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Relationship between glycated haemoglobin and fasting plasma glucose among diabetic out-patients at the University Teaching Hospital, Lusaka, Zambia

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Abstract
Background: Glycated haemoglobin (HbA_{1c}) measurement provides an accurate result of glycaemic levels from blood drawn at any time of day without reference to prandial state. We established the relationship between HbA_{1c} and fasting plasma glucose (FPG) in diabetic out-patients among diabetic outpatients in Lusaka, Zambia.
Methods: This cross-sectional study was carried out at the University Teaching Hospital diabetic clinic, Lusaka, Zambia. A total sample of 198 consenting participants was selected randomly from diabetic out-patients between September and December 2013. A structured interview schedule was used to capture data on socio-demographics and laboratory examination results. The Pearson's correlation coefficient, Student's t-test and Paired Samples t-test were used for data analysis.
Results: A total of 198 patients (mean age+SD= 53.19±13.32 years) were involved in the study. Majority (60.10%) of the patients were females while 39.90 per cent were males. The mean±SD of FPG of the patients slightly increased from the previous 10.75±7.78 mmo/L to the current 11.09±6.23 mmo/L (p = 0.592). The mean±SD of HbA_{1c} of the patients was 54.77±17.12 mmol/mol. There was a statistically significant weak and moderate positive correlation between HbA_{1c} and the previous and current FPG (r = 0.282, P = 0.001 and (r = 0.385, p = 0.001), respectively. However, there was a statistically significant but weak negative correlation between HbA_{1c} and age (r = -0.163, p = 0.023).
Conclusion: We found evidence of an association between HbA_{1c} and FPG proposing that as the FPG levels increase, the HbA_{1c} levels also increase in a predictable way. There is need to sensitise more especially the major stakeholders in the management of diabetes mellitus to consider FPG as an alternative in glycaemic control monitoring in the absence of HbA_{1c}.

Keywords: Diabetes mellitus, glycated haemoglobin, fasting plasma glucose, Zambia

Introduction

Diabetes mellitus (DM) is the most common metabolic disease (Haddadinezhad & Chazaleh, 2010) and is characterised by hyperglycaemia. The hyperglycaemia sufficient to cause pathological and functional changes in DM is frequently present for a long time before the complications appear (Agarwal *et al.,* 2013). The management of DM necessitates an accurate assessment of glycaemic control (Raja *et al.,* 2013). Glycaemic control monitoring can be achieved by HbA_{1c} and FPG among other tests. However, glycaemic control in diabetic patients can be best ascertained by HbA_{1c} levels (Kilpatrick *et al.,* 2009).

Glycated haemoglobin is formed by the non-enzymatic glycation of free amino groups at the N-terminus of the β-chain of HbA_{1c} by adult Hb's exposure to plasma glucose (Kilpatrick *et al.,* 2009). HbA_{1c} is a gold standard in analysis of patients' glycaemic control status, and is essential to ensure the optimal care of diabetic patients (Ghazanfari *et al.,* 2010; ADA, 2010). Because red blood cells (RBCs) in the human body survive for 8-12 weeks before renewal, measuring HbA_{1c} can be used to reflect average blood glucose levels over that duration, providing a useful longer-term gauge of glycaemic control (Roszyk *et al.,* 2007). As the average amount of plasma glucose

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increases, the fraction of HbA_{1c} increases in a predictable way (Roszyk *et al.,* 2007). However, the major proportion of its value is weighted toward the most recent two to four weeks (Sidorenkov *et al.,* 2011).

The long-term assessment of blood glucose is advantageous because it eliminates the large fluctuations that occur daily in blood glucose concentrations. In contrast to glucose measurements, HbA_{1c} also provides an accurate result from blood drawn at any time of day without reference to prandial state (Burtis *et al.,* 2006). In general, the frequency of plasma glucose testing depends on the type of DM the patient has and the treatment plan. However, the HbA_{1c} test should be done approximately every three months in uncontrolled or at least twice a year in well-controlled diabetic patients. The normal FPG levels are between 4.1 to 5.9 mmol/L when using the ABX Pentra 400 Clinical Chemistry Analyser (Burtis *et al.,* 2006). Also, the therapeutic objective of HbA_{1c} has been to obtain values ≤ 48 mmol/mol (IDF, 2009). However, patients with an HbA_{1c} ≥ 48 mmol/mol have an increased mortality rate (Roszyk *et al.,* 2007). In addition, a 1 per cent change in HbA_{1c} is equivalent to an approximately 1.94 mmol/L (Ghazanfari *et al.,* 2010) and 1.98 mmol/L (Saiedullah *et al.,* 2011) changes in mean plasma glucose (MPG). Thus, each 1 per cent reduction in the value of HbA_{1c}, results in risk of microvascular complications reduction by 40% (Ghazanfari *et al.,* 2010).

