ASSESSING THE VALIDITY OF RANDOM BLOOD GLUCOSE TESTING FOR MONITORING GLYCEMIC CONTROL AND PREDICTING HbA1c VALUES IN TYPE 2 DIABETICS AT KARL BREMER HOSPITAL

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DATE: December, 2012

DECLARATION

Declaration

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree. I also declare that ethical approval for the study was obtained from the Health Research Ethics Committee of Stellenbosch University (Reference number: N10/12/401).

Signature: .....……..... Date: ..…….....

ABSTRACT.

Background: The number of adults affected by diabetes mellitus in developing countries, such as South Africa, is projected to grow by 170%, from 84 to 228 million people between 1995 and 2025 .This high and increasing prevalence of diabetes worldwide, and the economic burden of diabetes on developing countries like South Africa emphasizes the importance of ensuring good glycemic control so as to slow down the rate of disease progression and prevent complications. The district health care facilities are the foundation of the health care system of South Africa. The current practice is that diabetics have a point of care random blood glucose (RBG) done on the morning of their clinic appointment and this is used as a form of assessment of glycemic control during the consultation. For further clinical decision making a HbA1c is done once a year as a benchmark of glycemic control. The practical clinical question that arises is whether the assumptions underlying local clinical decision making using the RBG are valid and to what extent RBG can be used to guide clinical management.

Aim and Objectives: The aim of this study was to assess the strength of the correlation between RBG and HbA1c and to make recommendations for the interpretation of RBG results in adult patients with Type 2 Diabetes taken at Karl Bremer District Hospital out-patient department. The objectives were: To determine glycaemic control in the study population and compare differences between age, sex and racial groups , and determine the RBG cut-off with the best sensitivity and specificity for predicting poor glycaemic control (HbA1c>7.0%) as well as the predictive value, likelihood ratio and pre/post-test odds and probability at this cut off.

Methods: A retrospective analysis of existing hospital data and the HbA1c tests requested from the NHLS by Karl Bremer Hospital over the 2011 year period. The data was analysed by means of a receiver operating characteristic (ROC) curve analysis to determine the value of RBG with the best combination of sensitivity and specificity to predict poor control of diabetes. A p-value of < 0.05 was assumed to represent statistical significance and 95% confidence intervals were used to describe the estimation of unknown parameters. HbA1c level of $< = 7\%$ was taken as representing good control and $> 7\%$ poor control.

Results: Data was obtained on 349 diabetic patients of whom 203 (58.2%) were female and 146 (41.8%) male. This study population had a mean age of 54.7 years, mean RBG of 13.0mmol/l and mean HBA1c of 9.4%. The total number of black patients was 79 (23%), coloured patients 147 (42%) and white patients 122 (35) % and their mean RBG were 15.4 mmol/l, 12.8 mmol/l and 11.9 mol/l respectively.

There was a statistically significant correlation between increasing RBG and increasing HbA1c ($p< 0.01$). The best value obtained on the ROC curve was an RBG of 9.8 mmol/l, which had a sensitivity of 77% and a specificity of 75%, positive predictive value of 0.88, positive likelihood ratio 3.08 and post-test probability of 88.2% for predicting an HbA1c above 7%.

Conclusion: It was concluded that a moderate correlation exists between RBG and HbA1c in this population of diabetic patients. .The best RBG for determining poor control, defined as a HbA1c>7.0%, was found to be 9.8mmol/l and this RBG had a sensitivity of 77% , specificity of 75% and positive predictive value of 88%. Significant differences were found in pre- and post -test probability for different racial groups. Point of care testing using this level of RBG for clinical decision making will

inappropriately categorise 23% of patients in this population and therefore introducing point of care testing for HbA1c is recommended.

Introduction

One of the major causes of death in South Africa (SA) is diabetes mellitus. Diabetes has the highest increase compared to HIV in number of deaths between 2004 and 2005, and there are an estimated 2 million people affected in SA, which corresponds to a prevalence of 5.5% in those aged 30 years and above.[1] Globally, a person dies from diabetes related causes every 10 seconds and each year 6 million people develop diabetes.[2]

The number of adults affected by diabetes mellitus in developing countries, such as South Africa, is projected to grow by 170%, from 84 to 228 million people between 1995 and 2025. In the same period, the developed world will only see a 41% increase, from 51 to 72 million people with diabetes.[3]

With this high and increasing prevalence of diabetes worldwide, and particularly with the economic burden of diabetes on developing countries like South Africa, it is important to ensure good glycemic control so as to prevent complications of diabetes and slow down the rate of disease progression.[4, 5] This will depend in part on the quality of care we render to our type 2 diabetic patients. In type 2 diabetic patients, the risk of complications is strongly associated with previous hyperglycemia and any reduction in the HbA1c value is likely to reduce the risk of complications, with the lowest risk in those having HbA1c values within the normal range (- <6.5%).[6] The incidence of microvascular and macrovascular diabetic complications is significantly associated with hyperglycemia and each 1% reduction in HbA1c is associated with a reduction in risk of 21% for diabetes related deaths, 37% for microvascular complications, 21% for any end points related to diabetes and 14% for macrovascular complications, such as myocardial infarction.[7]

Random blood glucose (RBG) and glycosylated haemoglobin (HbA1c) are two of the common ways that physicians assess glycemic control in diabetic patients.[8] Although the value of HbA1c varies from laboratory to laboratory, it correlates very well with a person's recent overall blood glucose levels (from the preceding 2-3 months) and thus is useful in predicting overall future diabetes morbidity and related complications.[8,9] HbA1c is a trusted gold standard for monitoring glycemic control and predicting complications and a HbA1c of <6.5% is regarded as normal, while the range from 6.5 – 7.5% is considered acceptable.[10] The Society of Endocrinology Metabolism and Diabetes of South Africa (SEMDSA) recommends a target HbA1c of 7%.[11] The reason for the more conservative goal is the disappointing results of recent trials which aimed for lower HbA1c values.[12] However, for carefully selected subgroups a lower HbA1c may be targeted, especially early in the course of the disease and in patients with a relatively long life expectancy.[13]

