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IDENTIFICATION OF PREDICTORS OF GLUCOSE CONTROL IN A COHORT OF ADULT PATIENTS WITH DIABETES MELLITUS AT KALAFONG HOSPITAL

By

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DECLARATION

I hereby declare that this dissertation submitted to the University of Pretoria for the Masters of Science in Clinical Epidemiology degree is my own work and has not been presented previously for any degree to any other tertiary institution.

ABSTRACT

Background and objectives of the study: Although it is known that good glycaemic control improves microvascular outcomes in diabetic patients, no local study has yet been undertaken to investigate the potential factors that influence poor or good blood glucose control. This research focused on the evaluation of blood glucose control as assessed by glycosylated haemoglobin (HbA_{1c}) levels in diabetic patients. In addition, certain determinants which contributed toward poor control at Kalafong Hospital were studied in a cohort of adults with diabetes mellitus for the year 2008. The aim of studying these determinants was to identify patients with a high risk of disease morbidity and barriers that prevent these patients from meeting their goals of improved health outcomes. The specific objectives were to estimate HbA_{1c} control of patients seen at the diabetic clinic at Kalafong Hospital Pretoria in 2008 and to assess any existing association between patient demographic characteristics and diabetes characteristics with HbA_{1c}.

Methods: The study was a retrospective cohort study. All diabetic patients aged 18 years and above, who had been registered in the 2008 dataset and who had come for at least one visit to the diabetic clinic and had at least one HbA_{1C} measurement, were included in the study. Patients who did not meet the above criteria were excluded from the study. A total of 942 patients seen in 2008 were selected, 801 patients met these inclusion criteria. The outcome variable HbA_{1c} was obtained by computing the mean of the two HbA_{1c} values collected for each participant for the year 2008, and used as a continuous dependent variable in multivariate linear regression. For descriptive purposes, HbA_{1c} values were categorised into good control (<7%), poor control (> or = 7 & < or =10%) and very poor control (>10%). Data analysis was performed using Stata version 10. Statistical significance was established at a threshold of 95% ($p < 0.05$).

Results: More than half of participants in the study were females (60.8%/39.2%). The mean age of participants in the study was 56 years (sd 14.1). With regard to race, the proportion of blacks was more than three quarters of the sample (93.1%/2.4%/2.4%). Our results showed that HbA_{1c} level decreased with increasing age, ($p = 0.016$). These results also showed that for every 1 mmol/l increase in total cholesterol, there was a 0.178% increase in HbA_{1c}, ($p = 0.019$; 95% confidence interval (CI): 0.030 - 0.327), suggesting that higher cholesterol was associated with poorer HbA_{1c} control. In addition, for every 1 mmol/l increase in capillary glucose, the HbA_{1c} increased by 0.276%, ($p = 0.000$; CI: 0.230 - 0.322) while for every one unit increase in BMI, the HbA_{1c} reduced by 0.032%, ($p = 0.017$; CI: -0.057 to -0.006). **Conclusion:** These results suggest that patients with higher total cholesterol and patients with higher capillary glucose level are more likely to exhibit poorer HbA_{1c} control, whereas, older patients and patients with a higher BMI are more likely to have better HbA_{1c} control.

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Abbreviations

- DM: Diabetes Mellitus
- HbA_{1c}: Glycolated haemoglobin
- SMBG: Self Monitoring of blood glucose
- SEMDSA: Society of Endocrinology, Metabolism and Diabetes of South Africa
- Type 2 DM: Type 2 Diabetes Mellitus
- Type 1 DM: Type 1 Diabetes Mellitus
- ADA: American Diabetes Association
- IGT: Impaired Glucose Tolerance
- IFG: Impaired Fasting Glucose
- WHO: World Health Organization
- CVD: Cardiovascular disease
- DCCT: Diabetes Control and Complications trial
- UKPDS: United Kingdom Prospective Diabetes Study
- USD: United State Dollars
- OR: Odd Ratio
- p: probability
- sd: Standard deviation
- BMI: Body Mass Index
- Std Err.: Standard Error
- Coef.: Coefficient
- R^2 : R squared

Glossary of Terms

Diabetes Mellitus: is a metabolic disorder of complex aetiology characterised by chronic hyperglycaemia, resulting from defects in insulin secretion, insulin action, or both. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. The long-term effects of DM include progressive development of retinopathy, nephropathy, neuropathy, and features of autonomic dysfunction, including sexual dysfunction.[1]

Type 1 Diabetes Mellitus: is the most common form of diabetes among children, teenagers, or young adults, although it can occur at any age and lasts a lifetime. It is caused by the auto-immune destruction of β-cells in the pancreatic Islets of Langerhans, with an absolute loss of insulin production. The disease is usually characterised by an abrupt onset of symptoms, dependence on exogenous insulin to sustain life, and proneness to ketosis even in basal state.

Type 2 Diabetes Mellitus: In contrast to type 1 DM, patients with type 2 DM do not depend on exogenous insulin and are not prone to ketosis. However, they may require insulin for correction of fasting hyperglycaemia, and ketosis may develop under special circumstances such as severe stress precipitated by infections or trauma. Although the etiology of type 2 DM is unclear, this type has a strong genetic basis as evidenced by a frequent familial pattern of occurrence. In addition, heterogeneous aetiology like obesity, increased age, a sedentary lifestyle and low birth weight have been identified as being risk factors of type 2 DM.[1,2]

Glycosylated hemoglobin (HbA_{1c})*:* is a laboratory value that indicates glycaemic control over a three-month period. A number of studies have shown that the HbA_{1c} can predict the risk for the development and/or progression of diabetic complications in patients with type 1 and type 2 DM.[3,4] The HbA_{1c} is a valuable indicator of treatment effectiveness, but also useful when the glycaemic target is not being met after adjustment of diabetes therapy.[5]

Chapter 1- Background

Research has shown that tight glycaemic control in patients with Diabetes Mellitus (DM) is important to prevent or delay complications of the disease. There is a direct relationship between the glycosylated haemoglobin (HbA_{1c}) and capillary glucose. Based on this association, glycaemic control of diabetic patients can be assessed using either the HbA_{1c} or frequently measured blood glucose as part of self monitoring (self monitoring of blood glucose – SMBG) or both. Since blood glucose levels can fluctuate widely, even frequent home glucose testing may not accurately reflect the degree of success in controlling blood sugar. The HbA_{1c} test is a valuable measure of the overall effectiveness of blood glucose control over a period of time. [3,6,7] However, the consensus amongst diabetologists is that follow up of glycaemic control in diabetic patients is recommended,[8] because a single HbA_{1c} measure reflects the glucose control in diabetic patients for the three months preceding the measurement. [9,10]

In the diabetic clinic at Kalafong Hospital, the Society for Endocrinology, Metabolism and Diabetes of South Africa's (SEMDSA) guideline is followed. Measures of HbA_{1c} are taken at least twice a year for every diabetic patient seen at the clinic. However, one problem that clinicians face is the non-attendance of follow-up appointments by patients.[11] A previous study carried out in 2004 at Kalafong Hospital diabetic clinic showed a significant improvement in the mean of HbA_{1c} measure amongst both the intervention and the control groups, after the intervention of a physician education programme and a structured consultation schedule for patients. The mean HbA_{1c} post intervention was 8.5% and 9.15% respectively in the intervention and control groups, which is generally not as good as the cut-off value recommended by the SEMDSA.[12,13] Not all the factors associated with poor HbA_{1c} control are known, owing to the unavailability of studies on the subject.

