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research

Glycaemic control and family history of diabetes mellitus: is it all in the genes?

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Background: Type 2 diabetes mellitus (T2DM) is a familial condition with a strong genetic component. International studies have highlighted associations between a positive family history of diabetes (FHD) and poorer glycaemic control. No current data are available on this association within the context of HIV.
Objectives: To determine a relationship between FHD and glycaemic control in patients living with DM (PLWD) in an HIV endemic area.
Methods: Standardised clinic sheets were used from the DM clinic at Edendale Hospital, Pietermaritzburg, South Africa, from January 1, 2019 to December 31, 2019. Statistical analysis was done.
Results: This study had 957 patients living with diabetes (PLWD); 498 (52.2%) had a positive FHD while 456 (47.8%) had no FHD. There were 146 (15.3%) HIV-infected patients; with 84 (57.5%) on a fixed dose combination (FDC) of anti-retroviral treatment (ART). Patients aged between 18 and 30 with a maternal FHD had significantly higher mean HbA1c levels than those without a maternal FHD (HbA1c: 10.80% vs. 9.72%, $p = 0.025$). Patients living with type 1 DM (PLWT1DM) in the HIV-uninfected cohort had significantly higher HbA1c levels than patients living with type 2 DM (PLWT2DM) (10.38% vs. 9.46%, $p = 0.002$). HIV-infected PLWD (PLWDH) on a FDC with a positive FHD had significantly higher HbA1c levels than those without a FHD (9.52% vs. 8.52%, $p = 0.04$). PLWDH with a positive maternal FHD on an FDC had increased HbA1c levels (9.81% vs. 8.55%, $p = 0.009$).
Conclusion: Genes significantly affect glycaemic control among PLWD. PLWT1DM and PLWDH with a positive FHD (especially a maternal FHD) should be regarded as being in a higher risk category requiring more intensive lifestyle and therapeutic intervention to achieve optimal diabetes control. Our study suggests that a positive FHD affects glycaemia in PLWT1DM as significantly, if not more, than in PLWT2DM and recommends screening for a FHD to be incorporated in the comprehensive management of DM.

Keywords: diabetes mellitus, glycaemic control, HbA1c, Family History, HIV, fixed-dose combination, patients living with diabetes and HIV

Introduction

It is well established that Type 2 diabetes mellitus (T2DM) is a familial condition with a strong genetic component,[1] with first-degree relatives of people with T2DM at increased risk of developing the disease.[2] Those with a family history of diabetes (FHD) have a 300–400% risk of developing DM when compared with those with no positive family history.[3] Globally, there are 463 million patients living with DM (PLWD), with more than 19 million patients living in Africa.[4] Estimates predict that by 2045 there will be approximately 47 million PLWD in Africa alone.[4]

Numerous international studies have highlighted associations between a positive FHD and poorer glycaemic control, [5–9]with variations occurring among patients from different demographic backgrounds.[10] Not all studies, however, have made this conclusion, with a Saudi Arabian study concluding that a FHD plays no significant role in glycaemic control in T2DM patients ($p < 0.39$).[11]

In South Africa, Erasmus *et al*. conducted a study in 2001 on the importance of FHD in Xhosa-speaking PLWD living in Transkei, which determined that patients with a positive FHD had an earlier onset of developing T2DM and that maternal influences play an important part in the development of T2DM.[1] They did not look at any association between FHD and glycaemic control, nor did they comment on any association with patient HIV status. No other local studies were done (to our knowledge) on associations between a positive FHD and glycaemic control.

Studies regarding which family member offered greater risk when having a positive FHD have identified maternal FHD as being more significant than a paternal FHD in various studies.[1,5–8] Erasmus *et al*. found that there was a significant maternal aggregation with 64.7% of patients having a diabetic mother compared with 27% who had a diabetic father ($p < 0.01$).[1] However, those with a combined maternal and paternal FHD are seen to have a greater risk where the combined risk equals the sum when either parent is affected.[12]

Glycaemic control in PLWD and HIV (PLWDH) has been shown to be suboptimal.[13–15] This can occur in those who are antiretroviral therapy (ART) naive, those on ART, as well as in those with a lower cluster of differentiation (CD4) level < 200 cell/μl.[14] Maganga *et al*. found that HIV-infected adults on long-term ART had a fivefold greater odds of glucose metabolism disorders than HIV-negative controls.[16] Khoza *et al*. postulated that the negative relationship between CD4 count and glucose levels may reflect viral removal and easing of the associated inflammatory response.[15]