The combined use of FPG and HbA_{1c} levels predicts the progression to DM in individuals with no apparent risk. In particular, the combination is recommended for individuals with a FPG ≥5.55 mmol/L (Inoue *et al.,* 2007). Most countries in the world are using HbA_{1c} for both diagnosis and long-term monitoring of DM to establish control status. However, due to the high cost, HbA_{1c} is limitedly used in many developing countries (Wiwanitkit, 2011) including Zambia. The old classical approach of FPG determination is still the standard method in those countries.

Furthermore, many studies (Rohlfing *et al.,* 2002; Kaur *et al.,* 2014; Hossain *et al.,* 2012; Haddadinezhad & Ghazaleh, 2010) have shown a relationship between HbA_{1c} and FPG and most clinicians would want to use the HbA_{1c} to monitor glycaemic control among their DM patients. Although, there is so much emphasis on HbA_{1c} as the best method to monitor glycaemic control, regular checking and good record keeping of FPG levels can be an alternative to those DM patients without access to HbA_{1c} measurement facilities. Therefore, the main objective of the study was to establish the relationship between HbA_{1c} and FPG in diabetic out-patients at the University Teaching Hospital (UTH), Lusaka, Zambia. The study will help diabetic patients and their healthcare providers set day-to-day targets for plasma glucose to achieve specific HbA_{1c} goals.

Materials and Methods

Study design

This cross-sectional study was carried out at UTH Diabetic Clinic, Lusaka, Zambia. The UTH has a bed capacity of 1800 and serves as the main tertiary referral hospital for Zambia (Lumba, 2014). The clinic manages patients with numerous diseases, including DM. The patients visit the clinic at appointed times advised by the medical officers for review and continuous monitoring their DM.

All the confirmed diabetic out-patients for at least two years and aged 15 years and above were included in the study. This is because patients with chronic illnesses tend to become non-compliant to medication with time. Also this age was chosen because the study was conducted at an adult clinic. Patients who were recruited in the previous month(s) were excluded from the study. This was to avoid studying the same patients over and over. A simple random sampling method was used in this study. The patients were selected consecutively from September to December, 2013 based on the daily sampling frame to avoid sampling bias. The sample size was calculated based on the 360 diabetic out-patients who passed through the diabetic clinic during

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the period of data collection. Based on Krejcie & Morgan's (1970) formula for calculating sample size of a finite population, a sample size of 186 participants was achieved.

Data collection

A structured interview schedule was used to capture data on socio-demographic characteristics and laboratory examination results. The interview schedule was developed based on the World Health Organization (WHO) stepwise survey (STEPS) instrument, version three (WHO, 2007). The same instruments were used on all the patients to ensure reliability and validity. The data on socio-demographic characteristics, FPG and HbA_{1c} were obtained by interview, review of medical records and laboratory measurements. Collecting blood for HbA_{1c} and FPG is part of the routine for these nurses. However, they were given a two-day orientation on how to use the data collection tool.

Laboratory examination

The quantitative determination of HbA_{1c} level in the collected blood from the diabetic patients was carried out by the immunoturbidimetry method using the ABX Pentra 400 Automated Clinical Chemistry Analyser (HORIBA ABX SAS, 34184 Montpellier, France). The technique has been certified by the National Glycohaemoglobin Standardisation Program (NGSP) of Australia (Burtis *et al.,* 2006). The FPG was measured by the enzymatic determination of glucose using the Trinder method with the same analyser (Arvind *et al,* 2004; Rvind, 2009).

Data analysis

Statistical analyses were carried out using IBM® SPSS® Statistics for Windows Version 20.0 (IBM Corp. Armonk, NY, USA). The Pearson's correlation coefficient and Student's t-test were used for bivariate analyses. The paired samples t-test was used for repeated measures of FPG to see whether there was a difference between the means. Statistical significance was considered at a *p*-value of < 0.05.

