The Relationship between Age and Diabetes Control in Patients Living with Diabetes Mellitus in Low-to-Middle Income Countries

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Submitted in fulfilment of the academic requirements

for the degree of Master of Medical Science

in the Department of Internal Medicine

School of Clinical Medicine

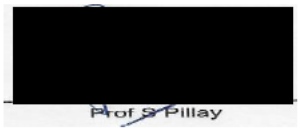
College of Health Sciences

University of KwaZulu-Natal

Durban

2021

As the candidate's supervisor, I have approved this thesis for submission.

Signed:  Name: Prof Somasundram Pillay Date: 27 September 2021

DEDICATION

I want to thank the Lord for giving me the courage and wisdom to undertake and complete this degree.

Thank you to my family and friends for all their support. My dad (U.P. Chetty), mum (S. Chetty), sister (Merishni) and fiancé (Kylie) – for your love, care and continuous support.

DECLARATION

I, Dr Rushern Ruvashin Chetty, declare that:

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ACKNOWLEDGEMENTS

- A big thank you to my supervisor, Professor Somasundram Pillay, for your excellent mentorship towards my research and future development. This project would not have been possible without your support and guidance.
- Mr Deepak Singh – statistician – for your expertise.
- Edendale Hospital and their staff for allowing the study to be conducted at their Diabetes Clinic.

ABBREVIATIONS

ART	Anti-retroviral treatment
BREC	Biomedial Research and Ethics Committee
DM	Diabetes Mellitus
EDH	Edendale Hospital
GFR	Glomerular Filtration Rate
HbA1c	Glycated Haemoglobin
HIC	High-income country
HIV	Human immuno-deficiency virus
JEMDSA	Journal of Endocrinology, Metabolism and Diabetes South Africa
LMIC	Low-and-middle-income countries
NCD	Non-communicable diseases
OGTT	Oral Glucose Tolerance Test
PLWD	Patients living with diabetes
PLWT1DM	Patients living with type 1 diabetes mellitus
PLWT2DM	Patients living with type 2 diabetes mellitus
PLWDH	Patients living with diabetes and HIV
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
SA	South Africa
SEMDSA	Society of Endocrinology, Metabolism and Diabetes South Africa
TB	Tuberculosis
T2DM	Type 2 Diabetes Mellitus
USA	United States of America
WHO	World Health Organisation

EXECUTIVE SUMMARY

Diabetes Mellitus (DM) is a chronic, metabolic disease characterised by raised blood glucose levels. In 2019, there were an estimated 463 million adult patients living with diabetes (PLWD), with this figure expected to reach around the 700 million mark by 2045. Patients living in low-income and middle-income countries comprise approximately 79% of global adult PLWD figures, with approximately 20% of these PLWD being older than 65 years. This illustrates that the burden of DM rests on the younger working-age population in low-to-middle-income (LMIC) countries. These patients living with type 1 and type 2 diabetes have reduced life expectancies of approximately 20 and 10 years, respectively. Unfortunately, this compounds the problem of further decreasing the life expectancy of the population of LMIC countries which are already being affected by communicable diseases like HIV infection.

South Africa has the highest prevalence of human immuno-deficiency virus (HIV) in the world at 13% with many PLWD also being HIV-infected. With the effective roll-out of anti-retroviral treatment (ART), patients are also able to live longer and can develop diabetes mellitus as a result of longevity, ART and the HIV-infection itself. With the prevalence of both these conditions and the numbers of DM expected to rise, determining relationships in PLWD in an HIV-endemic area would offer better knowledge and allow for better strategies to be implemented to effectively manage a significant proportion of patients in our setting.

A scoping review was conducted globally to identify associations between 'age' and 'glycaemic control' in HIV-infected PLWD. The review concluded that "varying data exists on the associations between glycaemic control and age in PLWD in the context of HIV infection (PLWDH). Further studies are recommended to determine associations in this regard, especially in LMIC where HIV and DM have a higher prevalence."

The lack of conclusive associations identified from the scoping review suggested that another study was warranted in an HIV-endemic region. A retrospective study was conducted among 957 PLWD of whom 146 patients were HIV-infected from the Edendale Hospital Diabetes Clinic, Pietermaritzburg, South Africa from 1 January 2019 to 31 December 2019. Statistical analysis was performed with a p value<0.05 being considered statistically significant. Our study showed that younger PLWD had poorer glycaemic control and were likely to develop diabetes-related complications later in life. Of note, older age was associated with improved mean glycated haemoglobin (HbA1c) levels after adjusting for glomerular filtration rate (GFR) [$r=-0.141$, $p<0.001$; (before adjustment: $r=-0.108$; $p=0.001$)]. In addition to this, PLWD with an HIV-infection who had a mean HbA1c>7% were significantly younger than those with HbA1c$\leq$7% (47.38 years vs. 52.77 years, $p=0.013$).

From this study, we evaluated associations between age and glycaemic control in PLWD has served to highlight that “more emphasis, in terms of diabetes education and management, needs to be placed in the younger age category of both PLWD and PLWDH”. This study, as well as future prospective studies, will assist with providing patients, healthcare workers and government with improved knowledge, thereby managing patients more effectively at any given age. Some of our recommendations from this study include: screening all patients for DM and implementing strategies to optimise glycaemic control and prevent complications; healthy diet to be implemented by patients of all ages; exercise as well as optimal pharmacological management and self-monitoring of glucose levels.

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CHAPTER 1: INTRODUCTION

Diabetes Mellitus (DM) is a chronic, metabolic disease characterised by raised blood glucose levels[1]. In 2019, there were an estimated 463 million adult patients living with diabetes (PLWD)[2], with this figure expected to reach around the 700 million mark by 2045[2].

Patients living in low-income and middle-income countries comprise approximately 79% of global adult PLWD figures, with approximately 20% of these PLWD being older than 65 years[2]. This contrasts with high-income countries which have greater than 50% of their PLWD older than 65 years[3]. This illustrates that the burden of DM rests on the younger working-age population in LMIC countries. These patients living with type 1 and type 2 diabetes have reduced life expectancies of approximately 20 and 10 years, respectively[4]. Unfortuately, this compounds the problem of further decreasing the life expectancy of the population of LMIC countries which are already being affected by communicable diseases like HIV infection and tuberculosis (TB). South Africa has the highest prevalence of HIV in the world at 13%[5], while TB was identified as the main cause of mortality in South Africa in 2019 with an estimated 58 000 deaths[6].

Literature has shown us that younger age is associated with poorer glycaemic control[7,8]. Considering this as well as younger patients experience a longer duration of DM, it would explain why there are increased complications in older patients[9]. In South Africa, it has already been demonstrated that older PLWD have a poorer quality of life and greater disability[10]. In addition to this, those with young-onset type 2 DM (T2DM) appear to have a more aggressive disease phenotype, leading to a poorer quality of life and unfavourable long-term outcomes[9]. This highlights the possibility of a future public health catastrophe[9]. Efforts should therefore be made to prevent this potential problem.

South Africa's mortality in older patients is transitioning from a country which mainly suffers from communicable disease (e.g. HIV and TB) to one of non-communicable diseases such as strokes and heart disease[11]. This underscores the importance of DM since strokes and heart disease are known complications of DM[8]. South Africa has a younger population with only 9.10% of the population being 60 years and older[11]. The working age in South Africa is between 15-64 years.[12] In addition, among those South Africans who are between 15-49 years old, approximately 18.70% have HIV-infection[5] while the prevalence of TB is estimated at 615 per 100 000 population[6]. Burgess et al. found that there was a greater than three-times higher mortality at 24-month follow up in PLWD who were HIV-infected when compared to those who were HIV-uninfected[13]. Furthermore, DM has been shown to increase the risk of developing TB by 300%[14]. Estimates from 2020 place the average South Africans' life expectancy at 62.50 years and 68.50 years for males and females, respectively[11]. This suggests that

the South African male life expectancy is lower than the retirement age of the population while females are expected to demise shortly after retirement age. The burden of this collision of non-communicable and communicable diseases in SA and its associated increase in earlier mortality has a significant impact on the working class, thereby reducing economic activity in the country.

In this study we aimed to perform a scoping review of what is currently known on 'The relationship between age and diabetes control in patients with diabetes mellitus in low-to-middle income countries' as well as determine if there are significant associations in patients living with diabetes (PLWD) between age and clinical and biochemical variables. This was done on PLWD who visited a regional hospital diabetes clinic in Pietermaritzburg, KwaZulu-Natal, South Africa. The results of this study can help the government to design and implement strategies to improve current diabetes care in patients targeting different age groups.

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CHAPTER 2: THE RELATIONSHIP BETWEEN AGE AND GLYCAEMIC CONTROL IN PATIENTS LIVING WITH DIABETES MELLITUS IN THE CONTEXT OF HIV INFECTION: A SCOPING REVIEW

This chapter focuses on a scoping review of the literature available on studies which include PLWD who are also HIV-infected to address relationships between ‘age’ and ‘glycaemic control’.

The study revealed that there were varying associations between ‘age’ and ‘glycaemic control’ in PLWDH.

(Some formatting changes and minor additions have been inserted from the original article published in JEMDSA)

Journal of Endocrinology, Metabolism and Diabetes of South Africa

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/oemd20

The relationship between age and glycaemic control in patients living with diabetes mellitus in the context of HIV infection: a scoping review

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To cite this article: RR Chetty & S Pillay (2021): The relationship between age and glycaemic control in patients living with diabetes mellitus in the context of HIV infection: a scoping review, Journal of Endocrinology, Metabolism and Diabetes of South Africa, DOI: 10.1080/16089677.2021.1945767

To link to this article: https://doi.org/10.1080/16089677.2021.1945767

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2021: 1–7

https://doi org/10 1080/16089677 2021 1945767

JEMDSA

ISSN 1608-9677 EISSN 2220-1009

ARTICLE

The relationship between age and glycaemic control in patients living with diabetes mellitus in the context of HIV infection: a scoping review

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Background: Patients living in low- and middle-income countries (LMIC) comprise approximately 79% of the global number of adult patients living with diabetes (PLWD). In addition, South Africa (SA), a LMIC, has the highest prevalence of HIV infection globally (13%). The literature suggests that poor glycaemic control is found in the younger PLWD while older PLWD have a poorer quality of life with greater disability. With the effective roll-out of anti-retroviral treatment (ART), patients are living longer and can develop diabetes mellitus as a result of longevity, ART and the HIV infection itself. Assessing the relationship between age in PLWD and HIV would help in developing effective strategies that can be implemented to optimise healthcare for this cohort of patients.

Objectives: A study was undertaken to summarise publications on age and glycaemic control in PLWD within the context of an HIV infection.

Methods: A scoping review was performed using online medical journal search engines with specific search terms according to the PRISMA guidelines. The Abstracts of articles were read and articles that matched the search criteria were downloaded and read in full. If they matched the chosen topic, they were summarised for analysis.

Results: There were 260 results found across 3 medical search engines (55 from Cochrane; 59 from PubMed; 101 from Scopus). A Google search was conducted for completeness (45 results). Seventeen journal articles were identified for the scoping review with 45 095 patients included in these studies from 7 countries. Associations between age and glycaemia differed greatly, being dispersed among the 'older age has worse glycaemia category', 'non-significant category' and 'older age has improved glycaemia category'.

Conclusion: Varying data exist on the associations between glycaemic control and age in PLWD in the context of HIV infection. Further studies are recommended to determine associations in this regard, especially in LMIC where HIV and DM have a higher prevalence.

Keywords: age, diabetes mellitus, glycaemic control, HIV, LMIC

Background

Diabetes mellitus (DM) is a chronic, metabolic disease characterised by raised blood glucose levels.[1] In 2019, there were an estimated 463 million adult patients living with diabetes (PLWD), with this figure expected to reach around the 700 million mark by 2045.[2]

Patients living in low- and middle-income countries (LMIC) comprise approximately 79% of the global adult PLWD figures, with approximately 20% of these PLWD being older than 65 years.[2] This contrasts with high income countries (HIC), where the majority of such patients are older than 64 years,[3] illustrating that the burden of DM rests on the shoulders of the younger working age population in these LMIC. These patients living with type 1 and type 2 diabetes already have reduced life expectancies of approximately 20 and 10 years respectively[4] and DM occurring at a younger age only serves to compound the problem of decreasing the life expectancy of the population in these LMIC, which are already being burdened by communicable diseases such as HIV infection and tuberculosis (TB). South Africa (SA) is classified as a LMIC and also has the highest prevalence of HIV infection in the world at 13%.[5] In addition, TB has been reported as the main cause of mortality in SA in 2019, with an estimated 58 000 annual TB-attributable deaths.[6]

Literature from both HIC and LMIC countries show us that poor glycaemic control is found in the younger PLWD.[7,8] Taking this finding into consideration and that younger patients are generally destined to have longer disease exposure, probably accounts for the increased risks of chronic complications found in older PLWD.[9] In SA, it has already been demonstrated that older PLWD have a poorer quality of life and greater disability.[10] In addition, those with young-onset type 2 DM (T2DM) appear to have a more aggressive disease phenotype, leading to a poorer quality of life and unfavourable long-term outcomes.[9] This serves to highlight the burden on the health system of DM in older patients.[9] Efforts should therefore be made to identify areas in diabetes control that can be targeted in the various age groups in order to prevent this potential problem.