Given that diabetes is a worldwide burden due to its prevalence and because of its complications and impact on the quality of life, it would be of utmost importance to improve the HbA_{1c} control in diabetic patients in South Africa and at Kalafong Hospital. [12]

The American Diabetes Association (ADA) classifies diabetes into five types:

- Type 1 Diabetes Mellitus or immune-mediated diabetes: account for only 5-10% of those with diabetes.
- Type 2 Diabetes Mellitus: accounts for 90-95% of those with diabetes.

- Other specific types of DM: for which causes include genetic defects affecting β-cell function and diseases of exocrine pancreas, endocrinopathies, drugs or chemical-induced diabetes, infections, uncommon forms of immune-mediated diabetes and other genetic syndromes associated with diabetes.
- Gestational DM: caused by insulin resistance and relative insulin deficiency associated with pregnancy. This type of diabetes occurs in approximately 3% to 5% of all pregnancies.
- Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).[2,14]

The goal of HbA_{1c} as recommended by the International Diabetes Federation (IDF) and American College of Endocrinology is below 6.5%, while that recommended by the ADA is less than or equal to 7%.[15,16,17]

The South African national guidelines and the SEMDSA's guidelines are in accordance with those of the ADA in terms of optimal values for HbA_{1c}[18,19] Consequently, good HbA_{1c} control was taken as a value of 7% and below in our study.

1.1 Literature Review

Diabetes Mellitus is the most common endocrine disorder affecting almost 6% of the world's population and therefore considered as a public health problem around the world. The total number of people with diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030.[20] More than 90% of these patients will have type 2 DM.[21] The number of people with diabetes is increasing due to population growth, aging, urbanization, an increasing prevalence of obesity and a sedentary lifestyles.[22,23]

The prevalence of diabetes is higher in men than women, but there are more women than men with diabetes, especially in developed countries.[24] The combined effect of a greater number of elderly women than men in most populations and the increasing prevalence of DM with age is the most likely explanation for this observation. The most important demographic change to DM prevalence across the world appears to be the increase in the proportion of people aged 65 years and above. The major concern is that this increase will occur in developed countries, with a growing incidence of type 2 DM. In developing countries those most frequently affected are in the middle, productive years of their lives, aged between 35 and 64. [20]

1.2 Diabetes in Africa

It has been found that the incidence of type 1 DM ranges from 1.9 to 7.0/100,000/yr. The prevalence of type 2 DM ranges from 0.3 to 17.9%.[1] At a more regional level, the prevalence in sub-Saharan Africa varies between 1.5% in Malawi and 3.6% in Botswana. [25] In South Africa the national prevalence is 3.4% and is expected to increase to 3.9% by 2025.[26] While many factors may contribute towards diabetic complications, non-adherence to diabetes treatment leads to poor glucose control and increases the risk of disease complications.[27]

1.3 Diabetes in South Africa

In 2007 the national prevalence of DM in adult South Africans aged 20 to 79 years was 4.5%. In the same age group 4.2% of all deaths were attributable to diabetes in males and 10.0% in females.[24] The prevalence of type 2 DM amongst different population groups varies extensively, ranging from 8% in urban blacks in Cape Town to 28.7% in a mixed population in Cape Town. Studies of the Indian population in Durban found a prevalence of 13%.[19] There is currently very little information on the prevalence of type 1 DM for South Africa.

1.4 Burden of Diabetes

Most people with diabetes will die or be disabled as a consequence of either macrovascular disease (atherosclerosis) or microvascular disease (retinopathy, nephropathy, and neuropathy) or both.[28] According to the World Health Organization (WHO), the number of deaths attributed annually to diabetes is around 3.2 million.[29] It is also estimated that 3.8 million men and women worldwide (6% of the total world mortality) died from diabetes-related causes in the year 2007. More than two-thirds of these deaths occurred in developing countries.[30] Shaw (2009)[23] estimates, that in developing countries, adult diabetes numbers are likely to increase by 69% from 2010 to 2030 for each age group with a doubling for the over-60-year age group, compared to 20% for developed countries with an increase of 38% only amongst the over 60s.

Diabetes has become one of the major causes of premature illness and death in most countries, mainly through the increased risk of cardiovascular disease (CVD). Studies such as the Diabetes Control and Complications Trial (DCCT),[6] the United Kingdom Prospective Diabetes Study (UKPDS),[5] and the Kumamoto study,[31] have shown that lowering levels of glycaemia could result in decreased rates of microvascular complications in type 1 and type 2 DM.

Glycaemic control, however, should not be considered the only goal of diabetes treatment. The focus of treatment should rather be on interventions that reduce morbidity and mortality.[32]

The financial burden of diabetes seems to be enormous, with the global health expenditure to treat and prevent diabetes and its complications expected to total at least USD 376 billion in 2010 and USD 490 billion in 2030. South Africa alone has spent about USD 865 million in 2010.[33] Considering these figures, as well as those cited earlier, it can be understood why DM should be considered a major public health problem.

1.5 Important findings from studies on diabetes worldwide

In addition to previously cited studies, other interventional studies on both type 1 and type 2 DM have demonstrated that tight glycaemic control significantly reduces the incidence and progression of macrovascular complications from hyperglycaemia in both type 1 and type 2 DM.[34,35,36]

Achieving glucose and HbA_{1c} goals remains one of the aims of diabetic therapy, but the bottom line should be a reduction in morbidity and mortality.

The importance of tight glycaemic control for protection against cardiovascular disease in diabetes has been established in the DCCT study for type 1 DM.[37]

The UKPDS which included 4,075 newly diagnosed patients with type 2 DM and who had HbA_{1c} levels of 7.5 to 10.7 %, demonstrated that improved glucose control decreased the frequency of microvascular complications (nephropathy and neuropathy).[7,38]

Selvin et al (2004)[39] showed in a meta-analysis of 10 prospective cohort studies that the relative risk for cardiovascular complications was 1.18 for each 1% increase in the HbA_{1c}. Which means, for every 1% increase in HbA_{1c} the risk of cardiovascular disease increases by 18%.

A meta-analysis of 16 randomised trials estimated that long-term intensive blood glucose control significantly reduced the odds of diabetic retinopathy (OR 0.49 [95% confidence interval 0.28-0.85], $p = 0.011$) and nephropathy progression (OR 0.34 [0.20-0.58], $p < 0.001$).[40]

Benoit et al (2005), in a longitudinal study, identified some factors including age, body mass index, total cholesterol, insurance status, disease duration and pharmacotherapy as predictors of glycaemic control type 2 DM.[41]

Motivation and aim of the study

Although it is known that a good glycaemic control improve microvascular outcomes, no local study has yet been undertaken to investigate the potential factors that influence poor or good blood glucose control. This research focused on the evaluation of blood glucose control as assessed by the HbA_{1c} level in diabetic patients. In addition, certain determinants which contributed to poor control at Kalafong Hospital were studied in a cohort of adults with DM during the year 2008. With this information, patients with high risk of disease morbidity could be identified; therefore, barriers that prevent these patients from meeting their goals could be explored in order to improve their health outcomes.

The aim of the study was to identify and assess the contribution of determinants of poor control at Kalafong Hospital in a cohort of adults with DM, for the year 2008.

The specific objectives of the study were to:

- Estimate HbA_{1c} control of patients seen at the diabetic clinics at Kalafong Hospital in 2008; and
- Assess any association between patient demographics or diabetes characteristics (i.e. type of DM, duration of disease and type of treatment) with HbA_{1c}.

