemia, South Africa, statin

## Background

Diabetes mellitus (DM) is on the increase globally and most alarmingly in the Africa region.[1] An estimated 463 million global adult population were living with diabetes in 2019 and the global prevalence has doubled to 9.3% since 2000.[1] Africa region has the highest proportion in the world of both undiagnosed DM (59.7%) and DM related deaths (73.1%) occurring under 60 years of age.[1] Atherosclerotic cardiovascular disease (ASCVD) is the largest contributor to both morbidity and mortality for people with DM with the relative risk of ASCVD between 1.6 and 2.6.[1]

Dyslipidaemia associated with DM is an important modifiable metabolic risk factor to reduce ASCVD.[1] Diabetic dyslipidaemia, also known as atherogenic lipoprotein phenotype (ALP) or atherogenic dyslipidaemia, manifests with elevated fasting and postprandial triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) and normal-to-mildly elevated low-density lipoprotein cholesterol (LDL-C) with the predominance of atherogenic small dense low-density lipoprotein (sdLDL) particles.[2–4] This pattern is mainly due to hepatic overproduction of TG-rich very-low-density lipoprotein (VLDL) particles and accelerated exchange of TG in VLDL for cholesteryl esters in HDL and LDL producing sdLDL.[2,3,5]

Elevated LDL-C, a form of dyslipidaemia, as the cause of ASCVD is unequivocal.[6,7] Coronary artery disease (CAD), ischaemic stroke and peripheral vascular disease (PVD) are all increased two- to four-fold in the DM population while heart failure risk is even greater with the risk reported as high as eight-fold in some studies.[8–11]

Lowering cholesterol levels, among other metabolic risk factors, can significantly reduce the risk of ASCVD outcomes.[1] Statin therapies have been shown to significantly reduce ASCVD events, including in people with type 2 diabetes mellitus (T2DM).[4,12,13] Amongst the DM population, cardiovascular (CV) benefits with the use of statins are seen for both primary and secondary prevention.[14,15] The 5-year incidence of major cardiovascular disease (CVD) events is reduced by 23% for every 1 mmol/L reduction in LDL-C.[4] As a result, statin therapy is recommended as a first-line treatment for primary and secondary prevention of ASCVD by major society guidelines.[4,16]

Ezetimibe, a non-statin therapy, has been proven to result in additional lowering of LDL-C levels when added to statin therapy and significantly reduced primary composite CV endpoint.[17] Approximately 27% of this study population had the diagnosis of DM.[17]

Both the South African (SA) dyslipidaemia and T2DM guidelines classify T2DM as a high CV risk condition and CV risk scoring is not needed to initiate statin therapy for primary CVD prevention.[18,19] Based on these guidelines, most T2DM patients' recommended LDL-C target is <1.8mmol/L.[18,19] Other recommended lipid targets are TG <1.7mmol/l, HDL-C of >1.2mmol/l in women and >1.0mmol/l in men.[18,19]

Despite the higher risk of ASCVD associated with an abnormal lipid profile, dyslipidaemia is undertreated. In one multi-centre study of over 7 000 participants in Europe, only 45% of the participants with atherogenic dyslipidaemia were on lipid-lowering therapy.[20] In another SA study that evaluated achievement of LDL-C targets in patients on lipid-lowering therapy in clinical practice, only 41.4% of patients achieved their LDL-C target.[21] In the Europe study

approximately 27% and in the SA study 64% of the participants had T2DM.[20,21] A previous report assessing lipid goal attainment in patients on lipid-lowering therapy in central SA was done in the private sector and included patients with and without DM.[21] In our setting, there is a lack of data regarding the prevalence and pattern of dyslipidaemia among T2DM patients on lipid-lowering therapy. Additionally, data regarding the attainability of lipid targets using lipid-lowering therapy is not available. Therefore, this study aimed to determine the pattern and prevalence of dyslipidaemia among T2DM patients on lipid-lowering therapy attending a public-sector tertiary Diabetes Clinic in the Free State province of SA. Also, the attainability of the LDL-C treatment target amongst other lipid level targets was investigated.

## Methods

### Study design and setting

It was a retrospective study based on patient records of T2DM patients that visited Universitas Academic Hospital Diabetes Clinic, Free State province in central South Africa, from 1 January to 31 March 2019. The Diabetes Clinic is based in the public sector and provides tertiary care service to a majority of the 2.9 million inhabitants of the province.

### Inclusion & exclusion criteria

Records of all T2DM patients of any age who consulted during the relevant period and on a minimum of 3 months of lipid-lowering therapy were enrolled in the study. Patients with T1DM, gestational diabetes, secondary causes of diabetes, patients not on lipid-lowering therapy for a minimum of 3 months, and missing patient records were excluded from the study.

**Population and sampling**

The files were sourced based on the Diabetes Clinic's diary that keeps a record of all the consultation visits. On average this referral clinic conducts 960 consultations per year and the majority of the patients are seen at least every six months and most have T2DM. Consecutive sampling was used and a total of 257 patient records were screened during the 3 months. The following clinical data were sourced from the patient records: age, gender, ethnicity, T2DM duration, presence or absence of ischaemic heart disease, peripheral vascular disease, stroke, hypothyroidism and current smoking status. Hypertension was recorded and graded according to the 2014 SA hypertension guidelines (Appendix F). The body mass index (BMI) was recorded and classified according to the World Health Organization (WHO) classification (Appendix G). Therapy for T2DM (oral, insulin or combination thereof) was also recorded. The following drug therapies that the patients were taking and could potentially influence the lipid profile were noted: beta-blockers, diuretics, corticosteroids, oestrogens and anti-retroviral therapy. The laboratory data included the fasting lipid profile that contained total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density cholesterol (LDL-C). LDL-C measured was indirect using Friedewald equation[18]. If TG exceeded 4.5mmol/L, LDL-C was not calculated by the laboratory as the equation relies on TG values $\leq$4.5mmol/L[18]. Lipid-lowering therapy type and dosage were also recorded. Data collected was recorded on the data collection sheet and transferred to a Microsoft Excel data spreadsheet for statistical analyses

**Definition of dyslipidaemia**

Optimal lipid targets for T2DM are defined in the 2018 dyslipidaemia guidelines by the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA)[18] as well as the 2017 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines for the management of T2DM[19] (Appendix H).

Dyslipidaemia was defined, using these guidelines, if one or more of the following are present: TC ≥4.5mmol/L, TG ≥1.7mmol/L, HDL-C ≤1.0mmol in males, ≤1.2mmol/l in females, and LDL-C ≥1.8mmol. If a single abnormal lipid parameter (TC, TG, HDL-C or LDL-C) was present, it was classified as isolated dyslipidaemia. When two lipid parameters (elevated TG, low HDL-C or elevated LDL-C) were detected, it was classified as combined dyslipidaemia. If all three lipid parameters were abnormal (elevated TG, low HDL-C and elevated LDL-C), it was classified as mixed dyslipidaemia.