The landscape of mortality in older patients in SA is changing from one of communicable diseases (e.g. HIV and TB) to that of non-communicable diseases (NCDs) such as strokes and heart disease.[11] This underscores the importance of DM, as strokes and heart disease are well recognised macrovascular complications of DM.[8] Epidemiologically, SA has a younger population with only 9.1% of the population being 60 years and older.[11] The working age in SA is generally defined as between 15 and 64 years.[12] South Africans who are 15–49 years old are also faced with an additional infectious diseases burden, especially that of HIV infection (with a prevalence of 18.7%[5]) and TB, which is estimated at 615 per 100 000 population.[6] Burgess et al. found that there was a greater than three times higher mortality at 24-month follow-up in PLWD who were HIV-infected when compared with those who were HIV-uninfected.[13] Moreover, people with an HIV infection are more likely to develop T2DM than HIV-uninfected patients.[14] Furthermore, DM has been shown to increase the risk of developing TB by

300%.[15] Estimates from 2020 place the average South African life expectancy at 62.5 and 68.5 years for males and females respectively.[11] This suggests that South African male life expectancy is lower than the retirement age of the population while females are expected to die shortly after retirement age. The burden of this collision of non-communicable and communicable diseases in SA and its associated increase in earlier mortality has a significant impact on the working class, thereby reducing economic activity in this country.

Aim

This scoping review aimed to summarise publications relating to age and glycaemic control in PLWD in HIV-infected patients (PLWDH) to identify a potential research gap on the topic by assessing associations between age and glycaemic control.

Methods

Search terms and data sources

For this scoping review, data were obtained using trusted online medical journal search engines. The Cochrane Library, PubMed and Scopus were utilised for this task. The following wording chosen was in the Boolean search format across the online search engine platforms in order to identify as many articles as possible on the topic: (‘diabetes’ OR ‘diabetes mellitus’ OR ‘insulin dependent diabetes mellitus’ OR ‘IDDM’ OR ‘insulin dependent diabetes’ OR ‘non-insulin dependent diabetes mellitus’ OR ‘non-insulin dependent diabetes’ OR ‘NIDDM’ OR ‘type 2 diabetes mellitus’ OR ‘type 2 diabetes’ OR ‘type 1 diabetes’ OR ‘type 1 diabetes mellitus’ OR ‘Age’ OR ‘elderly’ OR ‘young’) AND (‘increased age’ OR ‘decreased age’ OR ‘teenagers’ OR ‘teens’ OR ‘mature’ OR ‘old’ OR ‘pensioners’ OR ‘older’ OR ‘younger’) AND (‘HbA1c’ OR ‘glycaemic control’ OR ‘glycemic control’ OR ‘glycaemia’ OR ‘glycemia’ OR ‘glucose control’ OR ‘dysglycaemia’ OR ‘dysglycemia’) AND (‘HIV’ OR ‘AIDS’ OR ‘HIV-infection’ OR ‘HIV infection’ OR ‘HIV positive’ OR ‘HIV-positive’ OR ‘human immunodeficiency syndrome’).

A Google search was also done to find additional articles. Broader search terms were included: ‘diabetes’ and ‘HIV’ and ‘age’. From the results on Google, articles were identified by ‘title’ and if this included associations on ‘HIV’ and ‘diabetes’, the article was read in full to look for associations between glycaemic control and age in the study. Articles that had already been found on the other search engines were not read in the Google search. There were 110 articles evaluated by title while only 45 other articles were read in full for possible use in the study.

Study designs accepted were retrospective and prospective cohort studies where an identifiable DM group with an HIV infection was present. Any study, regardless of when or where it was conducted or published, was accepted provided that there was a relationship among the four variables (i.e. HIVinfected, DM, an association between 'age' and 'glycaemic control'). Only studies in English were read as the authors were only proficient in English.

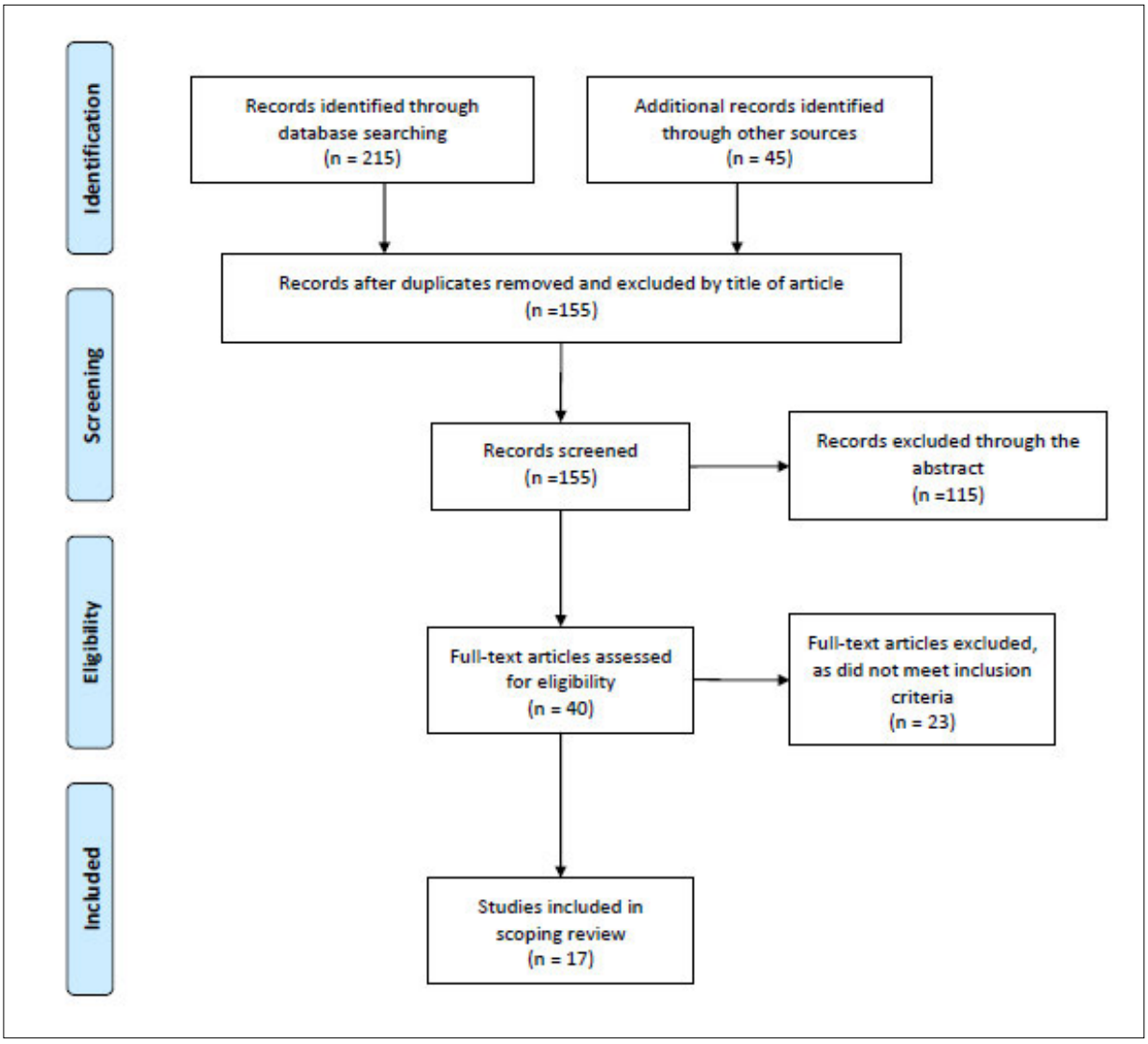

Figure 1: Flow diagram showing the eliminating process of articles to obtain final articles included in this scoping review

Data synthesis

As of April 15, 2021, there were 215 search results across three different search engines (55 from Cochrane Library; 59 from PubMed, and 101 from Scopus). An additional 45 articles were evaluated through the Google search. The articles' Abstract was read and those that met the criteria for our scoping review were downloaded and kept aside for full review of the entire article. Identical articles that were duplicated on the different search engines were omitted. We aimed to find studies from PLWDH cohorts (or alternatively DM cohorts or HIV cohorts where there were groups/subgroups that included PLWDH). We then determined whether there were clear relationships between 'age' and 'glycaemia' in such groups. Figure 1 is a flow diagram of the selection process followed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[16]

The selection of articles was done manually and no software program was utilised due to the limited number of results found. If articles were identified for inclusion in the scoping review, they were downloaded and kept in a folder, which was analysed later to be added to Table 1. This was done by author RRC and verified by co-author SP to ensure validity and standardisation of included studies.

There were a total of 17 articles that met our criteria for this study and these are summarised in Table 1 in chronological order.

Data were reported on year of publication, country, region, gender, type of study, patient selection and duration of both HIV and DM. These details highlighted that the earliest study found was in 2010 and since that time more than half of the publications have been within the last five years. The country and region were included to evaluate whether demographics or social factors had an impact on age and glycaemic control. As mentioned, the burden of disease of DM and HIV is in LMIC, hence we hoped to identify whether LMIC are adequately evaluating these associations, which is more relevant to them. The number of PLWDH showed the proportion of patients who suffered from both co-morbidities compared with the number of participants in the study and was included to determine the total number of patients that we used in this study. The type of study showed prospective vs. retrospective studies to allow causal relationships vs. associations to be drawn, respectively. The cohort selection was to determine whether patients were primarily from HIV clinics (who were also PLWD) or whether from a DM clinic who were also HIVinfected. The duration of HIV and DM was included to assess whether the duration of either co-morbidity had an effect on age.

Results

Demographics of the different studies

All of the studies had an association between age and glycaemic control in PLWDH. From the 17 studies that met our inclusion criteria, seven different countries were identified. There were six articles from the USA, five from South Africa, two from Malawi and one each from France, the Netherlands, Brazil and Iran. The studies ranged from 2010 to March 2021.

Nine of the studies were from LMIC while eight were from HIC countries. Locally in South Africa, there were five studies conducted (three in Pietermaritzburg [KwaZulu-Natal province]; one in East London [Eastern Cape province] and one in Soweto [Gauteng province]).

Glesby et al.[17] was the only study to be performed among a complete female cohort while Medapalli et al.[20] assessed US veterans and consisted almost entirely of males. All other studies conducted were done on cohorts of both sexes.

Number of patients identified and types of studies

There were 45 095 patients identified across the 17 included studies. In total, 5 060 patients were identified as having both HIV infection and being diagnosed with DM. Of these studies, there were five prospective and eight retrospective studies; the studies mentioned only that they were cross-sectional while one study did not mention the study design.

In terms of samples utilised, six of the studies identified included patients from HIV clinics and six studies identified patients from DM clinics. Two studies had cohorts of PLWDH. The other three studies comprised cohorts with TB and HIVinfected patients, newly diagnosed HIV-infected patients and women with or at high risk of contracting HIV infection.

Relationships between glycaemia, age and HIV infection

The results of the included studies varied as to the relationship between age and glycaemia. Some studies suggested that age and glycaemia have an inverse relationship, i.e. lower glycaemia occurs as age increases.[20,24,25,33] However, other studies suggested that glycaemia worsens with age.[19,23,26–29] To complicate this, there are also data to support there being no statistically significant differences that occur between age and glycaemia.[17,18,21,22,30–32]

In HIC countries, we found that in the ‘older has worse glycaemia category’ vs. ‘older has improved glycaemia category’ vs. ‘non-significant category’, there were two, two and four studies, respectively.

In LMIC, there were three studies in each of the categories. In Malawi, both of the studies suggested that age had no significance in glycaemia.[18,22] This contrasted with SA, where three studies suggested that there is an inverse relationship between age and glycaemia;[25,28,33] one study showed no significant relationship between age and glycaemia[31] while the last study showed that older patients had poorer glycaemia.[27] Overseas, both studies done in Brazil[26] and Iran[29] suggested that older age was associated with poorer glycaemia (see Table 2).

Table 1: Articles which met criteria of scoping review

No.	Author	Year of publication	Country	Region	Number of participants	No. of PLWDH	Gender	Type of study	Patient selection	Duration of HIV	Duration of DM	Associations found relevant to this scoping review
1	Glesby et al. [17]	2010	USA	6 urban sites	424	315	Females	Prospective	Women with or at high risk of HIV infection	X	X	HbA1c was lower in PLWHD compared to HIV-uninfected patients while there was no statistically significant differences in age.
2	Cohen et al. [18]	2010	Malawi	Blantyre	620	65	Both	Prospective	Diabetes Clinic	X	7.0	No statistical differences were seen between age and HbA1c values between PLWD and PLWDH; neuropathy was significantly associated with age or poor glycaemic control (fasting blood glucose but not HbA1c)
3	Capeau et al. [19]	2011	France	47 French clinics	1046	111	Both	Prospective	HIV-infected Cohort	3.6 (0.2–8.7)	X	Age is positively associated with PLWD compared to normoglycaemic patients; indinavir caused more hyperglycaemic episodes
4	Medapalli et al. [20]	2012	USA	New York	31072	1796	97% Male	X	HIV-infected	X	X	PLWDH had lower HbA1c at baseline compared to those without both co-morbidities; mean age of PLWDH were older than overall group