Chapter 2

2.1 Research question and hypothesis

In the diabetic clinic at Kalafong Hospital, the level of HbA_{1c} for each patient was often assessed. It was done at their first and third visits to the clinic through the year. This amounts to an interval of six months between HbA_{1c} measurements. We hypothesised that there could be an association between the level of HbA_{1c} and the patients demographic characteristics, diabetes characteristics, clinical complications and type of treatment.

2.2 Methods

Study design: A retrospective cohort study that assessed the HbA_{1C} and its determinants using data from Kalafong Hospital for the year 2008.

Study population:

Participants in this study were patients seen in the diabetic clinic at Kalafong Hospital Pretoria during the year 2008.

Inclusion criteria: All diabetic patients aged 18 years and above, who had been registered in the 2008 dataset, who had come for at least one visit to the diabetic clinic and had at least one HbA_{1C} measurement, were included in the study.

Exclusion criteria: patients who did not meet the above criteria were excluded from the study.

Research procedures

Clinic staff of the Kalafong Hospital prospectively collected and captured data for the year 2008 in a Microsoft Access database. One member of the research team was responsible for exporting the data to Microsoft Excel. The principal researcher was responsible for exporting these data into STATA for cleaning and analysis.

Variables

Outcome variable: The outcome variable HbA_{1c} was obtained by computing the mean of the two HbA_{1c} values collected for each participant annually, and used as a continuous variable in the multivariate linear regression. For descriptive purposes HbA_{1c} values were categorised into three categories namely: good control (<7%); poor control (> or = 7 & < or =10%); and very poor control

(>10%). Guidelines [13] suggest 7% as cut-off for good control and we added >7 to 10 and > than 10 as arbitrary levels of poor control (poor control and what we thought was clinically very poor control).

Explanatory variables: The variable "age" which was initially captured as a continuous variable was also categorised in quartiles. This was done to avoid any user defined cut point for age categories.

The variable "level of education" was categorised into four groups using the classification system of the South African department of education [42], namely, "No education" (reference group), "general education" (from reception year to grade 9), "further education" (from grade 10 to grade 12) and "higher education" (undergraduate and postgraduate degrees).

Race was categorised into three groups namely, "black" (reference group), "white" and "other" (including Indian and Coloured) Indians and Coloured were put together because of their small number (2.4%). Type of diabetes was categorised into two groups with type 2 DM and type 1 DM being the reference group. Other explanatory variables, included: gender, body mass index, capillary glucose, insulin users, dietician referral, systolic blood pressure, diastolic blood pressure, low density lipoprotein, high density lipoprotein, total cholesterol, triglycerides, and serum creatinine.

2.3 Data management

Data Collection: The dataset for 2008 contained more variables than were needed for the study. As a result, important variables necessary for this study were selected based on the literature review. The transfer of Kalafong Hospital data from a Microsoft Access database to Stata was done using the statistical software "Stat Transfer version 7".

Data analysis: Data analysis was performed using Stata version 10. Analysis was performed in various steps.

- *Univariate analysis*: To evaluate associations between the explanatory variables and HbA_{1C}. In order to select variables for multivariate analysis a liberal p value of < 0.15 was used as not to exclude any important variables.

- *Multivariate analysis*: We used two approaches: 1) using variables that would be available at the first visit of the year and be able to predict average HbA_{1C} during the year and 2) variables that became available during the year that could be associated with HbA_{1c} (used as a continuous variable).

- Model building: We started model building with the full model, the first approach included variables with a p-value < 0.15 from the univariate analysis but also variables available at first visit at the diabetic clinic (model of prediction). The second approach included variables with a p-value < 0.15 from the univariate analysis which were collected during the year 2008 and had an association with the HbA_{1c} (model of association). We first chose a clinical approach in selecting models then we did a backward stepwise elimination. Variables with the highest p-values (p>0.05) were removed from each model one at a time and changes in R square were evaluated.

2.4 Ethical considerations

Considering that patients had already given their informed consent for routine clinical data to be used for research purposes, this procedure was not necessary. Ethical considerations were therefore limited to the following procedures:

a) To ensure confidentiality, all data collected on participants remained anonymous. No information was divulged to any third party outside the study team;
b) Ethical approval was sought and obtained from the main ethics committee of the University of Pretoria; and
c) Written permission to use patient data was obtained from the superintendent of the Kalafong Hospital.

Chapter 3 - Results

In the study 942 patients were seen in 2008. A total of 801 patients met the inclusion criteria and 141 were excluded from our study (because they did not have a measure of HbA_{1c}).

Table 1 shows the socio-demographic distribution of research participants. More than half of participants in the study were females. Furthermore, participants were mostly in the age group 56 years and above.

Table 1: Descriptive table of the study participants for the year 2008 (n and mean (sd)).

Variables	**N**	**2008**
Gender (F/M)	573/369	60.8%/39.2%
Age (years)	865	56.0 (14.1)
Body mass index	769	31.3 (6.6)
Systolic blood pressure supine (mm Hg)	741	141.7 (23)
Diastolic blood pressure supine (mm Hg)	741	83.5(11.5)
Random capillary glucose level (mmol/l)	883	9.8 (4.1)
Race (black/white/other)	896/23/23	93.1%/2.4%/2.4%
Insulin users	697	74.1%
Type of diabetes mellitus (type1/type2)	307/620	33.1%/66.9%

Below is the table 2 which shows laboratory tests performed on patients for the year 2008.

Table 2: Table of laboratory tests: means (sd)

Laboratory test	n	Mean	Stand. deviation
Total cholesterol (mmol/l)	615	4.9	1.5
Low-density lipoprotein (mmol/l)	596	3.1	2.9
High-density lipoprotein (mmol/l)	608	1.3	0.4
Triglycerides* (mmol/l)	604	1.4	1.1
Serum-creatinine* (µmol/l)	593	78	32
Capillary glucose (mmol/l)	883	7.0	3.7
Glycosylated haemoglobin (%)	801	8.8	2.4

*Triglycerides and serum creatinine were skewed variables, and log transformed to meet the normal distribution assumption. In the table above, the median and inter-quartile range were reported for these two measurements.

The capillary glucose test was the most performed test (883), whereas the serum creatinine test was performed the least.

From Table 3 it can be seen that the variables that were most associated with HbA_{1c} control category included "age" (p=0.001), "type of DM" (p=0.005) and "treatment category" (p=0.002).

Table 3: Table of HbA_{1c} control category by gender, age, level of education, type of DM and treatment category for the year 2008

		HbA_{1c} control in 2008		
		GC[1]	PC[2]	VPC[3]
Gender	*Female*	133 (26.6%)	222 (44.4%)	145 (29.0%)
	Male	90 (29.9%)	126 (41.9%)	85 (28.2%)
	P	**0.591**		
Age	*18-48 yrs*	42 (22.2%)	76 (40.2%)	71 (37.6%)
	49-58 yrs	49 (24.3%)	85 (42.3%)	68 (33.7%)
	59-66 yrs	39 (23.8%)	89 (55.3%)	36 (21.9%)
	67-93 yrs	71 (39.0%)	77 (42.0%)	35 (19.1%)
	P	**<0.001**		
Level of education	*None.*	22 (31.9%)	28 (40.6%)	19 (27.5%)
	General	97 (28.0%)	157 (45.4%)	92 (26.6%)
	Further	74 (26.6%)	116 (41.7%)	88 (31.7%)
	Higher	-----	3 (60.0%)	2 (40.0%)
	P	**0.608**		
Type of DM	*DM type 1*	66 (26.0%)	96 (37.8%)	92 (36.2%)
	DM type 2	155 (28.7%)	250 (46.2%)	136 (25.1%)

[1] GC: Good control of HbA_{1c} in diabetic patient with values < 7%.