**Statistical Analysis**

Variables were reported according to the distribution of the sample and were not normally distributed. Descriptive statistics namely frequencies and percentages for categorical data and medians with interquartile ranges (IQR) and percentiles for numerical data were calculated. The prevalence of dyslipidaemia was calculated and described by means of 95% confidence for the prevalence.

Associations were calculated between gender and HT, HDL-C and BMI as well as between dyslipidaemia and the lipid profile indices, and described using the Chi-square test or Fisher's exact test for categorical data and Kruskal-Wallis test for numerical variables. For all the tests a two-sided *p*-value of <0.05 was considered to be statistically significant.

## Ethical clearance

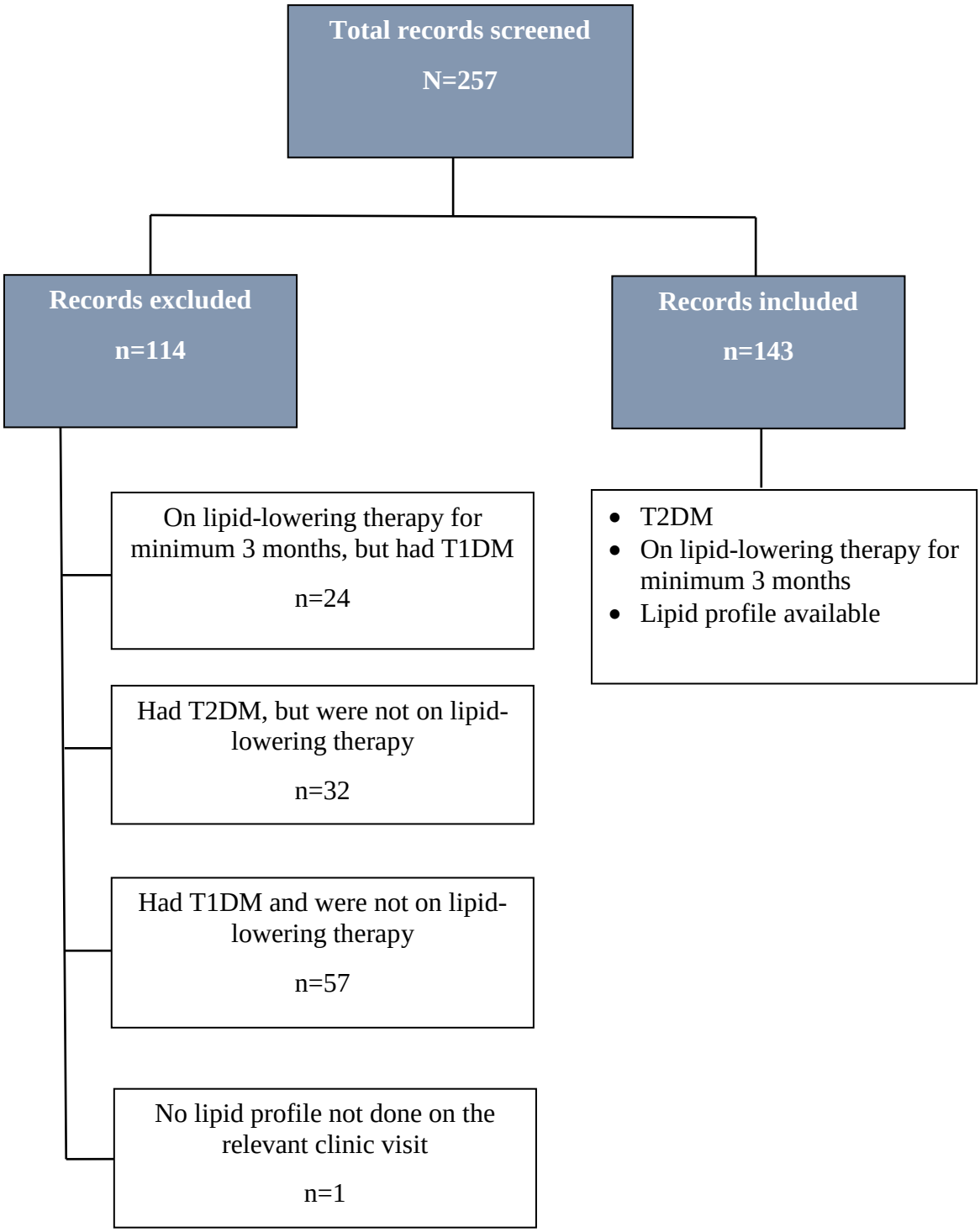
Ethics approval was obtained from the University of the Free State Health Sciences Research Ethics Committee before the commencement of the study (UFS-HSD2019/0869/2506, 04 June 2019). Permission to conduct the study was obtained from the Free State Provincial Health Department and the Head of the Internal Medicine department. The researcher ensured confidentiality by assigning the study number to each file to record clinical data on the datasheet without recording personal information. Because the information had been previously collected for routine clinical care and no further sample testing nor administration of treatment was done, informed consent was waived by the Ethics Committee. No conflict of interest is declared by the researcher.

## Results

### Overview of the included population

Of the 257 patient records screened over the 3-month study period, 114 were excluded from the study. The remaining 143 participants fulfilled the inclusion criteria (Figure 1). All but 2 participants (n = 141/143; 98.6%) were classified as very high-risk as per SA dyslipidaemia guidelines, thus requiring LDL-C of <1.8 mmol/L to be at target. The remaining 2 participants (1.4%) optimal LDL-C target was < 2.5mmol/L and both participants were within this target.

**Figure 1.** Strobe diagram depicting an overview of included & excluded records



## Demographics

The majority of the participants (n=133; 93.0%) were aged 40 years or more, with the median age of 63 years (IQR 52-71). Majority of the participants (n = 92; 64.3%) were female. Over half of the study participants (n = 74; 51.7%) were of the black ethnic group (Table 1).

## Clinical characteristics of the population

The median duration of DM diagnosis was 18 years (IQR 13-23). Of the 127 study participants whose anthropometry data was available, majority (n = 85; 66.9%) were obese with median BMI = 34.1 kg/m$^2$ (IQR 28.4-38.9). Female participants had higher median BMI than male participants (35.6 vs 31.6 kg/m$^2$; Kruskal-Wallis test, Chi-square ($x^2$) = 4.67, $p$ = 0.03). HbA1c >7%, implying poor control, was present in 113/143 (79%) with median HbA1c = 8.9% (IQR 7.4-10.1). Hypothyroidism diagnosis was present in 21.7% (n = 31/142) of participants with a median TSH level of 2.4 mIU/L (IQR 1.6-3.6) demonstrating good control of hypothyroidism. The demographic and clinical characteristics of the participants are summarised in Table 1.