This study aimed to determine a relationship between FHD and glycaemic control in an HIV-endemic area within South Africa, a

Table 1: Numbers of FHD vs. type of DM

	Family history of diabetes			
Type	**No, *n* (%)**	**Yes, *n* (%)**	p-*value*	**Total**
T1DM	62 (47%)	70 (53%)	0.486	132 (13.8%)
T2DM	394 (47.9%)	428 (52.1%)	0.236	822 (86.2%)
Total	456 (47.8%)	498 (52.2%)	0.173	954 (100%)
p-value	< 0.001	< 0.001	-	< 0.001

country with the highest reported prevalence of HIV infection (13%).[17]

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. The data for this study included all patients 18 years or older who attended the diabetes clinic at EDH between January 1, 2019 and December 31, 2019.

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

Good glycaemic control was defined as a HbA1c value < 7%.[18] The Bio-Rad D-10 machine (Bio-Rad Laboratories, Hercules, CA, USA) was used for analysing the HbA1c values at the laboratory. Both the laboratory and the machines are NGSP (National Glycohaemoglobin Standardization Program) accredited to maintain standardisation of HbA1c results, while the random glucose measurement (mmol/L) was determined using an Accu-Chek® glucometer (Roche, Basel, Switzerland).

Statistical analysis

Statistical analysis was conducted with numerical data using ANOVA, while 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 were analysed by Statistical Package for Social Science (SPSS) version 25 for Windows (IBM Corp, Armonk, NY, USA).

Table 2: Associations between FHD, age and HbA1c

Factor	**Age**	**18–30 HbA1c (%) ±SD**	**31–40 HbA1c (%) ±SD**	**41–50 HbA1c (%) ±SD**	**51–60 HbA1c (%) ±SD**	**61–70 HbA1c (%) ±SD**	**71–80 HbA1c (%) ±SD**	**81–90 HbA1c (%) ±SD**
Family history of diabetes	No	9.57 (2.25)	9.36 (2.32)	9.42 (2.01)	9.60 (2.35)	9.62 (2.60)	9.28 (±2.29)	8.62 (±1.73)
	Yes	10.44 (2.09)	9.79 (2.03)	9.87 (2.10)	9.67 (2.27)	8.75 (2.05)	8.91 (±1.75)	10.97 (±1.80)
	p-value	0.054	0.321	0.193	0.8	0.008	0.388	0.04
Mother	No	9.72 (2.20)	9.47 (2.32)	9.72 (2.02)	9.60 (2.37)	9.32 (2.46)	9.21 (±2.10)	8.62 (±1.73)
	Yes	10.80 (2.02)	9.83 (1.84)	9.68 (2.15)	9.71 (2.20)	8.92 (2.17)	8.80 (±1.85)	10.97 (±1.80)
	p-value	0.025	0.432	0.905	0.705	0.276	0.381	0.04
Father	No	10.06 (2.20)	9.54 (2.12)	9.64 (2.11)	9.63 (2.33)	9.28 (2.37)	9.28 (2.04)	8.74 (1.70)
	Yes	10.13 (2.22)	9.83 (2.38)	10.00 (1.88)	9.69 (2.23)	8.57 (2.45)	8.08 (1.69)	13.00 (0)
	p-value	0.902	0.6	0.393	0.874	0.187	0.041	0.023
Grandmother	No	10.00 (2.22)	9.61 (2.13)	9.70 (2.09)	9.63 (2.33)	9.22 (2.40)	9.13 (2.00)	8.94 (1.89)
	Yes	10.39 (2.08)	9.46 (2.61)	9.77 (1.97)	9.70 (2.07)	8.38 (1.85)	5.70 (0)	-
	p-value	0.489	0.844	0.908	0.892	0.438	0.453	-
Grandfather	No	9.98 (±2.19)	9.53 (2.16)	9.72 (2.06)	9.63 (2.31)	9.24 (2.39)	9.08 (2.03)	8.94 (1.89)
	Yes	11.98 (±0.89)	11.13 (1.82)	8.95 (2.65)	11.40 (0.14)	7.88 (2.15)	-	-
	p-value	0.019	0.148	0.465	0.28	0.209	-	-
Brother	No	10.11 (2.19)	9.65 (2.18)	9.70 (2.10)	9.64 (2.32)	9.20 (2.46)	9.13 (2.12)	8.94 (1.89)
	Yes	9.57 (2.29)	8.43 (1.45)	9.69 (1.77)	9.58 (2.11)	9.19 (1.17)	8.90 (1.65)	-
	p-value	0.533	0.22	0.988	0.92	0.991	0.677	-
Sister	No	10.05 (2.24)	9.60 (2.18)	9.73 (2.03)	9.55 (2.34)	9.30 (2.47)	9.10 (2.08)	8.94 (1.89)
	Yes	10.37 (1.48)	9.53 (2.08)	9.55 (2.41)	10.15 (2.06)	8.69 (1.87)	9.03 (1.85)	-
	p-value	0.732	0.935	0.724	0.124	0.179	0.899	-

