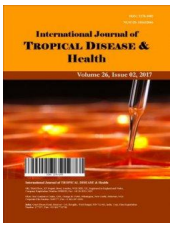

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The Effect of Age, Gender and Haemoglobin Variants on Glycated Haemoglobin

Taiwo Rachel Kotila[1*], Mabel Ayebatonyo Charles-Davies[2], Felix Rotimi Afolabi[3], Jokotade Oluremilekun Adeleye[4], Matthew Ogunlakin[2], Funmilola Mapayi[2] and Emmanuel Oluyemi Agbedana[2]

[1]Department of Haematology, College of Medicine, University of Ibadan, Nigeria.
[2]Department of Chemical Pathology, College of Medicine, University of Ibadan, Nigeria.
[3]Department of Epidemiology and Medical Statistics, College of Medicine, University of Ibadan, Nigeria.
[4]Department of Medicine, College of Medicine, University of Ibadan, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Glycated haemoglobin (HbA1c) is a useful screening, diagnostic and monitoring tool for diabetes. We present the effect of age, gender and haemoglobin variants on HbA1c in an African population with a high prevalence of sickle cell trait (SCT).
Study Design: An unmatched case-control study.
Place and Duration of Study: This was carried out in the out-patient clinic of a tertiary hospital over a one-year period.
Methods: After an overnight fast, blood samples for haemoglobin fractions and HbA1c were measured in 99 individuals with T2DM and 105 apparently healthy controls using HPLC (BioRad, variant II).
Results: The age for cases and controls were 25-80yrs and 30-80yrs respectively, male:female ratio were 1:3 and 1:1.4 respectively. Women were seven times more likely to have diabetes in the

**Corresponding author: Email: tkotila@com.ui.edu.ng;*

sixth decade than men. SCT was found in 31% of T2DM women but only in 20% of men (*P*=.33). T2DM women had a higher HbA1c (58mmol/mol (7.5%) vs 48mmol/mol (6.5%) (*P*=0.1)). Healthy women also had a significantly higher HbA1c than men, 38 mmol/mol (5.6%) vs 32 mmol/mol (5.1%) (*P*=.007). HbA1c was consistently higher in individuals with sickle cell trait (HbAS) than those without the trait in both groups. HbA1c did not differ between age groups in T2DM F (4, 92) =2.62, *P*= .81 nor in controls F (4, 96) =2.06, *P*=.09. There appears to be a complex interaction between gender and age groups on HbA1c in both T2DM and healthy controls, but the interaction was more pronounced in the T2DM group. There was a stronger correlation between fasting plasma glucose and HbA1C which was stronger controls than the T2DM group ((r= 0.23, *P*=.02) vs (r=0.12, *P*=.25)).

Conclusion: The association between age, gender and SCT on HbA1c was more pronounced in women, this may be an interplay between socioeconomic, hormonal and genetic factors.

Keywords: Epidemiology; gender disparities; haemoglobin variants; HbA1c; LMIC.

1. INTRODUCTION

Glycated haemoglobin (HbA1c) is the irreversible addition of a glucose residue to haemoglobin in a non-enzymatic reaction. It is not only useful as a screening and diagnostic tool for T2DM but also in long term monitoring of glycaemic control in individuals with diabetes [1,2]. Inconsistencies have been observed in the measurement of HbA1c such that it may sometimes not reflect the level of glycaemia. The presence of haemoglobin variants, age, gender and race are among many reasons why this may occur even though in some individuals this inconsistency cannot be explained [3,4]. The method employed in the determination of the HbA1c is also critical to its measurement and to its ability in detecting errors arising as a result of haemoglobin variants [5]. A high prevalence of haemoglobin variants has been reported in individuals with diabetes, also greater variations in HbA1c have been noted in populations with a high prevalence of haemoglobin variants [5,6]. We report here our observations on the differences noted in individuals with T2DM in comparison to apparently healthy individuals in an African community with a high prevalence of the sickle cell trait.

2. METHODS

This is an unmatched case-control study of 99 individuals with T2DM who were receiving treatment in a tertiary health centre and 105 apparently healthy individuals. Most of the healthy controls were volunteers from the workforce in the same tertiary centre from which the cases were selected. All the participants fasted overnight, after which a structured questionnaire was administered to them to obtain information on biodata, diet, lifestyle and past medical history. Anthropometric indices and blood pressure measurements were obtained from all the participants. Blood samples were obtained for haemoglobin fractions, glycated haemoglobin, complete blood count, lipid profile and some biochemical parameters. Haemoglobin fractions and glycated haemoglobin were measured using BioRad ® HPLC analyser (variant II).