5	Kim et al. [21]	2014	USA	New York	65	65	Both	Retrospective	PLWDH from clinic	X	X	There were no statistically significant differences in age when estimating glycaemia
6	Burgess et al. [22]	2014	Malawi	Blantyre	357	48	Both	prospective	DM Clinic	X	OR: 1.13	High HbA1c and an HIV-infection are risk factors for sight-threatening diabetic retinopathy while age is not significantly related
7	Roerink et al. [23]	2015	Nederlands	Nijmegen	518	28	Both	Retrospective	HIV clinic	12±7	9±5	PLWDH were older and had higher glucose and HbA1c levels
8	Zuniga et al. [24]	2016	USA	Urban	186	186	Both	Retrospective	HIV Clinic	X	X	Older age was significantly related to optimal HIV and DM control
9	Pillay et al. [25]	2016	SA	Pietermaritzburg	653	149	Both	Retrospective	DM Clinic	X	4.29± 4.65	Younger patients who were HIV-infected had higher mean HbA1c levels than older patients.
10	Moreira et al. [26]	2017	Brazil	Rio De Janero	473	10	Both	Retrospective	HIV and TB co-infection	X	X	PLWD were older and had a higher median glucose
11	Khoza et al. [27]	2018	SA	Soweto	320	106	Both	Prospective	DM clinic	5.35 ± 4.19 (Duration of ART)	11.9 ± 5.04	HIV-infected patients were younger and had lower HbA1c levels.
12	Sombanmu et al. [28]	2019	SA	East London	335	21	Both	Cross sectional	Newly diagnosed-HIV patients	X	X	Age <46 is significantly associated with fewer HbA1c levels ≥6.5%
13	Rasoolinejad et al. [29]	2019	Iran	Tehran	480	28	Both	cross-sectional study, retrospective	HIV- infected cohort	59.0 ± 35.9 months	x	Age greater than 40 was significantly associated with hyperglycaemia and DM

14	Zuniga et al. [30]	2020	USA	Center for AIDS Research Network of Integrated Clinic Systems	798	798	Both	Retrospective cross-sectional	PLWH and T2DM	X	X	No statistically significant differences in HbA1c between younger and older patients.
15	Pillay et al. [31]	2020	SA	Pietermaritzburg	915	165	Both	Cross-sectional	DM Clinic	6.5 years (IQR: 3-10) when on ART	Median 4 years; IQR:1-8	PLWDH were significantly younger than PLWD, there was no statistically significant difference in glycaemia between PLWD and PLWDH
16	Wallace et al. [32]	2020	USA	Washington	5876	1023	Both	Observational longitudinal, cross-sectional	HIV Cohort	Mean: 17.9 years	X	In PLWDH, age played no significance between well-controlled and non-controlled DM.
17	Chetty et al. [33]	2021	SA	Pietermaritzburg	957	146	Both	Retrospective	DM Clinic	X	X	Age categories and HbA1c values have an inverse relationship; a positive family history of diabetes has higher mean HbA1c levels in HIV-infected patients on a Fixed Dose Combination of ART

X=No information available on this association

Table 2: Summary of results of study by income type of country

	"older age has worse glycaemia category"	"non-significant category"	"older age has improved glycaemia category"
HIC	USA x 2 studies	USA x 4 studies	Netherlands x 1 study France x 1 study
LMIC	SA x 3 studies	SA x 1 study Malawi x 2 studies	SA x 1 study Brazil x 1 study Iran x 1 study

HIC = high-income countries; LMIC = low- and middle-income countries.

Discussion

Data vary on the associations between age and glycaemic control in PLWD within the context of HIV. An article published in 2018 by Fazekas-Lavu et al.[34] highlighted the limited data available on the associations between HIV and DM. Although literature is available, knowledge gaps are still widespread on this topic as there is no consensus on this association due to a paucity of studies. While performing this scoping review, multiple articles focused on the prevalence of DM or dysglycaemia within cohorts of HIV-infected patients rather than associations that occur in cohorts of patients with both these co-morbidities. We postulate that this is due to the lower prevalence of HIVinfected patients outside LMIC, thereby making it difficult to obtain a cohort of PLWD with an HIV infection in a sample size large enough to study. This is evident from our scoping review where only two studies had cohorts of PLWDH.

Kebbi et al. described that the rising number of younger patients with T2DM in the general population is associated with poorer glycaemic control.[35] Quah et al. concurred and suggested that targeted educational and behaviour modification programmes would be required to effectively manage younger PLWD.[36] In the context of an HIV infection, Chetty et al. found a similar association – younger patients had a higher mean HbA1c than older patients.[33] Al Lawati et al. highlighted that the poorer glycaemia seen in younger adults poses a formidable challenge to diabetes care teams.[37]

On the other end of the spectrum, Roerink et al. found that PLWDH were older and had higher HbA1c levels.[23] This could be attributed to older patients being at higher risk for the development of type 2 diabetes due to the combined effects of increasing insulin resistance and impaired pancreatic islet function.[17] When considering age and an HIV-infection, Kalra et al. highlighted that patients may develop DM due to normal ageing, the metabolic changes related to the HIV infection or due to HIV treatment.[39] This suggests that the occurrence of DM can be multifactorial in older patients. When considering the longer lifespan that PLWH have due to ART and the cardiovascular risks related to DM, effective strategies need to be implemented so that optimal care can be given to this cohort of PLWDH.

Glesby et al. conducted a study on a female cohort and suggested that the HIV infection was more significant than age when comparing glycaemic control. In this study, it was found that HIV-infected patients had lower mean HbA1c levels.[17] According to Monroe et al., HbA1c has been found to underestimate glycaemia in HIV-infected patients (both males and females).[40] This highlights the varying factors and challenges that can affect patients' glycaemia in the context of HIV.

Our study summarised associations but could not identify demographics or resources (seen through LMIC vs. HIC [high-income countries]) as a variable that could be associated with glycaemic control and age. For example, the countries that made up the 'older age has improved glycaemia category' consisted of the USA (two cases) and SA (three cases). This suggested that regardless of the region being developed or underdeveloped, associations may exist. This was evident in our South African setting where three studies were conducted in the same city (Pietermaritzburg) but the results of these studies did not correlate. It is evident from our findings that there are likely associations between age and glycaemic control that are not well understood at present. We postulate that this is attributed to the differing lifestyle habits (diet/exercise/medication adherence) of patients in the different age groups.

Conclusion

Varying data exist on the associations between glycaemic control and age in PLWD in the context of HIV. Further studies are recommended to determine associations in this regard, especially in LMIC where HIV and DM are highly prevalent.

Disclosure statement – No potential conflict of interest was reported by the authors.

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Received: 22-04-2021 Accepted: 17-06-2021

CHAPTER 3: AGE AND DIABETES CONTROL IN AN HIV-ENDEMIC COUNTRY: IS THERE AN ASSOCIATION? (RESEARCH ARTICLE)

This chapter focuses on original research on associations between Age and Diabetes Mellitus at the Diabetes Clinic at Edendale Hospital.

In this article we determined that younger PLWD have poorer glycaemic control and are likely to develop diabetes-related complications later in life. This study highlights that more emphasis needs to be placed on diabetes education and management in the younger age categories of both PLWD and PLWDH.

(Some formatting changes and minor additions have been inserted from the original article published in JEMDSA)

Age and Diabetes Control in an HIV-endemic country: Is there an association?

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[Article accepted by JEMDSA and published online on 2 December 2021]
https://www.tandfonline.com/doi/full/10.1080/16089677.2021.2002586

ABSTRACT

Background: The prevalence of diabetes mellitus (DM) in South Africa (SA) is 12.80% and is rising while that of HIV infection remains the highest globally (13%). Literature varies on the associations between glycaemic control and age in patients living with DM (PLWD). Through effective anti-retroviral treatment (ART), HIV-infected patients can now live longer and develop co-morbidities as experienced by HIV-uninfected patients. Identification of challenges faced in diabetes control within the various age groups would help in developing strategies to provide improved care to patients.

Objectives: This study aimed to determine an association between age and diabetes control in an HIV endemic area.

Methods: Data from standardised clinic sheets were used from the DM clinic at Edendale Hospital, Pietermaritzburg, South Africa, from 1 January 2019 to 31 December 2019.

Results: This study had 957 PLWD with 146 PLWD being HIV-infected (PLWDH). Older age was associated with improved mean glycated haemoglobin (HbA1c) levels after adjusting for glomerular filtration rate (GFR) [r=-0.141, p<0.001]. (Before adjustment: r=-0.108; p=0.001). HIV-infected patients had lower mean HbA1c levels than their HIV-uninfected counterparts while age was positively associated with BMI in patients (r=0.246, p<0.001). PLWDH with a mean HbA1c>7% were significantly younger than those with HbA1c≤7% (47.38 years vs. 52.77 years, p=0.013). GFR declined with age: PLWD with GFR<60ml/min were significantly older than those with GFR≥60ml/min (62.72 years vs. 48.30 years, p<0.001), this remaining significant after factoring in for HIV-infection and hypertension.

Conclusion: Younger PLWD have poorer glycaemic control and are likely to develop diabetes-related complications later in life. Notably, younger PLWDH also had poorer glycaemic control which places them at increased cardio-metabolic risk from sequelae of both the HIV-infection and DM. This study highlights that more emphasis needs to be placed on diabetes education and management in the younger age categories of both PLWD and PLWDH.

Keywords: Diabetes Mellitus, glycaemic control, age, HbA1c, HIV

Age and Diabetes Control in an HIV-endemic country: Is there an association?

Introduction

Globally, seventy-nine percent (79%) of adult patients living with diabetes mellitus (PLWD) are from low-and-middle-income countries (LMIC), with approximately 1 in 5 of these PLWD being older than 65 years[1]. In 2019, there were approximately 463 million PLWD and 4,2 million deaths that were related to diabetes mellitus (DM)[1]. These numbers are expected to rise to 700 million by 2045[1]. In South Africa (SA), a country classified as a LMIC, the prevalence of DM is 12.80%[2]. SA also has the highest prevalence of HIV infection globally (13%)[3]. Results from both high income contries (HIC) and LMIC countries suggest that younger age is associated with poorer glycaemic control[4,5]. This finding was contrasted by Roerink et al. who determined that older PLWD had poorer glycaemic control in a study conducted in Netherlands[6] while Zuniga et al. found that there were no statistically significant differences in HbA1c values between older and younger adults[7]. Additionally, a South African study showed that PLWD who were HIV-infected (PLWDH) were younger and had a lower mean HbA1c level[8]. This 2018 study by Khoza et al. conducted at the Chris Hani Baragwanath Academic Hospital DM Clinic, Soweto, SA, described 'The effect of HIV infection on glycaemia and renal function in type 2 diabetic patients'[8]. In another South African study, Werfalli et al. determined that older PLWD have a poorer quality of life and greater disability[9]. This is likely attributed to older PLWD being at increased risk for both acute and chronic microvascular and cardiovascular complications related to the disease[10].

With the effective rollout of anti-retro viral treatment (ART), HIV-infected patients can be expected to have a normal lifespan[11]. Kalra et al. highlighted the association between age and an HIV-infection in PLWD and mentioned that DM can develop as a result of the normal course of aging, metabolic factors related to the HIV-infection or due to ART[12]. As these patients can now live to an older age with co-morbidities, strategies need to be implemented to provide effective care to patients as they age.

Chetty et al. conducted a scoping review in 2021 describing the relationship between 'age' and 'glycaemic control' in PLWD in the context of HIV-infection. Results of this scoping review demonstrated that data varied significantly on the associations between glycaemic control and age in PLWD[13]. They recommended that additional studies be conducted in LMIC countries where there is a high prevalence of co-existent HIV and DM[13].

Methods

A retrospective, analytical cohort study was performed using data collected from patients who attend a specialised diabetes clinic at Edendale Hospital (EDH), Pietermaritzburg, KwaZulu-Natal. Clinicians used a standardised, comprehensive clinic sheet for all patients consulted in this clinic which has been approved by the University of KwaZulu-Natal Biomedical Research and Ethics Committee (BREC) – BCA 194/15 while the BREC approval number for this current study is 2645/2021. The data for this study included patients of all ages who attended the diabetes clinic at EDH between 1 January 2019 to 31 December 2019.

Patient demographics, age, mean HbA1c, random blood glucose, HIV status, type of DM were recorded in addition to other variables from the datasheet. Missing or incomplete or incorrectly completed data were not considered.

Age was divided into the following groups: 13-17 years; 18-30 years; 31-45 years; 46-60 years; 61-75 years and ≥76 years old.

Good glycaemic control was defined as a glycated haemoglobin (HbA1c) value ≤7.00% while poor glycaemic control was defined as HbA1c>7.00%[14]. The Bio-Rad D-10 machine (Bio-Rad, USA) was used for analysing the HbA1c values at the laboratory. Both the laboratory and the machines are NGSP (National Glycohemoglobin Standardization Program) accredited to maintain standardisation of HbA1c results while the random glucose measurement (mmol/L) was determined using an Accu-Chek® glucometer (Roche, Switzerland). All variables utilised in the study were determined using National Health Laboratory Services (NHLS) methodology and calibration by technicians in their lab.

Statistical analysis

Statistical analysis was conducted with numerical data using Analysis of Variance (ANOVA) whilst categorical data relationships were determined using either Chi-square or Fisher's Exact tests. A p-value<0.05 was used as indicator of significance. Data was analysed by Statistical Package for Social Science (SPSS) version 25 for Windows (SPSS Inc., Chicago, IL, USA). The original data was screened for completeness, with outliers being eliminated. Numerical data was tested for normality using the Kolmogorov Smirnov Test. Most of the variables were not normally distributed, hence non-parametric analysis was used. Descriptive measures included the use of central measures (mean, median), standard deviations and inter-quartile ranges. The relationships between numerical data was determined using

correlations, and those between categorical variables was done using chi square tests. Categorical data counts were represented using percentages. Binary logistic regression was used to determine the odds ratios for specified variables.