[2] PC: Poor control of HbA_{1c} in diabetic patient with values between 7-10%.

[3] VPC: Very poor control of HbA_{1c} in diabetic patient with values> 10%.

	P	**0.005**		
Insulin user	*None*	176 (78.9%)	247 (70.9%)	172 (75.4%)
	Insulin	47 (21%)	101 (29%)	56 (24.4%)
	P	**0.097**		

Univariate analysis

In some analysis data were missing, for example 22% of patients had missing blood pressure values and 26% did not have measure for the variable "insulin user".

Table 4 shows univariate analysis of associations between categorical variables and HbA_{1c} as a continuous variable.

Table 4: Univariate analysis of association

HbA_{1c}	Coef.	Std. Err.	P	95%Conf.Interval	
Gender male *(vs female)*	-0.180	0.175	0.304	-0.524	0.164
White race *(vs black)*	0.223	0.700	0.750	-1.150	1.596
Other race *(vs black)*	-0.504	0.560	0.367	-1.600	0.592
General education *(vs not being educated)*	0.245	0.320	0.444	-0.383	0.873
Further education *(vs not being educated)*	0.440	0.326	0.181	-0.204	1.080
Higher education *(vs not being educated)*	1.470	1.124	0.192	-0.740	3.674
Dietician referral *(vs no dietetician referral)*	0.291	0.170	0.086	-0.040	0.625
Presence of Cardio vascular disease *(vs absence)*	-0.290	0.260	0.271	-0.800	0.224
Patient is snuff user or smoking *(vs patient who does not snuff or smoke)*	0.211	0.234	0.367	-0.248	0.670
Type 2 Diabetes Mellitus *(vs other type of Diabetes Mellitus)*	-0.612	0.181	0.001	-0.970	-0.255

Patients with >1 visit to the clinic *(vs patients with 1 visit to the clinic)*	0.500	0.520	0.339	-0.522	1.520
Age category 49-58 yrs *(vs age category 18-48 yrs)*	-0.252	0.240	0.289	-0.718	0.214
Age category 59-66 yrs *(vs age category 18-48 yrs)*	-0.730	0.250	0.004	-1.219	-0.237
Age category 67-93 yrs *(vs age category 18-48 yrs)*	-1.185	0.243	0.000	-1.663	-0.707
Insulin users *(vs no insulin treatment)*	0.755	0.193	0.000	0.376	1.133

In the univariate analysis with categorical variables, categories of age of patients, type of diabetes mellitus, dietician referral and treatment category were kept as significant variables at 15% probability. The variable “age categories” was tested as a whole, with a p-value of <0.001.

Table 5 shows continuous variables, body mass index, total cholesterol and capillary glucose which were kept as significant variables at 15% probability from the univariate analysis.

Table 5: Univariate analysis of continuous variable associations:

HbA_{1c}	**Coef.**	**Std. Err.**	**P**	**95%Conf.Interval**	
Number of years since diagnostic of DM (years)	0.012	0.010	0.245	-0.008	0.033
Body mass index	-0.025	0.013	0.053	-0.510	0.000
Blood pressure systolic (mm Hg)	-0.003	0.002	0.235	-0.008	0.002
Blood pressure diastolic (mm Hg)	-0.006	0.004	0.161	-0.014	0.002

Serum creatinine*(umol/l)	22.982	20.253	0.257	-16.797	62.761
Total cholesterol (mmol/l)	0.340	0.080	0.000	0.181	0.500
High-density lipoprotein (mmol/l)	0.326	0.241	0.177	-0.148	0.800
Triglycerides*(mmol/l)	-0.106	0.152	0.483	-0.405	0.192
Capillary glucose (mmol/l)	0.239	0.022	0.000	0.196	0.282

Multivariate analysis

The approach based on baseline variables:

The first approach was to evaluate which factors would be predictive of the HbA_{1c} (as a continuous variable) from the factors that were available at the beginning of the year. In Model 1, the variables age; type of DM and the body mass index were available at first visit at the clinic.

Model 1 as a full model with type of diabetes included in the model

HbA_{1c}	Coef.	Std. Err.	P	95% Conf. Interval	
49-58 yrs	0.022	0.250	0.931	-0.469	0.512
59-66 yrs	-0.513	0.265	0.053	-1.032	0.006
67-9 3yrs	-0.987	0.254	<0.001	-1.486	-0.488
Type of DM *(type 2 vs type 1)*	-0.493	0.201	0.014	-0.888	-0.098
Body mass index	-0.015	0.013	0.259	-0.042	0.011

The variables we included in the multivariate analysis were those with a p-value < 0.15 from the univariate analysis. Factors available at first visit at the diabetic clinic visit were included irrespective of their p-value. We selected the following variables: age, type of diabetes and body mass index. This selection was made to study variables that are better predictors of HbA_{1c} control.(We called it the model of prediction.)

This first multivariate model included observations of 662 patients. All variables taken collectively were significant in this model ($p < 0.001$). This p-value indicates that the independent variables reliably predict the dependent variable.The explained variation (R^2) was 0.052, meaning that the variables within the model could only explain 5% of the variation in HbA_{1c} control. Even though the age categories 49-58 years and 59-66 years were not significant in this model, the Wald test showed that the variable "age of patient" taken as a whole was significant ($p < 0.001$). HbA_{1c} control in the age group 49-58 years was worse than the baseline category (18-48 years old), whereas it was better for the third and fourth age groups (>48 years). However, this difference was not statistically significant ($p = 0.931$). The variable "type of DM" was statistically significant in the model ($p = 0.014$, CI [-0.88,-0.09]). HbA_{1c} was lower by a multiplier of 0.49 in type 2 DM compared to HbA_{1c} in type 1 DM. Similarly, for every one unit increase in BMI, HbA_{1c} reduces by 0.015% when other variables in the model are kept constant. But this finding was not significant at the 5% level (p = 0.259).

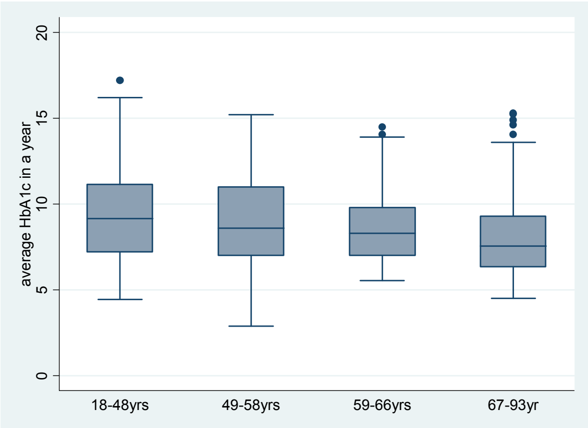

Figure 1: Boxplot comparing HbA_{1c} control across age categories

There was a significant trend ($p<0.05$) to lower HbA_{1c} over age categories adjusted for type of DM and BMI. The older a patient gets, the better his HbA_{1c} control becomes. Based on its p-value, we decided to remove the variable "BMI" from Model 1.

The test for trend of HbA_{1c} across age categories was performed and the p-value was significant at a 5% level. The older a patient gets, the better his HbA_{1c} control becomes ($F(1, 656) = 10.03$; p= 0.0016).

