ORIGINAL ARTICLE

Glycated Haemoglobin as an Index of Glycaemic Control: Ethnic Variation among Patients with Type 2 Diabetes Mellitus in a Malaysian Tertiary Hospital

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ABSTRACT

Introduction: Previous studies have revealed ethnic differences in glycated haemoglobin (HbA1c) value at the same glucose concentration. This study aimed to determine ethnic variation in HbA1c as an index of glycaemic control among type 2 diabetes mellitus (T2DM) patients. **Methods:** This cross-sectional, retrospective study recruited 293 T2DM patients by simple random sampling at the medical outpatient clinic of a tertiary hospital. **Results:** Ethnicity was equally distributed with 33.4% Malays and Indians, respectively, and 33.1% Chinese. Significant difference in ethnicity was noted between HbA1c groups ≤6.5% and >6.5%. Indians had the highest median HbA1c (8.3%), followed by Malays (7.7%) and Chinese (7.2%) [p=0.004]. Malays had lower HbA1c compared with Chinese at lower fasting plasma glucose (FPG) whereas Chinese had lower HbA1c compared with Malays at higher FPG, crossing over at FPG 2.8 mmol/L. Indians had higher HbA1c compared with Chinese and Malays except at FPG cross-over of 16 mmol/L where Malays were higher than Indians. FPG and ethnicity were independent predictors of HbA1c. An increase of 1 mmol/L in FPG resulted in an increase of 0.44% in HbA1c. Indians and Malays had 0.60% and 0.47% higher HbA1c, respectively, than Chinese. **Conclusion:** This pilot study in Malaysia examined ethnic variation in the relationship between FPG and HbA1c among T2DM patients. Since HbA1c is higher in Indians and Malays compared with Chinese at any given FPG, the hypoglycaemia risk may be increased in Indians and Malays when treatment strategies are focussed on using similar target HbA1c values to treat them.
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Keywords: Fasting plasma glucose, Glycated haemoglobin, Type 2 diabetes mellitus, Ethnicity, Malaysia

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INTRODUCTION

Diabetes mellitus (DM) is a prevalent non-communicable disease that is associated with significant mortality and morbidity. The National Health and Morbidity Survey 2019 (NHMS 2019) reported that the prevalence of DM among adults 18 years and above was 18.3%. The prevalence increased with age, from 5.4% (20-24 years old) to 43.4% (65-69 years old). NHMS 2019 also reported significant difference in the prevalence of DM among the local ethnicities with the highest being Indians at 31.4%, followed by the Malays, Chinese, Bumiputera Sarawak, Bumiputera Sabah and others at 21.6%, 15.1%, 12.3%, 11.1% and 8.7%, respectively (1).

Globally, diabetes is one of the main causes of chronic kidney disease (CKD). Within 20–25 years of the onset of DM, diabetic nephropathy occurs in 25 – 40% of patients. The National Kidney Foundation Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines has staged CKD using the following eGFR values: G1: ≥90 mL/min/1.73m^2; G2: 60-89 mL/min/1.73m^2; G3a: 45-59 mL/min/1.73m^2; G3b: 30-44 mL/min/1.73m^2; G4: 15-29 mL/min/1.73m^2 and G5: <15 mL/min/1.73m^2 (2).

HbA1c has been preferred for monitoring glycaemic control among patients with type 2 diabetes mellitus (T2DM) as it is a relatively convenient test with patients not required to fast and only a single blood sample needed. Besides, it is indicative of chronic glycaemia as it reflects the glucose level over the preceding 120 days. It is also used for diagnosing T2DM (3). The diagnostic value of HbA1c in T2DM in the Malaysian population is ≥6.3% (45 mmol/mol), whereas the target HbA1c value for glycaemic control is individualised based on patient

profile. HbA1c ≤6.5% (48 mmol/mol) is advocated for patients with a shorter duration of T2DM, longer life expectancy, no evidence of significant cardiovascular disease and have minimal risk of hypoglycaemia (3). The Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) analysis demonstrated the role of HbA1c as a valuable risk marker for diabetic complications (4).