For subgroups that are older, with advanced diabetic complications, especially renal failure or serious macrovascular disease, a more conservative HbA1c target may be appropriate. This is also the case in patients with serious recurring hypoglycaemic episodes, brittle diabetes, or hypoglycemic unawareness.[11-15]

In many African settings, RBG, and not HbA1c, is used for clinical decision making. A study in Kenya found that patients with type 1 or 2 diabetes mellitus came to the national hospital for follow-up visits very infrequently.[16] Indeed, for most of these patients their blood glucose monitoring was done only on the day of their visit to the doctor. It is imperative to note that the objective of the study was to determine how well the morning random blood level determined the quality of glycaemic control. The study showed that the morning random glucose level had a linear relationship with HbA1c taken simultaneously. A blood glucose level of 7 mmol/l had a 92.7% sensitivity for good control (HbA1c < or = 7.8%) and a 59.8% specificity. When the blood glucose cut-off level was raised to 10 mmol/l sensitivity fell to 66.3% (for HbA1c < or = 7.8%), and specificity increased to 83.2% .[16] There was a marked fall in sensitivity with an increasing cut off level for random blood glucose level in predicting good glycaemic control, and a concomitant rise in specificity.

The study therefore notes that morning random blood glucose in the ambulatory diabetic patients related well to simultaneously assayed HbA1c. Blood glucose within usual therapeutic targets of 4-8 mmol/l predicted good glycaemic control (HbA1c < or = 7.8%) with high sensitivity at the range of 86.3-98.4%.[16] Thus, in resource-poor settings, the morning random blood glucose assay, which is done in patients who may attend the diabetic clinic in the morning hours, may be used to predict the quality of their diabetic control. However caution should be exercised in its widespread use because its overall applicability may be clinic-specific depending largely on the average metabolic control of the diabetic population using that clinic. The study therefore note that further studies need to be done to relate HbA1c to blood glucose levels obtained at different times of the day in this population to determine the best predictor of good glycaemic control.

Type 2 diabetes constitutes the majority of diabetic patients seen at our public sector district hospitals. In the outpatient department of Karl Bremer District Hospital (KBDH), a RBG is the most frequently used test to determine whether diabetic care is optimal and to assess glycemic control. RBG is preferred to fasting blood glucose (FBG) because patients are seen in the late morning and most would have had some calorie intake –snack /breakfast - by this time. RBG is cheap, readily available as a point of care test, accessible, and instant interpretation can be done. The rule of thumb in the out patient clinic is that a RBG < 10mmol/l correlates with an acceptable HbA1c. HbA1c is more expensive, done occasionally (about once or at most twice yearly) and the result is not immediately available.[10] The current practice is that diabetics have an RBG (finger prick blood glucose estimation with a glucometer) done on the morning of their clinic appointment, and this is used as a form of assessment of glycemic control during the consultation and for further clinical decision making in the patient management. There is a growing trend towards also measuring HbA1c once a year as a benchmark of glycemic control.

The majority of patient consultations occur within the district health system and most diabetic care is offered there. It is important therefore that clinical practice is based on valid measurements of glycaemic control. The practical clinical question that arises in my setting is whether the assumptions underlying local clinical decision making are valid and to what extent RBG can be used to make an assessment of glycemic control. If there is a reliable correlation between the two measures then guidelines can be created for decision making based on RBG, but if no reliable correlation is proven then current practice should be reviewed.

Aim and objectives

The aim of this study was to assess the correlation between RBG and HbA1c and to make recommendations for the interpretation of RBG results in adult patients with Type 2 Diabetes taken at Karl Bremer District Hospital out-patient department. The objectives were:

•To determine glycaemic control in adult diabetic patients attending Karl Bremer Hospital and compare differences between age, sex and racial groups

•To determine the strength of the correlation between RBG and HbA1c

•To determine the RBG result with the best sensitivity and specificity for predicting poor glycaemic control (HbA1c<7.0%)

•To determine the predictive value, likelihood ratio and pre/post-test odds and probability when this level of RBG is used as a cut off to determine poor glycaemic control (HbA1c<7.0%)

•To make recommendations regarding the use of RBG for clinical decision making at Karl Bremer District Hospital.

Methods

Study design

The study was a retrospective analysis of existing hospital and laboratory data.

Setting

The study setting was the outpatient department (OPD) of Karl Bremer, a district level hospital that serves the Bellville area of the Cape Town Northern-Tygerberg sub-structure. The patients seen at the OPD have diverse chronic illnesses such as diabetes mellitus, hypertension, renal disease, ischemic heart disease, asthma and chronic obstructive airway disease and each one of these illnesses can be seen as a co-morbid condition with diabetes mellitus. They are usually referred from primary health care centres for better control and treatment optimization and then subsequently referred back to the primary health care centre. The majority of the patients are coloured (of mixed ancestry), white or Xhosa. In addition there are some Indian patients, as well as a minority of foreign immigrants (for example, Congolese and Somalis).

The diabetic patients are seen daily from Monday to Thursday. Patients include those with newly diagnosed diabetes mellitus , those referred with poor glycemic control from primary health care facilities in spite of treatment optimization or those coming for follow-up reviews at the outpatient clinic following recent hospitalization and discharge from the medical emergency or in-patient wards. They are all managed by the medical officers and a consultant who is in charge of the medical OPD. The patients have their RBG measured at each visit by a nurse via point of care capillary blood glucose estimation in the preparation room, before seeing a physician. The blood glucose value is recorded in the patient file. HbA1c should be ordered twice per year by the doctor and requires a venous blood sample that is sent to the laboratory.