RESULTS

(A) Epidemiology

Data of 957 PLWD were used for this study – there were 822 (86.20%) Type 2 DM (T2DM) patients while 132 (13.80%) patients had Type 1 DM (T1DM) [3 unknown]. Approximately one-sixth of the cohort had an HIV infection (146, 15.30%). Of this HIV-infected cohort with DM, 84 (57.50%) were on a fixed-dose combination (FDC) of ART, while the other patients were either not yet initiated or were on alternative ART regimens. The majority of patients were between 46-60 years in both the PLWD and the PLWDH cohorts. [See Table 1]

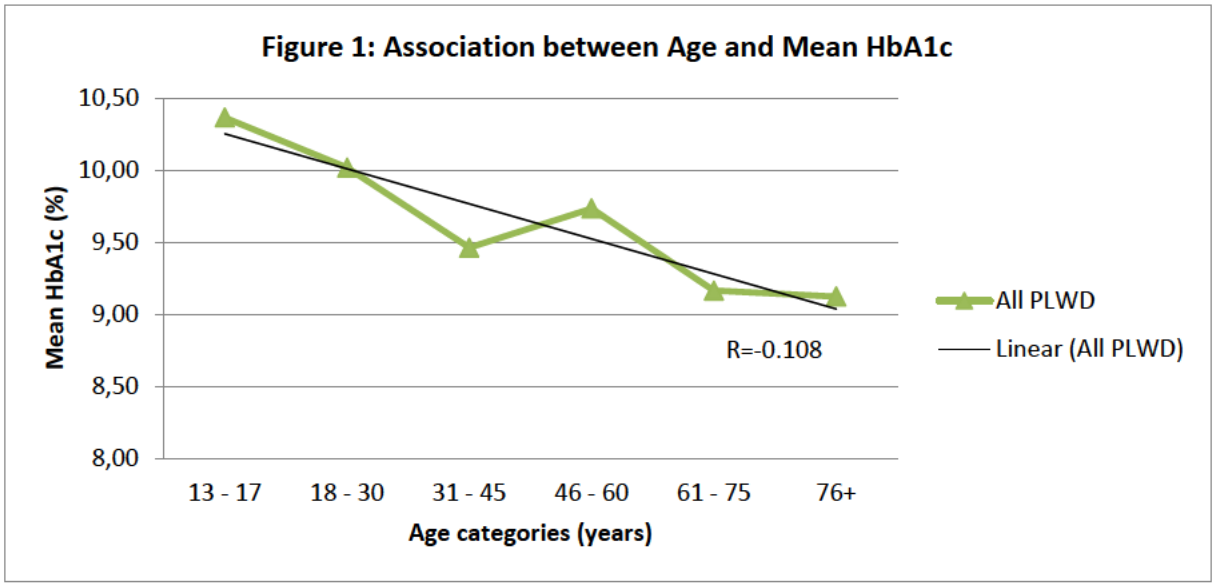
In the study the mean age of T1DM and T2DM was 29.33 years vs. 57.31 years, respectively. In PLWT1DM, there were 65 female patients while 67 patients were male. In PLWT2DM, females comprised of 596 patients while there were 226 male patients. In PLWT1DM there were 17 HIV-infected patients in contrast to 129 HIV-infected patients in PLWT2DM. With regards to hypertension, there were 30 PLWT1DM while there were 713 PLWT2DM.

(B) Age and HbA1c

The mean HbA1c had a weak negative correlation with age ($R=-0.108$; $p=0.001$) [figure 1]. There was a statistically significant difference noted between the mean HbA1c value in the 13-17 year category compared to the ≥76 year category (10.36% vs. 9.12%, respectively, $p=0.04$). All patients in the youngest and oldest age categories were HIV-uninfected. In addition to this, a statistically significant difference in HbA1c was observed between the 46-60 year and the 61–75-year age categories (9.73% vs. 9.16%, respectively, $p=0.002$). After adjusting for GFR, there was a stronger inverse correlation noted between age and HbA1c ($r=-0.141$, $p<0.001$) while HIV-infected patients had lower mean HbA1c levels than their HIV-uninfected counterparts. This association was highlighted in the 46–60-year age category (9.08% vs. 9.90%, respectively, $p=0.004$). There were significant differences noted in the mean HbA1c values between the age groups when considering all the patients together ($p=0.024$), within the HIV-uninfected group only ($p=0.026$), and within the HIV-Infected group only ($p=0.039$). [See Table 1]. Cross tabulation of BMI with HbA1c and HIV revealed non-significant results ($p>0.05$).

Table 1: Age and HbA1c levels of patients in the context of an HIV-infection

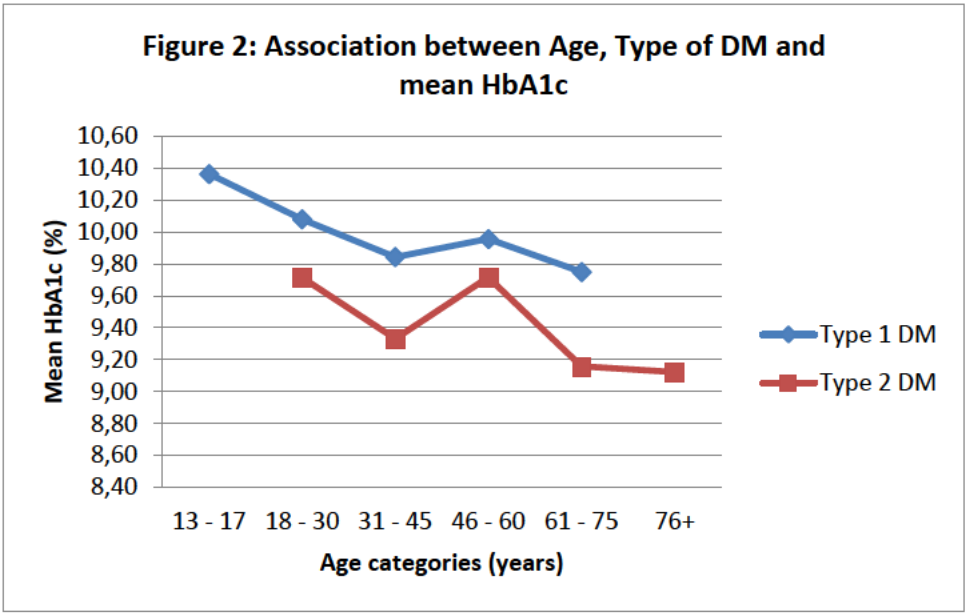
	All patients		HIV-Uninfected		HIV-Infected		
Age categories (years)	Count	Mean HbA1c (%)(±SD)	Count	Mean HbA1c (%) (±SD)	Count	Mean HbA1c (%) (±SD)	P values (HIV-uninfected vs. infected)
13 - 17	15	10.36 (1.96)	15	10.36 (1.96)	0	-	-
18 - 30	81	10.02 (2.24)	75	9.97 (2.27)	6	10.60 (1.93)	0.511
31 - 45	167	9.46 (2.19)	120	9.49 (2.17)	47	9.38 (2.28)	0.772
46 - 60	369	9.73 (2.22)	291	9.90 (2.18)	78	9.08 (2.25)	0.004
61 - 75	273	9.16 (2.30)	258	9.24 (2.30)	15	7.97 (1.87)	0.037
≥76	52	9.12 (2.04)	52	9.12 (2.04)	0	-	-
P values (across various age categories in column)		0.024		0.026		0.039	



(C) Type of Diabetes

There were significantly more patients with T2DM vs. T1DM (822 vs. 132: respectively, p<0.001). Patients living with type 2 diabetes mellitus (PLWT2DM) were significantly older than PLWT1DM (p<0.001).

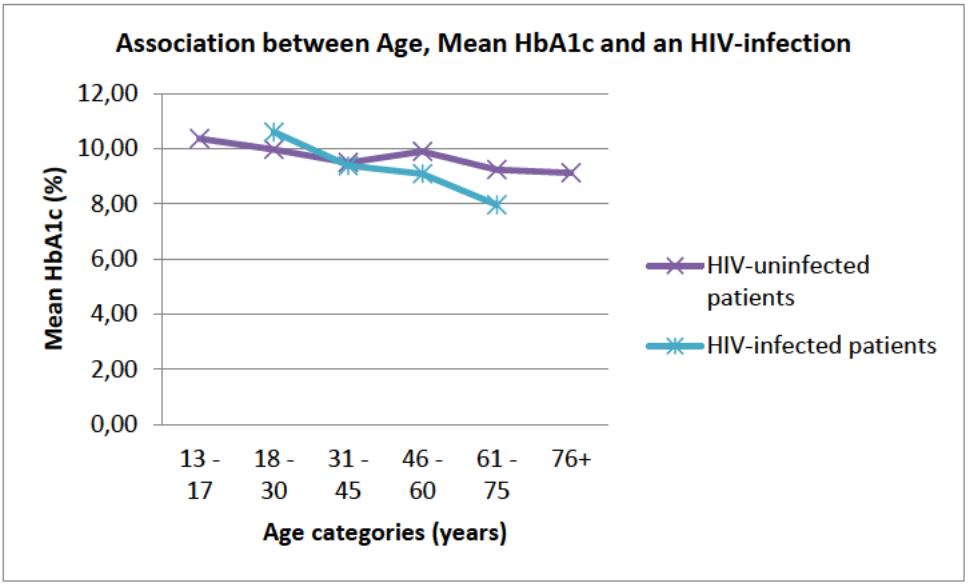
In PLWT1DM, younger patients had poorer glycaemic control (HbA1c>7.00%); however,.00 this was not statistically significant (28.85 years vs. 34.54 years, respectively, p=0.07). The mean age was also non-significant in PLWT2DM between those with good vs. poor glycaemic control (57.50 years vs. 57.41 years, respectively, p=0.942). The poorer glycaemic control in PLWT1DM compared to PLWT2DM across the age categories is illustrated in Figure 2.



(D) HIV Infection

A comparison between mean HbA1c>7.00% vs. HbA1c≤7.00% cohorts in PLWDH revealed that higher mean HbA1c values were associated with younger patients (47.38 years vs. 52.77 years, respectively, p=0.013). In those without an HIV-infection, there was no statistically significant difference between age and glycaemic control. PLWDH were younger than PLWD without an HIV infection in the cohort with HbA1c>7.00% (47.38 years vs. 54.18 years, respectively, p<0.001). Those with lower Cluster of Differentiation (CD4) counts were typically younger patients; however, this was not significant (p=0.075). The poorer glycaemic control in older HIV-uninfected PLWD is highlighted in Figure 2.

Figure 2: Association between Age, Mean HbA1c and HIV-infection



(E) Duration of DM

Overall, PLWD with good glycaemic control had a shorter duration of DM compared to those with sub-optimal control (7.24 years vs. 10.68 years, respectively, $p<0.001$). This significant finding was also observed in the HIV-uninfected group (7.07 years vs. 11.30 years, respectively, $p<0.001$). However, this did not occur in the HIV-infected group (7.92 years vs. 7.00 years, respectively, $p=0.513$). In addition to this, those with poor glycaemic control had a significantly longer duration of DM if they were HIV-uninfected (11.30 years vs. 7.00 years, respectively, $p<0.001$) [See Table 2].

Table 2: Duration of DM and mean HbA1c in the context of HIV-infection

	All patients		HIV-Uninfected		HIV-Infected		
Mean HbA1c (%)	Count	Mean duration of DM (±SD) in years	Count	Mean duration of DM (±SD) in years	Count	Mean duration of DM (±SD) in years	P values (HIV-uninfected vs. infected)
≤7.00	133	7.24 (7.68)	107	7.07 (7.89)	26	7.92 (6.84)	0.615
>7.00	761	10.68 (8.93)	655	11.30 (9.16)	106	7.00 (6.30)	<0.001
P values		<0.001		<0.001		0.513	

(F) Blood pressure

PLWD with elevated blood pressure [systolic blood pressure (SBP) ≥140mmHg] were significantly older than those with SBP<140mmHg (58.27 years vs. 50.25 years, respectively, p<0.001). This finding was present in both the HIV-infected and HIV-uninfected patients (p<0.001). HIV-uninfected patients with SBP≥140mmHg were significantly older than HIV-infected patients (59.08 years vs. 52.33 years, respectively, p=0.001).

Patients with elevated diastolic blood pressure (DBP) ≥90mmHg were significantly younger than those with DBP<90mmHg (50.36 years vs. 54.26 years, respectively, p=0.002). There was no significance noted in patients with DBP≥90mmHg between the HIV-infected and HIV-uninfected cohorts (p=0.457). Older patients had a significant positive correlation with mean SBP (r=0.298, p<0.001) while this association was not present with DBP (p>0.05) [See Table 3 and Figure 3]. Patients with hypertension were significantly older than those without (p<0.001). Furthermore, those patients with GFR<60ml/min, were significantly older than those with GFR≥60ml/min in both the hypertensive and non-hypertensive groups (p<0.001 vs. p=0.015, respectively) [See Table 4].