However, several studies have shown that HbA1c value varies between different ethnicities for a given glucose level. African Americans were reported to have a much increased HbA1c compared with the non-Hispanic whites and Mexican Americans (5). Furthermore, a study from Denmark demonstrated that Inuits have higher HbA1c compared with Caucasian Danes (6). These ethnic differences in HbA1c may, therefore, affect diagnostic and therapeutic targets.

Studies that evaluate HbA1c thresholds for diagnosing DM support this issue. Indeed, despite the criteria by American Diabetes Association (ADA) and World Health Organization (WHO) that have recommended the cut-off point ≥6.5% for diagnosing DM, various Asian countries have been using slightly different cut-off points. Studies in Asian population indicated that the ideal diagnostic cut-off point for HbA1c in T2DM differs with race as well as age, gender and prevalence of DM in a particular population (7-9). This includes a study in our local setting, which showed that HbA1c diagnostic cut-off point of 6.5% was less sensitive (36.7%) in diagnosing T2DM although highly specific (98.1%). Hence, HbA1c cut-off of 6.3% is preferred as it gives an acceptable specificity (97.4%) and sensitivity (42.5%) (8). This Malaysian study is comparable with that among Singaporeans, which found HbA1c diagnostic cut-off point of 6.2% or 6.3% to be more optimal (9). These findings of ethnic-specific HbA1c diagnostic cut-off may imply that ethnic-specific target HbA1c value for optimal glycaemic control may also be applicable. Nevertheless, ADA as well as the Malaysian clinical practice guidelines (CPG) have both recommended that the HbA1c goal should be individualised based on duration of DM, life expectancy, comorbidities, established vascular complications, patient preference and support system (3, 10).

To date, there is no data on HbA1c value as an index of glycaemic control in different ethnicities in Malaysia. Hence, the aim of this study was to determine ethnic variation in HbA1c as an index of glycaemic control among T2DM patients in a tertiary government hospital.

MATERIALS AND METHODS

Study population

This cross-sectional study was conducted using retrospective electronic data of patients who had attended the medical outpatient clinic at Hospital Kuala Lumpur (HKL) from December 2017 to December 2018. The sample size was calculated as follows: (11)

$$n = \frac{(\sigma_1^2 + \sigma_2^2/k)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

where n = number of sample; σ_1 = standard deviation (SD) of group 1; σ_2 = SD of group 2; Δ = difference in group means, assumed mean difference of 0.5 (11); k = ratio n1/ n2; $z_{1-\alpha/2}$ = 2 sided Z value ie. Z is 1.96 for confidence interval 95%; $z_{1-\beta}$ = power of 80%.

Using different combinations of HbA1c SD in Malays (1.5), Chinese (0.9) and Indians (1.4) (12) to substitute σ_1 and σ_2 in the above formula, the largest calculated sample size recommended was 291 with 97 for each ethnic population, i.e., Malay, Chinese and Indian. This study recruited a total of 293 subjects by simple random sampling.

The inclusion criteria was Malaysian subjects with T2DM aged 18 years and above. Subjects excluded were foreigners, pregnant women, patients with haemoglobinopathies or diseases affecting lifespan of red blood cells (RBC), e.g., nutritional anaemia, renal failure, splenectomised patient, haemolytic anaemia, thalassaemia, and other haemoglobinopathies (13), patients on medications known to affect HbA1c analysis such as corticosteroids, anti-psychotics, aspirin, high doses of vitamin C and E, antiretrovirals, ribavirin and dapsone as well as chronic opiate use (13), patients with severe hypertriglyceridaemia (>20 mmol/L) and severe hyperbilirubinaemia (total serum bilirubin >342 μmol/L) (14).

Data collection

Demographic factors (age, gender, and ethnicity) and laboratory data [HbA1c, FPG, serum creatinine, and estimated glomerular filtration rate (eGFR)] of patients who fulfilled the inclusion criteria were extracted from the laboratory information system (LIS) and recorded into the Pro-forma. Only the laboratory results from the first clinic visit were recorded for each patient during the study period. Approval to conduct the study was obtained from the Director of HKL (HKL/HCRC/AK-02-02) as well as the Malaysian Research Ethical Committee (MREC) Ministry of Health (NMRR-17-2813-38296).