Model 2: The model without the variable " BMI"

HbA_{1c}	**Coef.**	**Std. Err.**	**P**	**95% Conf. Interval**	
49-58 yrs	-0.189	0.239	0.430	-0.660	0.281
59-66 yrs	-0.577	0.255	0.024	-1.080	-0.076
67-93 yrs	-1.080	0.247	0.000	-1.564	-0.596
Type of DM *(type 2 DM vs type 1 DM)*	-0.492	0.193	0.011	-0.870	-0.114

After removing BMI from Model 1, R^2 decreased from 0.0520 to 0.0448. We could not compare this nested model with the full model considered as the reference model since the number of observations changed (due to BMI being missing in some individuals).

As we were unsure about whether the variable “type of DM” was always classified correctly we examined a simpler classification scheme, namely whether patients were using insulin or not.

Model 3: Model with insulin users included in the model

HbA_{1c}	**Coef.**	**Std. Err.**	**P**	**95% Conf. Interval**	
49-58 yrs	0.038	0.245	0.878	-0.444	0.520
59-66 yrs	-0.590	0.257	0.022	-1.095	-0.086
67-93 yrs	-0.972	0.250	<0.001	-1.461	-0.483
Insulin users	0.674	0.203	0.001	0.274	1.073
Body mass index	-0.019	0.013	0.142	-0450	0.006

This third multivariate model contained observations of 664 diabetic patients. The combination of all the variables included in this model was significant (p< 0.001). The variable “BMI” was not significant at the 5% level (p=0.142); therefore, we decided to drop it from the model. Even though the age category 49-58 years was not significant in this model, the Wald test showed that the categories of age of patient tested as a whole was significant (p= 0.000). The R^2 was 0.0577, which means the variables within the model could only explain 5.7% of the variation in HbA_{1c} control. The patients on insulin treatment were 0.674 times more likely to have a better HbA_{1c} than patients not on insulin treatment (p=0.001). There was a statistically significant decrease in HbA_{1c} by a multiplier of 0.59 in the age group 59-66 years (p=0.022) and by a multiplier of 0.972 in the age group 67-93 years (p<0.001) compared to the reference age category, suggesting that HbA_{1c} tends to improve with advancing age.

Checking for a trend between age categories and insulin users

There was a significant trend between age categories and insulin users (p= 0.001). This trend means that as patients on insulin grew older, their HbA_{1c} improved.

Model 4: Model without "BMI"

HbA_{1c}	Coef.	Std. Err.	P	95% Conf. Interval	
49-58 yrs	-0.178	0.236	0.450	-0.640	0.285
59-66 yrs	-0.647	0.248	0.009	-1.134	-0.160
67-93 yrs	-1.060	0.242	0.000	-1.537	-0.585
Insulin users	0.632	0.198	0.001	0.243	1.020

The variables age and insulin users were kept in the model based on their p-values. The age categories were tested as a whole. ($p < 0.001$). R^2 decreased from 0.0577 to 0.0478. This model could only explain 4.7% of the variation in HbA_{1c}. The patients on insulin treatment was 0.632 times more likely than that of patients not on insulin treatment to have a better HbA_{1c}, and this was statistically significant (p=0.001).

The approach based on values obtained during the year:

A second approach that we followed was to determine associations of variables that were collected during the year 2008 with the HbA_{1c}.

Model 5: Model including total cholesterol, dietician referral and capillary glucose

HbA_{1c}	**Coef.**	**Std. Err.**	**P**	**95% Conf. Interval**	
Age 49-58 yrs	0.052	0.239	0.829	-0.418	0.521
Age 59-66 yrs	-0.416	0.242	0.086	-0.892	0.060
Age 67-93 yrs	-0.745	0.236	0.002	-1.209	-0.281
Insulin users	0.255	0.195	0.191	-0.128	0.638
Dietician referral	0.034	0.173	0.845	0.306	0.373
Body mass index	-0.030	0.013	0.020	-0.056	-0.005
Total cholesterol	0.189	0.075	0.012	0.041	0.338
Capillary glucose	0.269	0.024	<0.001	0.223	0.316

For the model of association, we were interested in studying the variables that were associated with the HbA_{1c} from the univariate analysis. The variables "age", "dietician referral", "insulin users", "body mass index", "total cholesterol" and "capillary glucose" were eligible for inclusion in the multivariable model based on their p-value < 0.15. (refer table 4)

The R^2 for this model was 0.277, which means 27.7% of the variation in the HbA_{1c} was explained by this model (mostly by the capillary glucose). The variable "dietician referral" had the highest p-value (p=0.845) and was removed from the model. Total cholesterol, capillary glucose, body mass index and the categories of age variable were significantly associated with the HbA_{1c}.

These results also show that for every 1 mmol/l increase in total cholesterol, there was a 0.189% increase in HbA_{1c} (taken as a continuous outcome) if other variables in the model were kept constant, suggesting that higher cholesterol was associated with poorer HbA_{1c} control. Similarly, it was found that for every 1 mmol/l increase in capillary glucose, the HbA_{1c} increased by 0.269%, assuming that other variables in the model remained constant.

Model 6: Model without variable "dietician referral"

HbA_{1c}	**Coef.**	**Std. Err.**	**P**	**95% Conf. Interval**	
Age 49-58 yrs	0.054	0.240	0.822	-0.415	0.522
Age 59-66 yrs	-0.417	0.242	0.085	-0.893	0.058
Age 67-93 yrs	-0.743	0.236	0.002	-1.206	-0.280
Insulin users	0.255	0.195	0.190	-0.127	0.638
Body mass index	-0.030	0.013	0.019	-0.056	-0.005
Total cholesterol	0.190	0.075	0.012	0.042	0.338
Capillary glucose	0.270	0.024	<0.001	0.223	0.316

Considering the high p-value (p= 0.190) of the variable "insulin users", we also decided to remove it from the model .

Model 7: Model considered as the final model without “insulin users”

HbA_{1c}	Coef.	Std. Err.	P	95% Conf. Interval	
Age 49-58 yrs	0.016	0.239	0.946	-0.454	0.487
Age 59-66 yrs	-0.439	0.243	0.071	-0.917	0.038
Age 67-93 yrs	-0.785	0.237	0.001	-1.250	-0.320
Body mass index	-0.032	0.013	0.017	-0.057	-0.006
Total cholesterol	0.178	0.075	0.019	0.030	0.327
Capillary glucose	0.276	0.024	<0.001	0.230	0.322

The R^2 was 0.2767, which means 27% of the variation in HbA_{1c} control was explained by this model (mostly explained by the capillary glucose). The final model comprising all different variables predicts HbA_{1c} significantly, ($p<0.001$). And individually each variable in the model was statistically significant. From the table above it can be seen that for every 1 mmol/l increase in total cholesterol, there was a 0.178% increase in HbA_{1c}, suggesting that higher cholesterol was associated with higher HbA_{1c}. Similarly for every 1 mmol/l increase in capillary glucose, the HbA_{1c} increased by 0.276%, while for every one unit increase in BMI, the HbA_{1c} reduced by 0.032% ($p=0.017$). HbA_{1c} decreased by a multiplier of 0.785 in the age category (59-66 years) compared to the reference age category, and this was statistically significant ($p=0.001$); suggesting that older patients controlled better than younger ones.

Figure 2 shows that there is a linear trend between BMI and HbA_{1c}, the higher the BMI, the lower is the HbA_{1c}. However there is a huge variation around the regression line.