Table 3: Blood pressure and age in the context of an HIV infection

	All patients		HIV-Uninfected		HIV-Infected		
SBP (mmHg)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	P values (HIV-uninfected vs. infected)
< 140	567	50.25 (16.54)	467	51.08 (17.62)	100	46.35 (9.12)	0.009
≥ 140	382	58.27 (12.60)	336	59.08 (12.72)	46	52.33 (9.97)	0.001
p values		<0.001		<0.001		<0.001	
DBP (mmHg)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	p value
< 90	758	54.26 (16.10)	648	55.32 (16.71)	110	48.01 (9.81)	<0.001
≥ 90	191	50.36 (12.89)	155	50.70 (13.52)	36	48.92 (9.74)	0.457
p values		0.002		<0.001		0.629	

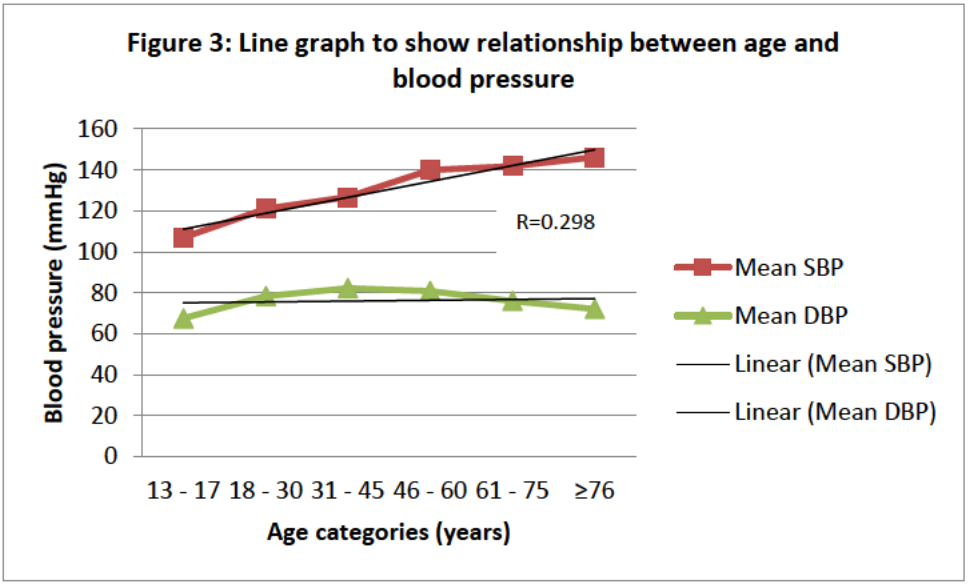


Table 4: Associations between age and GFR in hypertensive vs. non-hypertensive patients

	Non-hypertensive patients		Hypertensive Patients		
GFR (ml/min)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	P values
<60	10	45.10 (15.96)	271	64.83 (9.98)	<0.001
≥60	133	34.83 (12.41)	288	55.99 (11.32)	<0.001
P values		0.015		<0.001	

(G) Dyslipidaemia

Elevated triglycerides levels ≥ 1.7 mmol/L were associated with older age (55.72 years vs. 51.91 years, respectively, p<0.001). Decreased high density lipoproteins (HDL-cholesterol) levels in males were also significantly associated with older age (52.64 years vs. 47.78 years, respectively, p=0.032) [See Table 5].

Table 5: Associations between age and lipids

	All PLWD	
Total Cholesterol (mmol/L)	Count	Mean age (±SD)
< 4.5	444	53.16 (16.50)
≥ 4.5	436	53.97 (14.51)
P value		0.44
LDL (mmol/L)	Count	Mean age (±SD)
<1.8	154	54.69 (15.64)
≥ 1.8	420	53.64 (15.54)
P value		0.474
HDL (in females) (mmol/L)	Count	Mean age (±SD)
<1.2	239	55.37 (15.36)
≥ 1.2	269	55.67 (14.26)
P value		0.82
HDL (in males) (mmol/L)	Count	Mean age (±SD)
<1.0	76	52.64 (16.04)
≥ 1.0	155	47.78 (16.07)
P values		0.032
Triglycerides (mmol/L)	Count	Mean age (±SD)
<1.7	497	51.91 (16.74)
≥ 1.7	378	55.72 (13.52)
P values		<0.001

(H) Gender

There were no statistically significant differences documented between mean HbA1C and gender in the different age categories**.**

(I) Family History of DM (FHD)

Patients with a positive FHD and poor glycaemic control were significantly younger than those with good glycaemic control (51.57 years vs. 55.58 years, respectively, p=0.045). Furthermore, PLWD with HbA1c≤7.00% were usually younger if a positive FHD was present (51.57 years vs. 55.14 years, respectively, p=0.002) [Table 6].

Table 6: Associations between FHD, age and HbA1c

	Negative FHD		Positive FHD		
HbA1c (%)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	P value
≤7.00	69	54.96 (15.10)	64	55.58 (14.07)	0.807
>7.00	354	55.14 (16.50)	407	51.57 (14.95)	0.002
P values		0.933		0.045	

(J) Renal involvement

Patients with elevated creatinine≥104umol/l were significantly older than those with levels <104umol/l (62.01 years vs. 49.91 years, respectively, p<0.001). This association occurred in both PLWDH as well as in the HIV-uninfected patients (p<0.001) [See Table 7]. Glomerular filtration rate (GFR) declined with age. Those with a GFR<60ml/min were significantly older than those with GFR≥60ml/min (62.59 years vs. 48.30 years, respectively p<0.001) [Table 8]. When factoring in for co-morbidities, PLWD with co-morbid hypertension and an HIV-infection had a significantly lower age than PLWD without hypertension or an HIV-infection (45.10 years vs. 54.02 years, respectively, p=0.013).

Table 7: Association between creatinine and age in the context of an HIV-infection

	All patients		HIV-Uninfected		HIV-Infected		
Creatinine (umol/l)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	P values (HIV-uninfected vs. infected)
< 104	625	49.91 (15.53)	531	50.64 (16.25)	94	45.76 (9.63)	0.005
≥ 104	273	62.01 (11.72)	227	63.86 (11.40)	46	52.85 (8.60)	<0.001
P values		<0.001		<0.001		<0.001	

Table 8: Association between GFR and age

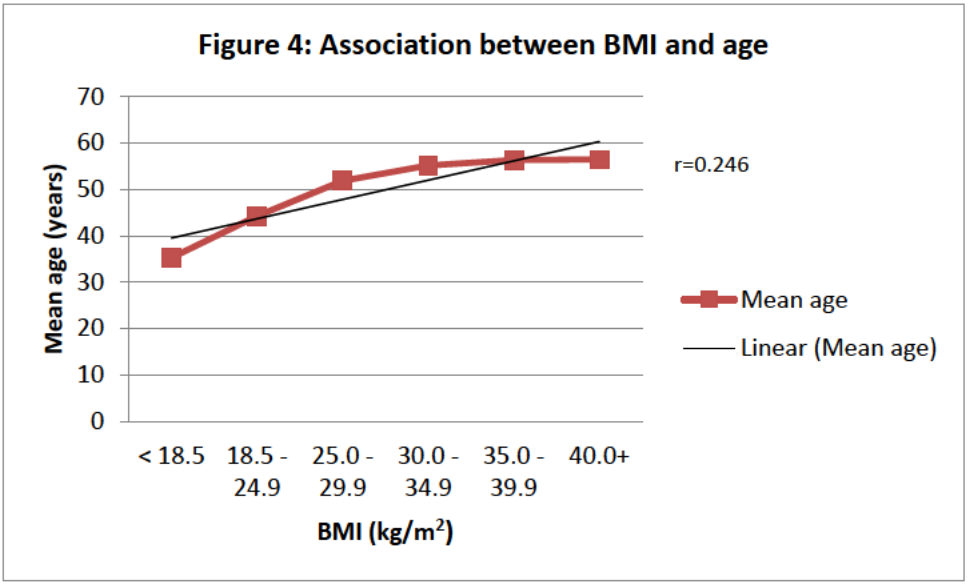
	All patients	
GFR (ml/min)	Count	Mean age in years (±SD)
<60	329	62.59 (11.14)
≥ 60	500	48.30 (14.42)
p values		<0.001
Breakdown of GFR		
<15	20	65.75 (9.61)
15-29	78	64.22 (11.90)
30-59	231	61.77 (10.93)

(K) Body Mass Index (BMI)

Patients with a BMI≥30kg/m^2 were typically older than those who had a BMI<30kg/m^2 (55.92 years vs. 48.12 years, respectively, p<0.001). This association of increased BMI and older age was also seen in the HIV-uninfected patients (57.17 years vs. 48.08 years, respectively, p<0.001) but did not occur in HIV-infected patients (p=0.775) [See Table 9]. There was a significant positive correlation noted between age and BMI in PLWD (r=0.246, p<0.001) [See Figure 4].

Table 9: Association between obesity and age in the context of an HIV-infection

	All patients		HIV-Uninfected		HIV-Infected		
BMI (kg/m^2)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	Count	Mean age in years (±SD)	P values (HIV-uninfected vs. infected)
<30	343	48.12 (17.21)	280	48.08 (18.39)	63	48.29 (10.63)	0.930
≥30	532	55.92 (13.57)	461	57.17 (13.80)	71	47.82 (8.35)	<0.001
P values		<0.001		<0.001		0.775	



DISCUSSION

Globally, results of studies have varied with regard to the relationship between age and glycaemic control. Results from both HIC and LMIC countries suggest that younger age is associated with poorer glycaemic control[4,5]. This finding was contrasted by Roerink et al. (Netherlands study) who determined that older PLWDH had poorer glycaemic control[6] while Zuninga et al. found that there were no statistically significant differences in HbA1c between older and younger adults[15]. In contrast to these, an Iraqi study found that younger patients were associated with poorer glycaemic control[16]. Our study yielded results which were similar to this Iraqi study. A South African study conducted by Khoza et al. showed that PLWDH were younger and had a lower mean HbA1c level[8]. Renal impairment decreases the clearance of insulin, thereby prolonging the half-life of the circulating insulin, resulting in decreased insulin requirements in PLWD[17]. After adjusting for GFR, older patients still had improved glycaemic control, becoming more significant after the adjustment. We postulate that older patients often having other co-morbidities might be more adherent to therapy and to clinic dates. Results of our study illustrate that we need to target improved glycaemic control in younger PLWD in order to prevent long-term complications.

The reason for younger patients with poorer glycaemic control is multi-factorial. Teenagers and younger adult patients often have T1DM where there is an absolute insulin deficiency[18]. Lack of adherence to insulin in PLWT1DM is frequent with estimates of adherence occurring in 23-77% of patients – with higher values predicted in LMIC[19]. Riaz et al. listed factors associated with non-adherence including: the educational level of the patients' parents, frequency of visiting DM clinics, knowledge regarding DM, lack of family support and the fear of hypoglycaemia[20]. Fu et al. suggested that non-adherence often resulted from a fear of needles or injections in patients[21] while Patton et al. described how PLWT1DM have issues relating to their diets which is a cause of poor glycaemic control[22]. It is thus essential to have good support with managing DM especially in the early stages of the disease as failure to adequately manage this condition can lead to poorer glycaemic control and resultant complications.

In older patients, there is improved glycaemic control compared to younger patients; however, glycaemic control is still not always optimal. In our study the older working group (46-60 year olds) had poorer glycaemia than the retirement group (61-75 year olds). We postulate that this is due to having poor eating patterns and consumption of unhealthy foods in the work environment. Work has been identified as a factor which leads to non-adherence due to a busy schedule[23]. Other factors which relate to poorer adherence include patient-related factors (e.g. forgetfulness or intentionally not taking medication) or drug-related (cost of medication or side effects)[23]. A South African study determined the cost of eating healthier foods was between 30-110% more expensive (on average 69% or more) than eating a non-healthy diet[24]. This would favour the purchase of non-healthy food which has adverse

effects on glycaemic control and health in general. This highlights the social challenges faced in managing DM (and other medical conditions) in all ages especially in a LMIC.

Our study demonstrated that there was an increased prevalence of renal complications (defined by significantly increased creatinine and lower GFR levels) in older patients. In a LMIC country (such as SA), limited resources result in fewer patients having access to these scarce life-saving treatment modalities. In 2017, the incidence of initiation of renal replacement therapy (RRT) in SA was 25 per million population (pmp) which was significantly lower than countries with greater resources such as the United States of America (370 pmp) or the United Kingdom (121 pmp)[25]. Furthermore, Maphumulo et al. described how the long waiting times for medical intervention in SA may lead to patients developing complications or succumbing to the disease process as a result of not receiving timeous intervention[26]. These findings emphasise the need for early implementation of effective management strategies in the younger PLWD to prevent or retard disease progression in order to decrease the burden on limited resources and treatment modalities.

It is well-established that there is an association between hypertension with cardio-vascular disease (CVD), commonly resulting in increased mortality[27]. PLWD have a 200-400% risk of dying from CVD[28], while some estimate that it can be as high as 10 times the risk of the general population[29]. In patients with hypertension and DM, the CVD risk increases by a further 75%[30]. In our study, systolic hypertension was positively associated with age. This is similar to what has been shown in other studies globally. An American study conducted by Ostchega et al. highlighted the increased prevalence of hypertension with age[31]. In contrast to this, our study found that the mean age of patients with increased DBP ≥90mmHg was younger than those with a DBP <90mmHg. According to Li et al., DBP is an important risk factor for coronary risk in younger patients[32]. It has also been shown to be a risk factor for formation of an abdominal aortic aneurysm[33]. Clinicians should be aware of this risk factor and pay special attention to diastolic blood pressures just as much in the younger PLWD as they do for older patients. In SA, Steyn et al. highlighted that the care of patients with DM and hypertension is suboptimal[34]. Strained healthcare systems are a major challenge, especially in Africa, with only 2% of patients having good control of hypertension[35]. It is therefore important to implement effective early interventions to manage non-communicable disease such as DM and HPT, especially when they co-exist.

Our study also demonstrated that elevated triglycerides and lower HDL values (in males) were present in older patients in the overall patient population. This is commonly found in T2DM and is associated with insulin resistance, obesity and metabolic syndrome phenotype[36]. It is worrying as this increases the risk of developing cardiovascular disease and increases the risk of all-cause mortality[37]. Feingold et al. found that approximately 60-70% of patients in the general population with obesity have dyslipidaemia[38]. Bekele et al. assessed this association of obesity and dyslipidaemia in PLWD and determined a similar finding[39]. In our study we found that older age is associated with increasing BMI. We postulate that the dyslipidaemia in older patients could be attributed to the increasing BMI values rather than due to glycaemic control.