Laboratory investigations

Plasma glucose and serum creatinine were measured by UV hexokinase and Jaffe methods, respectively, on the automated Cobas 8000 chemistry analyser (Roche Diagnostics GmbH, Mannheim, Germany). Calculated eGFR used the online Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (https://www.kidney.org/professionals/kdoqi/gfr_calculator). Plasma HbA1c was analysed by ion-exchange high performance liquid chromatography (HPLC) on the VARIANTTM II TURBO HbA1c Kit 2.0 (Biorad Laboratories, Hercules, California, USA).

Data analysis

Standard statistical software package, IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp) was used for data analysis. Categorical variables were described as frequencies and percentages whereas continuous variables were reported as mean ± SD for parametric data and median and interquartile range (IQR) for non-parametric data. Association of demographic factors and laboratory parameters with HbA1c groups was performed using Chi-square test and independent t-test / Mann-Whitney U test for categorical and continuous variables, respectively. Kruskal Wallis analysis determined the association of laboratory parameters between the Malays, Chinese and Indians. Linear regression analysis was done to examine the relationship between demographic factors as well as laboratory parameters with HbA1c. Subsequent multilinear regression analysis determined the independent predictors of HbA1c. A 'p' value of <0.05 (95% confidence interval) was considered to be statistically significant.

RESULTS

This study involved 293 T2DM patients in HKL. The median (IQR) age of patients was 60 (16) years old. There was almost equal gender and race distribution with males constituting 51.5%, Malays and Indians contributing 33.4%, respectively, and Chinese 33.1% of the study population. Majority had HbA1c >6.5%. The median (IQR) for HbA1c and FPG were 7.7 (2.7)% and 7.4 (3.7) mmol/L, respectively (Table I).

Table II shows significant difference among ethnicities between T2DM patients with HbA1c ≤6.5 and HbA1c >6.5. Patients with HbA1c >6.5% had significantly higher median FPG than patients with HbA1c ≤6.5%.

Significant difference in HbA1c between Malays, Chinese and Indians is demonstrated in Table III. Indians showed the highest median HbA1c, followed by Malays and Chinese. Although the median eGFR between the ethnic groups was significantly different, with Chinese having the lowest median eGFR, followed by Indians and Malays, the levels were still within category G1 (≥90 mL/min/1.73m^2) and G2 (60 – 89 mL/min/1.73m^2), which corresponds to normal and mildly decreased kidney function, respectively, based on KDIGO 2012 classification (2).

Figure 1 illustrates the estimation of the mean HbA1c over a FPG range of 1.0 to 25.0 mmol/L, and shows that Malays had lower HbA1c compared with Chinese at lower FPG whereas Chinese had lower HbA1c compared with Malays at higher FPG, crossing over at FPG 2.8 mmol/L. Similarly, at FPG targets for glycaemic control 4.4 – 7.0 mmol/L (3), Chinese had lower HbA1c compared with Malays with Indians having the highest value. Indians had higher HbA1c compared with Chinese and Malays except at FPG cross-over of 16 mmol/L where Malays were higher than Indians. These cross-over values (Table IV) were calculated using the ethnic-specific regression formula obtained from the linear regression analysis (Fig. 1).