Sampling procedure

Sample size was calculated by the Centre for Statistical Consultation to offer as much precision as possible to determine whether there was a significant correlation between HbA1c and RBG results. A sample size of 350 was recommended to achieve 80% power to detect a correlation of at least 0.2 using a two-sided hypothesis test with a significance level of 0.05.

Data collection

Data was obtained from the National Health Laboratory Service (NHLS) on all the HbA1c tests requested by Karl Bremer Hospital between January and December 2010. The patient record for each of the selected HbA1c test results were drawn and the corresponding RBG taken in the OPD was looked up and a pre-designed MS Excel data collection sheet was used to capture data on HbA1c, RBG and demographic/medical information that reflected the profile of the patient population.

Data analysis

There were two continuous variables, with the HbA1c being the dependent and the RBG the independent variable. The primary aim was to determine whether there was any significant correlation between RBG and HbA1c values and the strength and nature of the relationship. Age, race, and gender were also analysed to see if they affected the correlation between RBG and HbA1c. A HbA1c level of < = 7% was taken as representing good control and > 7% poor control , the sensitivity, specificity, predictive values and likelihood ratios of different threshold levels of RBG were then analysed. In addition the study population was also analysed by means of a receiver operating characteristic (ROC) curve to determine the value of RBG with the best combination of sensitivity and specificity to predict poor control of diabetes. A p-value of < 0.05 was assumed to represent statistical significance in hypothesis testing and 95% confidence intervals were used to describe the estimation of unknown parameters. STATISTICA version 9 was used to analyze the data with the assistance of the Centre for Statistical Consultation.

Ethical considerations

The research was a retrospective study involving an already existing database of routinely collected data and a waiver of informed consent was approved as no patient identifiers were analyzed or reported in the study. Patients' information was protected and confidentiality maintained with access restricted to myself and my supervisor. The patients were not at harm from the study and may also potentially benefit from a higher quality of care. Ethical approval was obtained from the Health Research Ethics Committee of Stellenbosch University (N10/12/401) and permission to conduct the study was granted by the Department of Health.

Results

Data was obtained on 349 diabetic patients of whom 203 (58.2%) were female and 146 (41.8%) male. This study population had a mean age of 54.7 years (SD 15.2, range-17.3 – 89.4), mean RBG of 13.0 mmol/l (SD 6.8, range-2.1-44.0mmol/l)and mean HBA1c of 9.4 %(SD 3.2, range: 3.5-21.2). The

distributions of RBG and HbA1c are shown in Figures 1 and 2. Out of this population of diabetic patients 247 (70.8%) were uncontrolled with an HbA1c > 7.0%.

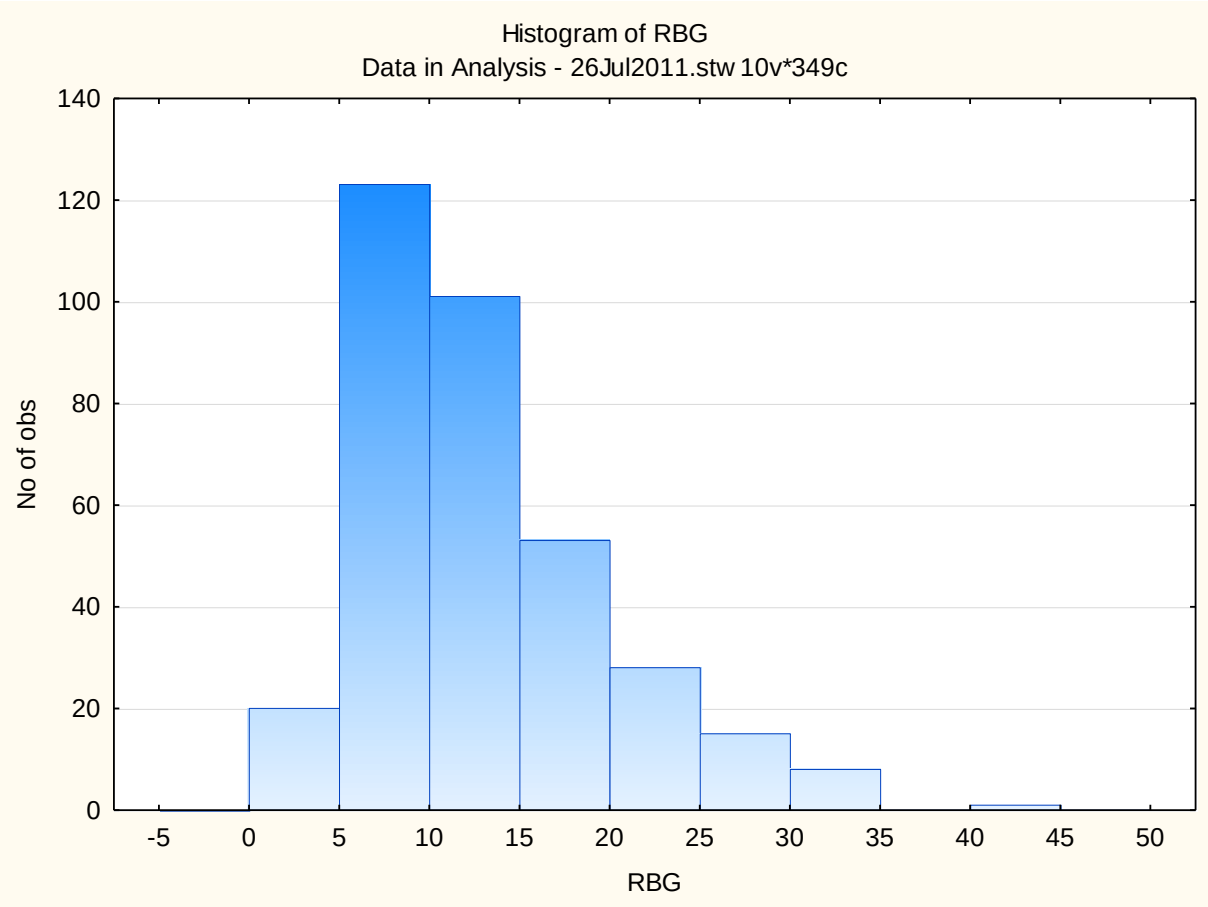

Figure 1: Distribution of random blood glucose results (mmol/l) (N=349)