**Table 1. Demographic & clinical data of the participants**

| *Variable | n (%) |
|---|---|
| **Age, median (years), with IQR** | 63 (52-71) |
| **Gender** | |
| **Male** | 51/143 (35.7) |
| **Female** | 92/143 (64.3) |
| **Ethnicity** | |
| **Black** | 74/143 (51.7) |
| **Coloured** | 11/143 (7.7) |
| **White** | 58/143 (40.6) |
| **Ischaemic heart disease** | 30/143 (21.0) |
| **Stroke** | 7/143 (4.9) |
| **Cigarette smoking** | 12/113 (10.6) |
| **Peripheral vascular disease** | 9/143 (6.3) |
| **Hypertension** | 131/143 (91.6) |
| **Hypothyroidism** | 31/143 (21.7) |
| **Body mass index ≥30kg/m$^2$** | 85/127 (66.9) |
| **Blood pressure** | |
| **Grade 1 hypertension** | 13/143 (9.1) |
| **Grade 2 hypertension** | 8/143 (5.6) |
| **Grade 3 hypertension** | 9/143 (6.3) |
| **Isolated systolic hypertension** | 45/143 (31.5) |

| | |
|---|---|
| **Oral antidiabetic therapy only** | 5/143 (3.5) |
| **Insulin therapy only** | 53/143 (37.1) |
| **Dual oral & insulin therapy** | 85/143 (59.4) |
| **HbA1c >7%** | 113/143 (79.0) |
| **Lipid-lowering therapy** | |
| **Statin only** | 135/143 (94.4) |
| **Fibrate only** | 3/143 (2.1) |
| **Dual statin & fibrate therapy** | 5/143 (3.5) |

*All variables expressed in numbers with percentages in brackets, unless otherwise specified

Nearly two thirds of the sample (n = 92; 64.3%) and just under one third (n = 45; 31.5%) were on diuretic and beta-blocker therapy, respectively (Table 2). Approximately a quarter of the patients (n = 37; 25.9%) were on a concomitant diuretic and beta-blocker therapy in keeping with the high rate of hypertension (n = 131; 91.6%) observed among the participants (Table 1). The prevalence of hypertension in males was similar to that in females (90.2 vs 92.4%; Fisher's exact test $p = 0.7$). Among 4 patients that were on HIV (human immunodeficiency virus) antiretroviral therapy (Table 2), one half were documented to be on efavirenz-based therapy, while in the remaining half antiretroviral therapy regimen information could not be retrieved from the records.

**Table 2.** Patient drug therapy list that may influence lipid profiles (n = 143)

| Year | n (%) |
|---|---|
| Corticosteroids | 2 (1.4) |
| Diuretics | 92 (64.3) |
| Oestrogens | 2 (1.4) |
| Beta-blockers | 45 (31.5) |
| HIV antiretroviral therapy | 4 (2.8) |

**Lipid-lowering therapy**

The most common lipid-lowering therapy among the participants was a statin monotherapy (n = 135; 94.4%), followed by dual statin and fibrate (n = 5; 3.5%), and lastly a fibrate monotherapy (n = 3; 2.1%) (Table 1). No patients were on any other type of lipid-lowering therapy including ezetimibe. The most commonly prescribed statin therapy was simvastatin (n = 128; 91.4%) followed by atorvastatin (n = 12; 8.6%). No patients were on rosuvastatin or any other type of statin. The median dose of simvastatin in 128 participants was 30mg (IQR 20-40), while in 12 participants on atorvastatin median dose was also 30mg (IQR 20-40). Among patients that were on a statin with or without a fibrate (n = 140), only 5% (n = 7) were on a high-intensity statin (Table 3).

**Table 3.** Classification of statins by potency of LDL-C lowering (n = 140)

| **High-intensity statin** | **Moderate-intensity statin** | **Low-intensity statin** |
|---|---|---|
| **n (%)** | **n (%)** | **n (%)** |
| 40mg Atorvastatin 6 (4.3) | 10mg Atorvastatin 2 (1.4) | 10mg Simvastatin 7 (5.0) |
| * 80mg Simvastatin 1 (0.7) | 20mg Atorvastatin 4 (2.9) | |
| | 20mg Simvastatin 57 (40.7) | |
| | 40mg Simvastatin 63 (45.0) | |

n = number. % in brackets. mg = milligrams

*80mg Simvastatin is no longer recommended due to high rates of adverse effects

**Dyslipidaemia pattern and prevalence**

The distribution of the pattern of dyslipidaemia is shown in Table 4. The prevalence of dyslipidaemia among the participants (n = 143) was 86.7% (95% confidence interval for the prevalence [80.2%; 91.3%]). The most frequent lipid abnormality was high LDL-C (n = 84/143) in 54.9 and 60.9% of males and females respectively (Figure 2).

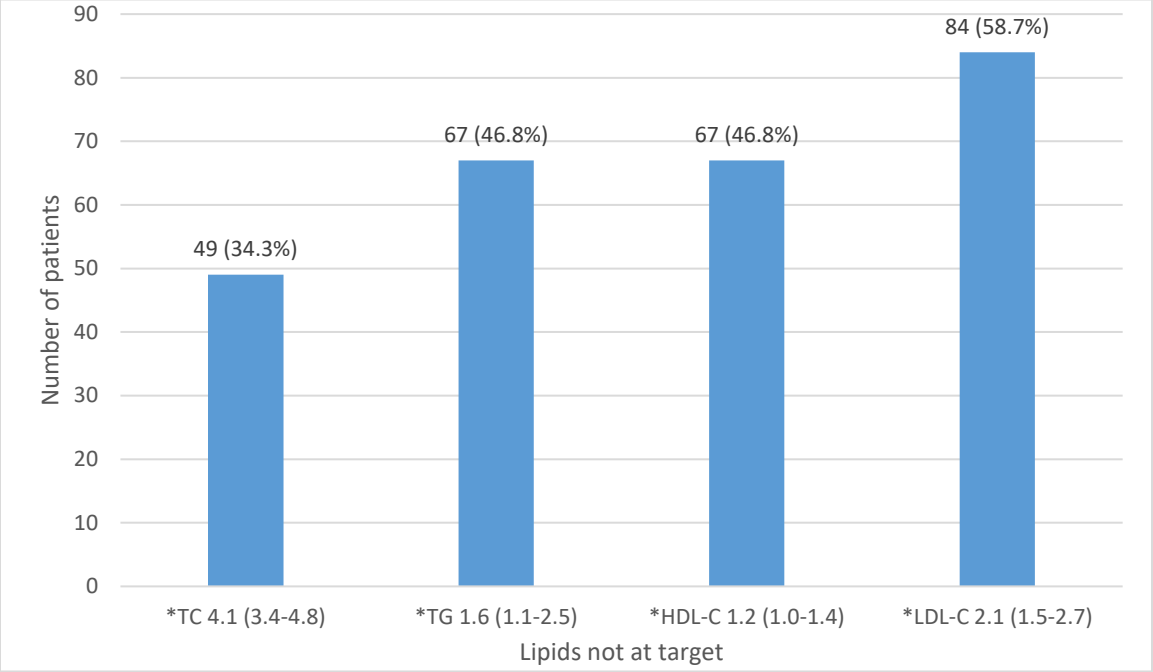
**Table 4.** Distribution of the pattern of dyslipidaemia among the study participants