Table 3: Associations between HbA1c and GFR

Age (years)	GFR < 60	GFR ≥ 60	*p*-value[a]	Mean HbA1c (%) ± SD
18–30	3	69	< 0.001	10.07 (2.19)
31–40	9	79	< 0.001	9.60 (2.16)
41–50	26	113	< 0.001	9.70 (2.07)
51–60	99	147	0.002	9.64 (2.31)
61–70	118	71	0.0006	9.20 (2.39)
71–80	56	23	0.0002	9.08 (2.03)
81–90	17	4	0.0045	8.94 (1.89)
≥90	1	0	0.317	10.10 (3.39)

[a]χ-square test between GFR groups.

Results

Epidemiology

Data of 957 PLWD were used for this study. Four hundred and ninety-eight PLWD (498/957, 52.2%) had a positive FHD while 456 (47.8%) PLWD had no FHD. A significant proportion of the patient cohort comprised T2DM (822, 86.2%) while 132 (13.8%) of PLWD had T1DM (with 3 remaining unknown) (Table 1). Almost one-sixth of the patient cohort had HIV infection (146, 15.3%). Of this HIV-infected cohort with DM, 84 (57.5%) were on a fixed-dose combination (FDC) anti-retroviral treatment (ART). The duration of DM when categorised into < 5 years, 5–10 years, 10–20 years and 20+ years had 349, 196, 265 and 109 patients respectively (38 patients had no documentation of duration recorded).

Family history and glycaemic control

FHD and glycaemic control varied with age and the patient's family members who had DM (Table 2). In adults aged between 18 and 30 years, patients with a maternal FHD showed significantly higher mean HbA1c and random blood glucose (RBG) levels when compared with those with no maternal FHD (HbA1c 10.80% vs. 9.72%, $p = 0.025$); and RBG (13.70 mmol/l vs. 10.70 mmol/l, $p = 0.039$). Higher HbA1c values were also observed in those PLWD who had a grandfather who had DM (11.98% vs. 9.98%, $p = 0.019$) in the 18–30-year age category.

Improved glycaemic control was present in those older patients with FHD. The 61–70-year age group had a lower mean HbA1c level in those patients with a positive FHD (8.75% vs. 9.62%, $p = 0.008$) while the 71–80-year age group showed that those with a paternal FHD had lower HbA1c levels (8.08% vs. 9.28%, $p = 0.04$).

When assessing age categories and HbA1c values (Table 3), an inverse relationship was observed between HbA1c values and age. A comparison between the age categories 18–30 and 81–90 age showed that the mean HbA1c was 10.07% and 8.94%, respectively ($p = 0.025$). Under the age of 60, there were significantly more patients with a GFR ≥ 60, compared with the over-60-year age categories, which had a greater number of patients with GFR values <60 ($p < 0.005$ for all age categories between 61 and 90).

Gender played no significant role on HbA1c levels between males and females with an FHD (9.53% vs. 9.57%, $p = 0.849$)

Table 4: Associations between HbA1c and FHD

		Family history of diabetes				
		No		Yes		
Factor		Count	Mean HbA1c (%) ± SD	Count	Mean HbA1c (%) ± SD	*p*-value for HbA1c %
DM type	T1DM	62	9.67 (2.09)	70	10.35 (2.05)	0.062
	T2DM	394	9.44 (2.37)	428	9.43 (2.15)	0.949
p-value			0.471		0.001	
Gender	Female	317	9.60 (2.39)	347	9.57 (2.19)	0.866
	Male	141	9.22 (2.17)	152	9.53 (2.09)	0.21
p-value			0.107		0.849	
Mother	No	458	9.48 (2.33)	179	9.46 (2.17)	0.92
	Yes	0	0.00	320	9.61 (2.15)	-
p-value			-		0.457	
Father	No	458	9.48 (2.33)	349	9.58 (2.12)	0.53
	Yes	0	0	150	9.50 (2.26)	-
p-value			-		0.705	
Grandmother	No	458	9.48 (2.33)	430	9.54 (2.15)	0.69
	Yes	0	0	69	9.70 (2.16)	-
p-value			-		0.567	
Grandfather	No	458	9.48 (2.33)	477	9.54 (2.15)	0.68
	Yes	0	0	22	10.02 (2.40)	-
p-value			-		0.309	
Brother	No	458	9.48 (2.33)	428	9.61 (2.22)	0.40
	Yes	0	0	71	9.27 (1.73)	-
p-value			-		0.219	
Sister	No	458	9.48 (2.33)	376	9.58 (2.19)	0.53
	Yes	0	0	123	9.49 (2.07)	-
p-value			-		0.689	