2.1 Statistical Analyses

Statistical analyses were performed using STATA version 13 (StataCorp, College Station, Texas). Continuous variables were expressed as mean ±SD. Haemoglobin variants were grouped into four: - the wild type (HbA), the heterozygote states HbAS (sickle cell trait), HbAC (HbC trait) and 'others' made up of the compound heterozygous state (HbS+C) and homozygous states (HbCC, HbSS). Because of the association of the sickle cell trait with T2DM in literature, [5] the effect of sickle cell trait (with and without the trait), age (grouped at intervals of 10 years), gender and haemoglobin variants on the outcome was analysed using independent t-test and F test as appropriate. Also, the interaction between age (in groups) and gender on HbA1c was investigated. Thereafter, post hoc analyses was carried out using Bonferroni multiple-comparison correction where necessary. In addition, Pearson's correlation was employed to investigate the relationship between HbA1c and FPG respectively in the two groups (T2DM and Control). *P*- value less than 5% were considered to be statistically significant across analyses.

3. RESULTS

The age range of the T2DM individuals was 25-80 years with a mean of 59.6±9.3 years while it

was 33-80 years with a mean of 46±9.4 years for the controls. There was no significant difference in the mean age of men and women with T2DM, 62.1yrs vs 58.6yrs respectively. The male/female ratio was 1:3 and 1:1.4 for T2DM and controls respectively, women were seven times more likely to have diabetes in the sixth decade with the likelihood becoming similar in both sexes by the eight decade (Table 1a) compared to controls (Table 1b).

Sickle cell trait was found in 31% of women with T2DM but in 20% of men (*P*=.33). Among the healthy controls, the prevalence of sickle cell trait was also higher in women 18% vs 11% (*P*=.31). The mean HbA1c was higher in T2DM than controls 55±3mmol/mol (7.2±0.3%) vs 34±1 mmol/mol (5.3±0.1%) (*P*<.001). Women with T2DM had a higher HbA1c than men with T2DM 58 mmol/mol (7.5%) vs 48 mmol/mol (6.5%) (*P*=.1), also apparently healthy women had a higher HbA1c 38 mmol/mol (5.6%) vs 32 mmol/mol (5.1%) (*P*=.007). HbA1c did not differ between age groups in T2DM F (4, 92) =2.62, *P*= .81 nor in controls F (4, 96)=2.06, *P*=.09. Glycated haemoglobin rose with age group in both cases and controls (Fig. 1).

Table 1a. Distribution of age and gender of individuals with T2DM

Age group (years)	Male (%)	Female (%)	M:F ratio	Total
≤40	0	2 (3)	-	2
41-50	6 (24)	12 (17)	1:2	18
51-60	4 (16)	27 (38)	1:7	31
61-70	10 (40)	26 (36)	1:2.5	36
71-80	5 (20)	5 (7)	1:1	10
	25	72	1:3	97

Age and gender were not recorded for two individuals

Table 1b. Distribution of age and gender of apparently healthy controls

Age group	Male (%)	Female (%)	M:F Ratio	Total
≤40	9 (21)	18 (30)	1:2	27
41-50	24 (57)	20 (34)	1:1	44
51-60	7 (17)	18 (30)	1:2	25
61-70	2 (5)	2 (3)	1:1	4
71-80	0	1(2)	-	1
Total	42	59	1:1.4	101

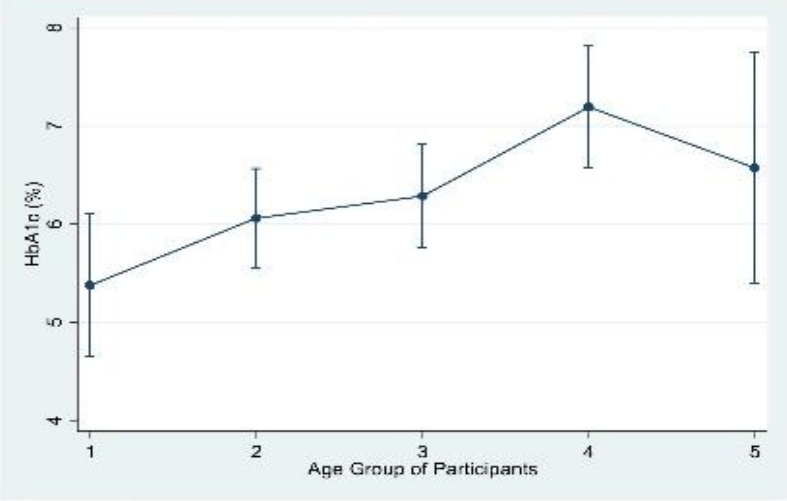

Fig. 1. The rise in HbA1c with age group in participants

The effect of gender on HbA1c was independent of age in both groups. There appears to be a complex interaction between gender and age groups on HbA1c in both T2DM and healthy controls, but the interaction was more pronounced in the T2DM group (Fig. 2). Women consistently showed a higher HbA1c except for the eight decade. Also, Hba1c varied greatly in men than women (Fig. 2).