| Lipid parameters at target definition | Pattern of dyslipidaemia | Parameters at target | Number | % |
|---|---|---|---|---|
| TG < 1.7 mmol/L<br>HDL > 1.0 mmol/L (males), > 1.2 mmol/L (females)<br>LDL <1.8 mmol/L | **No dyslipidaemia**<br>**13.3%** | TG+HDL+LDL | 19 | 13.3 |
| *Lipid parameters outside target definition | Pattern of dyslipidaemia | Parameters outside target | | |
| TG <1.7 mmol/L<br>HDL >1.0 mmol/L M, >1.2 mmol/L F<br>LDL <1.8 mmol/L | **Isolated dyslipidaemia**<br>**(n=49)**<br>**34.3%** | TG<br>HDL<br>LDL | 7<br>12<br>30 | 4.9<br>8.4<br>21.0 |
| | **Combined dyslipidaemia**<br>**(n=51)**<br>**35.7%** | TG+LDL<br>TG+HDL<br>HDL+LDL | 19<br>17<br>15 | 13.3<br>11.9<br>10.5 |
| | **Mixed dyslipidaemia**<br>**(n=20)**<br>**14.0%** | TG+HDL+LDL | 20 | 14.0 |
| | **Unclassified dyslipidaemia (n=4)** | LDL not calculated | 4 | 2.8 |
| | Total | | 143 | 100 |

*Prevalence of dyslipidaemia was 86.7% (95% CI[#] 80.2-91.3%) in 124/143 participants #confidence interval

The finding of 84 participants with elevated LDL-C meant that in 58.7% of the patients (70% of patients with dyslipidaemia and full lipid profile), LDL-C was not at target (Figure 2). Females had a significantly higher median LDL-C (2.2 vs 1.9 mmol/L; Kruskal-Wallis test, $x^2 = 4.38$, $p = 0.04$).

**Figure 2.** Individual lipid abnormalities and the median levels of the lipid profile among the study participants (n = 143)




*Median values with inter-quartile ranges in brackets in mmol/L. TC = total cholesterol ≥4.5mmol/L, TG = triglycerides ≥1.7mmol/L, HDL-C = high-density lipoprotein cholesterol ≥1.0mmol/L (M) & ≥1.2mmol/L F, LDL-C = low-density lipoprotein cholesterol ≥1.8mmol/L

The second most common lipid abnormality was both high TG & low HDL-C (n = 67 each), affecting 46.8% of the participants (Figure 2).For elevated TG, 37.2% of males and 52.2% of

females contributed to the prevalence with similar median TG (1.5 vs 1.8 mmol/L; Kruskal-Wallis test, $x^2 = 2.30$, $p = 0.1$). In 41.2% of males and 50% of females HDL-C was below target with median HDL-C significantly lower in males compared to females (1.1 vs 1.2 mmol/L, Kruskal-Wallis test, $x^2 = 5.44$, $p = 0.02$). The median lipid profile indices of the study participants are illustrated in Figure 2 and Table 5 shows the comparison between male and female participants.

**Table 5. Comparison of lipid profile in males and females**

| | *Total (n=143) | Male (M) (n=51) | Female (F) (n=92) | *p*-value |
|---|---|---|---|---|
| TG ≥ 1.7 mmol/L | 1.61 (1.15-2.49) | 1.55 (1.08-2.07) | 1.84 (1.17-2.76) | 0.1 |
| HDL-C<br>≤ 1.0mmol/L (M)<br>≤ 1.2 mmol/L (F) | 1.17 (0.97-1.39) | 1.09 (0.87-1.33) | 1.21 (1.00-1.43) | 0.02 |
| *LDL-C ≥1.8 mmol/L | 2.12 (1.48-2.67) | 1.87 (1.27-2.23) | 2.22 (1.52-2.77) | 0.04 |

*For LDL-C, total was n=139, M (n=50) & F (n=89)

Only 19 (13.3%) patients in the study (15.7% of males and 11.9% of females) had all 4 lipid parameters at target (Table 4). The most common dyslipidaemia pattern among patients with dyslipidaemia and full lipid indices (n = 51/120) was combined dyslipidaemia at 42.5%, representing 35.7% of all patients in the study (Table 4). It was followed by isolated (n = 49) and mixed (n = 20) dyslipidaemia patterns at 40.8% (34.3% of all patients) and 16.7% (14% of all

patients) respectively. High LDL-C plus either high TG or low HDL-C was common in males (32.6% of males), whereas in females high TG plus either low HDL-C or high LDL-C was most prevalent (29.6% of females) (Table 6).

In approximately 3% of the patients (2.8% of all study participants or 3.2% of patients with dyslipidaemia), the pattern of dyslipidaemia could not be classified (Table 4 and 6). This was due to LDL-C that was not calculated because TG was >4.5mmol/l making Friedewald equation estimation of LDL-C not reliable.

**Table 6.** Dyslipidaemia pattern among males and females with diabetic dyslipidaemia (n = 124)

| Pattern of dyslipidaemia | Males (n = 43)<br>n (%) | Females (n = 81)<br>n (%) | Total (n = 124)<br>n (%) |
|---|---|---|---|
| **Isolated** | 20 (46.5) | 29 (35.8) | 49 (39.5) |
| High TG | 3 (7.0) | 4 (4.9) | 7 (5.6) |
| Low HDL-C | 6 (13.9) | 6 (7.4) | 12 (9.7) |
| High LDL-C | 11 (25.6) | 19 (23.5) | 30 (24.2) |
| **Combined** | 19 (44.2) | 32 (39.5) | 51 (41.1) |
| High TG+Low HDL | 5 (11.6) | 12 (14.8) | 17 (13.7) |
| High TG+High LDL-C | 7 (16.3) | 12 (14.8) | 19 (15.3) |
| Low HDL+High LDL-C | 7 (16.3) | 8 (9.9) | 15 (12.1) |
| **Mixed** (High TG+Low HDL-C+High LDL-C) | 3 (7.0) | 17 (21.0) | 20 (16.1) |
| **Unclassified** | 1 (2.3) | 3 (3.7) | 4 (3.2) |

## Discussion

In this study of type 2 diabetes mellitus patients at high risk for cardiovascular disease, we report that 58.7% of the patients are not achieving the LDL-C target of <1.8 mmol/L as recommended by SA guidelines. We found a very high prevalence of dyslipidaemia (86.7% in our study) despite lipid-lowering therapy use. The most common lipid pattern abnormality we found was combined dyslipidaemia, largely due to TG and LDL-C above target.