Table 5: Type of DM and FHD in the context of HIV Infection

	Family history of diabetes					
Factor	**No, *n* (%)**	**Mean HbA1c (%) ± SD**	**Yes, *n* (%)**	**Mean HbA1c (%) ± SD**	***p*-value**	**Total**
HIV-infected	60 (6.3%)	8.69	86 (9%)	9.40	0.06	146 (15.3%)
Type 1 DM	7 (0.7%)	8.97 (1.88)	10 (1.0%)	10.18 (2.11)	0.24	17 (1.8%)
Type 2 DM	53 (5.5%)	8.64 (2.25)	76 (7.9%)	9.29 (2.27)	0.11	129 (13.5%)
P-value:		0.71		0.24		-
HIV-uninfected	398 (41.6%)	9.59 (2.33)	413 (43.1%)	9.59 (2.14)	Nil	811 (84.7%)
Type 1 DM	55 (5.7%)	9.77 (2.11)	60 (6.3%)	10.38 (2.05)	0.119	115 (12.0%)
Type 2 DM	341 (36.6%)	9.55 (2.37)	352 (36.8%)	9.46 (2.13)	0.60	693 (72.4%)
p-value		0.52		0.002		

Table 6: Associations between PLWDH and HbA1c in the context of being on a FDC (ART)

	On a FDC				
Family member	**No**	**HbA1c (%) ± SD**	**Yes**	**HbA1c (%) ± SD**	***p*-value**
FHD (any member)	34	8.52 (2.31)	50	9.52 (2.04)	0.04
Mother	49	8.55 (2.24)	35	9.81 (1.96)	0.009
Father	65	8.89 (2.17)	19	9.90 (2.21)	0.079
Grandmother	78	9.13 (2.18)	6	8.70 (2.70)	0.648
Grandfather	83	9.12 (2.21)	1	7.20 (0)	0.39
Brother	80	9.08 (2.25)	4	9.48 (1.23)	0.726
Sister	74	9.07 (2.22)	10	9.27 (2.21)	0.79

(Table 4). Furthermore, having a sibling or grandparent with a positive FHD also played no significant role in HbA1c levels (see Table 4).

Type 2 vs. Type 1 DM

When assessing PLWT2DM vs. PLWT1DM in the HIV-uninfected cohort, significantly lower HbA1c levels were found (HbA1c 9.46% vs. 10.38%, $p = 0.002$) (Table 5). A lower RBG level was also observed when comparing between the patients living with type 2 and 1 DM with a positive FHD (11.24 mmol/l vs. 11.40 mmol/l, respectively); however, this was not statistically significant ($p = 0.818$). PLWT2DM with a maternal FHD had lower HbA1c levels when compared with PLWT1DM with maternal FHD (9.51% vs. 10.29%, respectively ($p = 0.034$); a maternal FHD was associated with higher HbA1c levels than a general FHD in PLWT2DM (9.51% vs. 9.43%, $p = 0.627$).

HIV and glycaemic control

Differences in glycaemic control were noted between PLWD without an HIV infection compared with PLWD with an HIV infection (PLWDH). Although marginally not statistically significant, HbA1c levels show that PLWDH with a positive FHD have higher HbA1c levels than PLWDH with no FHD (9.40% vs. 8.69%, $p = 0.06$). PLWDH who were taking ART (FDC) and who had a positive FHD were found to have significantly higher HbA1c levels when compared with those without a positive FHD (9.52% vs. 8.52%, $p = 0.04$) (Table 6) — this was particularly prevalent in those PLWDH with a positive maternal FHD (HbA1c 9.81% vs 8.55%, $p = 0.009$). When comparing those with a positive FHD in the HIV-uninfected cohort (see Table 5), PLWT1DM had higher HbA1c levels than those with T2DM (10.38% vs. 9.46%, $p = 0.002$). This contrasted with the findings when no FHD was present in the HIV-uninfected cohort when comparing T1DM vs. T2DM ($p = 0.52$).