Table I: Demographic factors and laboratory parameters of study population

Variables	N = 293 n (%)
Age (years): Median (IQR) = 60 (16) (range 20 - 87)	
<60	139 (47.4)
≥60	154 (52.6)
Gender:	
Male	151 (51.5%)
Female	142 (48.5%)
Ethnicity:	
Malay	98 (33.4%)
Chinese	97 (33.1%)
Indian	98 (33.4%)
HbA1c:	
≤6.5%	65 (22.2%)
>6.5%	228 (77.8%)

	Median (IQR) Mean ±SD[a]	Min - Max	Reference range
HbA1c:			
NGSP (%)	7.7 (2.7)	4.5 - 16.0	≤ 6.5*
IFCC (mmol/mol)	60.7 (29.5)	25.7 - 151.4	≤ 47.5*
FPG (mmol/L)	7.4 (3.7)	2.7 - 22.4	3.0 - 6.1†
Creatinine (µmol/L)	74.90 ± 17.97[a]		62 - 106†
eGFR (ml/min/1.73 m^2)	91.7 (24.8)	60.0 - 155.1	≥ 90†

*targets for control of T2DM (3)
†reference range used in HKL

Table II: Association of demographic factors and laboratory parameters between T2DM patients with HbA1c ≤6.5 and HbA1c >6.5

Demographic factors	HbA1c ≤6.5 n=65 n (%)	HbA1c >6.5 n=228 n (%)	χ^2	p value*
Gender				
Male	32 (49.2)	120 (52.6)	0.234	0.628
Female	33 (50.8)	108 (47.4)		
Age (years)	Median age 60 (IQR =19)	Median age 60 (IQR =16)		
< 60	30 (46.2)	109 (47.8)	0.055	0.814
≥ 60	35 (53.8)	119 (52.2)		
Ethnicity				
Malay	25 (38.5)	73(32.0)	6.938	0.031
Chinese	27 (41.5)	70 (30.7)		
Indian	13 (20.0)	85 (37.3)		

Laboratory Parameters	HbA1c ≤ 6.5 n=65 Median (IQR) Mean ±SD[a]	HbA1c > 6.5 n=228 Median (IQR) Mean ±SD[a]	z or t†	p value*	Reference range
FPG (mmoll/L)	6.0 (1.30)	8.5 (4.5)	-8.430	<0.001	4.4 - 7.0
Serum creatinine (µmol/L)	74.7 ± 17.8[a]	75.0 ± 18.1[a]	-0.145†	0.885	62 - 106
eGFR (ml/min/ 1.73m^2)	90.3 (28.9)	92.3 (24.0)	-0.852	0.394	≥ 90

Chi-Square statistical test (χ^2); Mann-Whitney statistical test (z) ; independent t test†; statistical significance at p <0.05*

Table III: Comparison of laboratory parameters between ethnicities

Laboratory parameters	Malay	Chinese	Indian	H/ F†	p value*
	Median (IQR) Mean ±SD[a]	Median (IQR) Mean ±SD[a]	Median (IQR) Mean ±SD[a]		
HbA1c:					
NGSP (%)	7.7 (3.4)	7.2 (2.3)	8.3 (2.6)	11.293	0.004
IFCC (mmol/mol)	60.7 (37.1)	55.2 (25.1)	67.2 (28.4)		
FPG (mmol/L)	7.1 (3.5)	7.2 (3.0)	8.4 (4.4)	3.552	0.169
Serum creatinine (µmol/L)	73.2 ± 17.4[a]	74.8 ± 18.5[a]	78.0 ± 24.3[a]	0.863†	0.423
eGFR (ml/ min/1.73m^2)	94.5 (19.3)	87.9 (17.2)	92.6 (22)	6.954	0.031

Kruskal Wallis test (H); One-way ANOVA test (F)†; statistical significance at p <0.05*