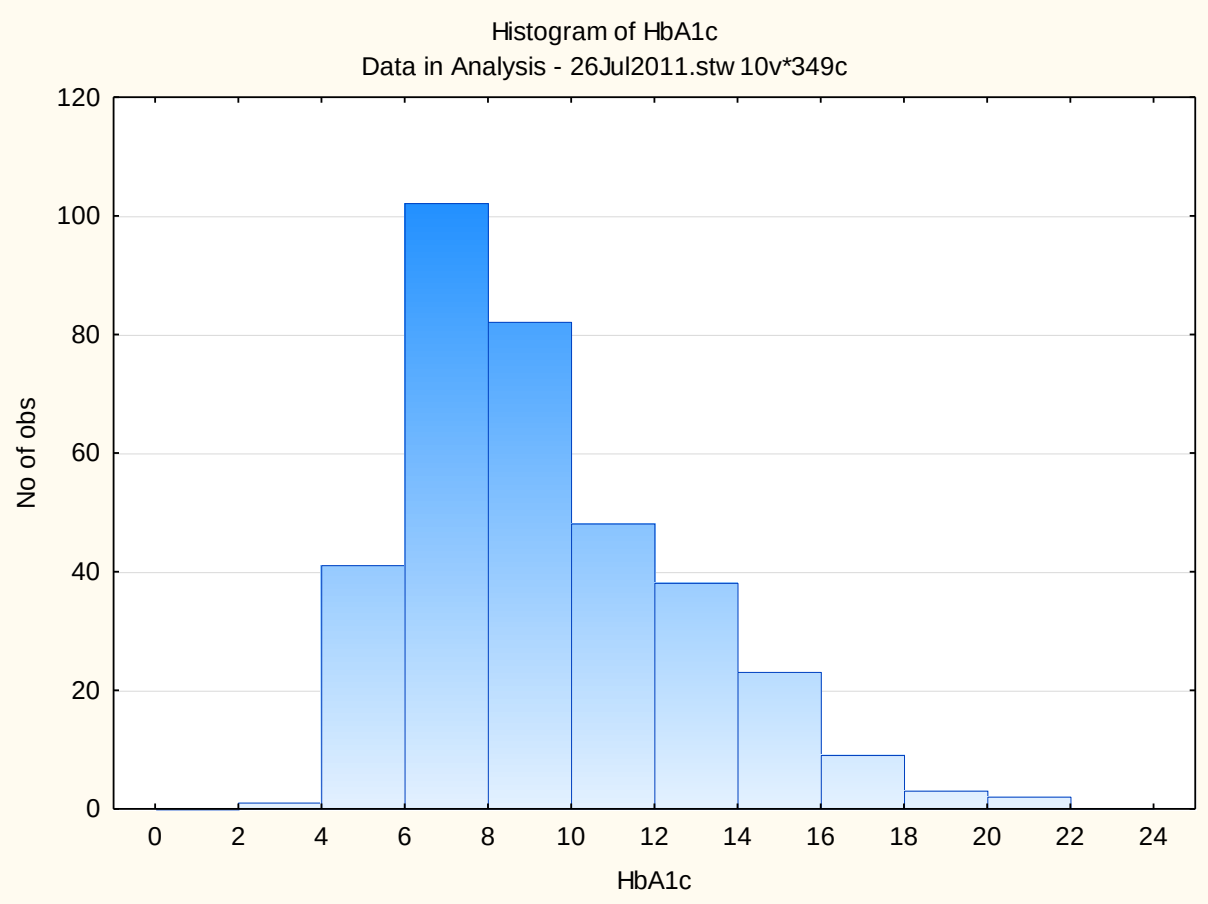

Figure 2: Distribution of HbA1c in the study population (%) (N=349)

The total number of white patients was 122 (34.9%), coloured patients 147 (42.1%) and black patients 79 (22.6%). Black patients had a significantly higher mean RBG (15.4 mmol/l) compared with the coloured (12.8 mmol/l) and white (11.9 mol/l) patients ($p<0.01$). There was no significant difference, however, between the coloured and white patients. All three racial groups had a significantly different mean HbA1c implying that black patients were most likely to be uncontrolled, followed by coloured and then white patients as shown in Table 1. The number of patients who were uncontrolled was 77 (63.1%) in the white population, 106 (72.1%) in the coloured and 64 (81.0%) in the black population.

Table 1: Diabetic control (HbA1c) in different racial groups.

Race	Mean HbA1c (%)	95% Confidence Intervals	P value
White	8.3	7.8 – 8.9	<0.01
Coloured	9.5	9.0-10.0	
Black	10.8	10.1-11.5	

The mean RBG for males and females was 13.0 mmol/l in both (p=0.99) and the mean HbA1c for males was 9.2% vs. 9.5% for females (p= 0.39). There was a statistically significant association between increasing patient age and decreasing RBG (p<0.01), but the correlation coefficient was low at 0.15 and only 2% of the variation in RBG was explained by age as shown in Figure 3.