Duration of DM

FHD and the duration of DM showed little significance in glycaemic control. PLWD who had been diagnosed with DM for between 11 and 20 years and who had a brother with DM had statistically higher RBG levels than those without a brother who had DM (13.18 mmol/l vs. 10.84 mmol/l, $p = 0.034$); however, no significance was found when assessing HbA1c levels in this group (9.66% vs. 9.57%, $p = 0.848$).

Table 7: Associations between FHD, BMI and HbA1c

Family history of diabetes					
	No		**Yes**		
BMI	**Count**	**Mean HbA1c (%) ±SD**	**Count**	**Mean HbA1c (%) ±SD**	***p*-value**
< 18.5	7	11.50 (2.10)	8	11.18 (2.78)	0.808
18.5–24.9	69	10.11 (2.02)	67	10.00 (2.25)	0.764
25.0–29.9	94	9.44 (2.26)	98	9.88 (2.33)	0.186
30.0–34.9	109	9.42 (2.47)	109	9.78 (2.09)	0.247
35.0–39.9	72	9.19 (2.20)	89	9.12 (1.83)	0.826
40.0+	68	9.09 (2.54)	85	9.02 (1.94)	0.847

Body mass index (BMI)

There were no significant associations between FHD, BMI and HbA1c in our study ($p > 0.05$) (Table 7).

Discussion

Glycaemic control in PLWD varies by age, duration, type and HIV status of patients.

T1DM, a multifactorial disease with a strong genetic component, is caused by the autoimmune destruction of pancreatic beta cells,[19] while T2DM is the result of interaction between environmental factors with a strong hereditary component[20]. T2DM has been reported to have a stronger link to family history and lineage than T1DM;[21] however, our study found that a positive FHD was present almost equally in both types of DM (53% in T1DM and 52.1% in T2DM). We also found that glycaemic control (as defined by higher HbA1c levels) was significantly poorer in PLWT1DM than in those PLWT2DM when both groups had a positive FHD in the HIV uninfected cohort. We postulate that the reason may be due to a greater genetic influence on PLWT1DM than is currently thought. Pillay *et al*. found a similar finding of elevated HbA1c levels in T1DM compared with T2DM,[22] which supports this idea that genes may play a stronger role in T1DM.

Several studies have suggested that a maternal FHD increases transmission of T2DM (unknown underlying mechanism).[23] It now appears that a maternal FHD is also associated with poorer glycaemic control in PLWD in the different age groups as well as in those who are HIV infected on treatment. An adjusted odds ratio (OR) showed that there were no significant results on whether FHD, HIV or ART played a greater role in the influence of HbA1c levels; however, patients with an FHD were 2.086 times more likely than those who did not have a FHD to have HbA1c levels > 7%.

HIV and ART have been implicated in the aetiology of DM and suboptimal glycaemic control.[14,24] Although this has been commented on, the role of how FHD changes this equation has not been given much attention previously. A positive maternal FHD, especially if patients are taking ART (FDC comprising tenofovir®/emtricitabine®/efavirenz® [TEE]), appears to be associated with significantly higher HbA1c levels. This highlights the need to identify a positive FHD and to be more aggressive with investigating and managing those with it. In HIV-infected patients taking an FDC, the mean HbA1c level was found to be 1.00% higher in those who had a positive FHD compared with those without an FHD. It suggests that the influence of genetic factors on HbA1c may be confounded by other factors such as an HIV infection or ART. This serves to highlight the need to incorporate FHD into the comprehensive assessment of glycaemic control in PLWHD who are on ART to identify suboptimal glycaemic control across the various regimens and offer alternatives.

Limitations of study

- As this was a retrospective study no causal relationships could be determined; rather, associations were defined.
- Misclassification of FHD may impact on the data.
- Data on the mortality of patients were not reported on as this was a retrospective chart study conducted over a one-year period.

Other lifestyle factors (such as compliance) may have influenced glycaemia.

Conclusion

Genes play a significant role in glycaemic control among PLWD. PLWT1DM and PLWDH who have a positive FHD (especially a maternal FHD) should be regarded as being in a higher risk category requiring more intensive lifestyle and therapeutic intervention to achieve optimal diabetes control. Our study contrasts the idea that T2DM has a stronger hereditary linkage and suggests that a positive FHD affects glycaemia in PLWT1DM just as significantly, if not more so, than in PLWT2DM. We recommend that screening for a FHD should be made part of the comprehensive management of PLWD. We further recommend that future studies with a larger cohort are warranted to determine the strength of association of FHD in diabetes particularly between PLWT1DM and PLWT2DM.

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