Dyslipidaemia prevalence remains high in our study population despite the use of lipid-lowering therapy. Given hypercholesterolaemia caused 4.4 million deaths as reported in the 2016 Global Burden of Disease study,[22] 86.7% of patients in our study remain at high risk for mortality. Elsewhere in South Africa similar prevalence has been reported, ranging between 87.5-93.5% in T2DM patients.[23,24] It is worth noting that even though the two SA studies are in the public sector, the use of lipid lowering therapy magnitude was different from our study. In the Naidoo study[24] 83% of the participants were on any lipid-lowering therapy and in the Daya study[23] all patients were only on simvastatin. In our study in comparison, all patients were on lipid-lowering therapy consisting of simvastatin, atorvastatin or bezafibrate. The observation may account for lower dyslipidaemia prevalence in our study. The high prevalence of dyslipidaemia among DM patients on lipid-lowering therapy is not unique to SA and has been seen in international studies with varying prevalence. One large retrospective study in the United Kingdom reported dyslipidaemia prevalence of 77.1% in the DM population while in China there was a 70.9% overall prevalence.[25,26]

Of note, over half of the patients with T2DM in our study had LDL-C above target and remain at risk of major cardiovascular events despite the use of statin therapy. This finding is similar to an

observational study that examined the management of LDL-C levels in SA. This study found that 58.6% of the patients on lipid-lowering therapy did not reach the LDL-C target.[21] Similar to our study, 98.7% (97.9% in our study) of participants were on statin therapy in this study.[21] In contrast, however, approximately two-thirds of patients in this study (65.2%) had DM compared to 100% in our study and 57.9% were patients managed in a private sector compared to 100% in the public sector in our study.[21] When focusing on the under-resourced South African public healthcare setting only, as is the case with our study, two other SA studies have found an even higher proportion of patients not meeting target LDL-C of <1.8mol/L ranging from 73.5%-76.5%.[23,24] Of note, in the Daya study, only simvastatin was used by all patients at a mean dose of 20mg[23], whereas in our study 128 out of 140 patients on statin therapy (89.5% of the patients) used simvastatin at the higher median dose of 30mg. The remaining 10.5% of patients in our study were on fibrates (2.1%) and higher potency atorvastatin (8.4%). The use of the higher median dose of simvastatin and high-potency atorvastatin may account for the higher proportion of patients achieving LDL-C of <1.8mmol/L in our study. In the Naidoo study, only 83% of patients with DM[24] (compared to 100% in our study) were on any lipid-lowering therapy. Again, there was a higher percentage of patients on lipid-lowering therapy in our study and that may explain the higher proportion of patients reaching the target LDL-C compared to the Naidoo study. Nonetheless, over 50% of patients in our study are still undertreated despite 97.9% of them being on statin therapy. Globally, the success rate for LDL-C goal attainment differs from the 41.3% in our study and has ranged from 39.9% to 61.5% with the highest success rate among the lowest CV risk groups.[26,27] Numerous high-quality studies have proven elevated LDL-C as a cause of ASCVD[6,7] and the risk of CAD, stroke and heart failure are increased at least four-fold

in DM.[8] Patients in our study remain at high risk for the adverse CV events and would benefit from the lowering of LDL-C. The observation of the above target LDL-C and overall high prevalence of dyslipidaemia in our study highlights the lack of optimal management of dyslipidaemia despite the high use of statin therapy.

Although we did not test the reasons behind this poor management of dyslipidaemia in our study, we note that various possibilities are contributing to our findings. We noted in our study that only 5% of patients receiving statins were on a high-intensity statin. This is surprisingly low given the high dyslipidaemia prevalence and lack of achievement of LDL-C targets. This may be due to clinician inertia and lack of awareness regarding the appropriate use of statin potency and dose titration. Lack of physician awareness of treatment guidelines, underestimation of patient's CV risk and clinician inertia to titrate statins have been observed before.[26] In SA, the use of high-intensity statin use has ranged from 8.8% to 25.1%, with improved use observed in the private sector clinical practice than in the public sector.[21,24]

Access to high-intensity statins remains a challenge in our low-resource setting. At the time of our study, high-intensity statins such as atorvastatin and rosuvastatin were available only on a motivational basis. Additionally, the supply of the high-intensity statins at the primary care level remains inadequate despite successful motivation and approval for use in selected individual patients. Cholesterol absorption inhibitor was not used in any of the patients despite a high prevalence of dyslipidaemia in our study, particularly the LDL-C above target. This is comparable to other local studies with ezetimibe only used in one (2.6% of all participants in that study) out of the three studies of patients with a high prevalence of dyslipidaemia.[21,23,24] Ezetimibe was shown to have additional LDL-C lowering when added to statin and improved

cardiovascular outcomes.[17] Ezetimibe is accessible only at a tertiary care level on an individual motivated basis. Lack of access is also likely contributing to poor use of high-intensity statin and non-use of ezetimibe in our study despite the poor achievement of LDL-C target.

We found a high rate of obesity and this may contribute to the high prevalence of dyslipidaemia, particularly the combined dyslipidaemia pattern that was most prevalent in our study. 66.9% of patients in our study had BMI $\geq$ 30 kg/m$^2$ and combined dyslipidaemia (mainly high TG plus LDL) was the commonest pattern of dyslipidaemia. Obesity is associated with insulin resistance in T2DM leading to hypertriglyceridaemia, low HDL-C and high LDL-C, particularly sdLDL-C.[5]

We also note in our study that there was poor T2DM control with a median HbA1c of 8.9% likely contributing to the lipid abnormalities observed. Poor T2DM control has been shown to correlate positively with unfavourable lipid profile.[28]

We did not test poor treatment adherence by the patients as a contributor but lack of adherence is known as a contributor to the underachievement of LDL-C target and may have contributed to our study findings.[26]

Regardless of the reason for patients failing to meet the LDL-C target, it is clear that the residual diabetic dyslipidaemia is associated with high cardiovascular morbidity and mortality[29,30]. Patients with T2DM would benefit greatly from the appropriate use of lipid-lowering therapy, particularly statins.[30]

Combined dyslipidaemia was the most common pattern of dyslipidaemia observed, accounting for 42.5% of patients with dyslipidaemia and full lipid profiles. This is similar to findings

observed elsewhere in South Africa. Daya et al observed that among T2DM patients with dyslipidaemia, 43.8% had combined dyslipidaemia and this was the commonest pattern observed.[23] In our study, the combined dyslipidaemia pattern was driven largely by LDL-C and TG levels not at a target in 37.2% of patients with the combined pattern. This likely reflects residual atherogenic diabetic dyslipidaemia that is not fully treated by pharmacological and non-pharmacological interventions. It has been previously documented that overproduction of hepatic TG-rich VLDL and decreased degradation of apoB, a major component of VLDL, in insulin-deficient and/or resistant individuals contribute significantly to hypertriglyceridaemia.[5] Additionally, elevated LDL largely sdLDL, and glycated LDL that participate in atherosclerosis are observed in individuals with T2DM, obesity and insulin resistance.[5] This atherogenic LDL is the hallmark of diabetic dyslipidaemia.[5] Indeed patients in our study had high rates of obesity (median BMI 34.1 kg/m$^2$) and poorly controlled T2DM (HbA1c >7% in 79% of patients) that could explain the observed dyslipidaemia pattern.

