GLYCAEMIC CONTROL DURING SURGERY IN DIABETIC PATIENTS AT KENYATTA NATIONAL HOSPITAL

A dissertation submitted in part fulfillment of the requirement for the Degree of Masters of Medicine in Anaesthesia, University of Nairobi.

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DECLARATION

This thesis report is my original work and to my knowledge has not been presented for any award in any university.

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DEDICATION

To my parents, my sister Esther, my two brothers Patrick and Henry, and my best friend, Fred, who have all inspired me greatly and offered their endless support.

LIST OF ABBREVIATIONS

HbA1c : Glycated haemoglobin A1c

CABG : Coronary artery bypass grafting

ICU : Intensive Care Unit

WHO : World Health Organization

Hb : Haemoglobin

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ABSTRACT

Objective – To study the patterns of glycaemic control in diabetic patients undergoing surgery in Kenyatta National Hospital.

Design – A cross sectional, prospective study.

Setting – Kenyatta National Hospital operating rooms

Subjects – Diabetic patients undergoing emergency or elective surgery

Methods – Over five months, November 2005 to March 2006. Glycated haemoglobin was determined as well as blood sugar levels pre-operatively, at half hourly or hourly intervals intra-operatively and at reversal from anaesthesia. The vital signs of the patients at reversal were noted.

Results – The mean HbA1c was 4.17%, and the mean pre-operative blood sugar was 8.7 mmol/l, and the mean intra-operative blood sugar was 9.14 mmol/l. There was no statistically significant correlation between HbA1c and age, sex and duration of diabetes, but there was statistically significant correlation between HbA1c and random blood sugar taken at interval intra-operatively. Most of the patients managed on diet, did not receive insulin intra-operatively. The mean total amount of insulin used intra-operatively was 6.7 units. 6.2% of patients reversed poorly from anaesthesia and their mean blood sugar was 10.1 mmol/l. 14.8% of patients who reversed poorly had HbA1c > 6.4%. 4.4 % of patients were admitted into the intensive care unit due to respiratory distress and septic shock.

Conclusion – Pre-operative glycaemic control was optimal and patients managed on diet had the best control and did not require insulin during surgery. Glycaemic control (mean blood sugar < 10 mmol/l) was achieved intra-operatively through use of insulin and this was not associated with immediate post-operative complications.

INTRODUCTION

Diabetes mellitus is a challenge in the medical field, especially continuous glycaemic control that aims to avoid the associated complications and resultant morbidity and mortality.

Diabetes mellitus describes a metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

Diabetes mellitus as defined by the World Health Organisation (WHO) is fasting venous plasma glucose concentration $\geq$ 7.0 mmol/l on at least two separate occasions; or venous plasma glucose concentration of $\geq$ 11.1 mmol/l at 2 hours following ingestion of 75 g of glucose and on at least one other occasion during the 2 hour test.

Measurement of glycated haemoglobin (HbA1c) is used to determine average glycaemic control over an 8 to 12 week period. The glycated haemoglobin level has been linked to development of microvascular complications such as neuropathy, nephropathy and retinopathy. In certain cases the HbA1c level gives equal or almost equal sensitivity and specificity to glucose measurement, however it is not available in many parts of the world.

The acute metabolic complications of diabetes include diabetic ketoacidosis, and hyperosmolar non ketotic diabetic coma. Diabetic ketoacidosis is caused by cessation of insulin intake, or infection, surgical or emotional stress despite continued insulin therapy and is characterized by severe hyperglycaemia with activation of the ketogenic process that initiates the development of metabolic acidosis.
In hyperosmolar coma, there is profound dehydration resulting from a sustained hyperglycaemic diuresis in the elderly diabetic patient who is unable to balance fluid intake with the urinary fluid losses, and is not associated with ketoacidosis.

Diabetes mellitus also results in progressive development of specific long term complications that include retinopathy with potential blindness; nephropathy that may lead to renal failure; neuropathy with risk of foot ulcers, amputation, Charcot joints, features of autonomic dysfunction; and circulatory abnormalities especially atherosclerosis predisposing to coronary artery disease and stroke.

Diabetes thus potentially increases the possibility of surgery in affected individuals and also is a major risk factor for post-operative surgical and anaesthetic complications, but meticulous control substantially reduces this risk.

The stress response to surgery further worsens hyperglycaemia. Lack of monitoring and glycaemic control during surgery can result in hyperglycaemia which causes delayed emergence from anaesthesia especially if the patient develops ketotic coma. The hyperglycaemia also results in delayed wound healing and prolonged hospital stay.

The reverse can occur. Lack of monitoring may fail to detect hypoglycaemia, which is also almost impossible to diagnose clinically in the unconscious patient, and is a serious hazard, that can be the cause of delayed awakening and even death.

Thus aggressive blood sugar normalization with frequent monitoring can improve outcome following surgery and in critical illness.

Intra-operative insulin infusion via pump, or bolus, or glucose-insulin-potassium infusion can be administered with the aim of achieving a target of 6.67 – 10 mmol/l.

The blood sugar can be monitored half hourly or hourly and adjustments to insulin made depending on the blood glucose level obtained.

LITERATURE REVIEW

Patients with diabetes undergo surgical procedures at a higher rate than do non-diabetic patients[1] for diabetic and non-diabetic related illnesses. Due to a combination of angiopathy, neuropathy, hyperglycaemia and impaired immune response, diabetic patients are predisposed to infections including foot infection, skin infections, soft tissue infections (necrotizing fasciitis, abscesses, hand infections), urinary tract infections, respiratory tract infections, metastatic septic infections (liver), invasive external otitis and mucormycosis,[2] some of which require surgical intervention. Diabetes also increases the risk for coronary artery, cerebrovascular and peripheral vascular disease and nephropathy[3] which predispose to elective surgery including coronary artery bypass grafting[4] and renal transplant.[5]

Emergency surgical procedures that diabetic patients commonly undergo include laparotomy, appendectomy, cholecystectomy; and diabetes related procedures such as abscess drainage, ulcer care and lower extremity amputation.[6]

Even in pregnancy, diabetes is associated with more complications and increased rate of surgery than in the normal population. Dunne et al[7] carried out a study regarding pregnancy outcome in all women with insulin dependent diabetes mellitus complicated by diabetic nephropathy, who attended joint diabetic-antenatal clinic over a 7 year period between 1990 and 1997. 21 pregnancies in women were followed up and at delivery, 76% of babies were appropriate in size for gestational age whereas 9.5% were large for gestational age and 14% were small for gestational age. 57% of babies were preterm and all required neonatal unit care. There was a high frequency of obstetric complications; one woman had a sudden antepartum haemorrhage due to placental abruption, while 50% of pregnancies were complicated by worsening proteinuria and hypertension and/or fetal distress requiring preterm delivery. The caesarean section rate was 90.5% versus 20% in the background population.

The stress of surgery itself results in metabolic disturbances that alter glucose homeostasis,[6] and hence interfere with glycaemic control in the otherwise well controlled

patient undergoing surgery.[8] It also poses a serious threat to glucose homeostasis in the poorly controlled diabetic patient, hence the increased requirement of insulin therapy peri-operatively.[6] Persistent hyperglycaemia is a risk factor for endothelial dysfunction,[9] post-operative sepsis,[10] cerebral ischaemia[11] and inhibits host defences against infection[12,13] including many leucocytes function[14,15] as well as impairing wound healing because of its detrimental effects on collagen formation and the resulting diminished wound tensile strength.[16] Hyperglycaemia also increases the risk of renal allograft rejection.[17]

Impaired wound healing contributes to increased rate of post-operative infections in patients with diabetes mellitus including wound infections, skin infections, pneumonia and urinary tract infections and these are a major cause of morbidity accounting for two thirds of all post-operative complications and 20% of all post-operative deaths in patients with diabetes.[18,19]

The metabolic stress response to anaesthesia and surgery also include release of catabolic counter regulatory hormones epinephrine, norepinephrine, cortisol, glucagon and growth hormone.[20, 21] Raucoules-Aime et al[22] studied non-insulin dependent diabetes mellitus patients undergoing major surgery, and measured counter regulatory hormones. He found that plasma concentrations of growth hormone increased significantly during surgery.

Several factors complicate the metabolic management of the diabetic patient in the peri-operative period. These include starvation, before and after operation, the endocrine and consequent metabolic responses to surgery; and immobilisaton.[23] The stress response itself may precipitate diabetic crises such as diabetic ketoacidosis, hyperglycaemia hyperosmolar syndrome during surgery or post-operatively with negative prognostic consequences.[24,25]

Insulin requirements will be increased by infection; in pain and trauma; in patients with burns; in hypoxia; in patients with hepatic disease; in obese patients; in steroid treated patients; in cardiovascular surgery; in mental stresses; in poor pre-operative metabolic control and in recent ketoacidosis.[26,27,28]

The Diabetic Control and Complications Trial (DCCT), a multicenter randomised clinical trial designed to compare intensive with conventional diabetes therapy, has shown that improved glycaemic control lowers the risk of secondary diabetic complications.[29]

Thourani et al[30] reported that diabetes is an independent predictor of morbidity and/or mortality in patients undergoing surgical procedures. Specifically, glycated haemoglobin (HbA1c) has been shown to be a predictor of death in diabetes. In a prospective study carried out by Khaw et al,[31] 4662 diabetic men aged 45-79 were followed up from November 1995 to December 1999. HbA1c was measured and men with HbA1c concentrations of 5% - 6.9% had 82% mortality from cardiovascular and ischaemic heart disease and non cardiovascular causes. Lowest rates occurred in men with HbA1c concentrations below 5%.

In another prospective study, the UK prospective diabetes study (UKPDS),[32] 4585 patients were followed up with the aim of determining the relation between development of complications of diabetes including mortality, and the exposure to glycaemia over time in patients with type 2 diabetes mellitus as measured by updated mean haemoglobin A1c. Each 1% reduction in HbA1c was associated with a 37% decrease in risk for microvascular complications (predominantly retinopathy; decreasing the requirement for laser photo-coagulation therapy) and a 21% decrease in the risk of any end point (such as amputation) or death related to diabetes (such as death from peripheral vascular disease). The lowest risk of complications was in patients with HbA1c in the normal range (< 6.0%).