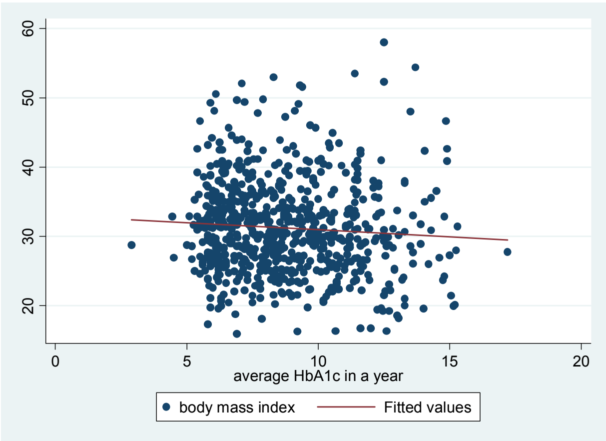

Figure 2: Scatterplot correlating BMI and HbA_{1c} (correlation for BMI= -0.074 and p= 0.05).

Because the average capillary glucose explains most of the variation of the HbA_{1c} we examined this with a scatterplot.

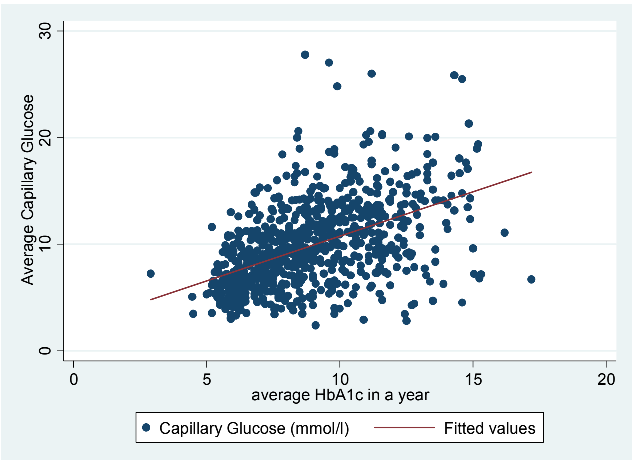

Figure 3. Scatterplot correlating capillary glucose and HbA_{1c} (correlation for capillary glucose= 0.363 and p<0.001).

Figure 3 shows a large variation around the regression line. In general the higher the glucose the higher the HbA_{1c} will be. However for individual values of capillary glucose the ability to predict HbA_{1c} is poor (especially at the higher range of HbA_{1c}).

Below is the summary table of all four models as described above.

Table 6: Summary of all four models

Variables	***Model 1***	***P***	***Model 2***	***P***	***Model 3***	***P***	***Model 4***	***P***
Age 49-58 yrs	0.022(0.250)	0.931	-0.189(0.239)	0.430	0.038(0.247)	0.927	-0.208(0.237)	0.379
Age 59-66 yrs	-0.513(0.264)	0.053	-0.577(0.255)	0.024	-0.590(0.259)	0.015	-0.705(0.250)	0.005
Age 67-93 yrs	-0.987(0.254)	<0.001	-1.080(0.247)	<0.001	-0.972(0.250)	<0.001	-1.161(0.243)	<0.001
Type of DM (type 1 vs type 2 DM)	-0.493(0.201)	0.014	-0.492(0.193)	0.011				
Body mass index	-0.015(0.013)	0.259			-0.019(0.013)	0.144		
Insulin users patients					0.674(0.203)	0.001	0.632(0.198)	0.001
R^2	0.0520		0.0448		0.0577		0.0478	
Prob>F	<0.001		<0.001		<0.001		<0.001	

The first four models are all significant in their their ability to predict HbA_{1c}. ($p<0.001$).

Model 3 has the highest R^2 and is therefore considered as better than models 1, 2 and 4.

Below in table 7 is a summary of models 5-6-7 seen above.

Table 7: Models 5-6-7:

Variables	***Model 5***	***P***	***Model 6***	***P***	***Model 7***	***P***
Age 49-58 yrs	0.052 (0.240)	0.829	0.054 (0.239)	0.822	0.164 (0.239)	0.946
Age 59-66 yrs	-0.416 (0.242)	0.086	-0.417 (0.242)	0.085	-0.439 (0.243)	0.071
Age 67-93 yrs	-0.745 (0.236)	0.002	-0.743 (0.236)	0.002	-0.785 (0.237)	0.001
Body mass index	-0.030 (0.013)	0.020	-0.030 (0.013)	0.019	-0.032 (0.013)	0.017
Insulin users patients	0.255 (0.195)	0.191	0.255 (0.195)	0.190		
Dietician referral: patient with >1 visit	0.034 (0.173)	0.845				
Total cholesterol	0.189 (0.075)	0.012	0.190 (0.075)	0.012	0.178 (0.075)	0.019
Capillary glucose	0.270 (0.024)	<0.001	0.270 (0.024)	<0.001	0.276 (0.024)	<0.001
R^2	0.2770		0.2769		0.2767	
Prob>F	<0.001		<0.001		<0.001	

As can be seen in table 6, model 5 has the highest R^2. All the models are significant in their ability to predict HbA_{1c} ($p<0.001$).

Regression diagnostics:

- Checking for outliers

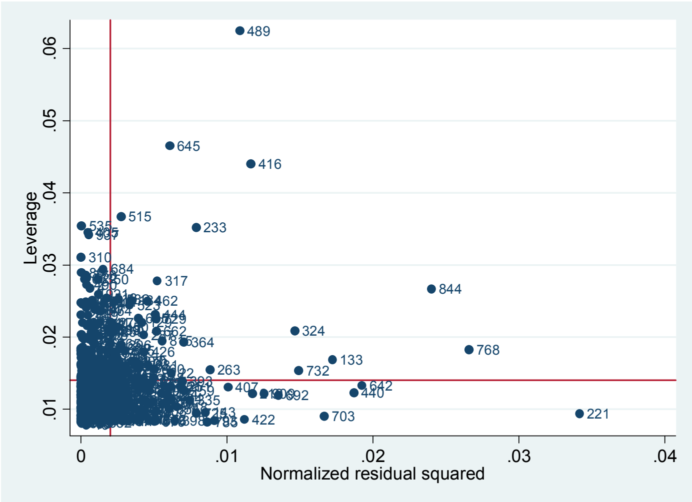

Figure 4: Residuals versus fitted values plot

The output shown in Figure 4 identifies some individuals with high leverage (outliers) that could have contributed towards a poorer fitting model.

Model 8: Model without the outliers

HbA_{1c}	**Coef.**	**Std. Err.**	**P**	**95% Conf. Interval**	
Age 49-58 yrs	-0.018	0.238	0.939	-0.486	0.449
Age 59-66 yrs	-0.432	0.240	0.074	-0.905	0.042
Age 67-93 yrs	-0.769	0.234	0.001	-1.230	-0.308
Body mass index	-0.046	0.014	0.001	-0.072	-0.019
Total cholesterol	0.174	0.075	0.020	0.027	0.321
Capillary glucose	0.279	0.024	<0.001	0.232	0.327

In Model 8, the tendency towards a decrease in HbA_{1c} with increasing age can still be seen, but now the difference is only significant for the age group 67-93 years. The regression coefficient for BMI is negative, meaning that an increase in BMI results in a decrease in HbA_{1c} (p = 0.001). Both the total cholesterol and capillary glucose have positive regression coefficients, with statistically significant p-values and confidence intervals. Thus an increase in total cholesterol and / or capillary glucose is associated with an increase in HbA_{1c}.

- Checking for heteroscedasticity: The Breusch-Pagan / Cook-Weisberg test for heteroscedasticity showed a p-value of 0.115. We thus failed to reject the null hypothesis for homoscedasticity, which states that the variance of errors remains constant.