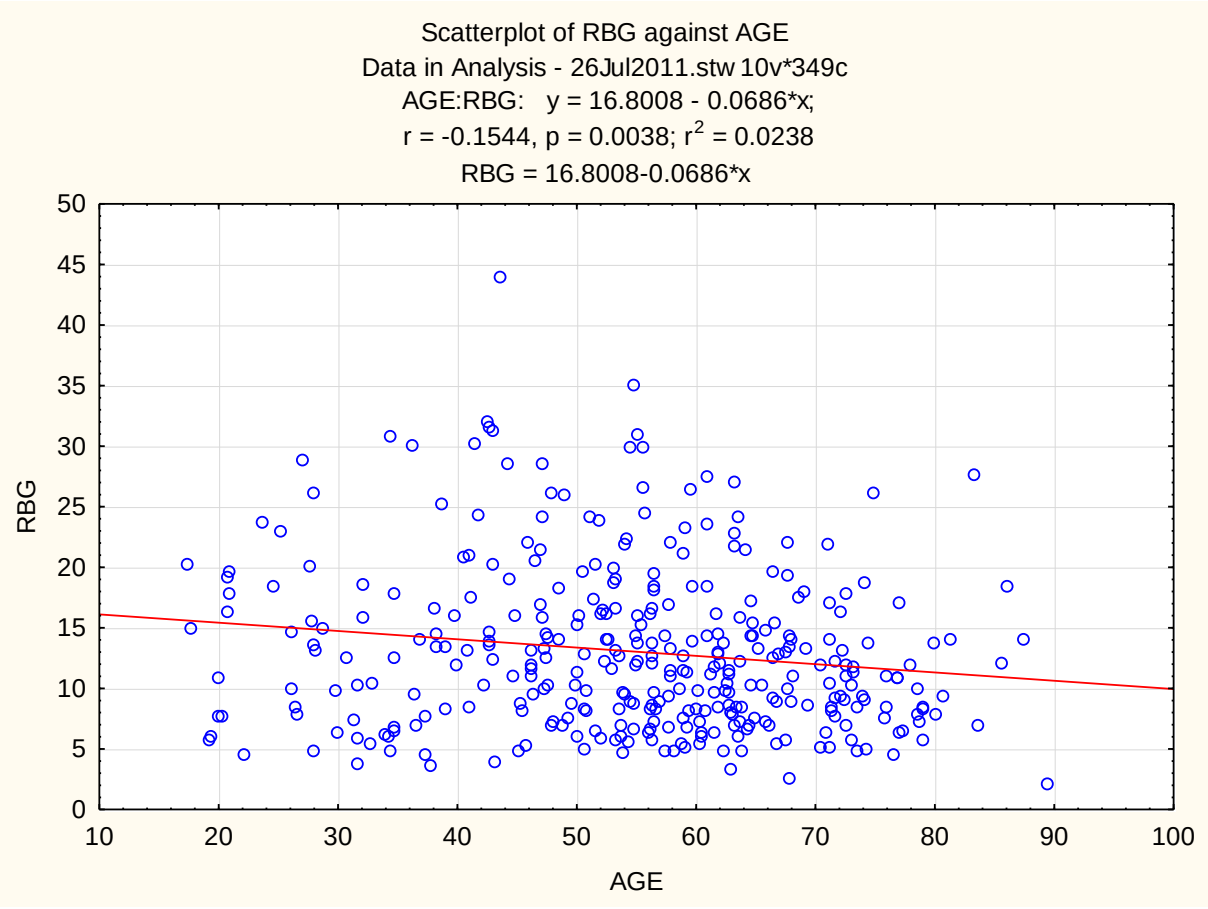

Figure 3: Correlation of RBG (mmol/l) and age (years).

The HbA1c scatter plot in Figure 4 shows that there was a significant association ($p< 0.01$) between decreasing HbA1c and increasing patient age with a low correlation coefficient of 0.19 and only 3% of the variation in HbA1c was explained by age. Therefore, although there was a statistically significant correlation between RBG and HbA1c with age this is probably not of much clinical significance.