Ethical considerations

This study was approved by the University of Zambia Biomedical Research Ethics Committee (Reference number 005-07-13). The patients who were willing to participate in the study were asked to give informed and written consent.

Results

Participants and distribution

A total of 198 out-patients were involved in the study. The mean±SD of age of the total study patients were 53.19±13.32 ranging from 19 to 82 years. Of the total patients, 79 (39.90%) were males and 119 (60.10%) were females. The mean±SD of FPG of the patients for the previous three months and current was higher (10.75±7.78 mmo/L and 11.09±6.23 mmo/L) than the normal (4.1-5.9 mmol/L). Using the paired samples t-test, there was a very slight increase in the FPG from the previous (10.75± 7.78 mmo/L) to the current (11.09±6.23 mmo/L). However, the difference was not statistically significant ($p = 0.592$). The mean±SD of HbA_{1c} of the patients was 54.77±17.12 mmol/mol.

Comparison of the glycaemic parameter levels and age

The mean±SD levels of HbA_{1c}, current FPG and age were higher in females than in males except for the previous FPG (Table 1). However, there was no significant gender difference for the glycaemic parameter levels except for age when the student's t-test was used (Table 1).

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Table 1: Comparison of the glycaemic parameter levels and age in males and females (n=198)

Parameter	Male	Female	*P*-value*
	N (Mean±SD)	N (Mean+SD)	
HbA_{1c} (mmol/mol)	76 (53.19±15.52)	118 (55.80+18.05)	0.301
Previous FPG (mmol/L)	76 (11.50±10.60)	117 (10.20±5.12)	0.258
Current FPG (mmol/L)	77 (10.50±7.35)	118 (11.30±5.36)	0.377
Age (Years)	79 (50.84±15.32)	119 (54.75±11.61)	0.043

Key: N=number of patients; SD= Standard deviation; * = significant P-value at p<0.05

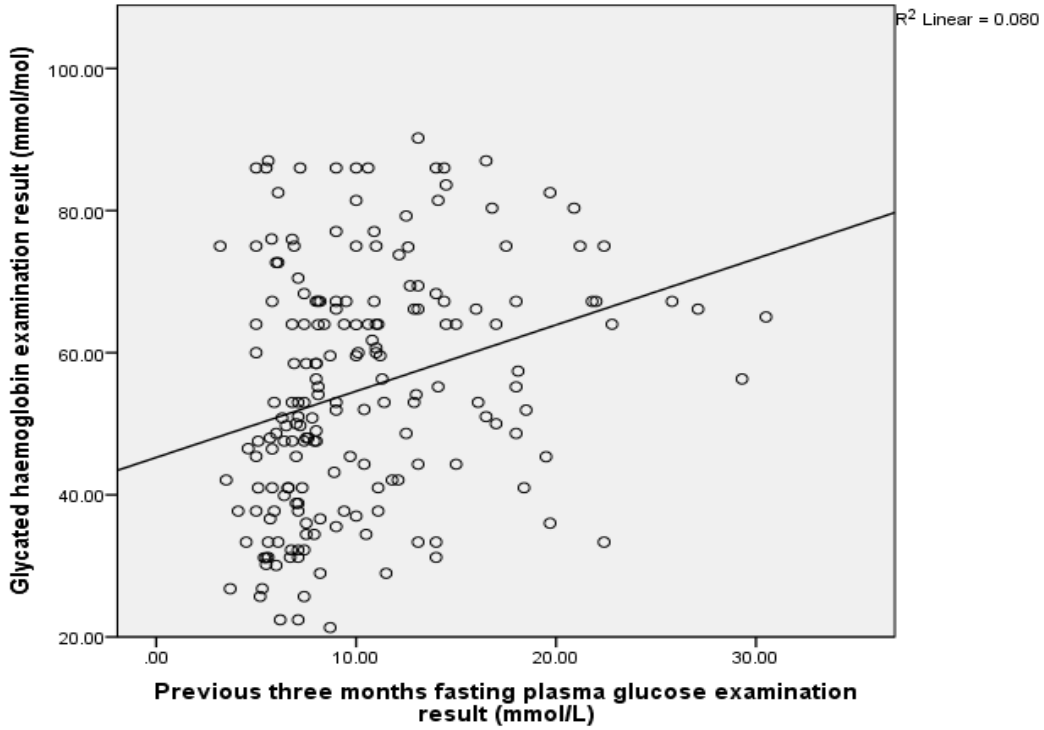

Figure 1: A scatter-plot of HbA_{1c} *versus* previous three months FPG (p < 0.01)