Diabetic patients are also at risk of hypoglycaemia in the peri-operative period. Hypoglycaemia in the anaesthetized or sedated patient may be unrecognized if appropriate glucose monitoring is not performed. An article by Schiff and Welsch[33] cited factors that may contribute to peri-operative hypoglycaemia as being prolonged fasting, hypoglycaemic medication, inadequate nutritional therapy, sedation and post-operative gastrointestinal problems such as vomiting, gastroparesis and ileus.

Various regimens exist for glycaemic control but no data is available to demonstrate superiority of one method over another.

Any regimen should maintain good glycaemic control to avoid hyperglycaemia or hypoglycaemia; prevent other metabolic disturbances, be relatively easy to understand and applicable to a variety of situations (operation room, recovery room, general medicine and surgical wards).[8] The key success of any regimen is careful, frequent monitoring to detect any alterations in metabolic control and correct them before they become severe.

Glucose-insulin-potassium infusion

Many authorities have suggested a glucose-insulin-potassium infusion for major operations for well controlled non-insulin dependent diabetes mellitus patients, for all minor and major operations for insulin dependent diabetes mellitus and poorly controlled non-insulin dependent diabetes mellitus.[6,8,26,34,35,36] The infusion is efficient, safe, simple and effective as it delivers the glucose, potassium and insulin at an even rate.[36] 15 units of insulin in 500 mls of 10% dextrose with 10 mEq potassium chloride is infused at 100 mls/hr[2] in adults and should be continued until oral feeding recommences.[26,34]

Thai et al[37] carried out a retrospective study of 112 diabetic patients undergoing surgery. 68 of the patients were managed by a diabetes team and received glucose-insulin-potassium infusion (16 units of rapid acting insulin plus 10 mEq potassium chloride plus 500 mls 10% dextrose). 44 of the patients were managed by the surgeon and anaesthetist and received a wide variety of regimens. Glycaemic control was significantly poor in the patients who did not receive glucose-insulin-potassium infusion, whereas better glycaemic control was obtained in the patients who received the infusion.

Intravenous insulin versus subcutaneous insulin

Sliding scale use of subcutaneous insulin has long been a standard method of glucose control in hospitalized patients, however many authorities on diabetic care have recently promoted the use of a variable rate intravenous insulin infusion as a more effective

approach to peri-operative diabetic management.[8] The disadvantage of the subcutaneous regimen is that it is based on an anticipated 2- to 4-hour peak effect of regular insulin and its absorption is erratic in the peri-operative period.[38]

In a study carried out by Pezzarossa et al,[39] in a university in Italy, intravenous insulin administration achieved better control than the subcutaneous during the intra-operative period, whereas it did not offer advantages over the subcutaneous route during the pre- and post-operative periods.

Intravenous insulin infusion is simple and has a more predictable absorption compared with that of subcutaneous injections.[8] In type 1 diabetes mellitus, the recommended insulin rate is 0.5 – 1 units/hr.[6,8] In patients with poor control or type 2 diabetes mellitus, the recommended dose is higher, 2-3 units/hr.[8,26,34] The insulin infusion rate is adjusted according to the hourly capillary glucose measurement, guided by the existing algorithm or sliding scale.

The goal is to maintain blood glucose levels within a target range of 6.67 – 10 mmol/l (adequate < 10 mmol/l) during the peri-operative period.[6,8,36]

Kaufman et al[40] retrospectively reviewed surgical admissions at the children's hospital of Los Angeles in patients with type 1 diabetes mellitus from July 1989 to June 1992 and evaluated subcutaneous insulin versus intravenous insulin use.

In group 1 patients received 0.06-0.1 units regular insulin/kg/hour intravenous infusion beginning 2 hours prior to surgery and lasting 2-3 days post-operative. In group 2 patients were given subcutaneous regular and intermediate acting insulin as 2-4 injections daily with regular insulin dose prior to surgery decreased to 66-75% of usual. Blood glucose levels were determined at bedside at hourly intervals. Insulin dose adjustments were made with aim of achieving blood sugar levels between 5.5-8.3 mmol/l. The mean bedside glucose levels for group 2 were significantly higher during the intra-operative period. It was concluded that meticulous glycaemic control was readily achieved peri-operatively with a constant intravenous insulin infusion.

In a prospective study by Furnary et al[41] of 2467 consecutive diabetic patients who underwent open heart surgical procedures between 1987 and 1997, daily mean blood glucose levels were calculated from glucose levels obtained during the day of surgery, and from the first to the fifth post-operative days. The development of deep sternal wound infections was also recorded. The patients were classified into two sequential groups: a control group and a study group. The control group included 968 patients operated on between January 1, 1987 and September 1, 1991; and these patients received individualized sliding scale guided intermittent subcutaneous insulin injections to control blood glucose post-operatively. Treatment was administered every 4 hours with the aim of keeping blood sugar levels at or below 11.1 mmol/l.

The study group included 1499 patients who underwent open heart surgical procedures between September 1, 1991 and November 1, 1997. The patients were treated with a continuous insulin infusion titrated to maintain blood glucose levels between 8.3-11.1 mmol/l.

85% of patients in the continuous insulin infusion study group successfully achieved levels below 11.1 mmol/l, whereas only 47% in the subcutaneous insulin group reached this target level. Continuous insulin infusion achieved tighter glucose control.

Mean blood glucose levels on the day of surgery through to the third post-operative day were significantly lower within the continuous insulin infusion group compared to the subcutaneous insulin group (day of surgery- 11.0 mmol/l versus 13.4 mmol/l; day 1- 9.8 mmol/l versus 11.4 mmol/l; day 2- 10.1 mmol/l versus 10.8 mmol/l; day 3- 9.9 mmol/l versus 10.4 mmol/l).

Patients with deep sternal wound infections had higher blood sugar levels than patients without deep sternal wound infections.

The rate of deep sternal wound infections in patients who received subcutaneous insulin was 1.9% (19 of 968) compared to that in patients who received continuous insulin infusion which was 0.8% (12 of 1499). Thus implementation of the continuous insulin infusion protocol resulted in a 2.5 fold decrease in the rate of deep sternal wound infections compared with that of subcutaneous insulin.

This showed that continuous intravenous insulin induced a significant reduction in peri-operative blood glucose levels which led to a significant reduction in incidence of deep sternal wound infections compared to subcutaneous insulin.

Dextrose infusion

Diabetic patients undergoing surgery are kept nil by mouth thus require intravenous glucose as their caloric source.[42] Adequate glucose is provided peri-operatively to prevent catabolism, starvation ketosis and insulin induced hypoglycaemia.[8]

The caloric requirement is increased due to the stress of surgery.

Caloric requirement in most diabetic patients averages 5-10 g/hr glucose (1.1-2.1mg/kg/min) and 5% dextrose at 100 mls/hr delivers 5 g/hr glucose.[6,42]

The practice is to give 5% dextrose at 100-125 mls/hr or 10% dextrose at 100 mls/hr.[6,8,26,34] A 20-50% dextrose solution can be given through a central venous catheter if fluid restriction is critical.[8]

Intravenous fluids

Fluids should be used as in non-diabetic patients preferably normal saline and dextrose in water avoiding lactate containing solutions such as Ringer's lactate and Hartmann's solution as these cause exacerbation of hyperglycaemia[43] due to lactate converting rapidly to glucose in the fasting state.

Adequate fluids should be administered to maintain intravascular volume and correct fluid deficits;[6] with modifications in patients with renal failure or congestive heart failure.

Insulin dependent diabetes mellitus versus non-insulin dependent diabetes mellitus

Raucoules et al[44] compared intra-operative glycaemic control and insulin requirements in 40 non-insulin dependent diabetes mellitus and 40 insulin dependent diabetes mellitus patients undergoing general anaesthesia for elective procedures, also comparing continuous intravenous insulin infusion versus insulin boluses. Continuous intravenous

infusion was 1.2 units per hour and repeated intravenous boluses were at 10 units every 2 hours. They found out that glycaemia and insulin requirements did not differ significantly in the two types of diabetes mellitus, regardless of insulin therapy used. The conclusion was that it is not necessary to modify the insulin regimen according to the type of diabetes.

Major versus minor surgery in diabetic patients

Major surgery is that surgery involving penetration of a body cavity or transection of a major limb bone, whereas minor surgery is that surgery that does not involve penetration of a body cavity or transection of major limb bone.[45] Diabetic patients undergoing minor surgery with good glycaemic control can be managed satisfactorily without insulin and usually do not have restrictions to eating in the post-operative period thus return to routine diabetic dietary schedule very soon after surgery, whereas patients undergoing major surgery who are receiving hypoglycaemic treatment or have poor glycaemic control should be established on insulin therapy pre-operatively preferably continuous intravenous insulin infusion.[35,36] Patients who have undergone major surgery have restrictions to feeding in the immediate post-operative period, thus glucose and insulin infusions are continued post-operatively.[36]

Insulin requirements were evaluated in 36 insulin dependent diabetic patients undergoing elective surgery under general anaesthesia; 18 undergoing minor surgery (vitrectomy) – group A; and the other 18, major surgery – group B (gastrectomy - 4 patients, bowel resection - 6 patients and hip replacement – 8 patients).[46] The patients received continuous intravenous infusion of short acting insulin (Actrapid) at 1.25 units/hr with additional bolus of insulin 5 units if intra-operative blood glucose exceeded 11.1 mmol/l. Capillary blood glucose concentrations were measured every 15 minutes. There was no significant difference in the time course of blood concentration between the two groups. However, total amount of insulin given and the rate of administration of insulin (group A: 1.7 units/hr; group B: 3.0 units/hr) were significantly higher in the major surgery group.

Oral hypoglycaemic agents are stopped before surgery. Long acting sulfonylureas such as chlorpropamide are stopped 48 to 72 hours before surgery, while short acting sulfonylureas and metformin are withheld the night before or on the day of surgery, whereas there is no rationale for stopping thiazolidinediones.[6,8,35,38]

Patients undergoing surgery under general anaesthesia especially major surgery, are usually starved. Starvation results in inadvertent hypoglycaemia and excessive catabolism thus parenteral carbohydrate in form of dextrose should be administered to safeguard this.[35] It should be noted that starvation is not an acceptable method of maintaining glucose values within the reference range.[38]

Diabetic patients who have surgery performed under regional anaesthesia will usually resume oral intake earlier than after general anaesthesia. Regional anaesthesia modulates secretion of catabolic hormones (released during the stress response to surgery and exacerbate hyperglycaemia) and any residual insulin secretion.[35]

Patients with diabetes have an increased incidence of acute rejection following renal transplantation.[47] However patients with optimal glycaemic control have less rejection episode than those with poor control. In a study by Thomas et al,[48] of diabetic patients undergoing renal transplant; 11% of patients with optimal control (mean glucose concentration < 11.2 mmol/l over the first 100 hours) had a rejection episode compared to 58% with poor early control (mean glucose concentration > 11.2 mmol/l over the first 100 hours).