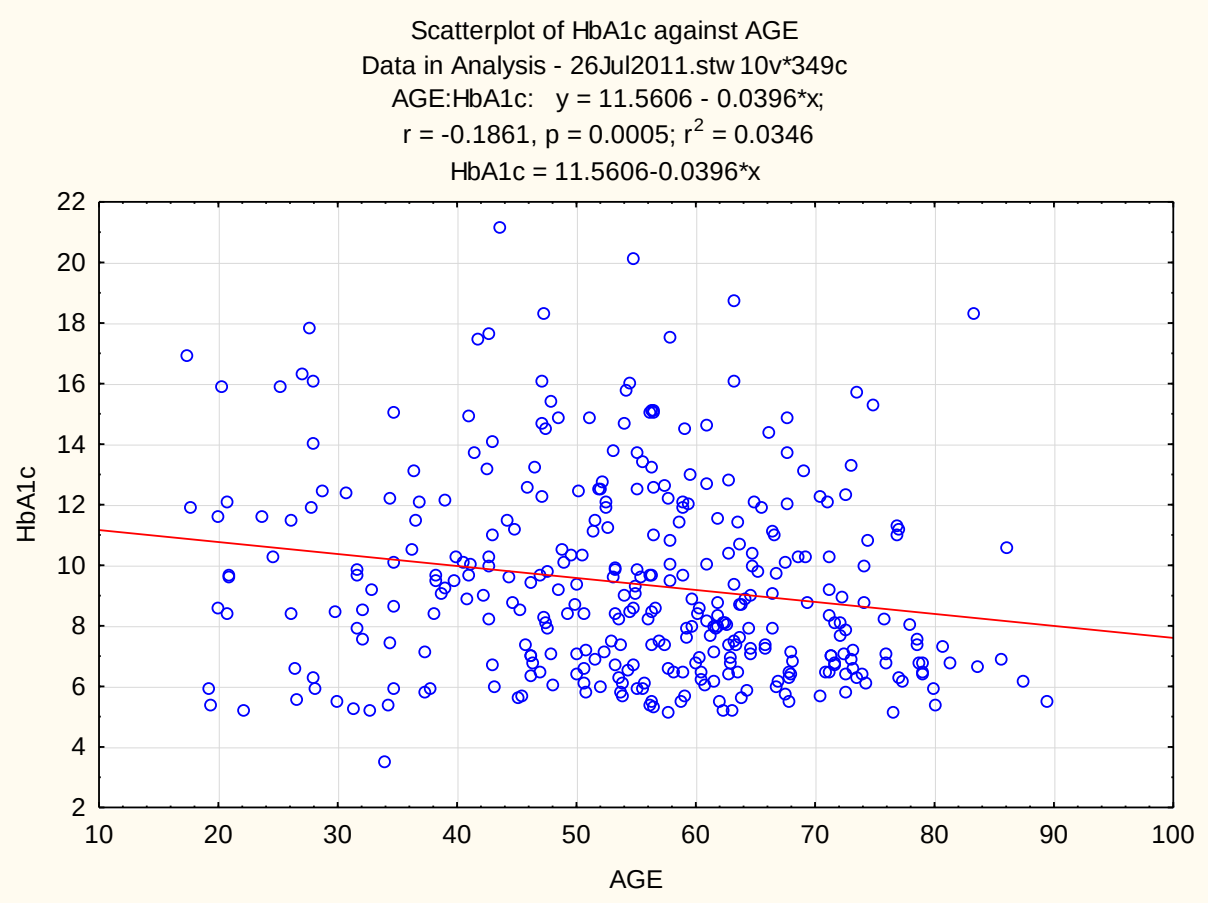

Figure 4: Association between HbA1c (%) and age (years).

There was a statistically significant correlation between increasing RBG and increasing HbA1c as shown in Figure 5 ($p< 0.01$). The correlation coefficient was 0.6 and this implies a moderate correlation between the two variables, with 45% of the variation in RBG due to the relationship with HbA1c.

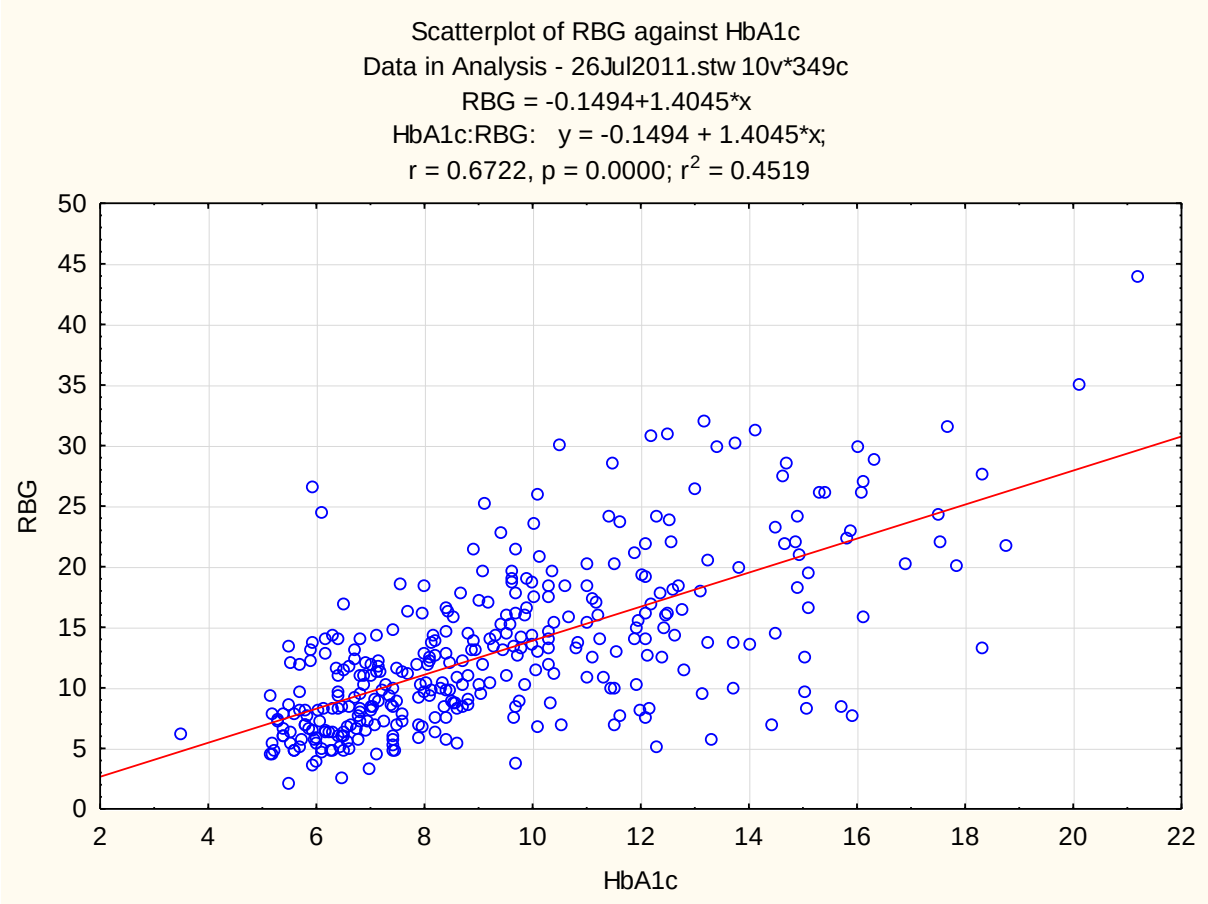

Figure 5: Correlation between RBG (mmol/l) and HbA1c (%).