Relationship between HbA1c versus FPG and age

The Pearson's correlation coefficient test was run to establish the relationship between HbA_{1c}, FPG and age. There was a statistically significant but weak positive correlation between HbA_{1c} mean±SD (54.77±17.12 mmol/mol) and the previous FPG mean±SD (10.75±7.78 mmo/L) (r = 0.282, P = 0.001) (Figure 1). However, there was a statistically significant moderate positive correlation between HbA_{1c} (54.77±17.12 mmol/mol) and the current FPG (11.09±6.23 mmo/L) (r = 0.385, P = 0.001) (Figure 2). There was a statistically significant but weak negative correlation between HbA_{1c} mean±SD (54.77±17.12 mmol/mol) and the age mean±SD (53.19±13.32 years) (r = -0.163, P = 0.023) (Figure 3).

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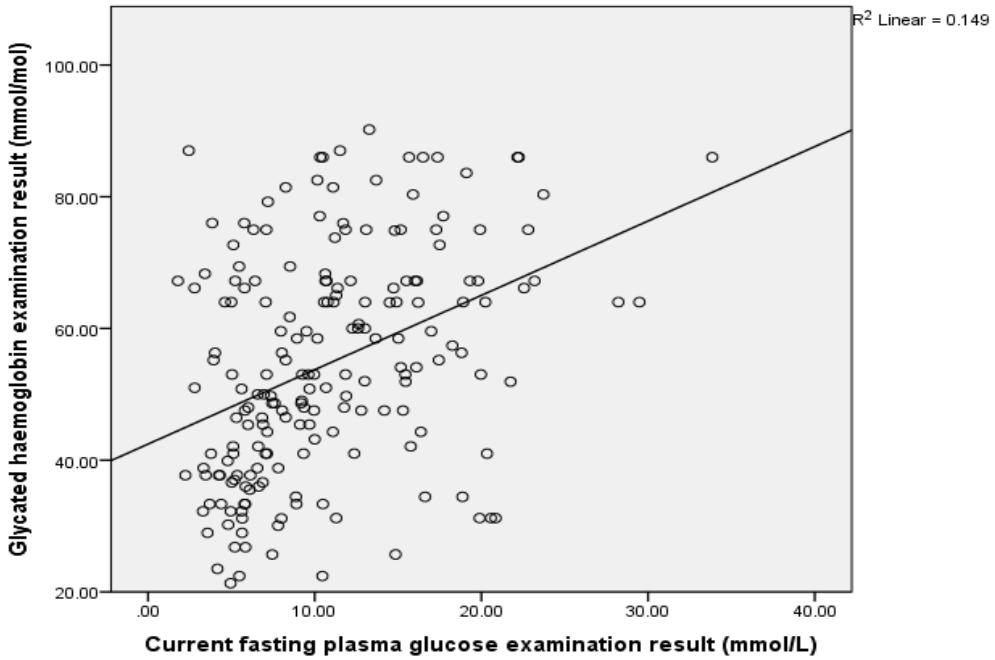

Figure 2: A scatter-plot of HbA_{1c} *versus* current FPG ($p < 0.01$)