Though HbA1c was consistently higher in individuals with sickle cell trait (HbAS) than those without the trait in both groups, these differences were not significant (57 mmol/mol (7.4%) vs 54 mmol/mol (7.1%), *P*=.54 in T2DM and 37 mmol/mol (5.5%) vs 34 mmol/mol (5.3%), *P*=.48 in controls). However, HbA1c differ significantly between the different haemoglobin variants in T2DM F (3, 95) = 8.38; *P*< .001 but not in controls F(3,101) = .73; *P*= .54.The mean HbA1c of each haemoglobin variant group is shown in Table 2.

The post hoc analysis showed that the 'others' haemoglobin variant group was solely responsible for the differences in both T2DM and controls. (Among the T2DM, an individual with HbCC had an HbA1c of 175 mmol/mol (18.2%) whilst an individual with HbS+C among the controls had HbA1c of 42 mmol/mol (6.0%)). These two individuals had FPG of 6.87mmol/L (123.9mg/dL) and 4.2mmol/L (76mg/dL) respectively. The correlation between Fasting Plasma Glucose (FPG) and HbA1c was stronger in controls than T2DM ((r= 0.23, *P*=.02) vs (r=0.12, *P*=.25)) (Fig. 3).

4. DISCUSSION

The effect of gender and age on glycated haemoglobin is better appreciated in the control group which is representative of the general population. Though the trends were similar in both the T2DM and control groups, the control group showed a more statistically significant differences than the T2DM group in these variables. Correlations between glycated haemoglobin and FPG was also more pronounced in the controls. The use of

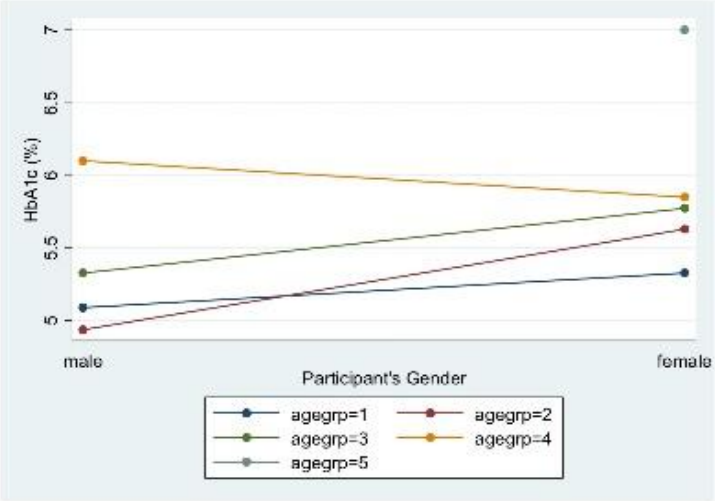

Fig. 2. Interaction of age and gender on HbA1c

Table 2. Distribution of haemoglobin variants by Glycated Haemoglobin (HbA1c) among T2DM and apparently healthy controls

	Mean HbA1c					
	Patients			Controls		
Hb Variants	**N**	**mmol/mol (SD)**	**% (SD)**	**N**	**mmol/mol (SD)**	**% (SD)**
HbA	67	52±26	6.9±2.4	83	34±13	5.3±1.2
HbAS	27	58±20	7.5±1.8	16	37±7	5.5±0.6
HbAC	4	58±20	7.5±1.8	5	40±8	5.8±0.7
Others	1	175	18.2	1	42	6.0

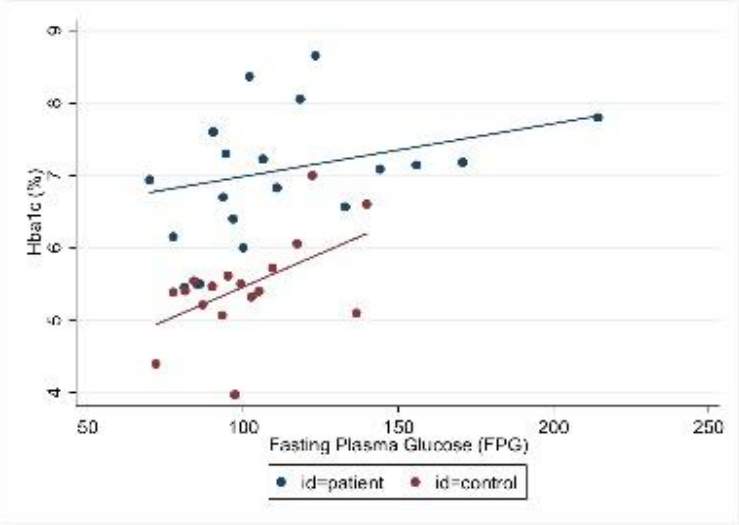

Fig. 3. Correlation between fasting plasma glucose and HbA1c differ between T2DM and controls