As expected, we found that poorly controlled HbA1c was associated with a longer duration of DM. Mamo et al. also found that a duration of DM greater than 7 years led to poorer glycaemic control[40]. This is likely due to progressive damage to insulin ß-cell secretion with time and an increase in insulin resistance[40]. Worsening glycaemic control with increased duration of DM plus advancing age increases the risk of cardiovascular morbidity and mortality. In our study, younger patients had significantly higher mean HbA1c levels than their older counterparts. Ramanathan et al. highlighted that a long duration of DM with poor glycaemic control increases the microvascular complications of DM[41]. Petitti et al. recommended that poorly controlled glycaemia in younger patients warrants an urgent need for effective strategies to improve the metabolic status of patients[42]. This was confirmed by Toh et al. who found that younger patients had poorer glycaemic control than older patients and should receive targeted interventions to achieve 'optimal' glycaemic control[43]. Our study findings suggest that more emphasis needs to be placed on intervention strategies targeting this group of PLWD this in order to decrease long term diabetes-related complications resulting from poor glycaemic control.

The combination of HIV infection and DM remains a major concern for LMIC. We showed that those with an HIV-infection were younger than their HIV-uninfected counterpart, implying longer future disease duration. Our study found that the younger PLWDH had poorer glycaemic control. This coupled with increased disease duration secondary to young age and availability of ART increases the risk of development of diabetes related complications.

Overall, HbA1c was lower in HIV-infected patients when compared to PLWD without an HIV-infection. Our results contrasted that of a study conducted in Netherlands which found that PLWDH had higher glucose levels and were older[6]. This is a significant finding in our study and we postulate that this improved glycaemic control in HIV-infected patients could be attributed to either the quality of a specialised, diabetes clinic which offers co-monitoring of the HIV infection and DM or could be as a result of HIV-infected patients being more compliant to their medication resulting in them taking both their ART and DM medication.

Within the PLWDH cohort, renal disease occurred at a younger age. Although no histological diagnosis of HIV-associated nephropathy (HIVAN) was obtained in these patients, we suspect that this could be as a result of an HIV-infection as all patients in the cohort were PLWD. This is important as the development of renal disease at a younger age will result in more patients requiring renal replacement therapy, placing an increasing burden on the state and its limited resources.

In addition to this, those with elevated blood pressures were younger in HIV-infected patients compared to HIV-uninfected patients. A study conducted by Olaiya et al. found out that younger patients with undiagnosed and untreated hypertension had a longer duration of disease during which they developed complications from hypertension[44]. This suggests that regardless of the co-morbidity, undiagnosed and untreated disease in youth can have complications later on in life. This emphasises the challenges that arise when HIV infection and non-communicable diseases interact.

LIMITATIONS

- Not all patients had all results filled in their datasheets.
- As this was a retrospective study, no causal relationships could be determined; rather, associations were defined.
- A single-centre was utilised in this study.

CONCLUSION

Younger PLWD have poorer glycaemic control and are likely to develop diabetes-related complications later in life. Notably, younger PLWDH also had poorer glycaemic control which places them at increased risk from sequelae of both HIV and DM. This study has served to highlight that more emphasis in terms of diabetes education and management needs to be placed in the younger age category of PLWD and PLWDH.

Acknowledgements

- Mr D Singh for his help in generating statistical analyses for the study.
- Sister Lungi Ndaba and her nursing team at the Edendale Hospital diabetes clinic.

Conflict of Interest

None

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CHAPTER 4: CONCLUSION

This research project aimed to address two primary aims: firstly, to perform a scoping review on the relationship between Age and Diabetes Control in Patients Living with Diabetes Mellitus in an HIV-endemic area and, secondly, to conduct original research on this topic.

The scoping review highlighted that "varying data exists on the associations between glycaemic control and age in PLWD in the context of HIV infection". It was also suggested in this scoping review that "further studies are recommended to determine associations in this regard, especially in LMIC where HIV and DM have a higher prevalence". This highlighted to us that relationships between the above-mentioned variables are not well understood. This made the research article (Chapter 3) more relevant to the study as associations in our setting would offer greater insight to our population.

Our research article determined that "younger PLWD have poorer glycaemic control and are likely to develop diabetes-related complications later in life". We established that it was important to highlight that "more emphasis, in terms of diabetes education and management, needs to be placed in the younger age category of both PLWD and PLWDH". By doing this we hope that younger patients optimise lifestyle changes (in terms of diet and exercise) as well as medical treatment in order to improve glycaemic control to live longer (with fewer complications) thus leading to an improved quality of life.

The latest 2019 International Diabetes Federation statistics suggest that approximately 12,8% of South Africans are PLWD[1] which is more than double the number of cases since 2017[2]. This shows a significant increase in numbers and suggests that greater efforts need to put in place to prevent and manage this deadly non-communicable disease. In June 2021, SA was ranked 49th out of 95 countries (which was the top ranked African country) according to the 'Health Care Index by Country 2021 Mid-Year' statistics[3]. Considering the prevalence of DM and HIV throughout the African continent and the sample utilised for this study, this suggests that the results obtained from this study will be relevant not only locally in SA but also to other countries throughout Africa (and LMIC countries worldwide).

From this study we agree that it is useful to screen all patients for DM and that in younger patients who are diagnosed with DM it is imperative to implement strategies to optimise glycaemic control to prevent

complications. In the context of a LMIC, we recommend that a holistic approach be utilised in the management of DM. Sami et al. highlighted that diet and a sedentary lifestyle are main factors for developing DM within LMIC countries[4]. Although our study is conducted in patients already diagnosed with DM, these same factors should be considered in order to prevent worsened glycaemic control. We advocate for a healthy diet to be implemented by patients of all ages despite realising that this is not always possible in a LMIC country since healthier foods are nearly twice as expensive as unhealthier foods[5]. In addition to this, we recommend that exercise should be done by PLWD in all ages in order to promote good glycaemic control. The current recommendation according to the SEMDSA 2017 guidelines is that exercise should be done for at least 30 minutes a day, 5 times a week[6]. This is a cost-effective, non-pharmacological method to manage DM and can be done at all ages. The advice recommended is also true for all HIV-infected patients living with DM.

Optimal pharmacological management is another key aspect to maintaining good glycaemic control and preventing complications. Efforts to promote this include adherence to medication as well as self-monitoring of glucose levels[7]. Again, we recommend that these measures should be done by PLWD of all ages. Through good adherence measures and self-monitoring glucose levels, patients would often be able to detect higher glycaemic control and inform their healthcare provider – who would then be able to appropriately adjust or up-refer in order to optimise pharmacological intervention. By instilling these methods from a younger age, it would drastically improve the glycaemic control and ultimately allow for PLWD to live longer with fewer complications and have a better quality of life.

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APPENDIX 1: THE STUDY PROTOCOL

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School of Clinical Medicine

The Relationship between Age and Diabetes Control in Patients Living with Diabetes Mellitus in Low-to-Middle Income Countries

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(February 2021)

EXECUTIVE SUMMARY

The purpose of this retrospective, observational study will be to determine if a relationship exists between age and diabetes control in patients presenting to the diabetes clinic at Edendale Hospital in KwaZulu-Natal between 1 January 2019 and 31 December 2019.

Diabetes Mellitus (DM) is a chronic, metabolic disease characterised by raised blood glucose levels. In 2019, there were an estimated 463 million adult patients living with diabetes (PLWD), with this figure expecting to reach around the 700 million mark by 2045. Patients living in low-income and middle-income countries comprise approximately 79% of global adult PLWD figures, with only 20% of these PLWD being older than 65 years. This illustrates that the burden of DM in LMIC countries rests on the younger working-age population. Younger age is associated with poorer glycaemic control and also implies a longer duration of disease exposure. This often results in increased risks of complications which can be encountered in older patients and can drastically reduce life-expectancy by approximately 10-20 years.

In this study we will assess the effect of age on clinical and biochemical variables in PLWD who visit a regional hospital diabetes clinic in Pietermaritzburg, KwaZulu-Natal, South Africa. The results of this study can help the government to design and implement strategies to improve current diabetes care in patients targeting different age groups.

1. BACKGROUND AND LITERATURE REVIEW

1.1 Defining the Clinical Problem

Diabetes Mellitus (DM) is a chronic, metabolic disease characterised by raised blood glucose levels[1]. In 2019, there were an estimated 463 million adult patients living with diabetes (PLWD), with this figure expected to reach around the 700 million mark by 2045[2].

Patients living in low-income and middle-income countries (LMIC) comprise approximately 79% of the global adult PLWD figures, with approximately 20% of these PLWD being older than 65 years[2]. This contrasts with high-income countries which have greater than 50% of their PLWD older than 65 years[3], illustrating that the burden of DM rests on the shoulders of the younger working-age population in these LMIC. These patients living with type 1 and type 2 diabetes already have reduced life expectancies of approximately 20 and 10 years respectively[4] and DM occurring at a younger age only serves to compound the problem of decreasing the life expectancy of the population in these LMIC, countries which are already being burdened by communicable diseases like HIV infection and tuberculosis (TB). South Africa, classified as a LMIC, has the highest prevalence of HIV in the world at 13%[5] with TB being reported as the main cause of mortality in South Africa in 2019, with an estimated 58 000 annual TB-attributable deaths[6].

1.2 The literature review

Literature shows us that poor glycaemic control is found in the younger PWLD[7,8]. Taking this abovementioned finding into consideration and that younger patients are generally destined to have a longer disease exposure, probably accounts for the increased risks of chronic complications found in older PLWD[9]. In South Africa (SA), it has already been demonstrated that older PLWD have a poorer quality of life and greater disability[10]. In addition to this, those with young-onset type 2 DM (T2DM) appear to have a more aggressive disease phenotype, leading to a poorer quality of life and unfavourable long-term outcomes[9]. This highlights the possibility of a public health catastrophe in older PLWD[9]. Efforts should therefore be made to identify areas in diabetes control which can be targeted in the various age groups in order to prevent this potential problem.

The landscape of mortality in older patients in SA is transitioning from one of communicable diseases (e.g., HIV and TB) to that of non-communicable diseases (NCDs) such as strokes and heart disease[11]. This underscores the importance of DM since strokes and heart disease are recognised macrovascular

complications of DM[8]. Epidemiologically, South Africa has a younger population with only 9.1% of the population being 60 years and older[11]. The working age in South Africa is generally between 15-64 years[12]. South Africans between 15-49 years old are faced with additional infectious diseases burden that of HIV-infection with a prevalence of 18.7%[5] and TB which is estimated at 615 per 100 000 population[6]. Burgess et al. found that there was greater than three-times higher mortality at 24-month follow up in PLWD who were HIV-infected when compared to those who were HIV-uninfected[13]. In addition to this, people with an HIV-infection are more likely to develop T2DM than HIV-uninfected patients[14]. Moreover, DM has been shown to increase the risk of developing TB by 300%[15]. Estimates from 2020 place the average South Africans' life expectancy at 62.5 years and 68.5 years for males and females, respectively[11]. This suggests that the South African male life expectancy is lower than the retirement age of the population while females are expected to demise shortly after retirement age. The burden of this collision of non-communicable and communicable diseases in SA and its associated increase in earlier mortality, has a significant impact on the working class, thereby reducing economic activity in the country.

The prevalence of DM is generally equal between males and females in most populations[16]. However, it has also been suggested that males have a higher prevalence of DM than females across all age groups[17]. It has been traditionally accepted that an age of <40 years is usually associated with T1DM while those with an age of >40 years is associated with T2DM[18]. In a Trinidadian study, age was found to be the most significant risk factor for T2DM[19]. These findings were echoed by Suastika et al. who highlighted age as an important risk factor for both T2DM and cardiovascular disease[20]. This underscores the importance of age on DM. In Kwa-Zulu Natal (KZN), SA, Govender et al. assessed a cohort of PLWD under 35 years of age and found that the majority of younger patients with DM had T1DM and these patients often had a lower BMI than those with T2DM[21]. No mention of HIV was mentioned in the article published by Govender et al.

Elevated triglyceride levels are commonly associated with T2DM[22]. Gao et al. found that triglyceride levels were related to diabetes progression in an elderly Chinese population ≥ 65 years[23]. This was likely due to the elevated triglyceride levels being strongly associated with inadequate glycaemic control in PLWD[24]. Hayashi et al. conducted a study in Japan and suggested that if high-density lipoprotein (HDL) cholesterol is well controlled in elderly PLWD then complications such as ischemic heart disease might be decreased to the levels found in middle-aged cohorts of PLWD[25]. Russo et al. found that women with T2DM had poorer control of low density lipoproprotein (LDL) than men in general, and that discrepancies were more significant in older patients[26]. Dyslipidaemia is important to diagnose and manage as it is a major risk factor for cardio-vascular events[27]. A study conducted in Johannesburg, SA,

assessed lipid levels in Black South Africans with T2DM and found that socio-economic status played little role on dyslipidaemia; however, no mention of associations between age and dyslipidaemia were present in this study[28]. In addition to this study, Omodanisi et al. conducted a study in Western Cape, SA, on the prevalence of dyslipidaemia in T2DM[29]. It was found that male and female PLWD had dyslipidaemia of 94% and 84% respectively – again, no mention of associations with age were described[29]. Limited data is available on associations between age and dyslipidaemia in a resource-limited setting, with there being no relationships offered from the above South African studies.

