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CLINICAL REVIEW

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 developed countries, 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 developed and developing 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

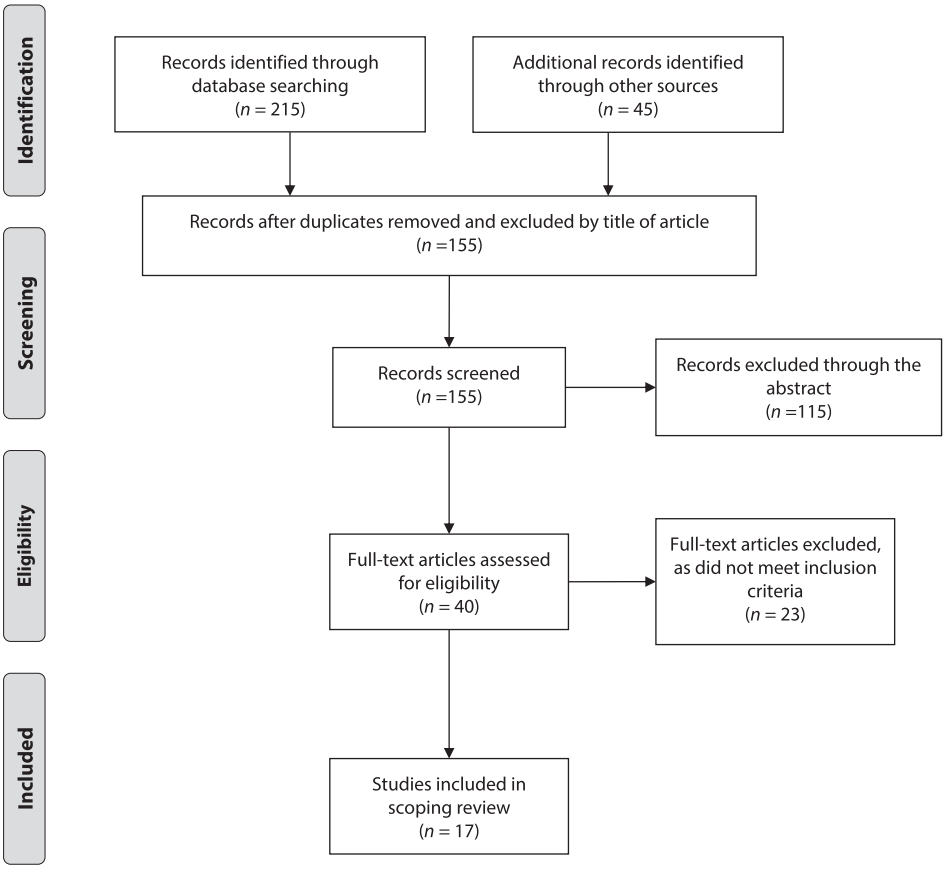

Figure 1: Flow diagram showing the article elimination process to obtain final articles included in this scoping review.

it was conducted or published, was accepted provided that there was a relationship among the four variables (i.e. HIV-infected, DM, an association between 'age' and 'glycaemic control'). Only studies in English were read as the authors were only proficient in English.

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 HIV-infected. 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 developed 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 HIV-infected 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 developed 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).

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.

Table 1: Articles that met criteria of the 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	Six urban sites	424	315	Females	Prospective	Women with or at high risk of HIV infection	X	X	HbA1c was lower in PLWHD compared with 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 with 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 with 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	Netherlands	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 Janeiro	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.

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
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

Category	'Older age has worse glycaemia category'	'Non-significant category'	'Older age has improved glycaemia category'
HIC	USA × 2 studies	USA × 4 studies	Netherlands × 1 study; France × 1 study
LMIC	SA × 3 studies	SA × 1 study; Malawi × 2 studies	SA × 1 study; Brazil × 1 study; Iran × 1 study

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

We postulate that this is due to the lower prevalence of HIV-infected 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.

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