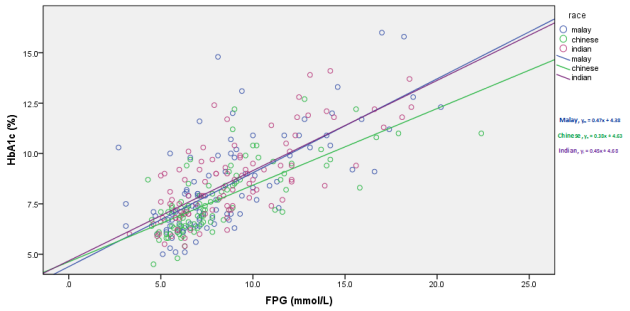

Figure 1: Relationship between HbA1c and FPG according to ethnicity

Simple linear regression analysis showed that age, ethnicity, FPG and eGFR have a significant relationship with HbA1c. However, only FPG and ethnicity remained independent predictors of HbA1c with multivariate linear regression analysis (Table V). FPG (Beta = 0.710) had a heavier influence on HbA1c than ethnicity (Beta = Indian 0.137, Malay 0.106) [data not shown]. FPG and ethnicity explained 53.1% of the variance on HbA1c (R^2 = 0.531). An increase of 1 mmol/L in FPG resulted in an increase of 0.44% in HbA1c. Indians and Malays had 0.60% and 0.47% higher HbA1c, respectively, than Chinese (Table V).

DISCUSSION

This pilot study in Malaysia examined ethnic variation in the relationship between FPG and HbA1c among T2DM patients. There are numerous reports in literature indicating variation of HbA1c among different ethnic groups, mostly comparing between Caucasians and non-Caucasians (15-17). There was significant difference in HbA1c values between Malays, Chinese and Indians in this study, concurring with previous research looking into the effect of ethnicity on the variation of HbA1c (15, 18, 19).

Using the target HbA1c value of 6.5% for glycaemic control, majority of patients with HbA1c >6.5% were Indians while Chinese mainly had HbA1c ≤6.5%. These findings are comparable with a previous study done in Singapore, which also has a multiethnic population and demonstrated that Chinese had the lowest HbA1c compared with Indians and Malays (18). Ismail and colleagues postulated that factors that protect the Chinese from DM, either genetic, cultural or both, may have contributed to the better glycaemic control as reflected by the lower HbA1c (20). It has been suggested that the Asian Indian phenotype consisting of central obesity and increased visceral fat contribute to the increased insulin resistance (21). Indians have also been found to have the lowest concentration of plasma adiponectin, an adipocyte-specific gene product efficient in lowering blood glucose and improving insulin sensitivity among diabetic patients, compared with Malays and Chinese (22).

Table IV: HbA1c versus FPG based on ethnic-specific regression formula

FPG (x)	2.7	**2.8**	2.9	3.0	4.4	7.0	**16**	25
HbA1c Malay (y_m) y_m = 0.47x + 4.38	5.649	**5.696**	5.743	5.790	6.448	7.67	**11.90**	16.13
HbA1c Chinese (y_c) y_c = 0.38x + 4.63	5.656	**5.694**	5.732	5.770	6.302	7.29	10.71	14.13
HbA1c Indian (y_i) y_i = 0.45x + 4.68	5.895	5.940	5.985	6.030	6.660	7.83	**11.88**	15.93

Table V: Simple linear regression analysis and Multivariate linear regression analysis with HbA1c as the dependent variable

	Simple linear regression			Multivariate linear regression		
Variables	**b (95% CI)**	**t statistic**	**p value***	**B (95% CI)**	**t statistic**	**p value***
Age	-0.022 (-0.039- -0.004)	-2.456	0.015			
Ethnicity: (vs Chinese)						
Malay	0.659 (0.080-1.239)	2.239	0.026	0.467 (0.064- 0.871)	2.280	0.023
Indian	0.942 (0.362- 1.521)	3.199	0.002	0.604 (0.199- 1.009)	2.938	0.004
FPG	0.442 (0.393- 0.491)	17.765	<0.001	0.435 (0.386-0.483)	17.633	<0.001
eGFR	0.016 (0.003- 0.029)	2.499	0.013			