Hypertension (HPT) is twice as frequent in PLWD compared with those without DM[30]. In young adults, elevated blood pressure often precedes the development of DM by 20-25 years[31]. In older patients, there is often age-related stiffening of the major arteries leading to isolated systolic HPT[32]. This is significant as it leads to adverse complications such as strokes, cardiac and renal disease[32]. Moreover, in Finland, elevated diastolic blood pressure has been found in younger PLWD, with the peak in the 40-44 year-old category[33]. This type of HPT (diastolic HPT) also leads to increased total and cardio-vascular mortality[34]. A study from India found that co-morbid DM and HPT were associated with older age, obesity and dyslipidaemia[35]. In Mthatha, Eastern Cape, SA, a study conducted on PLWD with co-morbid HPT highlighted that male gender and age ≥65 years were associated with uncontrolled HPT[36]. Another South African study performed in Mpumza, KZN, assessed that the prevalence of HPT with co-morbid DM was 6%, and was higher in older female patients[37]. This KZN study was, however, conducted on a general population rather in PLWD. Limited data is available on associations between DM and HPT in a cohort of PLWD factoring in age with and without HIV-infection.

Older age is associated with increased HbA1c levels[38]. This is likely due to impaired glucose tolerance, impaired fasting glucose, and an increased prevalence of patients with T2DM[39]. In Denmark, Ghouse et al. studied elderly individuals (≥65 years) with T2DM and determined that the effect of glycaemic control (measured by HbA1c) on all-cause mortality depended on the duration of diabetes[40]. Baptista et al. performed a study among Brazilian adults and elderly PLWD and found that patients living with Type 1 DM (PLWT1DM) had significantly higher HbA1c levels than PLWT2DM ($p<0.01$)[41]. Locally, within, Mpumalanga, SA, Masilela et al. concluded that age was a significant determinant of poor glycaemic control among PLWD[42]. There was no mention of the patient's HIV in Masilela's study.

Thyroid disease is commonly found in most types of DM and is associated with advanced age, particularly in T2DM and underlying autoimmune disease in T1DM[43]. The prevalence of thyroid

disease in females appears to be greater than males and in PLWD[44]. Ravishankar et al. found that the prevalence of thyroid disorders in PLWD was 29% and that those with hyperthyroidism had poorer glycaemic control[45]. They concurred that elderly patients had a greater prevalence of thyroid disease than those under 60 years[45]. A South African study conducted by Pillay et al. determined that there was an increased prevalence of thyroid disorders (especially sub-clinical hypothyroidism) in PLWD and this was even higher in HIV-infected PLWD (PLWDH)[46]. This study also suggested that young, overweight, female PLWDH were at risk of sub-clinical hypothyroidism[46]. In our current study we will further assess associations in PLWD with co-morbid thyroid disease (PLWDT) in the various age categories by factoring in additional variables.

In this study we will assess the effect of age on clinical and biochemical variables in PLWD (within an HIV-endemic area) who visit a regional hospital diabetes clinic in Pietermaritzburg, KZN, SA. The results of this study can help the government to design and implement strategies to improve current diabetes care in patients targeting different age groups.

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1. RESEARCH QUESTIONS:

What, if any, is the relationship between age and diabetes control in patients living with diabetes mellitus in low-to-middle income countries?

What will a ‘scoping review’ reveal about what is already known on this topic and what deficiencies will be identified ?

2. AIMS AND OBJECTIVES

AIMS:

- To perform a scoping review of what is currently known on 'The relationship between age and diabetes control in patients with diabetes mellitus in low-to-middle income countries'
- To determine if there are significant associations in patients living with diabetes (PLWD) between age and clinical and biochemical variables.
- Associations* will be sought between age and:
    - Glycaemic control (HbA1c and random blood glucose)
    - HIV status
    - Demographics (Gender/Family History of Diabetes)
    - Body mass Index (BMI) (kg/m^2)
    - Type of DM (Type 1 and Type 2 DM)
    - Dyslipidaemia (Total Cholesterol, Triglyceride, HDL and LDL- Cholesterol)
    - Blood pressure (mmHg)
    - Kidney function (Glomerular Filtration Rate-GFR)
    - Thyroid function (TSH)
    - Electrolytes (Calcium, Magnesium, Phosphate)
    - Social factors (diet adherence, exercise and home glucose monitoring)
    - Microvascular complications of DM (nephropathy, neuropathy, retinopathy)
    - Macrovascular complications of DM (Stroke, IHD, MI)
- To determine/postulate why these associations occur.

*the author will analyse and choose the best, most relevant associations to include in the study

OBJECTIVES:

In order to achieve the above aims, I will:

- Utilise relevant electronic search engines to perform a thorough scoping review of what is currently known on the association between age and DM.
- Capture clinical and biochemical variables from the Edendale Hospital diabetes datasheet for all patients consulted between 1 January 2019 to 31 December 2019.
- Use this data to determine any associations that may exist between these variables and age.

Variables to be included in the study will include:

- Mean HbA1c (%)
- Mean Random Blood Glucose (mmol/l)
- HIV status (positive or negative)
- CD4 count (cells/mm^3)
- Duration of HIV diagnosis (years)
- Duration of antiretrovirals (ARVs) in years
- Names of ARVs
- Family History
    - Maternal
    - Paternal
    - Grandmother
    - Grandfather
    - Brother
    - Sister
- Gender (male/female)
- BMI (kg/m^2)
- Type of DM (Type 1 or Type 2)
- Duration of DM (years)
- Mean Total Cholesterol (mmol/l)
- Mean Triglyceride (mmol/l)
- Mean HDL (mmol/l)
- Mean LDL (mmol/l)
- Mean systolic blood pressure (mmHg)
- Mean systolic diastolic blood pressure (mmHg)
- GFR (ml/minute/$1.73m^2$)
- Creatinine (mmol/L)
- Urine dipstick
- TSH (mIU/L)
- Calcium (mmol/L)
- Magnesium (mmol/L)
- Phosphate (mmol/L)
- Diet control (yes or no)
- Exercise (yes or no)
- Home Glucose Monitoring (yes or no)

- Sensory-neuro examination (intact or not)
- Glaucoma (yes or no)
- Cataract (yes or no)
- Non-proliferative retinopathy (yes or no)
- Proliferative retinopathy (yes or no)
- Cerebral Vascular Event (yes or no)
- Ischemic Heart Disease (yes or no)
- Myocardial Infarction (yes or no)

3. METHODS

3.1. Study design

A retrospective, quantitative, observational, analytical cohort study will be performed.

3.2. Setting

This study will be conducted at the diabetes clinic at Edendale Hospital (EDH) which is a regional hospital based in Pietermaritzburg, Kwa-Zulu Natal (KZN).

3.3. Participant selection and sampling strategy

Inclusion criteria

- Data of all patients who attended the diabetes clinic at EDH between 1 January 2019 to 31 December 2019 will be used in the study.

Exclusion criteria

- Incompletely filled datasheets

The EDH diabetes clinic uses a comprehensive diabetes datasheet for all patients consulted in this clinic. This datasheet has been approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee BREC - BCA 194/15. Data for my aims will be accessed from this datasheet and captured on an Excel document.

3.4. Measurements

All data will be captured from the Edendale diabetes datasheet. Any datasheets with missing information will be omitted from the analysis.

3.5. Data Collection and statistical analysis

The data will be collected and inserted into an Excel datasheet by using patients 'Folder Number' and not their name to maintain confidentiality. Continuous variables will be documented as mean values ± standard deviations (SD). Numbers (n) and percentages (%) will be expressed for categorical variables. Numerical data will be compared using Anova, whilst categorical data relationships will be determined using either Chi-square or Fisher's Exact tests. A p-value < 0.05 will be used as indicator of significance. Data will be analysed by Statistical Package for Social Science (SPSS) version 25 for windows (SPSS Inc., Chicago, IL, USA).

When analysing the data, age will be analysed in the categories of 13-18 years, 19-30 years, 31-45 years, 46-60 years, 61-75 years and 76+ years.

3.6. Sample size, statistical power and variable selection

Data of all patients who meet inclusion criteria will be captured for the study time period 1 January 2019 till 31 December 2019.

4. ETHICAL CONSIDERATIONS

4.1. Community participation

Gatekeeper permission will be required from EDH and the Department of Health to use data from their diabetes clinic (see below for Gatekeeper permission)

4.2. Social Value

A local study would be useful in providing patients with knowledge of how age affects diabetes control in the South African context. The results of this study can help the government to design and implement strategies to improve current diabetes care in patients targeting different age groups.

4.3. Scientific validity

The datasheets will be analysed and it will be subjected to statistical analysis taking into account the aims of the study.

4.4. Fair selection of participants

All patients who meet the inclusion criteria will be included in the study.

4.5. Risk/benefit balance

Biologically, there is will be no risk or discomfort on any patients that will result from this study.

Psychologically, no fear/distress/anxiety will be experienced by patients as this is a retrospective study.

Socially, all patients will be identified by their 'Folder Number' when capturing data thereby maintaining confidentiality of patients' details.

4.6. Independent ethic review

Ethics approval will be obtained from BREC prior to conducting the study.

4.7. Informed consent

No informed consent will be required as the data required will be retrospective and taken from datasheets.

4.8 Ongoing respect for participants

Data will be processed without using the patients' name or details which can identify them to protect their confidentiality.

5. METHODOLOGICAL CHALLENGES AND STUDY LIMITATIONS

Obtaining a representative sample and an adequate sample size: The study will use the datasheet, approved by BREC, which is used for all patients who attended the EDH diabetes clinic. It will sample a 12-month period which should offer an adequate representation and sample size of the population.

Managing missing data from datasheets: Not all sheets will have all data filled in. Due to this, those which are incompletely filled will be excluded from the study.

6. FEASIBILITY

6.1. Time lines and project management

Tasks	Time period
Topic and literature review	20 January –10 February 2021
Protocol	15 February – 31 March 2021
Scoping review	1 April – 30 April 2021
BREC approval	1 May – 31 May 2021
Permission from EDH	1 June – 15 June
Data capturing	15 June – 30 June 2021
Statistical analysis	1 July – 31 July 2021
Results and Discussion	1 August – 31 August 2021

6.2. Study team, contributors and authorship.

Name	Department	Contribution	Author or acknowledgement
RR Chetty	2nd year Intern, Addington Hospital, KZN	Concept Sheet, Protocol, BREC approval Permission from EDH Results and Discussion	Author
Professor S. Pillay	Department of Internal Medicine at King Edward Hospital (KEH), Clinical Lecturer NRM SCM, UKZN	Supervisor – make recommendations for all work	Supervisor

6.3. Participating Centres

Diabetes Clinic, Edendale Hospital

6.4. Study Funding and Progress

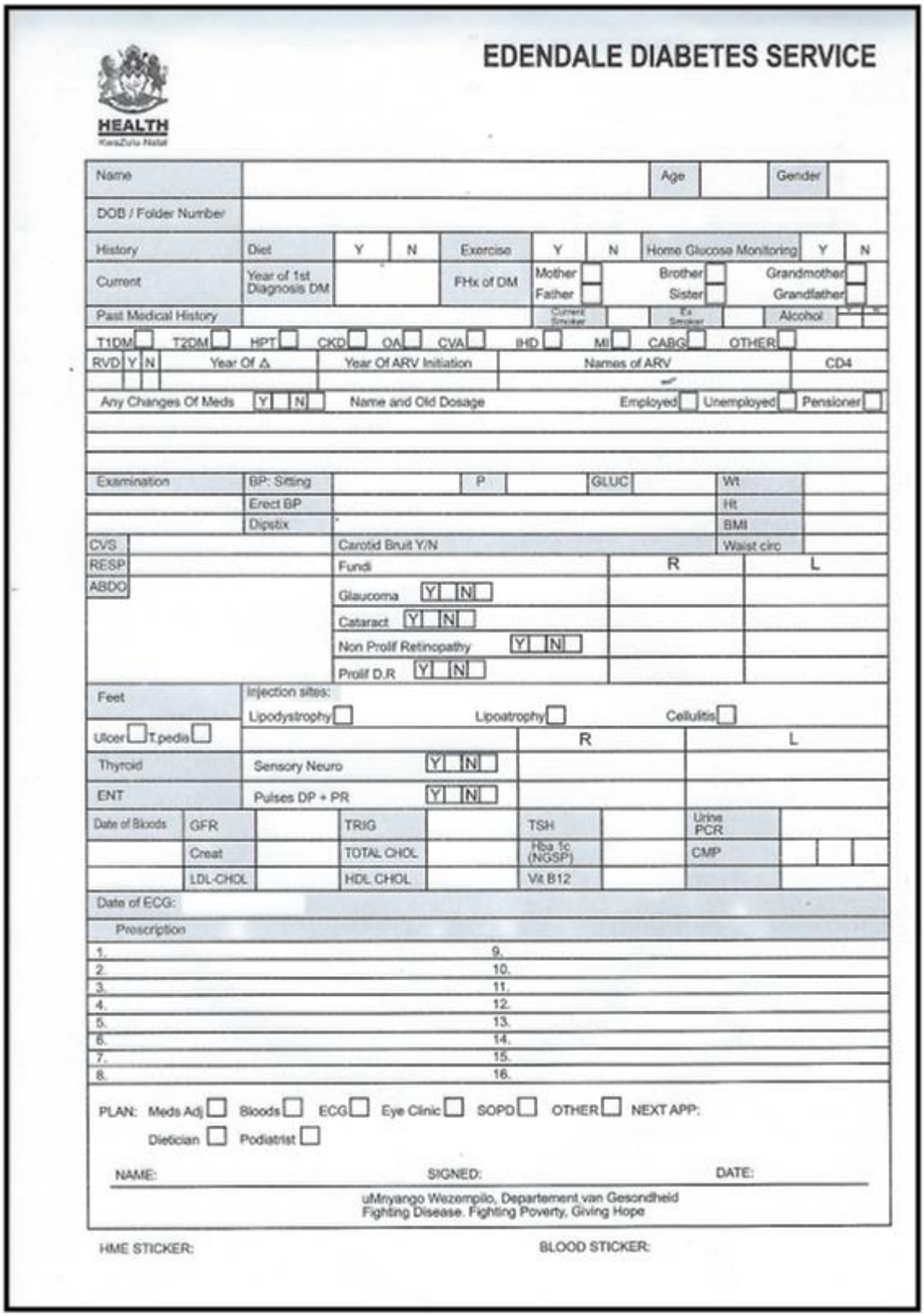
ITEM DESCRIPTION	COST
Registration Fees	R4 000
Data Capturer	R4 000
Statistician	R4 000
Transport costs	R1 500
Stationary and Printing	R1 000
Publishing costs (for possible publication in peer-reviewed journals)	R20 000
Sundry expenses	R1 500
TOTAL COST	R36 000

7. STUDY SIGNIFICANCE

In this study we will assess the effect of age on clinical and biochemical variables in PLWD who visit a regional hospital diabetes clinic in Pietermaritzburg, KwaZulu-Natal, South Africa. The results of this study can help the government to design and implement strategies to improve current diabetes care in patients targeting different age groups.