antidiabetic medication among the cases could be a reason for the non-significant difference in T2DM compared to control since the medications could cause a reduced variation in the glycated haemoglobin in the cases compared to the control who would have a greater variation. More so, a study on incident diabetes showed that the gap in HbA1c between the sexes had closed up after one year of medication showing that medication modifies the variation in glycated haemoglobin [7]. In addition, the response of women to antidiabetic medication may differ from the response of men because the use of antidiabetic medication predisposes female patients with T2DM more to hypoglycaemia than male patients. The use of medication is also negatively associated with HbA1c in men but positively associated in women [8,9]. The ability of antidiabetic medication to reduce the variability of glycated haemoglobin in the cases may also be affected by the presence of haemoglobin variants since HbA1c greatly differ between haemoglobin variants in cases but not in controls. The higher prevalence of the sickle cell trait in women with T2DM could also contribute to the significantly higher glycated haemoglobin in the T2DM group and may play a role for the higher excess risk in some complications seen in women [7,10,11]. The interaction between age and gender on glycated haemoglobin was not significant in our study which could be because of the small sample size, since another study noted a similar but significant interaction between the two emphasising that gender differences change as the population changes [7]. Though the risk conferred by diabetes and gender on cardiovascular diseases have been studied extensively, it was recently, that the interaction between gender and diabetes was found to be more pronounced in black women than white women [12]. Thus introducing the possibility of racial differences in the interaction.

We observed that the prevalence of T2DM was three times higher in women which is at variance with the epidemiology in high income countries where the prevalence is only slightly higher in men [13-15]. In the USA, the overall lifetime risk of diabetes for 2000-2011 was 40.2% in men and 39.6% in women, this is in contrast to African Americans where the risk is higher in women 55.3% vs 44.7%, though the risk is similar in Hispanics 51.8% vs 51.5% for men and women respectively [16]. In other low/middle income countries (LMICs) the trend is similar to what we observed in our study. In Saudi Arabia, the prevalence was 73.3% vs 26.7% in women and men respectively, while in Pakistan it was 59.1% vs 40.9% respectively [17,18]. The higher prevalence in women from LMICs has been attributed to socioeconomic barriers in accessing good nutrition, healthcare and less opportunities for physical activity [11]. The differences could also be genetic since the difference in the two sexes are not pronounced in Hispanics who share similar socioeconomic status with African Americans. The possibility of the observed

differences to glycaemic control have also been attributed to biology, therefore there is a call for more research on sex-specific differences to bridge the gap in the observed gender disparities [11].

It is necessary to explore further, possible reasons for the seven-fold risk observed in women with T2DM in the sixth decade which drastically reduced to unity in the eighth decade. Similarly, women who were at least 80years old showed six times the risk of leg ulcers than men, though men had shown a higher risk a decade earlier. Also, it was observed that baseline gender differences which initially was limited to the young and middle age group at diagnosis had disappeared in the middle age group after one year of follow up [7,10]. These show that the gender differences are not unrelated to age, which could be why hormonal differences have been used to explain gender differences in glucose homeostasis [19]. Though the direct mechanism involved is not known, the hormonal effect has been thought to be due to the beneficial effect of oestradiol before menopause [20]. It could also be that women respond differently to antidiabetic agents during and after menopause since the differences between the genders become more pronounced after menopause. A difference in the response of both gender to antidiabetic medication and glucose homeostasis could also explain the better correlation between FPG and HbA1c in the control group compared to the T2DM group [19,20]. In addition, other hormonal problems in T2DM, like subclinical hypothyroidism which has been shown to be significantly associated with glycated haemoglobin [21] is a discriminatory factor in women with concomitant hypertension, diabetes and dyslipidaemia [22].

5. CONCLUSION

The higher HbA1c and prevalence of diabetes in the middle and older age group is a known observation globally but the higher prevalence in women, also found in other LMICs may not be due to socioeconomic reasons alone but could also have both hormonal and genetic components. This study also observed a higher prevalence of the sickle cell trait among women with T2DM which would suggest the possibility of a genetic component to the gender disparities. We therefore agree that there is a need to further study the gender disparities in the epidemiology of T2DM [11].

CONSENT

All participants gave a written informed consent before the questionnaire was administered to them and blood samples taken for the study.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the Institutional Review board, the study was also conducted in conformity with the declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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