R^2 = 0.531; CI: confidence interval; statistical significance at p <0.05*

Multivariate linear regression analysis revealed that only FPG and ethnicity remained independent predictors of HbA1c. Indians and Malays had significantly higher HbA1c than Chinese at a given FPG (Table IV), a finding consistent with the previous study done in Singapore (18). Possible explanations are that the variation in HbA1c among Malays, Chinese and Indians could be due to biological factors that include glycaemic-dependent or non-glycaemic dependent, or other non-biological factors such as access to treatment, body composition, lifestyle or environment factors (18). Glycaemic-dependent factors include a) differences in the daily glycaemic exposure among the different ethnicities, which may contribute to the differences in HbA1c at the same FPG (18) and b) differences in glycaemic responses. The latter had been excluded in A1C-derived average glucose (ADAG) study by multiple glucose measurements (23). The non-glycaemic dependent factors include a) variable glycation among individuals; b) variable rates of deglycation, i.e., the rate of glucose removed from HbA1c; c) genetics, whereby there are approximately 15 genomic loci found to influence HbA1c based on large-scale, genome-wide association studies, which may have a measurable effect on the HbA1c (24) and d) RBC lifespan. Reduced removal of senescent RBC from the circulation causes higher HbA1c, and thus variation in RBC turnover may contribute to the variation in HbA1c among ethnic groups (24).

The most important question in the observation of ethnic variation in HbA1c among Malays, Chinese and Indians is whether the observed difference bears clinical significance. At FPG targets for glycaemic control 4.4 – 7.0 mmol/L, Chinese had lower HbA1c compared with Malays, with Indians having the highest value. Thus, compared with FPG-based criteria, a single HbA1c cut-off for T2DM diagnosis may reclassify more Indians and Malays as having T2DM than Chinese. Failure to consider the ethnicity-associated differences in glucose level and HbA1c and by using a single target HbA1c value for all populations may lead to an increased incidence of hypoglycaemia among Malays and Indians. Results from the DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) trial proves this point. They showed that by accomplishing the same target HbA1c value in whites and in African Americans may result in lower plasma glucose in African Americans than in whites (25). Other studies have also demonstrated that African Americans experience hypoglycaemia more than whites (15).

In this study for example, at a FPG of 6.0 mmol/L, HbA1c will be higher in Malays and Indians compared with Chinese. Hence, more aggressive treatment will be administered to Malays and Indians to reach the target glycaemic value of 6.5%. If their FPG is already at 6.0 mmol/L, there is a risk of reducing the plasma glucose drastically to a hypoglycaemia level. Hence, considering HbA1c is higher in Indians and Malays compared with Chinese at any given FPG, the hypoglycaemia risk may be increased in Indians and Malays when treatment strategies are focussed on using similar target HbA1c values to treat them.

The strengths of this study include provision of additional evidence for ethnic variation in HbA1c, particularly in South East Asia. To our knowledge, this is the first study in Malaysia, examining ethnic difference in the relationship of FPG and HbA1c among T2DM. Equal number of samples obtained from the three major ethnic groups in Malaysia allowed better observation and comparison of HbA1c and its associated factors between ethnicities.

This study has a few limitations. Firstly, the sample size is arguably small. Secondly, as this study was done retrospectively and only depended on the available data from the LIS of patients with known T2DM, other confounders that may influence the glycaemic status, glycaemic control and thus HbA1c, such as socioeconomic status, duration of DM, level of physical activity, body mass index, insulin level and relevant medications could not be evaluated and excluded.

Further studies are required in a larger population to determine the possible contributing factors to ethnic differences in HbA1c such as RBC survival, the intracellular and extracellular environment and also the genetic determinants of haemoglobin glycation (17). As per the Malaysian CPG on the Management of T2DM, HbA1c ≤6.5%, as a target for glycaemic control is advocated for patients with a shorter duration of T2DM, longer life expectancy, no evidence of significant cardiovascular disease and have minimal risk of hypoglycaemia (3). Otherwise, HbA1c targets should be personalised and individualised according to patients' comorbidities and other risk factors (3). Further studies should be done to investigate the possible causes of such differences and to determine if ethnic differences in HbA1c are associated with diabetic complications, so that prevention and management strategies can be tailored to specific ethnic groups accordingly.

CONCLUSION

As diabetes is projected to increase worldwide in the next decade (26), it is timely that ethnicity-targeted preventive measures and management is undertaken, upon knowing the effect of ethnicity on HbA1c. The findings in this study may also provide important information and source of comparison for other Asian countries with similar ethnic groups. However, the underlying possible causes of such difference need to be addressed.

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