8. APPENDICES

APPENDIX 1: EDENDALE HOSPITAL DIABETES CLINIC DATASHEET



HEALTH
KwaZulu-Natal

EDENDALE DIABETES SERVICE

Name						Age		Gender			
DOB / Folder Number											
History	Diet	Y	N	Exercise	Y	N	Home Glucose Monitoring	Y	N		
Current	Year of 1st Diagnosis DM			FHx of DM	Mother ☐ Father ☐		Brother ☐ Sister ☐		Grandmother ☐ Grandfather ☐		
Past Medical History					Current Smoker		Ex Smoker		Alcohol		
T1DM ☐ T2DM ☐ HPT ☐ CKD ☐ OA ☐ CVA ☐ IHD ☐ MI ☐ CABG ☐ OTHER ☐											
RVD	Y	N	Year Of Δ		Year Of ARV Initiation		Names of ARV			CD4	
Any Changes Of Meds	Y ☐ N ☐		Name and Old Dosage				Employed ☐	Unemployed ☐	Pensioner ☐		

Examination	BP: Sitting		P		GLUC	Wt	
	Erect BP					Ht	
	Dipstix					BMI	
CVS		Carotid Bruit Y/N				Waist circ	
RESP		Fundi				R	L
ABDO		Glaucoma Y ☐ N ☐					
		Cataract Y ☐ N ☐					
		Non Prolif Retinopathy Y ☐ N ☐					
		Prolif D.R Y ☐ N ☐					

Feet	Injection sites: Lipodystrophy ☐	Lipoatrophy ☐	Cellulitis ☐
Ulcer ☐ T.pedis ☐		R	L
Thyroid	Sensory Neuro Y ☐ N ☐		
ENT	Pulses DP + PR Y ☐ N ☐		

Date of Bloods	GFR		TRIG		TSH		Urine PCR	
	Creat		TOTAL CHOL		Hba 1c (NGSP)		CMP	
	LDL-CHOL		HDL CHOL		Vit B12			

Date of ECG:

Prescription

1.	9.
2.	10.
3.	11.
4.	12.
5.	13.
6.	14.
7.	15.
8.	16.

PLAN: Meds Adj ☐ Bloods ☐ ECG ☐ Eye Clinic ☐ SOPD ☐ OTHER ☐ NEXT APP:
Dietician ☐ Podiatrist ☐

NAME: SIGNED: DATE:

uMnyango Wezempilo, Departement van Gesondheid
Fighting Disease. Fighting Poverty, Giving Hope

HME STICKER: BLOOD STICKER:

APPENDIX 2: BIOMEDICAL RESEARCH AND ETHICS COMMITTEE (BREC) APPROVAL LETTER

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

21 August 2021

Dr Rushern Ruvashin Chetty (214516475)
School of Clinical Medicine
Medical School

Dear Dr Chetty,

Protocol reference number: BREC/00002645/2021
Project title: The Relationship between Age and Diabetes Control in Patients Living with Diabetes Mellitus in Low-to-Middle Income Countries
Degree: MMedSc

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 21 August 2021. Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Amended_Lockdown_Level_3_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 21 August 2021. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 14 September 2021.

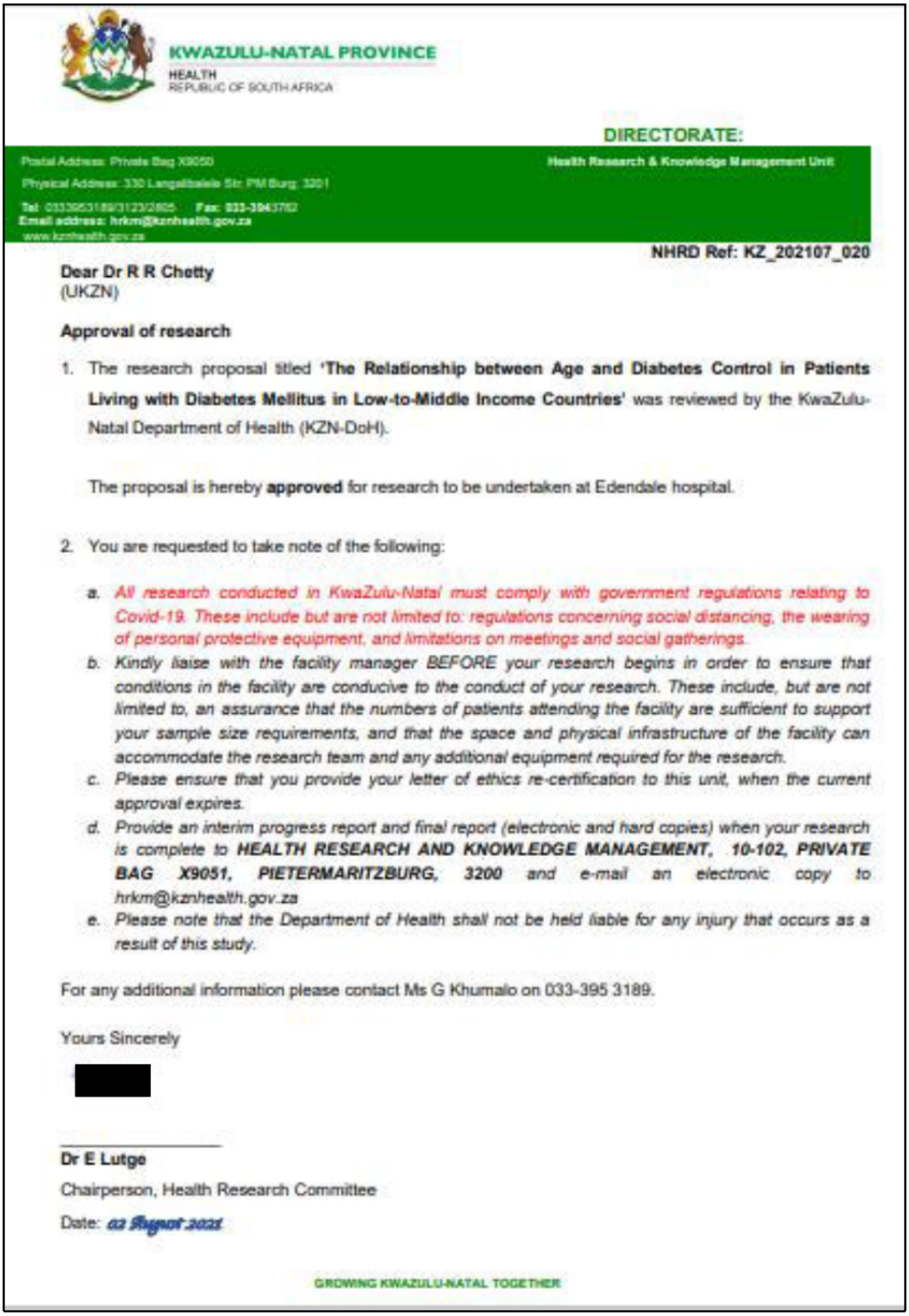
Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

APPENDIX 3: KWA-ZULU NATAL DEPARTMENT OF HEALTH APPROVAL LETTER



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
Health Research & Knowledge Management Unit

Postal Address: Private Bag X9051
Physical Address: 330 Langalibalele Str, PM Burg, 3201
Tel: 033 3953189/3123/2805 Fax: 033-3943782
Email address: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

NHRD Ref: KZ_202107_020

Dear Dr R R Chetty
(UKZN)

Approval of research

1. The research proposal titled **'The Relationship between Age and Diabetes Control in Patients Living with Diabetes Mellitus in Low-to-Middle Income Countries'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Edendale hospital.

2. You are requested to take note of the following:

   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Ms G Khumalo on 033-395 3189.

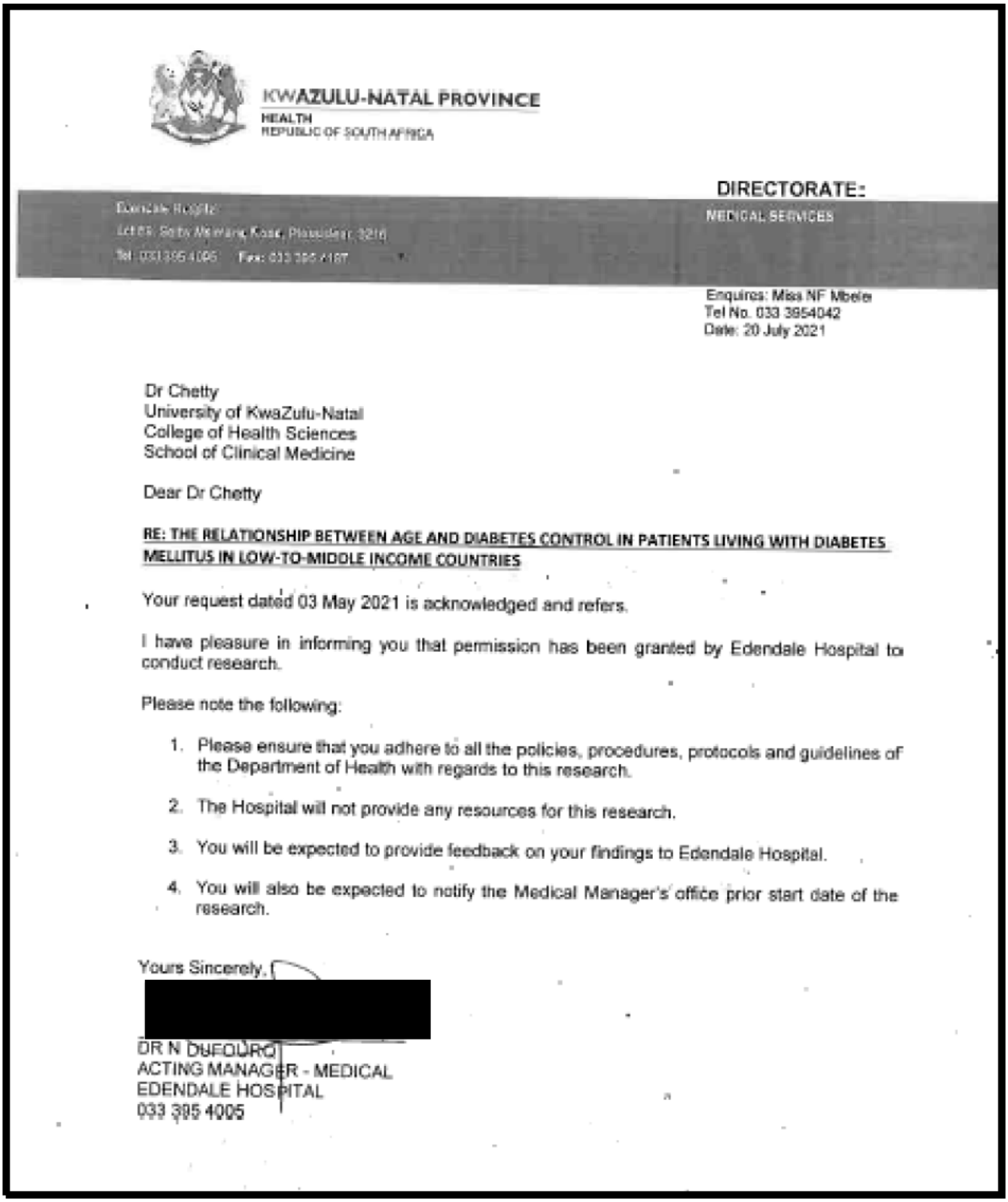
Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 02 August 2021

GROWING KWAZULU-NATAL TOGETHER

APPENDIX 4: EDENDALE HOSPITAL (GATEKEEPER) APPROVAL LETTER



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
MEDICAL SERVICES

Enquires: Miss NF Mbele
Tel No. 033 3954042
Date: 20 July 2021

Dr Chetty
University of KwaZulu-Natal
College of Health Sciences
School of Clinical Medicine

Dear Dr Chetty

RE: THE RELATIONSHIP BETWEEN AGE AND DIABETES CONTROL IN PATIENTS LIVING WITH DIABETES MELLITUS IN LOW-TO-MIDDLE INCOME COUNTRIES

Your request dated 03 May 2021 is acknowledged and refers.

I have pleasure in informing you that permission has been granted by Edendale Hospital to conduct research.

Please note the following:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. The Hospital will not provide any resources for this research.
3. You will be expected to provide feedback on your findings to Edendale Hospital.
4. You will also be expected to notify the Medical Manager's office prior start date of the research.

Yours Sincerely,

[redacted]

DR N DUFOURQ
ACTING MANAGER - MEDICAL
EDENDALE HOSPITAL
033 395 4005