McAlister et al[4] did a retrospective cohort study of 291 consecutive patients with diabetes undergoing coronary artery bypass grafting (CABG) in a tertiary care facility between April 2000 and March 2001. The patients studied were those who survived at least 24 hours post-operatively. His findings were that 78 patients (27%) suffered "adverse outcomes": 7 patients suffered a non-fatal stroke or myocardial infarction, 63 of the patients had a septic complication and 8 patients died. Median duration of hospital stay was 7 days (interquartile range 6-13 days) and the median time for complication was 6

days (interquartile range 4-11 days). The average capillary blood glucose on the first post-operative day was significantly associated with subsequent adverse outcomes. Compared with patients in the lowest quartile (blood glucose 4.8-10.1 mmol/l on the first post-operative day), patients in the highest quartile range (blood glucose $\geq$ 12.5 mmol/l) exhibited a significant increase in non fatal stroke, septic complications or death after 24 hours. It was thus concluded that glycaemic control was suboptimal with average glucose on first post-operative day being 11.4 mmol/l and was significantly associated with adverse outcomes post-CABG.

Glycaemic control is also important in critically ill patients in the surgical unit. Van den Berghe et al[49] performed a prospective, randomized controlled study involving 1548 critically ill adults admitted to a Belgian surgical intensive care unit. Patients were randomly assigned to receive intensive insulin therapy to maintain blood glucose between 4.4 - 6.1mmol/l or conventional treatment involving infusion of insulin only if the blood glucose level exceeded 11.9 mmol/l. The blood glucose was maintained between 10 – 11 mmol/l. The study showed that intensive insulin therapy reduced mortality during intensive care from 8% with conventional treatment to 4.6%.

RATIONALE

Diabetic patients are at risk for surgical exposure due to microvascular complications. Sugar control peri-operatively will determine outcome following surgery and it provides a challenge to the anaesthetist.

Poor peri-operative glycaemic control results in inadequate reversal from anaesthesia, and thus necessitating admission to the Intensive Care Unit (ICU) or High Dependency Unit (HDU) post-operatively with resultant increase in post-operative infections and delayed wound healing culminating in prolonged hospital stay and even death.

On the other hand, good glycaemic control during surgery, will enable a smooth reversal from anaesthesia, and reduce the number of patients admitted to the Intensive Care Unit as well as post-operative mortality.

Lack of blood sugar monitoring during surgery may result in hypoglycaemia, which may also delay reversal from anaesthesia, in turn resulting in a hypoxic event, that will cause cerebral damage, prolonged coma and admission in the ICU and eventual demise.

The requirements for insulin and glucose are unpredictable in the unconscious diabetic patient undergoing surgery hence the need for close monitoring intraoperatively.

No local study of intraoperative glycaemic levels has been performed. Looking at glycaemia, and relating it to outcome at reversal from anaesthesia, will enable audit of available patterns and recommendations of appropriate measures can be made.

GOALS AND OBJECTIVES

Goal

Improve intra-operative glycaemic monitoring, control and outcome following anaesthesia

General objective

Study patterns of glycaemic control in diabetics patients undergoing surgery in Kenyatta National hospital

Specific objective

- Determine quality of medium term glycaemic control (pre-operative) through estimation of HbA1c

- Determine levels of glycaemia intra-operatively in patients undergoing surgery and relate it to HbA1c
- Determine insulin administered intra-operatively and relate it to HbA1c
- Relate intra-operative glycaemic levels and HbA1c to age, gender, duration of diabetes
- Relate intra-operative glycaemic levels to immediate post-operative events
- Relate immediate post-operative events to HbA1c

  Immediate post-operative events considered in the study:

  Haemodynamics : bradycardia, hypotension, respiratory distress

  Reversal : easy or poor

  Admission to intensive care unit

  Death

Research Question

Is poor glycaemic control (HbA1c > 7%) associated with poor post-operative outcome?

METHODOLOGY

Study design

The study design was a cross-sectional, prospective study of intra-operative glycaemia and control.

Study Population

Diabetics undergoing elective or emergency surgery

Site of Study

Kenyatta National Hospital operating rooms.

Sampling

Consecutive sampling of all diabetic patients presenting for emergency or elective surgery was performed.

Sample size

The following formula was used to determine sample size.[50]

$$n = Z^2_{(1-\alpha/2)} \frac{P(1-P)}{d^2}$$

n = sample size

$Z^2_{(1-\alpha/2)}$ is the standard error of the mean corresponding to 95% confidence interval. This limit is given by p=0.05 and the corresponding value determined from a t-table is 1.96

d = the target margin of error or the absolute precision which is 5%

P = the percentage adverse outcome (including mortality) following poor glycaemic control in this case 8% (derived from literature)

Thus: $n = 1.96^2 \times \frac{0.08(1-0.08)}{0.05^2} = 113$

Eligibility criteria

- All diabetic patients (as defined by WHO) presenting for elective or emergency surgery at the Kenyatta National Hospital theatres.
- Informed written consent

Exclusion criteria

- Non-consenting patients
- Non-diabetics or patients whose hyperglycaemia is discovered intra-operatively
- Pre-operative altered sensorium or overt confusion in patients

Study Procedure

113 diabetic patients undergoing emergency and elective surgery in the Kenyatta National hospital theatre were included in the study.

Informed consent was obtained from the patients prior to surgery.

Capillary blood sugar levels were determined 15 minutes pre-operatively for each patient enrolled in the study.

1 ml of blood was drawn in EDTA bottle for the purpose of estimation of HbA1c, which was performed at the Immuno-Molecular Diagnostic Laboratory at Kenyatta National Hospital.

Under general anaesthesia, or regional anaesthesia, the surgical procedure was performed. During this period, capillary blood sugar levels were determined every half hour to one hour intervals (onset of action of Actrapid insulin is within 30 minutes) and at reversal from anaesthesia.

The vital signs of the patients; pulse rate, blood pressure were recorded as routinely done, and at reversal from anaesthesia these were noted.

To determine blood sugar measurements use was made of a Hemocue Glucose® 201+ blood glucose analyzer with cuvettes from Hemocue Limited (Angelholm, Sweden). The sample consisted of 5μL of capillary blood. The analyzer has a measuring range of 0-22.2 mmol/l (which may be extended to 44.4 mmol/l by dilution) and an internal electronic self test that verifies the performance of the optronic unit of analyzer.

Capillary whole blood was utilized in glucose estimation and this is equivalent to venous plasma.[51]

For HbA1c determination, use was made of HbA1c % liquidirect from Human Gesselschaft Biochemical and Diagnostics (Germany), which is an immunoassay for direct photometric determination. It utilizes linkage of antigen and antibody to directly determine the percentage of HbA1c in whole blood. Both total Hb and HbA1c bind competitively to specific latex particles, proportional to their concentration. Monoclonal antibodies against HbA1c are cross linked by anti-monoclonal antibodies and react specifically with HbA1c resulting in an agglutination of the latex particles. The degree of agglutination depends on the amount of HbA1c. The increase of turbidity in the reaction mixture is measured photometrically. The HbA1c % value is extrapolated from a curve established with the calibrators.

The normal range for the method used at the Immuno-Molecular Diagnostics Laboratory, Kenyatta National Hospital for HbA1c is 4.4 – 6.4%.

Data Analysis

Data coded in questionnaires was entered into the computer, cleaned, verified, and stored in hard and soft copies.

The mean, median, mode, and standard deviation were calculated, and data was presented in form of graphs, tables, scatter diagrams, and pie charts as appropriate.

Chi-square test was used to analyse the relationship between categorical variables and Student's t-test for differences in means (continuous variables). Pearson correlation was used to analyse the relationship between numerical variables. Statistical analysis of the difference between HbA1c and age, sex, duration of diabetes, surgical diagnosis, and type of anaesthesia was made using two-way analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

All analyses were performed using SPSS statistical software (version 11).

ETHICAL ISSUES

The procedure was harmless as it involved routine measurements of blood sugars that constitute regular monitoring. Measurement of capillary blood sugar was performed pre-operatively, at intervals intra-operatively, at reversal from anaesthesia. HbA1c was also estimated as a pre-operative value.

Only 5µL of blood for capillary blood sugar, and 1 ml for HbA1c was obtained, with minimal discomfort to the patient.

The close intra-operative metabolic and haemodynamic monitoring was very useful to the patient.