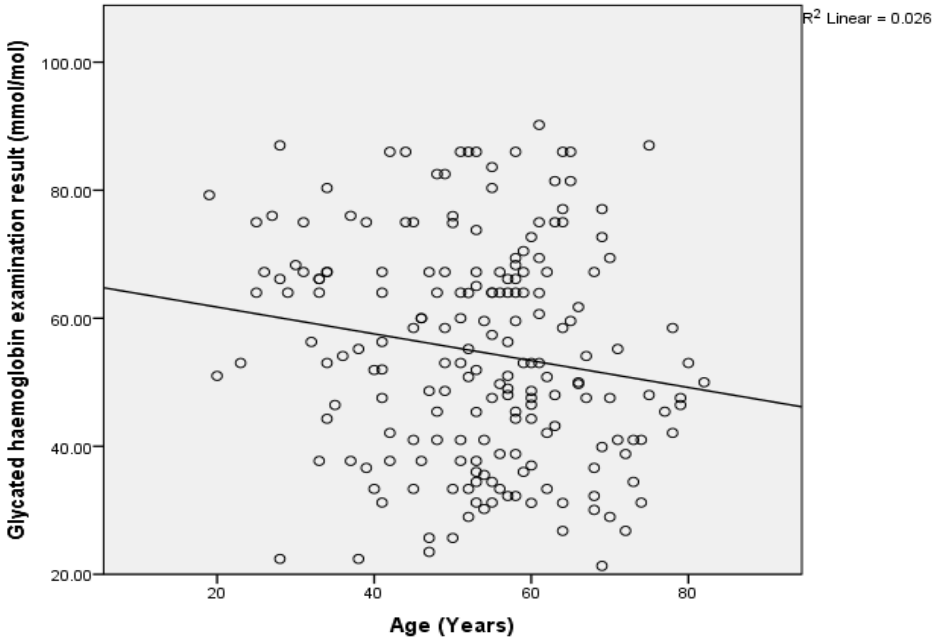

Figure 3: A scatter-plot of HbA_{1c} *versus* age ($p < 0.01$)

Discussion

The HbA_{1c} is a product of non-enzymatic reaction between glucose and free amino groups of Hb involving lots of other proteins, too and it is the principal mechanism through which glucotoxicity

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is formed. HbA_{1c} measurement is now considered as the best index for the control of diabetes as well as for preventing its complications (Saiedullah *et al.,* 2011). However, HbA_{1c} test is subject to certain limitations in conditions that affect RBC turnover. Haemoglobin variants must be considered, particularly when the HbA_{1c} result does not correlate with the patient's clinical situation (Sacks *et al.,* 2002) and this makes the relationship between HbA_{1c} and FPG complex.

The current study revealed that the FPG of the patients for the previous three months and current was higher than the normal; and there was a slight increase in the FPG from the previous to the current which difference was not statistically significant. The HbA_{1c} of the patients was also higher than the normal. Similarly, Haddadinezhad & Ghazaleh (2010) and Saiedullah *et al.* (2011) reported a higher than normal HbA_{1c} and FPG of the patients.

This study revealed a weak negative correlation between HbA_{1c} and age. On the other hand, Rohlfing *et al.* (2002), Kaur *et al.* (2014) and Saiedullah *et al.* (2011) reported a higher correlation between HbA_{1c} and FPG. The correlation was strongest in the age group below 30 years but the difference was insignificant between males and females (Haddadinezhad & Ghazaheh, 2010; Mo *et al.,* 2013; Liang *et al.,* 2010; Rajal Reddy *et al.,* 2013; Kaur *et al.,* 2014). In addition, some studies reported strong positive correlation between HbA_{1c} and FPG (DCCT/NGSP, 2005; Pani *et al.,* 2008; Liang *et al.*, 2010;). However, Wiener & Roberts (1999) and Mo *et al.* (2013) reported a non-significant correlation between age and HbA_{1c}. It appears that HbA_{1c}-age represents only the metabolic status (Turk *et al.,* 1998). The prevalence of such abnormality would be expected to be greater amongst older subjects, falsely suggesting a correlation between HbA_{1c} and age (Wiener & Roberts, 1999). The combined screening with FPG and HbA_{1c} may identify older adults at very high risk for diabetes when FPG and HbA_{1c} are considered together. Thus, the selection of subjects may be the key to the differences in the influence of age on HbA_{1c} (Wiener & Roberts, 1999).

Most importantly, the current study revealed a weak and moderate positive correlation between HbA_{1c} and previous and current FPG. The results are similar to those by Hossain *et al.* (2012), Haddadinezhad & Ghazaleh (2010) and Wiwanitkit (2012), who reported moderate correlations between HbA_{1c} and FPG. The poor correlation might be due to the high prevalence of Hb disorder in the study setting. Thus, FPG might not be used to imply HbA_{1c} in the areas with the background of endemic Hb disorder (Wiwanitkit, 2012).