The output shown in Figure 5 omits individuals with high leverage.

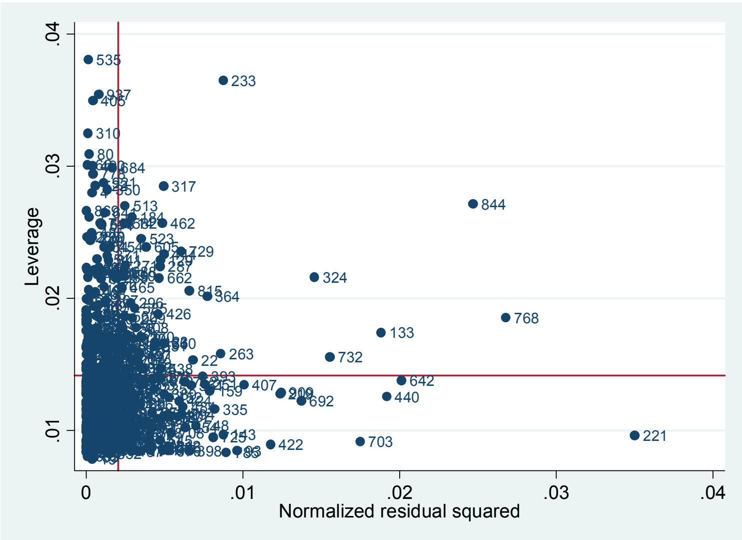

Figure 5: Residuals versus fitted values plot

Since the graph of residuals versus fitted (or actual) values is highly suggestive of heteroscedasticity, we decided to determine robust estimates on the model without the outliers.

- Correcting the heteroscedasticity: The option HC3 used is suitable for small samples.

Heteroscedasticity is something that we need to routinely examine in each model, since its presence will produce results that can lead to errors in inferences with hypothesis testing. The null hypothesis for the test of heteroscedasticity states that the variance of errors is constant. If the null hypothesis is rejected (p<0.05), as in the above model, the variance of errors cannot be considered to be constant.

In other words, there is a risk of making erroneous inferences from our hypothesis tests. When heteroscedasticity is severe and not corrected, this may result in biased standard errors and *p* values. The direction of the bias depends on the pattern of heteroscedasticity, which may be too large or too small.

Model 9: Model with robust standard error estimates

HbA_{1c}	Coef.	Robust HC3 Std. Err.	P	95% Conf. Interval	
Age 49-58 yrs	-0.018	0.265	0.945	-0.538	0.502
Age 59-66 yrs	-0.432	0.230	0.062	-0.885	0.022
Age 67-93 yrs	-0.769	0.233	0.001	-1.227	-0.310
Body mass index	-0.046	0.013	0.001	-0.072	-0.019
Total cholesterol	0.174	0.077	0.023	0.024	0.325
Capillary glucose	0.279	0.027	<0.001	0.227	0.332

The coefficients of the variables remained the same but the standard errors and confidence intervals were wider. The correction for heteroscedasticity is a method suggested by Long and Ervin (2000) in stata package to correct for heteroscedasticity whereby standard errors become more robust.[43]

Chapter 4

4.1 Discussion of results

Diabetic patients need regular follow up of their HbA_{1c} value, which leads to therapeutic adjustments to their treatment regimen in order to achieve better control of blood glucose levels. Blood glucose that are too high (hyperglycaemia) or too low (hypoglycaemia) increase the risk of disease morbidity.

The main results of the research can be summarised as follows:

Based on the 1st approach with factors available at the beginning of the year (model of prediction), BMI was found to be significantly associated with HbA_{1c} control.

While in the 2nd approach, among variables collected during the year 2008 (model of association), total cholesterol and capillary glucose predicted better the HbA_{1c}.

An increase in the BMI predicted the HbA_{1c} better. There have been some studies, however, that showed better levels of HbA_{1c} with higher BMI. One such study was reported by Acharya (2008) in young male adults aged between 15 to 25 years with type 1 DM. [44] Since HbA_{1c} control was related to the type of DM, a possible explanation would be that older patients were more likely to have type 2 DM and consequently get a poor control. The heavier is a patient, the more likely he will have a type 2 DM and a poor glucose control.[45, 46]

The fact that a significant association between HbA_{1c} and capillary glucose was found in our study is quite logical. Capillary glucose levels are used for daily adjustments of therapy in the follow up of diabetic patients. Most studies have found an association between HbA_{1c} and capillary glucose, and recently some authors have described a new formula, according to which the average blood glucose could be estimated from HbA_{1c}[47,48]

Regarding the correlation that was found between total cholesterol and HbA_{1c}, Khan et al. (2007) [49] had similar findings, and concluded that HbA_{1c} can provide information about the circulating lipid profile in addition to its primary role in monitoring long-term glycaemic control.

We also showed that one of the diabetic characteristic "insulin users" was not a significant predictor of HbA_{1c}, in spite of the fact that insulin users constituted almost three-quarters of the study sample. This finding does not agree with most studies consulted. A possible explanation could be in the way the variable “insulin user” was generated: patients on oral treatment, combined oral and insulin treatment and no treatment were all categorized as “non-insulin users”. We only considered as insulin users patients who were exclusively on insulin treatment. Subsequent diabetic studies involving the variable “non-insulin users” would need to analyse the different type of treatment separately.

The overwhelming evidence from the literature shows that there is a positive association between insulin intake and improvement of HbA_{1c}. It is logical to expect a correlation between these two variables because the goal of monitoring diabetic patients through the HbA_{1c} marker is to ensure that treatment leads to improved blood glucose. Dandona et al. (2008) found that the use of glucose lowering drugs prevented macrovascular complications in type 2 diabetes in addition to the control of co-morbid conditions (hypertension and dyslipidemia) associated with this disease.[50] There were no available studies from South Africa using a similar study population with which to compare our results.

No studies were found in the existing literature describing any prediction of HbA_{1c} control based on type of DM. It is worth noting that most studies consulted looked at samples in which participants were either type1 diabetics or type 2 diabetic patients and only very few studies have investigated samples with both type 1 and type 2 diabetic patients as we did in our study.

The finding that sex was not a significant demographic predictor of HbA_{1c} was similar to the findings from most of the studies consulted such as Chan et al. (2000).[51] In South Africa, a study conducted by Erasmus et al. (1999) also found that sex was not significantly associated with HbA_{1c}.[52] However, both studies were carried out in patients with type 2 DM only.

Finally with regards to demographic characteristics, race was not a significant predictor of HbA_{1c} control even though black patients appeared to have higher HbA_{1c} than patients of other races. Some studies have shown that HbA_{1c} varies with race and ethnicity, poorer glycaemic control are common among black patients.[53,54] It is worth noting that, in our study, the proportion of black patients was much higher than all other racial groups put together. This could have potentially prevented the detection of any differences in HbA_{1c} based on race group.

The findings that “age” was a significant predictor of HbA_{1c} agrees with the results of Gilliland et al. (2002), which showed that HbA_{1c} level decreased with increasing age. However, an important observation in the above-mentioned study was that there could be a possible survival bias, whereby older patients with poorly controlled diabetes died at younger ages. [55,56]

It is important to mention that missing values were not imputed and non linear relationship were not investigated. It would have also been useful to do a logistic regression to determine factors associated with poor control versus good control in order to guide the clinician as to who should receive more attention.