Our study had limitations that must be noted. As a retrospective study selection or information bias is inherent. And cross-sectional design precludes any temporal association between baseline and subsequent LDL-C levels following lipid-lowering therapy. Dyslipidaemia due to secondary drug causes like thiazide diuretics and beta-blockers cannot be completely ruled out as a confounder. We did not collect data on lipid-lowering therapy contraindications, adverse effects nor adherence to treatment that may impact the use of lipid-lowering therapy. We also did not collect data on how long the patients were taking lipid-lowering medication for and that may influence lipid profiles. Because it was conducted in a tertiary diabetes clinic, the study may represent a particular population that is at the highest CV risk and with difficult to control lipid

profiles. As a result, the findings may not be generalizable to the entire South African T2DM population. Further large prospective studies reflecting prevalence in secondary care and district hospitals, as well as primary health care clinics in a public sector setting, is recommended to determine the pattern and prevalence of dyslipidaemia. These studies should also assess the availability, access and use of lipid-lowering therapy among the South African T2DM population.

## Conclusions

Our study highlights the underachievement of lipid targets in patients with T2DM who are already taking lipid-lowering therapy. There is also a high prevalence of dyslipidaemia (86.7%) despite available clinical guidelines. We highlight the need for education of both healthcare providers at all levels of care and patients regarding the intensification of lipid-lowering therapy among T2DM as appropriate and when indicated. Our study also informs the health policymakers to make accessible more potent lipid-lowering therapy such as high potency-statins and additional lipid-lowering therapy like ezetimibe in the public sector healthcare setting to improve clinical management of diabetic dyslipidaemia. These measures along with improved strategies to address poor glycaemic control and modifiable lifestyle factors such as the high rate of obesity and hypertension could help to reduce excess ASCVD morbidity and mortality associated with residual diabetic dyslipidaemia. A large prospective study in the public sector setting is needed to further evaluate the prevalence and pattern of dyslipidaemia, as well as appropriate use and availability of lipid-lowering therapy among T2DM patients.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

## Abbreviations

| | |
|---|---|
| apoB | Apolipoprotein B |
| ASCVD | Atherosclerotic cardiovascular disease |
| BMI | Body mass index |
| CAD | Coronary artery disease |
| CEPHEUS SA | CEntralised Pan-South African survey on tHE Undertreatment of hypercholeSterolaemia (CEPHEUS SA) |
| CETP | Cholesteryl ester transfer protein |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DM | Diabetes mellitus |
| DYSIS | DYSlipidemia International Study |
| HbA1c | Glycated haemoglobin |
| HDL-C | High-density lipoprotein cholesterol |
| HT | Hypertension |

| | |
|---|---|
| LDL-C | Low-density lipoprotein cholesterol |
| SA | South Africa |
| sdLDL | Small dense low-density lipoprotein cholesterol |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| TG | Triglyceride |
| TSH | Thyroid-stimulating hormone |
| VLDL | Very low-density lipoprotein |

**Acknowledgements**

Not applicable

**Funding**

Not applicable

**Authors' contributions**

LP conceptualised, designed and executed the study and was the primary author of the manuscript. LP wrote the manuscript. TRPM assisted with the editing of the article. RN performed the statistical analyses and assisted with the editing of the article. LP, TRPM & RN contributed to the interpretation of data and analyses. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study was approved by the University of the Free State's Health Sciences Research Ethics Committee on the 4th of June 2019 with ethical clearance number UFS-HSD2019/0869/2506. The permission to use hospital data was granted by the Department of Health, Free State Province, South Africa. Due to the retrospective nature of the study, the need to obtain informed consent requirement was waived by the Health Sciences Research Ethics Committee.

## Consent for publication

Not applicable

## Competing interests

The authors declare that they have no competing interests

**References**


1. International Diabetes Federation. *IDF Diabetes Atlas Ninth Edition 2019*.; 2019. http://www.idf.org/about-diabetes/facts-figures. Accessed March 21, 2021.

2. Blom DJ. Dyslipidaemia in Type 2 Diabetes. *S Afr J Diabetes Vasc Dis*. 2013;10(2):48-50. https://0-journals.co.za.wagtail.ufs.ac.za/docserver/fulltext/sajdvd/10/2/sajdvd_v10_n2_a2.pdf?expires=1538597176&id=id&accname=57783&checksum=B9DF8F8B6E090721DE5BAE1B2DE75E14. Accessed October 3, 2018.

3. Athyros VG, Doumas M, Imprialos KP, et al. Diabetes and lipid metabolism. *Hormones*. 2018;17(1):61-67. doi:10.1007/s42000-018-0014-8

4. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455

5. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes Dyslipidemia. *Diabetes Ther*. 2016;7(2):203-219. doi:10.1007/s13300-016-0167-x

6. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

7. Michos ED, McEvoy JW, Blumenthal RS. Lipid Management for the Prevention of Atherosclerotic Cardiovascular Disease. Jarcho JA, ed. *N Engl J Med*. 2019;381(16):1557-

1567. doi:10.1056/NEJMra1806939

8. Martín-Timón I. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes*. 2014;5(4):444. doi:10.4239/wjd.v5.i4.444

9. Kamil S, Sehested TSG, Carlson N, et al. Diabetes and risk of peripheral artery disease in patients undergoing first-time coronary angiography between 2000 and 2012 - A nationwide study. *BMC Cardiovasc Disord*. 2019;19(1):234. doi:10.1186/s12872-019-1213-1

10. Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 Diabetes Mellitus and Heart Failure, A Scientific Statement From the American Heart Association and Heart Failure Society of America. *J Card Fail*. 2019;25(8):584-619. doi:10.1016/j.cardfail.2019.05.007

11. Kenny HC, Abel ED. Heart Failure in Type 2 Diabetes Mellitus: Impact of Glucose-Lowering Agents, Heart Failure Therapies, and Novel Therapeutic Strategies. *Circ Res*. 2019;124(1):121-141. doi:10.1161/CIRCRESAHA.118.311371

12. Koskinas KC, Siontis GCM, Piccolo R, et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. *Eur Heart J*. 2018;39(14):1172-1180. doi:10.1093/eurheartj/ehx566

13. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532-2561. doi:10.1016/S0140-6736(16)31357-5

14. Naeem F, McKay G, Fisher M. Cardiovascular outcomes trials with statins in diabetes. *Br J Diabetes*. 2018;18(1):7-13. doi:10.15277/bjd.2018.161

15. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: Evidence report and systematic review for the US preventive services task force. *JAMA - J Am Med Assoc*. 2016;316(19):2008-2024. doi:10.1001/jama.2015.15629

16. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678

17. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489

18. Kluq E, Raal F, Marais D, et al. South African dyslipidaemia guideline consensus statement: 2018 update A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA). *South African Med J*. 2018;108 (Part 2):973-1000. doi:DOI:10.7196/SAMJ.2018.v108i11.13383

19. Amod A (Ed.). SEMDSA 2017 Guidelines for the Management of Type 2 diabetes mellitus. *JEMDSA*. 2017;22(1 (Supplement 1)):S1-S196. https://www.semdsa.org.za/images/647-4385-1-pb.pdf. Accessed March 4, 2019.