Figure 6 is a receiver operator characteristic (ROC) curve that was used to determine the best RBG value to predict patients with an HbA1c above 7%. The ROC curve compares the sensitivity on the Y axis to (1-specificity) on the X-axis. A perfect RBG value should lie in the left upper corner where sensitivity and specificity is 100%. However the best value obtained on this ROC curve was a RBG of 9.8 mmol/l, which had a sensitivity of 77% and a specificity of 75% for predicting HbA1c above 7%.

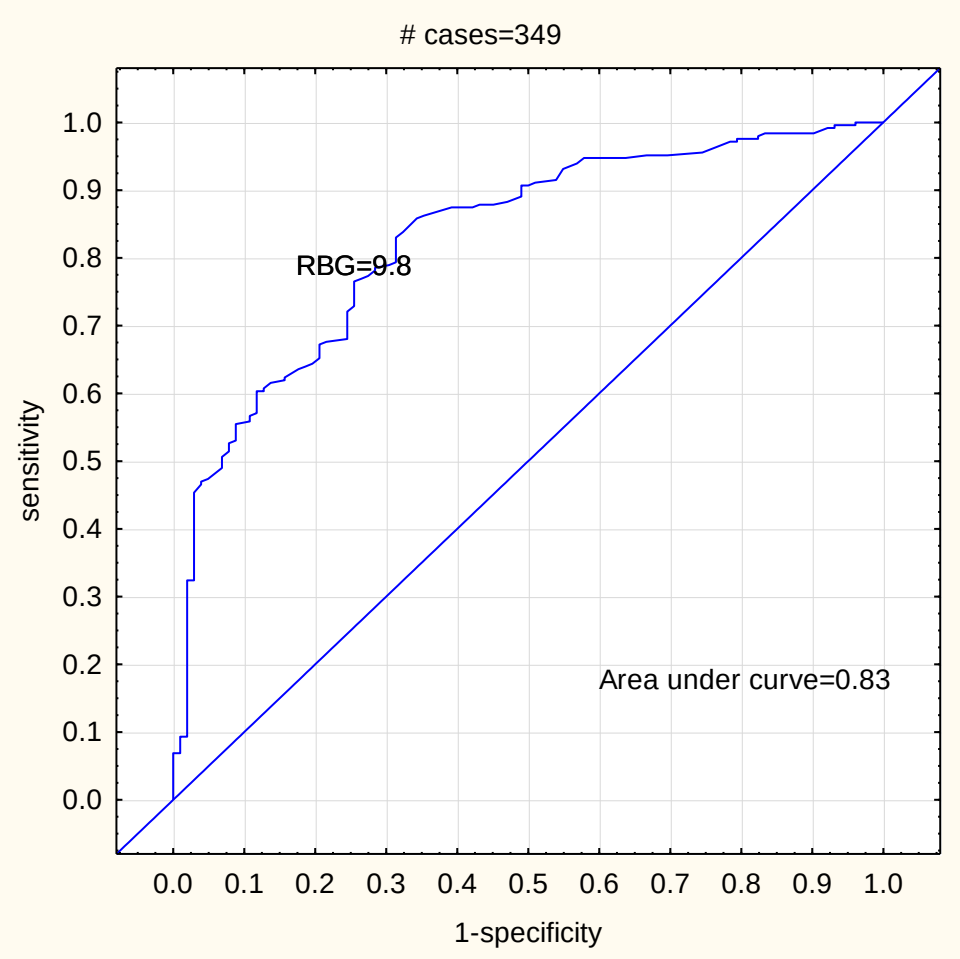

Figure 6: Receiver operator characteristic curve for random blood glucose

This implies that 23% of patients with poor control (HbA1c>7.0%) will not be identified and will have a RBG less than 9.8 mmol/l. It also implies that 25% of patients with good control will be wrongly identified by having an RBG greater than 9.8mmol/l on the day they are seen. The predictive properties of a RBG threshold of 9.8mmol/l are shown in Table 2.

Table 2: Predictive properties of a RBG threshold of 9.8mmol/l

Indicator	Result
Sensitivity	77%
Specificity	75%
Positive predictive value	0.88
Positive likelihood ratio	3.08
Prevalence of poor control	70.8%
Pre-test odds	2.42
Post-test odds	7.45
Post-test probability	88.2%

This means that in the outpatient diabetic population, a patient with a RBG greater than 9.8 mmol/l has 88.2% probability of also having an HbA1c greater than 7%. It is clear from Table 1 above that the pre-test odds of a high HbA1c is significantly different between racial groups. The post-test odds and probability of uncontrolled diabetes will therefore also differ between these groups as shown in Table 3. The post-test probability in Table 3 shows that a white patient with RBG greater than 9.8 mmol/l has a 84.0% probability of also having HbA1c greater than 7%, a coloured patient a 88.8% probability and a black patient a 92.9% probability.

Table 3: The glycemic control and prevalence in the three racial groups

Indicator	White (n=77)	Coloured(n=106)	Black(n=64)
Prevalence of HbA1c > 7%	63.1%	72.1%	81.0%
Pre-test odds	1.71	2.58	4.26
Post-test odds	5.27	7.95	13.12
Post-test probability	84.0%	88.8%	92.9%

Discussion

Key findings

The best RBG value to predict an uncontrolled HbA1c was found to be 9.8 mmol/l, which is very close to the value of 10.0 mmol/l that is currently used by most clinicians at the hospital. This confirms that current decision making is made on the best available value of RBG. However decisions made on this basis will miss 23% of the 70.8% of patients with poor control and implies that out of 100 patients seen in the outpatients 16 that are poorly controlled will be missed and have a RBG less than 9.8 mmol/l. On the other hand 25% of the 29.2% of patients with good control will be inappropriately labeled as poorly controlled and this implies that out of 100 patients 7 will fall into this category with a RBG greater than 9.8mmol/l when seen. Overall therefore a decision made on the basis of RBG will inappropriately categorise 23 out of every 100 patients seen. Thus, although decision making using RBG is currently based on the best possible cut off value, almost a quarter of patients will be mismanaged on this system. The post-test probability does vary however between racial groups and will be slightly better for coloured and black patients. Although there was a statistically significant correlation between RBG and HbA1c with age this was not of much clinical significance.