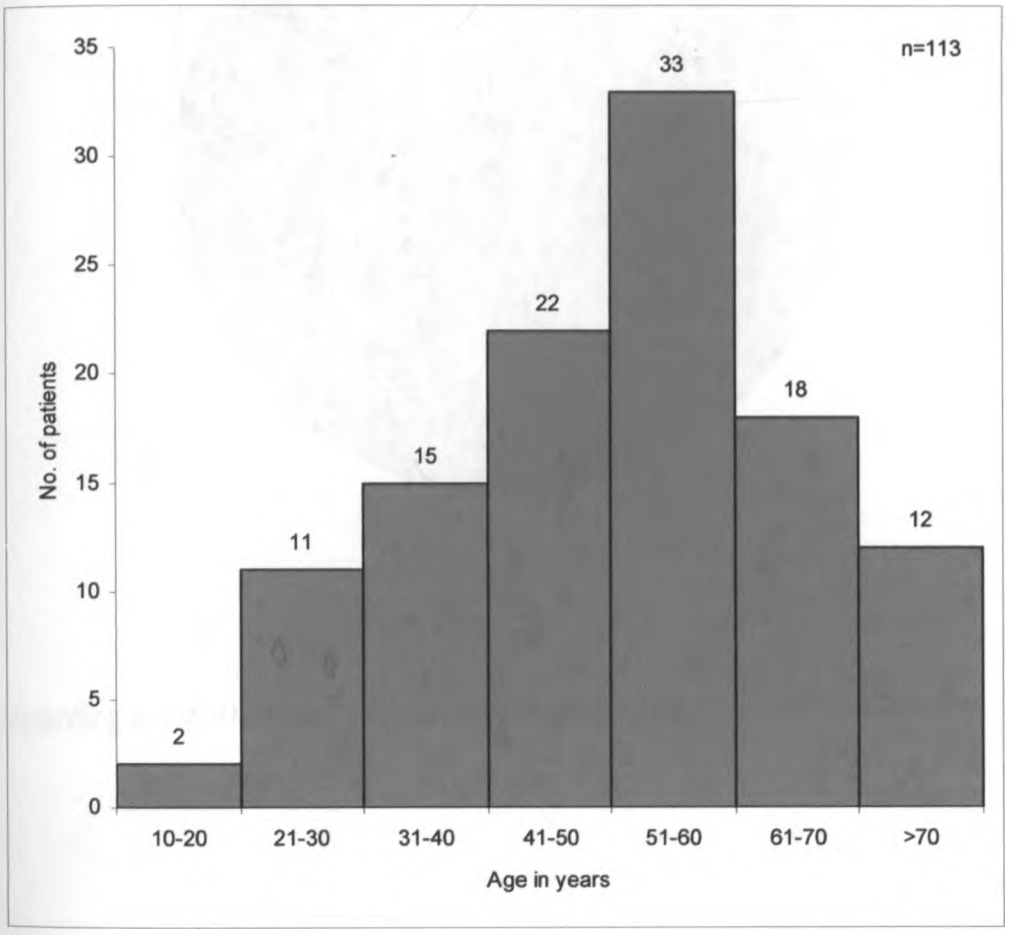
The information about the patient was handled with utmost confidentiality and only used for the intended purpose.

Permission to carry out the study was sought from Kenyatta National Hospital Ethics and Research Committee.

RESULTS

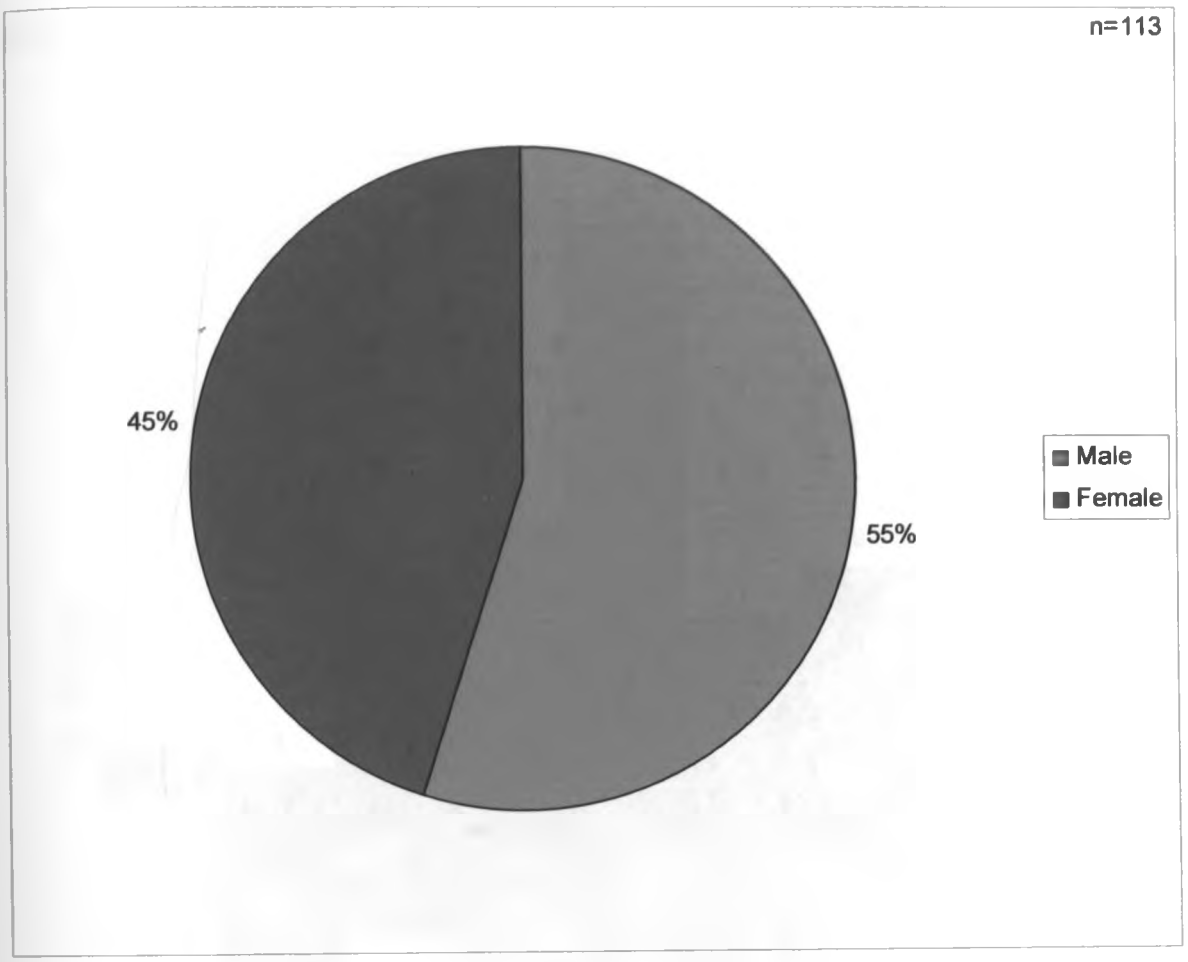
113 diabetic patients presenting for emergency or elective surgery were enrolled to the study between November 2005 and March 2006. Figure 1 below shows the age distribution.

Figure 1 – Age distribution



The mean age was 51.75 years, the median was 53 years, the mode was 60 years. The standard deviation was 15.941 with a range of 12 to 90 years. 1.8% were less than 21 years, 10.6% more than 70 years, majority, 29.2% were between 51 and 60 years.

Figure 2 – Sex Distribution



Regarding sex distribution, 54.9 % were males and 45.1 % were females.

There were more females aged between 21 and 30 years, and more males aged between 51 and 60 years. The overall sex-age ratio fell short of being statistically significant (p = 0.06).

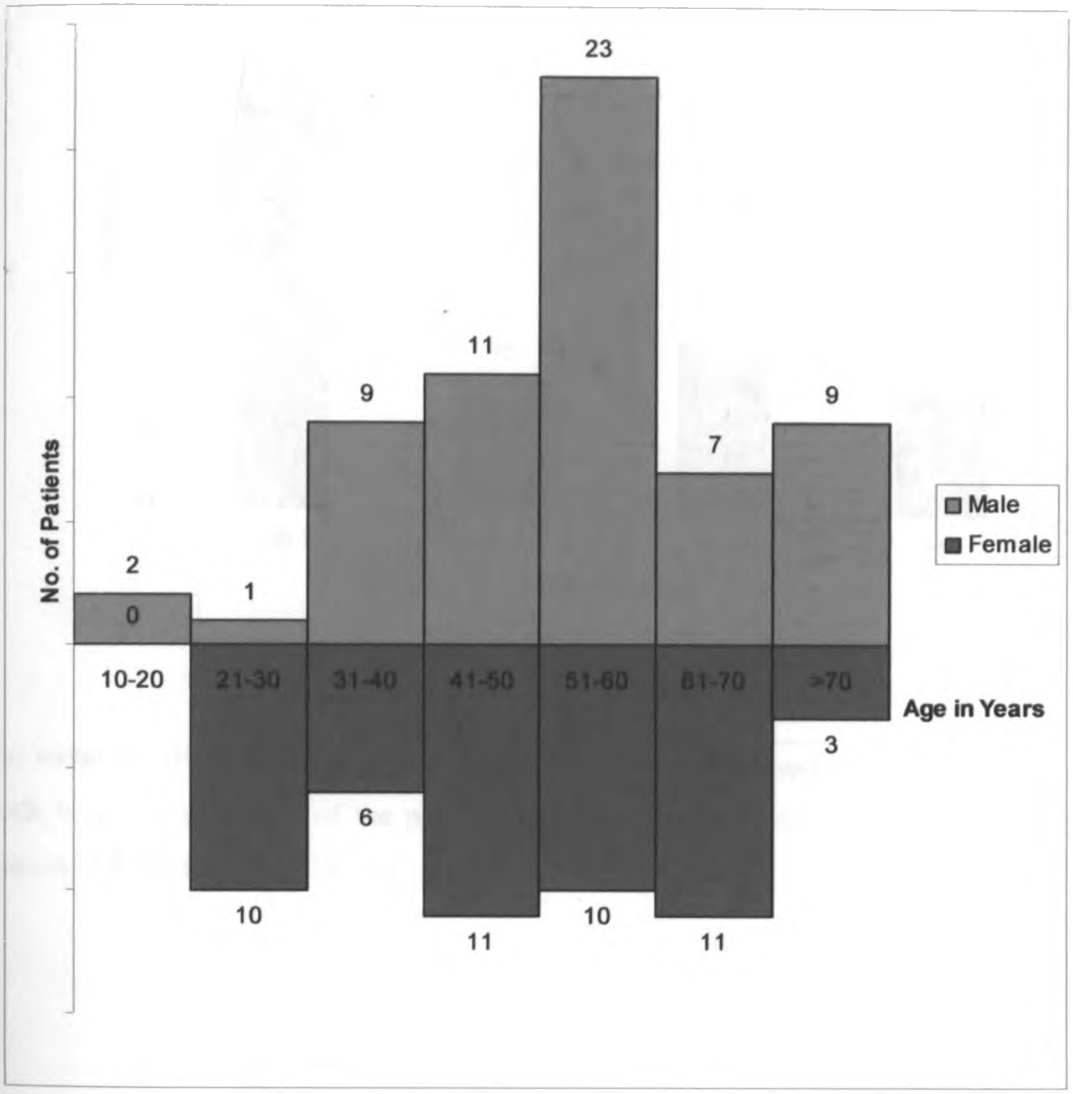
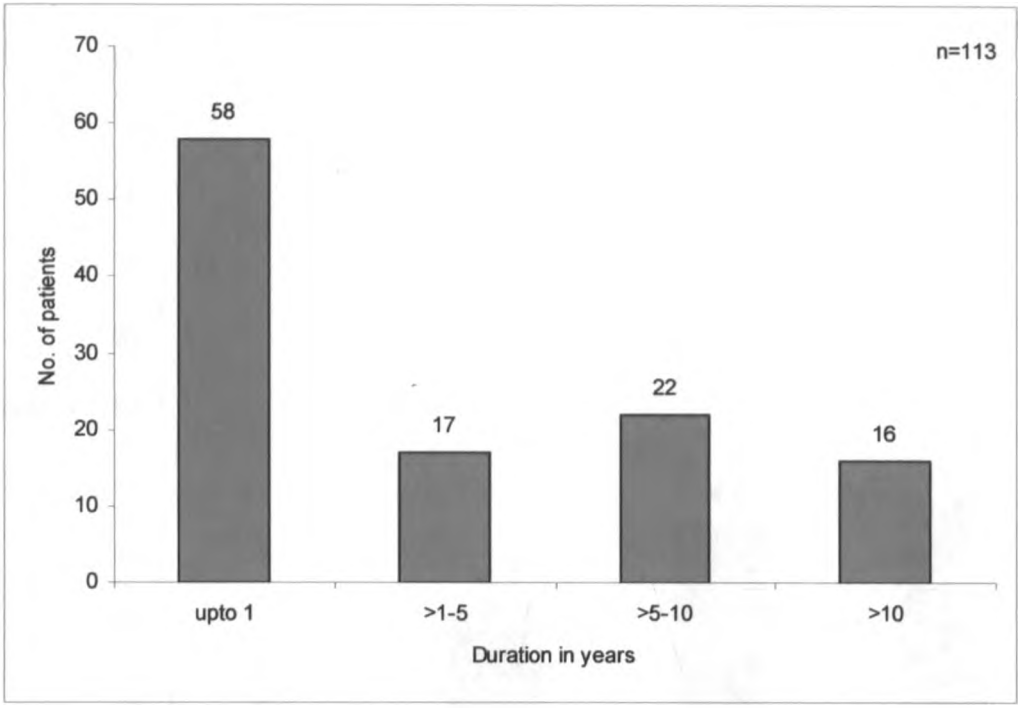