20. Halcox JP, Banegas JR, Roy C, et al. Prevalence and treatment of atherogenic

dyslipidemia in the primary prevention of cardiovascular disease in Europe: EURIKA, a cross-sectional observational study. *BMC Cardiovasc Disord*. 2017;17(1):160. doi:10.1186/s12872-017-0591-5

21. Blom DJ, Raal F, Amod A, Naidoo P, Lai Y. Management of low-density lipoprotein cholesterol levels in South Africa: the International ChoLesterol management Practice Study (ICLPS). *Cardiovasc J AFRICA* •. 2019;30(1):15-23. doi:10.5830/CVJA-2018-054

22. Noubiap JJ, Bigna JJ, Nansseu JR, et al. Prevalence of dyslipidaemia among adults in Africa: a systematic review and meta-analysis. *Lancet Glob Heal*. 2018;6(9):e998-e1007. doi:10.1016/S2214-109X(18)30275-4

23. Daya R, Bayat Z, Raal F. Prevalence and pattern of dyslipidaemia in type 2 diabetes mellitus patients at a tertiary care hospital. *J Endocrinol Metab Diabetes South Africa*. 2017;22(3):31-35. doi:10.1080/16089677.2017.1360064

24. Naidoo S, Raal F. Pattern of dyslipidaemia in relation to statin use in patients with type 2 diabetes mellitus attending a tertiary care hospital. *J Endocrinol Metab Diabetes South Africa*. 2020;25(1):6-11. doi:10.1080/16089677.2019.1686869

25. Jameson K, Amber V, D'Oca K, Mills D, Giles A, Ambegaonkar B. Impact of lipid-lowering therapy on the prevalence of dyslipidaemia in patients at high-risk of cardiovascular events in UK primary care - A retrospective database study. *Int J Clin Pract*. 2013;67(12):1228-1237. doi:10.1111/ijcp.12238

26. Zhao S, Wang Y, Mu Y, et al. Prevalence of dyslipidaemia in patients treated with lipid-lowering agents in China: Results of the DYSlipidemia International Study (DYSIS).

*Atherosclerosis*. 2014;235(2):463-469. doi:10.1016/j.atherosclerosis.2014.05.916

27. Danchin N, Almahmeed W, Al-Rasadi K, et al. Achievement of low-density lipoprotein cholesterol goals in 18 countries outside Western Europe: The International ChoLesterol management Practice Study (ICLPS). *Eur J Prev Cardiol*. 2018;25(10):1087-1094. doi:10.1177/2047487318777079

28. Mahajan R, Koley S. Association of HbA1c with Lipid profiles in patients with type 2 diabetes mellitus. *Int J Biomed Res*. 2016;7(3):139-143. doi:10.7439/ijbr

29. Warraich HJ, Rana JS. Dyslipidemia in diabetes mellitus and cardiovascular disease. *Cardiovasc Endocrinol*. 2017;6(1):27-32. doi:10.1097/XCE.0000000000000120

30. Jialal I, Singh G. Management of diabetic dyslipidemia: An update. *World J Diabetes*. 2019;10(5):280-290. doi:10.4239/wjd.v10.i5.280

## APPENDICES

### Appendix A

Letter of approval from the Health Sciences Research Ethics Committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

**Health Sciences Research Ethics Committee**

04-Jun-2019

Dear **Dr Lebohang Pitso**

Ethics Clearance: **Dyslipidaemia pattern and prevalence among type 2 diabetes mellitus patients on lipid-lowering therapy at a tertiary central South African hospital**

Principal Investigator: **Dr Lebohang Pitso**

Department: **Internal Medicine Department (Bloemfontein Campus)**

**APPLICATION APPROVED**

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/0869/2506**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

**Health Sciences Research Ethics Committee**
**Office of the Dean: Health Sciences**
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

**Appendix B**

Letter of permission from the Department of Health, Free State Province

health
Department of Health
FREE STATE PROVINCE

29 May 2019

**Dr L Pitso**
**Dept. of Internal Medicine**
**UFS**

**Dear Dr L Pitso**

**Subject: Dyslipidaemia pattern and prevalence among type 2 diabetes mellitus patients on lipid-lowering therapy at a tertiary central South Africa hospital.**

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / lithekom@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Universitas Hospital CEO's on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

**Dr D Motau**
**HEAD: HEALTH**
**Date:** 30/05/19

**Head : Health**
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

**Appendix C**

Letter of permission from the Head of Internal Medicine Department

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

2 May 2019

Dr E le Grange
The Chairperson,
Ethics Committee' Faculty of Health Sciences
University of the Free State

Dear Dr Le Grange

I hereby give **Dr L Pitso** (Endocrinology Fellow) permission to conduct research for his MPhil degree.

**Title:** : DYSLIPIDAEMIA PATTERN AND PREVALENCE AMONG TYPE 2 DIABETES MELLITUS PATIENTS ON LIPID-LOWERING THERAPY AT A TERTIARY CENTRAL SOUTH AFRICAN HOSPITAL

Kind regards

.....
**Dr TRP MOFOKENG : HOD**
**Dept of Internal Medicine**

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MBChB (UCT), Cert Endocrinolog + Met(SA)
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Data collection sheet sample 1

## Diabetic dyslipidaemia study data sheet

Visit Date: Study No:

**DEMOGRAPHY**

Age (in years): Gender: Male ☐ Female ☐

Ethnicity: Black ☐ White ☐ Coloured ☐ Indian/Asian ☐ Other ☐ Unknown ☐

**CO-MORBIDITIES AND COMPLICATIONS**

Diabetes duration since diagnosis (in years):

IHD (ischaemic heart disease): Yes ☐ No ☐ Unknown ☐
Stroke: Yes ☐ No ☐ Unknown ☐

Smoking: Yes ☐ No ☐ Unknown ☐

PVD (peripheral vascular disease): Yes ☐ No ☐ Unknown ☐
HT (hypertension): Yes ☐ No ☐ Unknown ☐
Hypothyroidism: Yes ☐ No ☐ Unknown ☐