Conclusion and Recommendation

The main findings are that baseline variables only explain very little of the variation in HbA_{1c}. Of the other variables captured during the year the major contributor to the R^2 was capillary glucose (as can be expected). Thus there does not appear to be major predictors of HbA_{1c} besides capillary glucose and the scatter and diagnostic plots suggest that on an individual level capillary glucose poorly predicts whether HbA_{1c} is in the poor or excellent range. The measurement of HbA_{1c} therefore, is crucial in determining which patients need more attention.

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ANNEXURE

1. Informed consent

Ingeligde toestemming vir versameling en gebruik van roetine kliniese pasient inligting.

Hiermee verleen ek (volle naam en van) ____________________, Hospitaal nommer ____________ toestemming dat gegewens ingewin rakende ondersoeke en uitkomste van behandeling wat tydens my behandeling in die departement Interne geneeskunde, Kalafong Hospitaal verkry word, vir mediese opleiding en/of navorsing in die Fakulteit van Gesondheidswetenskappe , Universiteit van Pretoria, gebruik mag word. Sodanige toestemming word verleen met dien verstande dat my identiteit onder alle omstandighede anoniem sal bly en dat my persoonlike inligting streng vertroulik hanteer sal word.

Pasiënt Handtekening:___________________ Datum: _______________

Nasionale Identiteits nommer: ___________________

Getuie Handtekening:___________________ Datum: _______________

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Informed consent to the collection and use of routine clinical information.

I ___________________ (full name and surname), Hospital number____________hereby give consent that information pertaining to evaluations, tests and outcomes of my treatment in the department of Internal medicine, Kalafong hospital, may be used for training and research in the Faculty of Health Sciences, University of Pretoria. This consent is given with the understanding that my identity will under all circumstances be kept anonymous and that all my personal information will be managed strictly confidential.

Patient Signature: ____________________ Date: ________________

National ID number: ____________________

Witness Signature: ____________________ Date: ________________

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

* FWA 00002567, Approved dd 22 May 2002 and Expires 13 Jan 2012.
* IRB 0000 2235 IORG0001762 Approved dd Jan 2006 and Expires 13 Aug 2011.

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Faculty of Health Sciences Research Ethics Committee
Fakulteit Gesondheidswetenskappe Navorsingsetiekkomitee

DATE: 26/02/2010

PROTOCOL NO.	**137/2007**
OLD TITLE	~~Identification Of Predictors Of Long-Term Glucose Control In A Cohort Of Adult Patients With Diabetes Mellitus At Kalafong Hospital~~
NEW TITLE	Identification of predictors of glucose control in a cohort of adult patients with diabetes mellitus at Kalafong Hospital.
INVESTIGATOR	**Person:** Dr TK Mutembe **Phone:**012-3426536 **Fax:** 012-3420160 **E-Mail:** tessy.dr@gmail.com **Cell:**0782155212
DEPARTMENT	School of Health Systems and Public Health; University of Pretoria
STUDY DEGREE	M.Sc (Clin Epi)
SUPERVISOR	Prof P Rheeder
SPONSOR	None.
MEETING DATE	31/10/2007

The Protocol Amendment was approved on 24/02/2010 by a properly constituted meeting of the Ethics Committee.

Members of the Research Ethics Committee:

Prof VOL Karusseit	MBChB; MFGP(SA); MMed(Chir); FCS(SA) - Surgeon
Prof JA Ker	MBChB; MMed(Int); MD – Vice-Dean (ex officio)
Dr NK Likibi	MBBCh – Representing Gauteng Department of Health)
Prof TS Marcus	(female) BSc(LSE), PhD (University of Lodz, Poland) – Social scientist
Dr MP Mathebula	Deputy CEO: Steve Biko Academic Hospital
Prof A Nienaber	(female) BA(Hons)(Wits); LLB; LLM(UP); PhD; Dipl.Datametrics(UNISA) – Legal advisor
Mrs MC Nzeku	(female) BSc(NUL); MSc(Biochem)(UCL, UK) – Community representative
Snr Sr J Phatoli	(female) BCur(Eet.A); BTec(Oncology Nursing Science) – Nursing representative
Dr L Schoeman	(female) B.Pharm, BA(Hons)(Psych), PhD – Chairperson: Subcommittee for students' research
Mr Y Sikweyiya	MPH; SARETI Fellowship in Research Ethics; SARETI ERCTP; BSc(Health Promotion) Postgraduate Dip (Health Promotion) – Community representative
Dr R Sommers	(female) MBChB; MMed(Int); MPharmMed – **Deputy Chairperson**
Prof TJP Swart	BChD, MSc (Odont), MChD (Oral Path), PGCHE – School of Dentistry representative
Prof C W van Staden	MBChB; MMed (Psych); MD; FCPsych; FTCL; UPLM - **Chairperson**

Sommers

DR R SOMMERS; MBChB; MMed(Int); MPharmMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

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Permission to access Records / Files / Data base at Kalafong Hospital

TO: Dr L M PHALATSI...........
Chief Executive Officer/Information Officer
Kalafong Hospital

FROM: Tessy Karimba Mutembe
Investigator
618 Verdi Street, Constantia Park, Pretoria

Re: Permission to do research at Kalafong Hospital

TITLE OF STUDY: Identification of predictors of long-term glucose control in a cohort of adult patients with diabetes mellitus at Kalafong Hospital.

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

I am a student at the Department of S.H.S.P.H. at the University of Pretoria. I am Working with **Prof Paul RHEEDER**. I herewith request permission on behalf of all of us to conduct a study on the above topic at your Diabetes Clinic. This study involves access to patient records.

The researchers request access to the following information: patient files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Signature of the Principal Investigator

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Permission to do the research study at this institution / facility and to access the information as requested is hereby approved.

Title and name of Chief Executive Officer: Dr L.M. PHALATSI

Name of institution: KALAFONG HOSP

Signature: [signature]

Date: 25/9/07

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INITIAL CONSENT BY DEPARTMENTAL HEAD

I JH Retief head of Internal Medicine department of Kalafong hospital in consultation with the Chief Executive Officer / Superintendent of this Hospital grant permission to submit an application to conduct a clinical trial/evaluation to the Chairperson (s) of the relevant Ethics, Research and Therapeutic Committees of this Hospital.

The officer conducting the trial/evaluation will be ______

Designation / Rank MSc. Clin. Epi Student

THE HEAD OF THE DEPARTMENT MUST SIGN HERE!

HEAD OF DEPARTMENT			DATE		
Signature	Initial(s)	Surname	Day	Month	Year
[signature]	JH	Retief	20	09	2007

THE APPLICANT MUST SIGN HERE

	TRIALIST INVESTIGATOR			DATE		
	Signature	Initial(s)	Surname	Day	Month	Year
1.	[signature]	T.K.	Etty Kukembe	20	09	2007
2.	[signature]	DC	van Zyl	20	09	2007

THE APPLICANT THAT APPLY FOR THIS STUDY MUST SEE TO IT THAT THE SUPERINTENDENT / C.E.O. OF THE HOSPITAL WHERE THE STUDY WILL BE DONE, SIGN HERE BEFORE THE ETHICAL COMMITTEE RECEIVE THIS APPLICATION FORM.

APPROVAL BY HOSPITAL CHIEF EXECUTIVE OFFICER:

I L.M. PHALATSE Chief ~~Executive Officer /~~ superintendent of KALAFONG Hospital, hereby agree that this trial / evaluation be conducted in the Internal Medicine Department of this hospital.

The officer conducting the trial will be : ______

The officer controlling supplies will be: ______

HOSPITAL C.E.O. / Superintendent			DATE		
Signature	Initial(s)	Surname	Day	Month	Year
[signature]	L.M.	PHALATSI	25th	Sept	2007