Silverman *et al.* (2008) and Haddadinezhad & Ghazaleh (2010) reported a moderate to strong positive correlation between HbA_{1c} levels and FPG. Several studies have revealed a strong positive correlation between HbA_{1c} and FPG (Rohlfing *et al.,* 2002; Liang *et al.,* 2010; Bozkaya *et al.,* 2010; Raja *et al.,* 2013; Lipska *et al.* 2013; Kaur *et al*. 2014). This is because the level of HbA_{1c} is proportional to the level of glucose in the blood and normal levels of glucose produce a normal amount of HbA_{1c}. Thus, as the average amount of plasma glucose increases, the fraction of HbA_{1c} increases in a predictable way and this serves as a marker for average blood glucose levels over the previous 8 to 12 weeks prior to the measurement (Roszyk *et al.,* 2007). It is important to note that FPG test ascertains the glucose levels for the past few days but since blood glucose levels fluctuate throughout the day, glucose records are imperfect indicators of changes in the body due to hyperglycaemia. However, this does not mean that FPG cannot be used among DM patients who do not have access to HbA_{1c} measurement facilities.

There is an increase in the use of HbA_{1c} to monitor long-term glycaemic control in diabetic patients (Rohlfing *et al.,* 2002) as there is a strongly correlation between HbA_{1c} with adverse outcome risks. The addition of elevated HbA_{1c} to the model with raised FPG resulted in improved discrimination and calibration. In particular, the combination is recommended for individuals with a FPG > or =5.55 mmol/L (Kazuo *et al.,* 2007).

The level of HbA_{1c} at any point in time is contributed to by all circulating RBCs, from the oldest (120 days old) to the youngest (NGSP, 2010). However, HbA_{1c} is a "weighted" average of blood glucose levels during the preceding 120 days, meaning that glucose levels in the preceding

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30 days contribute substantially more to the level of HbA_{1c} than do glucose levels 90-120 days earlier. This is supported by data from actual practice showing that HbA_{1c} level improved significantly already after 20 days since glucose-lowering treatment intensification (Sidorenkov *et al.,* 2011). This explains why the level of HbA_{1c} can increase or decrease relatively quickly with large changes in plasma glucose; it does not take 120 days to detect a clinically meaningful change in HbA_{1c} after a change in mean plasma glucose (Rohlfing *et al.,* 2002; NGSP, 2010). Thus, calculated HbA_{1c} levels can be used with regular check-ups of FPG and HbA_{1c} levels in diabetic patients at lesser cost (Manjunatha *et al.,* 2011).

The association between the FPG and HbA_{1c} level depends on the extent of glycaemic control. A clear understanding of the relationship between HbA_{1c} and FPG is necessary for setting appropriate day-to-day FPG testing goals with the expectation of achieving specific HbA_{1c} targets. There is need for patients and healthcare providers to include HbA_{1c} in the monitoring of diabetic out-patients to determine the effectiveness of glycaemic control measures. As long as the patients and healthcare providers continue to use plasma glucose tests alone, which fluctuate daily, it will be difficult to monitor glycaemic control adequately.

This study had limitations such as the time between the previous and current estimation of FPG was not the same for all patients. Some patients had their previous FPG reading taken four to six months prior to the study. Also, the establishment of the associated between HbA_{1c} and FPG did not take into consideration the confounding factors. Furthermore, this study was carried out on a finite study population illustrated by the fact that only the participants who visited the UTH diabetic clinic during the period of data collection were included in the sample. Since the data on medical records of the diabetic patients at the clinic were incomplete; it was difficult to capture the previous FPG for some patients.

In conclusion, this study showed an association between HbA_{1c} and FPG suggesting that the level of the former is directly proportionate to the level of the later. Therefore, normal levels of FPG produce a normal amount of HbA_{1c} and vice versa. The study will enable health care providers and DM patients to review the monitoring of glycaemic control by not only emphasising on HbA_{1c} even if it is not possible but to look at FPG as an alternative. This will be achieved through sensitisation especially among the major stakeholders in the management of diabetes mellitus.

Competing interests

The authors declare no competing interests.

Authors' contributions

EMM conceived the study. EMM, AM and CM designed the study. EMM collected and analysed the data and wrote the manuscript. AM, BM and CM supervised the whole study process, including the writing of the manuscript. All the authors read and approved the final manuscript. All the authors contributed equally and as stated in the manuscript.

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