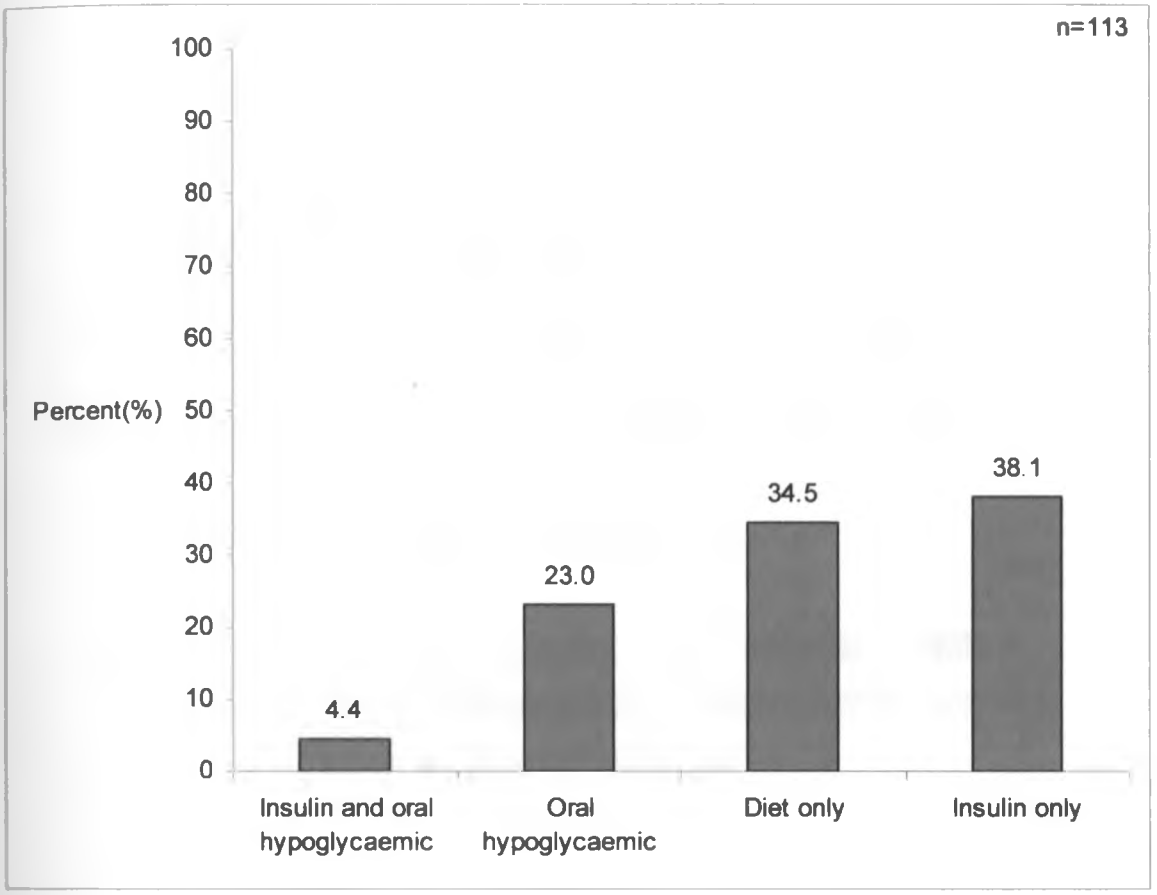
Figure 3 – Age and Sex distribution ($X^2 = 18.07$, $p = 0.06$)

Figure 4 – Duration of diabetes



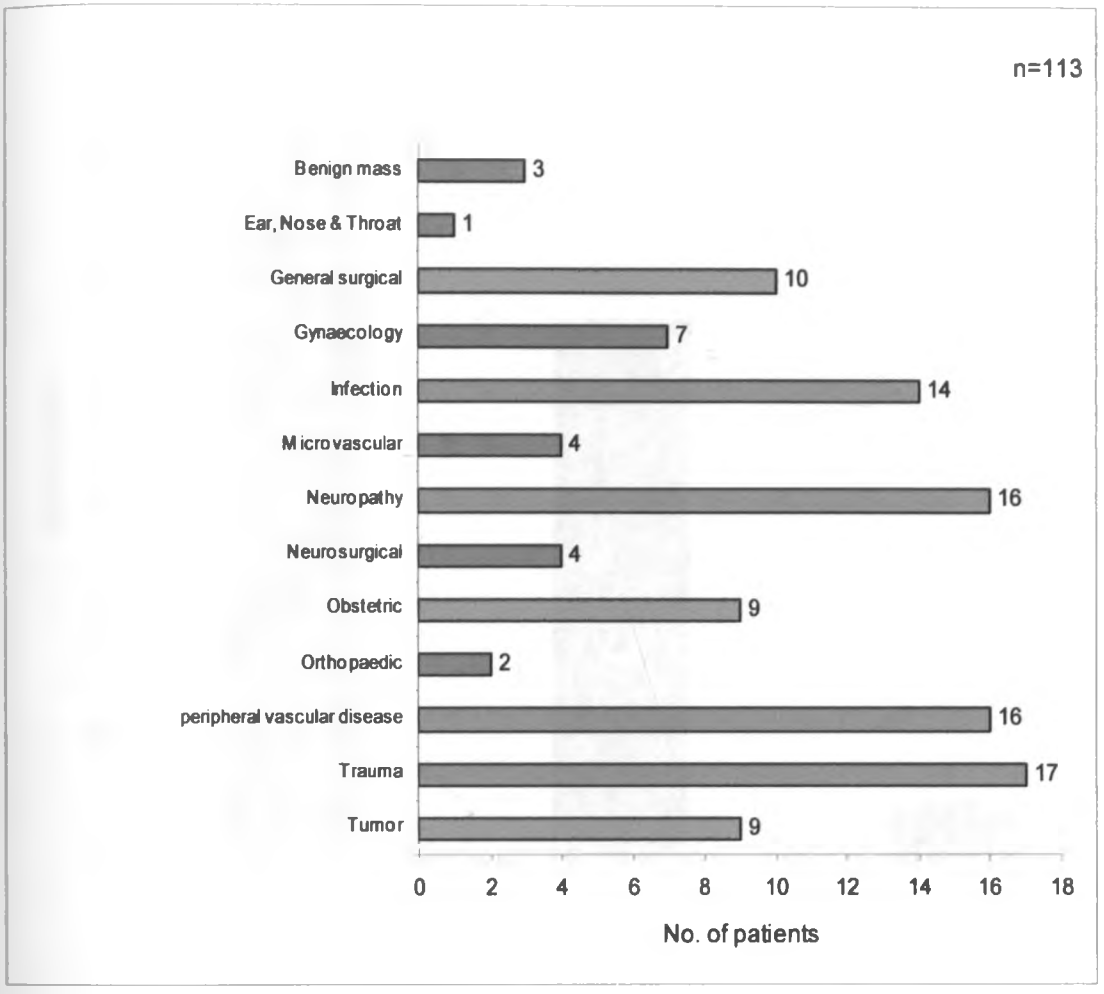
The mean duration of diabetes was 4.9 years, whereas the median was 2 years and the mode was 1 year. 51.3% of the patients had been managed for diabetes for less than 1 year and 14.2% for more than 10 years.

Figure 5 – Pre-operative diabetes treatment used



Regarding pre-operative diabetes therapy used, 34.5% were on diet only, 38.1% were on insulin only, 4.4% were on insulin and oral hypoglycaemic agents, and 23% were on oral hypoglycaemic agents.