Comparison to the literature

A study examined the reliability of random venous or capillary blood glucose testing, random urine glucose testing, and a current symptom history in predicting a high HbA1c in Type 2 diabetic patients taking oral hypoglycaemic agents in a poorly controlled rural African population.[17] The study shows that for a cut-off point for HbA1c of > or = 8%, a random venous plasma glucose of > or = 14 mmol/L (present in 47.2% of subjects), gives a specificity of 97.1% (95% CI 85.1-99.9), sensitivity 56.8% (48.8-64.5) and positive predictive value (PPV) 98.9% (94.2-99.9).[17] If the random capillary blood glucose is increased to 17 mmol/L (present in 28.4% of subjects) then the specificity is 100% (90.0-100.0), PPV 100% (93.7-100.0) and sensitivity 34.3% (27.2-42.1). The study therefore notes that where resources are limited, a high random glucose can be used to detect a significant proportion of those with the worst

control with a high degree of specificity enabling primary care staff to modify treatment safely. However increasing specificity in this way leads to a significant decrease in sensitivity (34%) and so a large number of poorly controlled patients would be missed.[17] Similarly another study conducted in a Kenyan district hospital showed that decreasing the cut off value of RBG to 7mmol/l increased sensitivity to 92.7%, but at the cost of decreasing specificity to only 59.8%.[16] In this same study a cut-off for RBG of 10 mmol/l demonstrated a sensitivity of 66.3%, which is lower than Karl Bremer. The lower sensitivity may be due to differences in the prevalence of poorly controlled type 2 diabetes.

Another study found that hemoglobin A1c (HbA1c) values are influenced by analytical interferences such as HbF and hemoglobin variants and clinical factors such as increased red cell turnover, as well as less well-known, demographic factors such as race, age, and sex.[18] Haemoglobinopathies and malaria (increased red cell turnover) are not commonly found in Cape Town's patient population. The prevalence of anemia in the study population was not recorded. The significant association of race with glycemic control was an interesting finding. Studies in non-diabetic populations find that HbA1c levels are on average higher in black communities. [18, 19, 20, 21,22] Reasons for these differences may be genetic as well as related to lifestyle choices and poverty.[6] The relationship between blood glucose and HbA1c may also be different in black patients.[24] The annual audit of the quality of care at different health centres in Cape Town does not support the hypothesis that differences in control are due to differences in quality of care between health centres that serve predominantly white, coloured or black communities. [25]

Limitations of the study

The measurements of HbA1c and RBG were done on the same day, but not at the same time and variations will occur if patients had a high calorie intake in between the two. It is imperative to note that the sample was designed to obtain sufficient paired data (RBG and HbA1c) to analyse the relationship not to be representative of the diabetic population. Descriptive data therefore regarding levels of control, age, race and sex may not be representative of the outpatient population as a whole. The study population was not differentiated into those with type2 diabetes alone or those with type 2 diabetes and other chronic diseases that might influence HbA1c results.

Implications and recommendations

Current decision making, which is based on point of care testing for RBG, is not an acceptable practice as decision making will be based on a false assessment in 23% of patients seen. Nevertheless the current rule of thumb to determine poor control (10mmol/l) has the best sensitivity and specificity. I have argued that the FBG is not a practical option in our setting and home blood glucose monitoring is not recommended for the majority of type 2 diabetics. Further studies could investigate whether the mean of serial RBG readings over several visits has a better sensitivity and specificity than a single reading. The district health services have committed to the cost of HbA1c testing annually, but not to more frequent testing and cost remains an issue for HbA1c tests. In addition the practical use of the HbA1c test is limited by its unavailability at the time of decision making and therefore point of care testing should be considered. More frequent HbA1c testing has been linked with better glycaemic control.[25] It may be more cost effective to introduce point of care testing in the larger picture of preventing diabetic complications and mortality and this should be further studied as an alternative approach.

Conclusion

The majority (71%) of patient receiving an HbA1c test at Karl Bremer Hospital were poorly controlled. Racial differences existed in levels of control with black patients having the worst control, followed by coloured and then white patients. There were no differences between males and females and a small but significant improvement with age. It was concluded that a moderate correlation exists between RBG and HbA1c in this population of diabetic patients. The best RBG for determining poor control, defined as a HbA1c<7.0%, was found to be 9.8mmol/l and this RBG had a sensitivity of 77% , specificity of 75% and positive predictive value of 88%. Significant differences in pre- and post -test probability for different racial groups were found. Point of care testing using this level of RBG for clinical decision making will inappropriately determine control in 23% of patients in this population and the Department of Health should explore the option of point of care testing for HbA1c.

Acknowledgement

My appreciation to the medical record staff of Karl Bremer for provision of reviewed folders and to DOH for granting me the permission to conduct the study. My sincere appreciation to my supervisor Professor R Mash for his prompt feedbacks, guidance and support. My deepest gratitude to my husband Oladeji Daramola for supporting me throughout the period of my residency programme and my daughters – Toni and Derin and Son –Simi. Overall, my thanks to God Almighty for keeping and strengthening me.

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