**DIABETES TREATMENT**

Oral: Yes ☐ No ☐ Unknown ☐ Insulin: Yes ☐ No ☐ Unknown ☐
Oral/Insulin: Yes ☐ No ☐ Unknown ☐

**OTHER TREATMENT**

GCS (gluco-corticosteroids): Yes ☐ No ☐ Unknown ☐
Diuretics: Yes ☐ No ☐ Unknown ☐ Oestrogens: Yes ☐ No ☐ Unknown ☐
BB (beta-blockers): Yes ☐ No ☐ Unknown ☐

HIV (human immunodeficiency virus) treatment: Yes ☐ No ☐ Unknown ☐ If Yes, *type:

**LIPID-LOWERING THERAPY (TYPE & DOSAGE IN MG)**

Statin: Simvastatin ☐, dose Atorvastatin ☐, dose Rosuvastatin ☐, dose

Fibrates: Bezafibrate ☐, dose Fenofibrate ☐, dose Gemfibrozil ☐, dose

Statin/Fibrates combination: Yes ☐ No ☐ Ezetimibe: Yes ☐ No ☐, dose

Other:

*HIV treatment: LPV/r (lopinavir/ritonavir), AZT (zidovudine), EFV (efavirenz), d4T (stavudine), ATV/r (atazanavir/ritonavir), DTG (dolutegravir), RPV (rilpivirine).

1

**Appendix E**

Data collection sheet sample 2

## Diabetic dyslipidaemia study data sheet template

**CLINICAL FACTORS**

Weight (in kg): Height (in m):

SBP (systolic blood pressure in mmHg):

DBP (diastolic blood pressure in mmHg):

**LABORATORY DATA**

*Kidney Indices

Microalbumin (in mg/mmol creat): Macroalbumin (in g/mmol creat):

eGFR (estimated glomerular filtration rate in mL/min/1.73m$^2$):

Diabetes Indices

HbA1c (glycated haemoglobin in %): FPG (fasting plasma glucose in mmol/L):

Thyroid Indices

TSH (thyroid stimulating hormone in mIU/L): free T4 (thyroxine in pmol/L):

Lipid Profile Indices

TC (total cholesterol in mmol/L):

TG (triglyceride in mmol/L):

HDL-C (high-density lipoprotein cholesterol in mmol/L):

LDL-C (low-density lipoprotein cholesterol in mmol/L):

*Microalbumin or albumin creatinine ratio. Macroalbumin or protein creatinine ratio. 2

**Appendix F**

South African (SA) hypertension practice guidelines 2014

**Table 1. Definitions and classification of office BP (mmHg). Adapted from ref 9**

| *Stage* | *Systolic BP (mmHg)* | *Diastolic BP (mmHg)* |
|---|---|---|
| Normal | < 120 | < 80 |
| Optimal | 120–129 | 80–84 |
| High normal | 130–139 | 85–89 |
| Grade 1 | 140–159 | 90–99 |
| Grade 2 | 160–179 | 100–109 |
| Grade 3 | ≥ 180 | ≥ 110 |
| Isolated systolic | ≥ 140 | < 90 |

BP should be categorised into the highest level of BP whether systolic or diastolic.

Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014.Cardiovasc J Afr [Internet]. 2014 [cited 2019 May 1];25(6):288–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25629715

**Appendix G**

The World Health Organization (WHO) body mass index (BMI) classification

Table 2.1
**Classification of adults according to BMI**[a]

| Classification | BMI | Risk of comorbidities |
|---|---|---|
| Underweight | <18.50 | Low (but risk of other clinical problems increased) |
| Normal range | 18.50–24.99 | Average |
| Overweight: | ≥25.00 | |
| Preobese | 25.00–29.99 | Increased |
| Obese class I | 30.00–34.99 | Moderate |
| Obese class II | 35.00–39.99 | Severe |
| Obese class III | ≥40.00 | Very severe |

[a] These BMI values are age-independent and the same for both sexes. However, BMI may not correspond to the same degree of fatness in different populations due, in part, to differences in body proportions (see section 2.3.2). The table shows a simplistic relationship between BMI and the risk of comorbidity, which can be affected by a range of factors, including the nature of the diet, ethnic group and activity level. The risks associated with increasing BMI are continuous and graded and begin at a BMI above 25. The interpretation of BMI gradings in relation to risk may differ for different populations. Both BMI and a measure of fat distribution (waist circumference or waist : hip ratio (WHR)) are important in calculating the risk of obesity comorbidities.

World Health Organization. Obesity : preventing and managing the global epidemic: report of a WHO consultation. Geneva; 2000.

**Appendix H**

The SEMDSA (Society for Endocrinology, Metabolism and Diabetes of South Africa) recommended lipid value targets and other modifiable risk factors targets in type 2 diabetes mellitus (T2DM)

**Table I:** CVD risk factors and targets for patients with type 2 diabetes

| Traditional CVD risk factors | | Targets |
|---|---|---|
| Cigarette smoking | | Cessation |
| Dyslipidaemia | | |
| | Total cholesterol | <4.5 mmol/L |
| | LDL cholesterol | <1.8 mmol/L |
| | HDL cholesterol | > 1.0 mmol/L (men)<br>>1.2 mmol/L (women) |
| | Triglycerides | <1.7 mmol/L |
| Obesity | | |
| | Waist circumference | <94 cm (men); <90 cm (men of South Asian descent)<br><80 cm (women) |
| | Body mass index | <25 kg/m$^2$ |
| Hypertension | | |
| | Systolic blood pressure | <140 mmHg |
| | Diastolic blood pressure | <90 mmHg |

LDL = low density lipoprotein; HDL = high density lipoprotein

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. “Chapter 16: Cardiovascular risk and the management of dyslipidaemia in patients with type 2 diabetes mellitus” in 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1) (Supplement 1): S1-S196.

**Appendix I**

The Turnitin summary report

# DYSLIPIDAEMIA PATTERN AND PREVALENCE AMONG TYPE 2 DIABETES MELLITUS PATIENTS ON LIPID-LOWERING THERAPY AT A TERTIARY CENTRAL SOUTH AFRICAN HOSPITAL

*by* Lebohang Pitso

**Submission date:** 14-Sep-2020 07:34PM (UTC+0200)
**Submission ID:** 1386943839
**File name:** WERING_THERAPY_AT_A_TERTIARY_CENTRAL_SOUTH_AFRICAN_HOSPITAL.docx (343.09K)
**Word count:** 7671
**Character count:** 44885

DYSLIPIDAEMIA PATTERN AND PREVALENCE AMONG TYPE 2 DIABETES MELLITUS PATIENTS ON LIPID-LOWERING THERAPY AT A TERTIARY CENTRAL SOUTH AFRICAN HOSPITAL

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