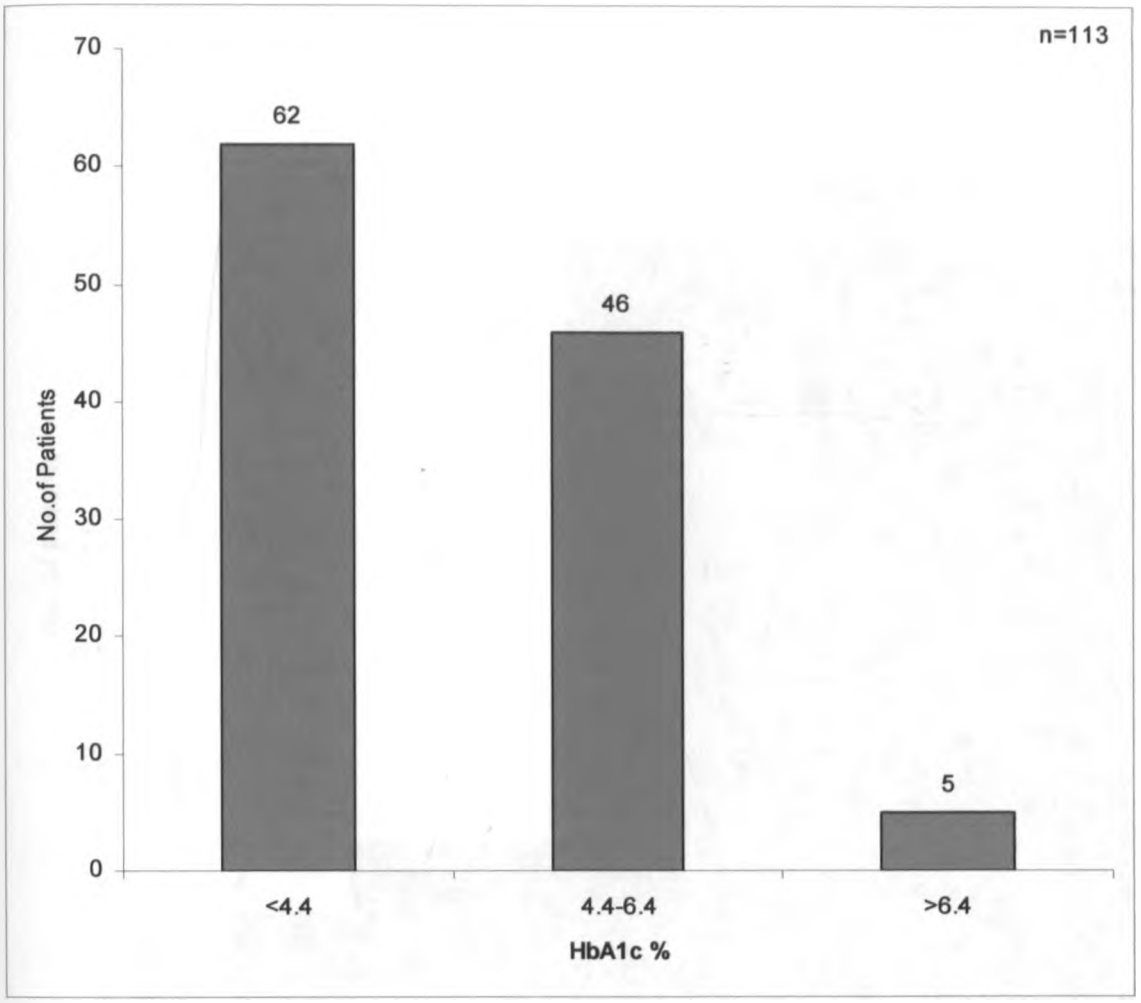
Figure 6 – Surgical diagnosis



The diabetic patients presented with different surgical diagnoses, including trauma such as head injury, fractures and gunshot wounds; neuropathy and peripheral vascular disease such as diabetic foot, cataract, glaucoma; infections; general surgical such as intestinal obstruction; obstetric and gynaecological procedures such as abnormal uterine bleeding, fetal distress; microvascular such as retinopathy; benign masses and tumors; neurosurgical; and orthopaedic.

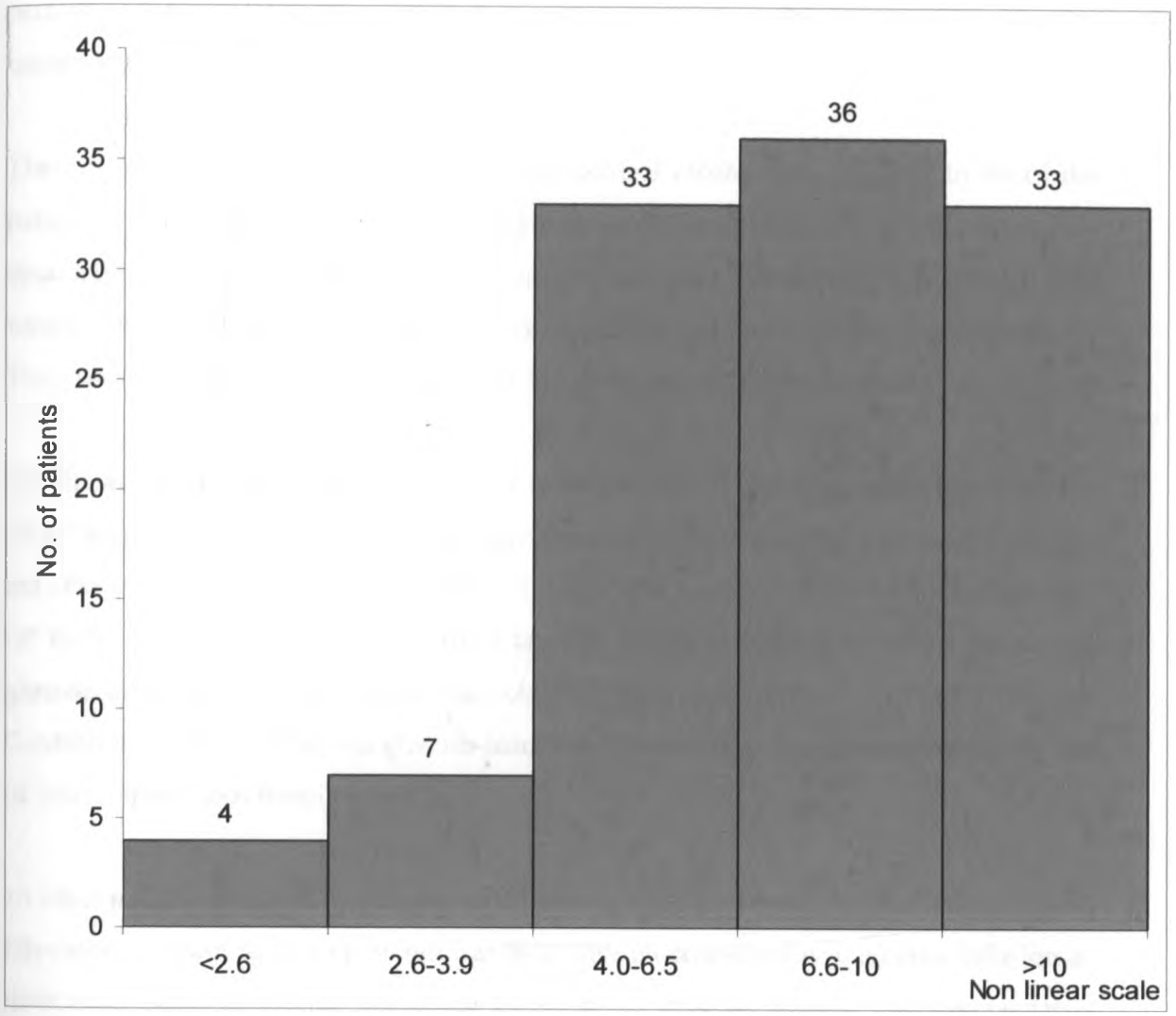
55 patients presented with conditions that were a complication of diabetes, whereas in 58 patients the conditions had no relation to diabetes.

Figure 7 – Mean HbA1c



The mean HbA1c was 4.173% with a median of 4.1% and a mode of 3.5%. The standard deviation was 1.3045. 62 (54.9%) patients had HbA1c of less than 4.4% , 46 (40.7%) had HbA1c between 4.4 and 6.4% whereas only 5 patients (4.4%) had HbA1c of more than 6.4%.

Figure 8 – Pre-operative blood sugar



Results of pre-operative blood sugars are illustrated above, and the mean pre-operative blood sugar was 8.7 mmol/l.

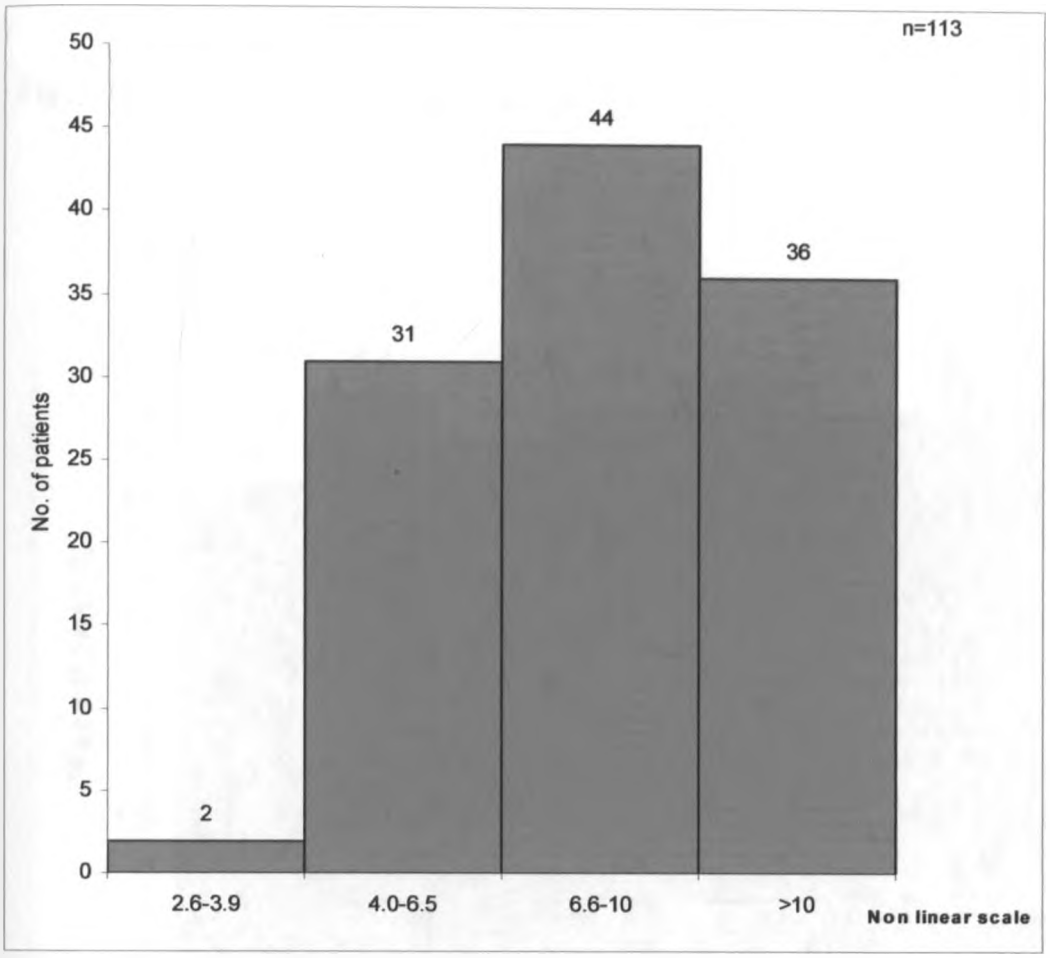
One patient had his surgery deferred for a few hours due to a random blood sugar of 21 mmol/l and severe dehydration with altered level of consciousness. Surgery was performed 4 hours later, after, rehydration with normal saline and control of blood sugar using intravenous insulin boluses.

There were varied intra-operative glycaemic control mechanisms applied. In 64 of the patients (54%), no insulin therapy was administered. These patients had prior good pre-operative glucose levels (their mean pre-operative blood glucose being 6.6 mmol/l), and were mainly controlled pre-operatively on diet, insulin and oral hypoglycaemic agents. They were maintained on normal saline or 5% dextrose intra-operatively.

Insulin was administered intra-operatively in 49 patients (43%); their mean pre-operative blood sugar was 11.1 mmol/l (pre-operative control of these patients was mainly insulin, but also oral hypoglycaemic agents and combined oral hypoglycaemic agent and insulin). Of these, 35 had the glucose-insulin-potassium infusion running at varied rates. The glucose-insulin-potassium infusion was continued post-operatively.
Control in 4 of the patients on glucose-insulin-potassium infusion was augmented by use of bolus intravenous insulin injections.

14 other patients received insulin via subcutaneous and intravenous bolus administration. Glycaemic control in these patients was best with glucose-insulin-potassium infusion as their rates could be altered according to the blood glucose results. The subcutaneous insulin resulted in hypoglycaemic episodes requiring bolus dextrose administration.

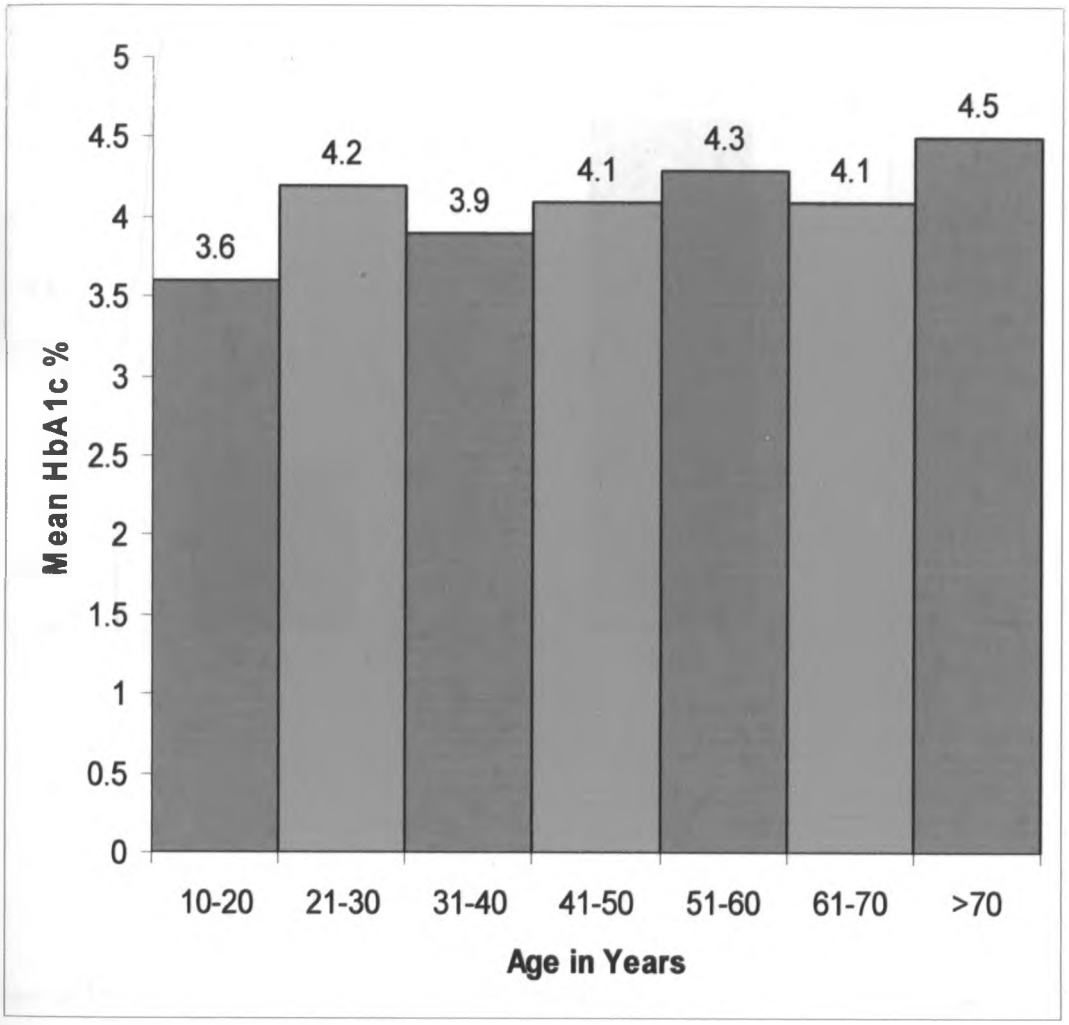
Figure 9 – Mean intra-operative blood sugar



The mean intraoperative blood sugar was 9.14 mmol/l. The median was 8.55 mmol/l and the mode was 4.0 mmol/l with a range of 4 – 19 mmol/l.

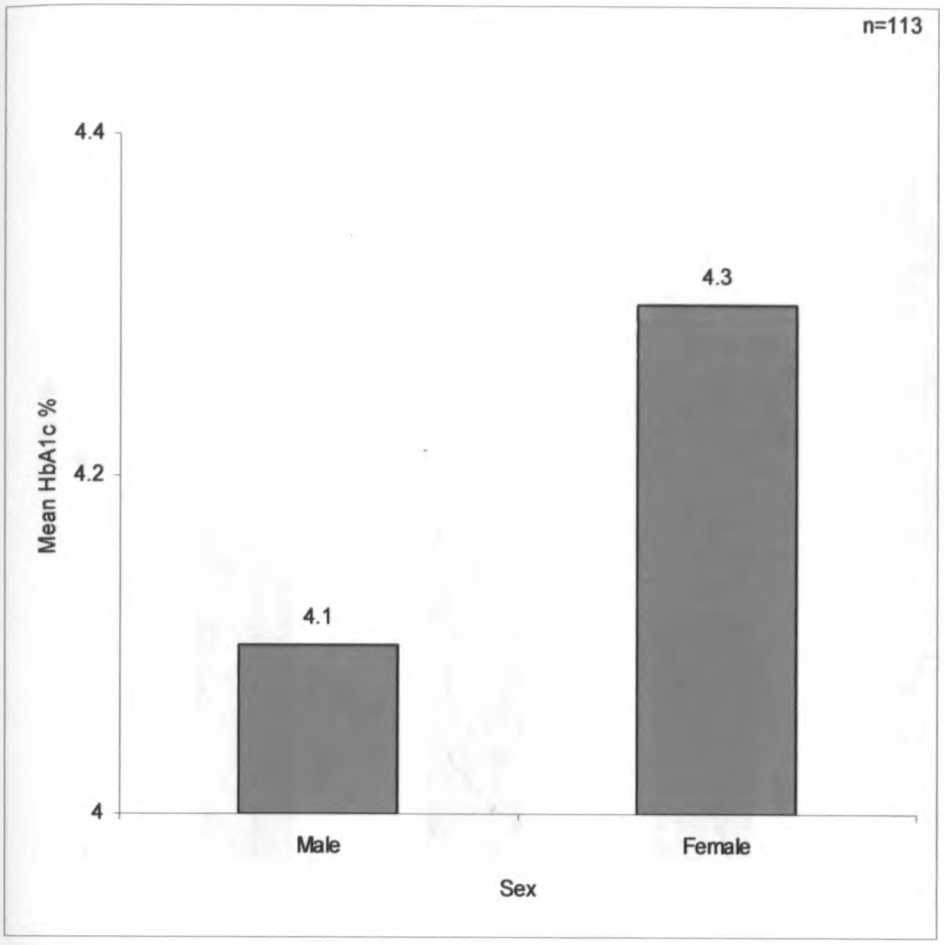
There was no association between glycated haemoglobin (HbA1c) and age, sex and duration of diabetes [figures 10, 11, and 12].

Figure 10 – Mean HbA1c in relation to age



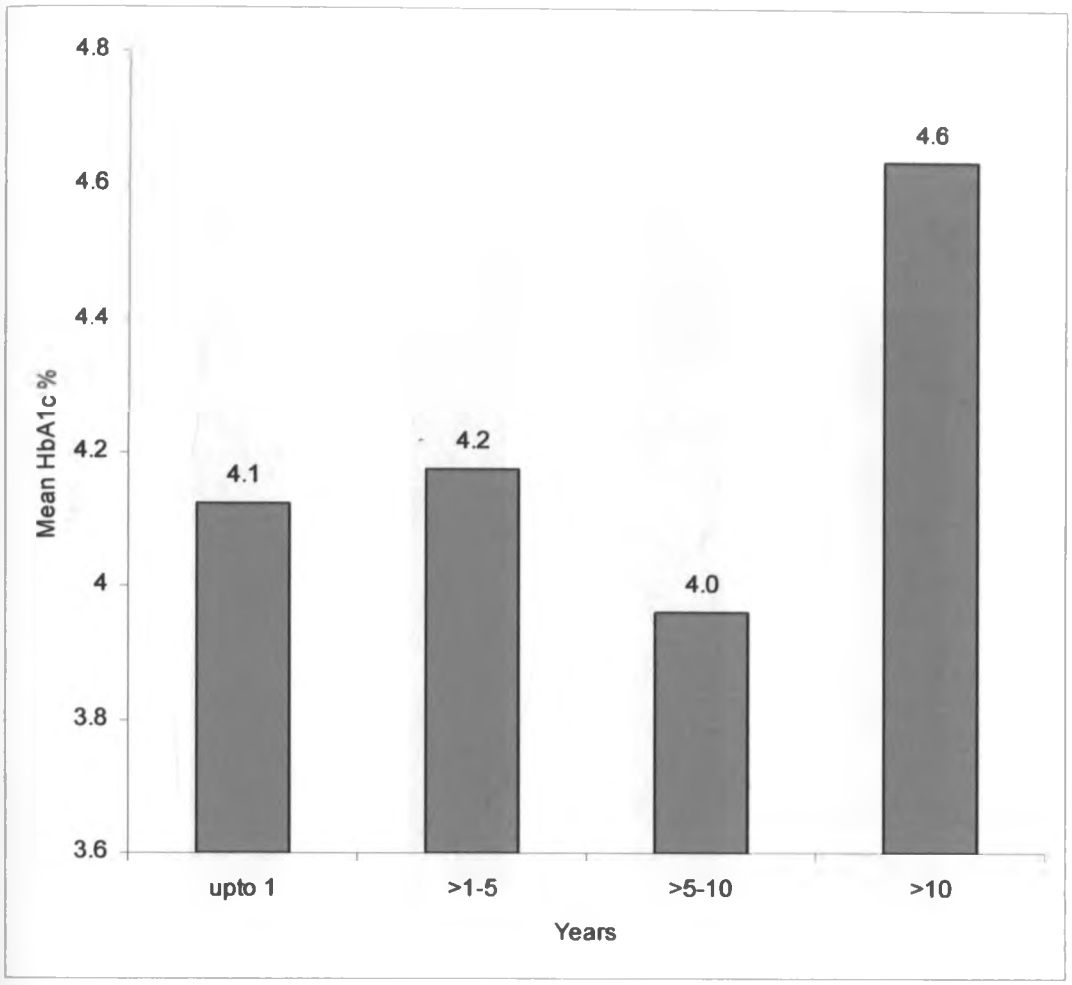
There was no statistical significance between HbA1c and age of the patient ($p = 0.915$).

Figure 11 – Mean HbA1c in relation to sex



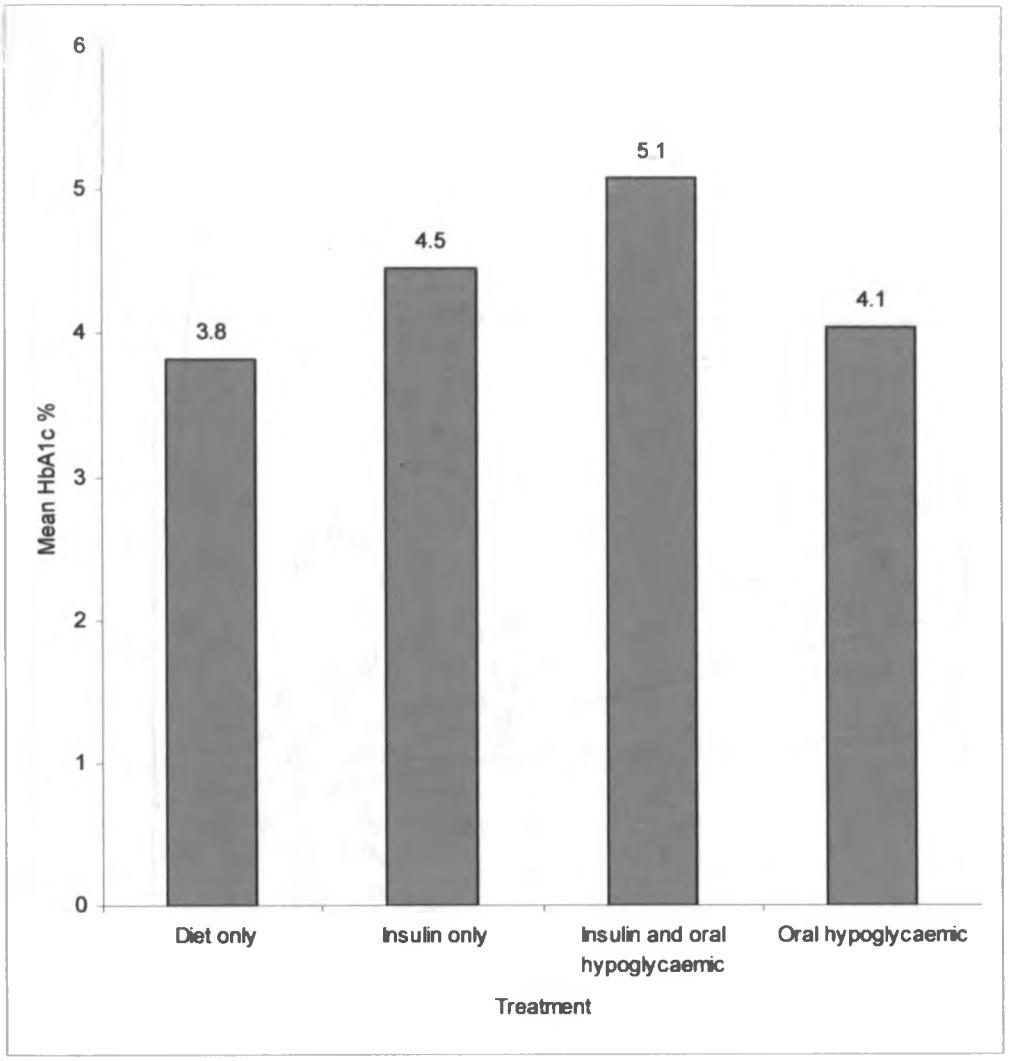
In general levels of HbA1c were higher in females by 0.2% but this difference was not statistically significant ($p = 0.553$).

Figure 12 – Mean HbA1c in relation to duration of diabetes



There was no statistically significant difference among means of HbA1c in various groups of duration of diabetes, even though patients with longer term diabetes seemed to show higher levels of HbA1c ($p = 0.447$).

Figure 13 – Mean HbA1c in relation to pre-operative diabetes treatment used



There was statistically significant variation of means of HbA1c within the treatment used ($p = 0.059$). The patients on diet, insulin and oral hypoglycaemic agents had better pre-operative glycaemic control compared to patients on combined oral hypoglycaemic agent and insulin. Intra-operative glycaemic control of patients on combined oral hypoglycaemic agent and insulin was expected to be relatively difficult.

The random blood sugars which had been recorded at intervals were compared with the HbA1c. There was statistically significant correlation between HbA1c and interval random blood sugars at 0 hour to 1 hour ($p < 0.05$). This correlation was lost for blood sugars at 1.5 hours and beyond [figures 14 – 18].

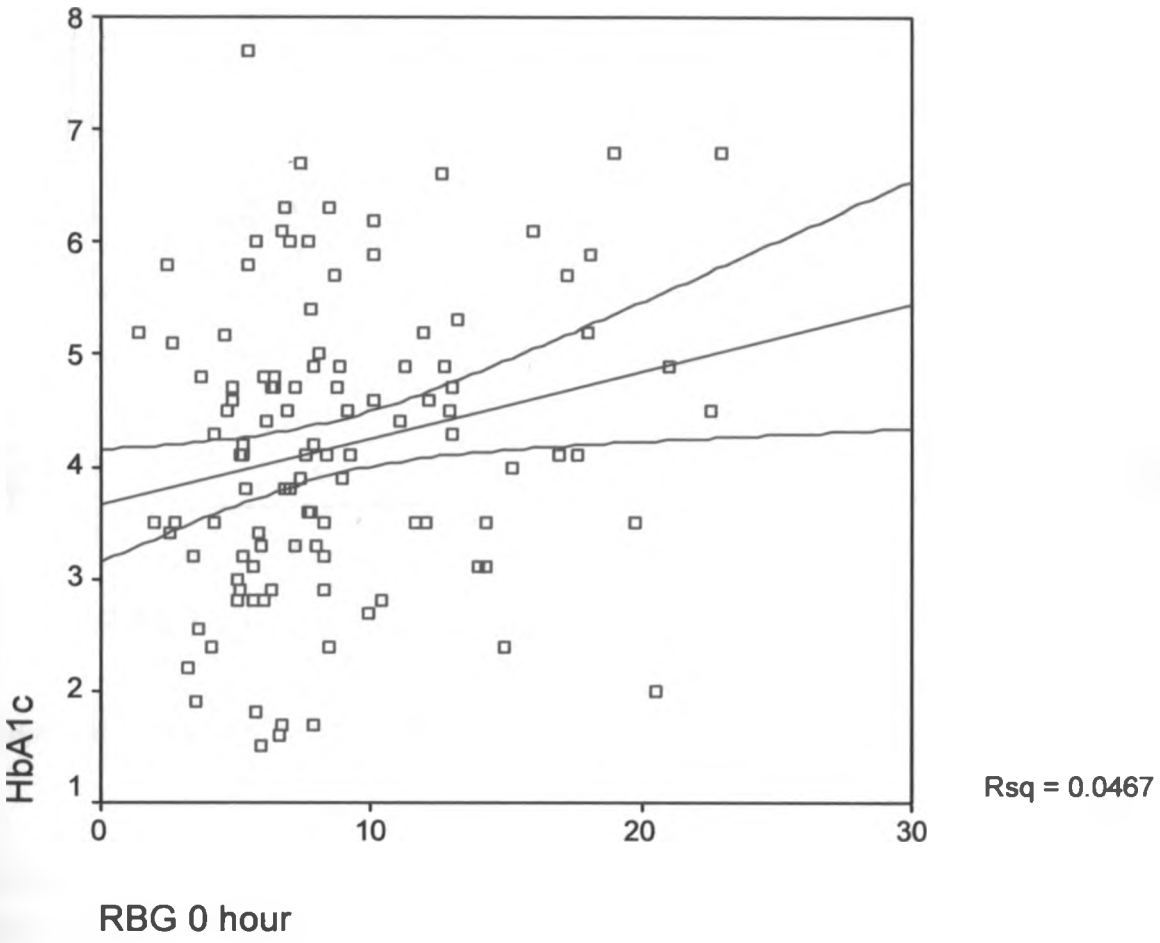


Figure 14 - Scatter diagram of HbA1c in relation to random blood sugar at 0 hour

Regarding HbA1c and random blood sugar at 0 hour, there was statistically significant correlation between the two ($r = 0.227$, $p = 0.016$).

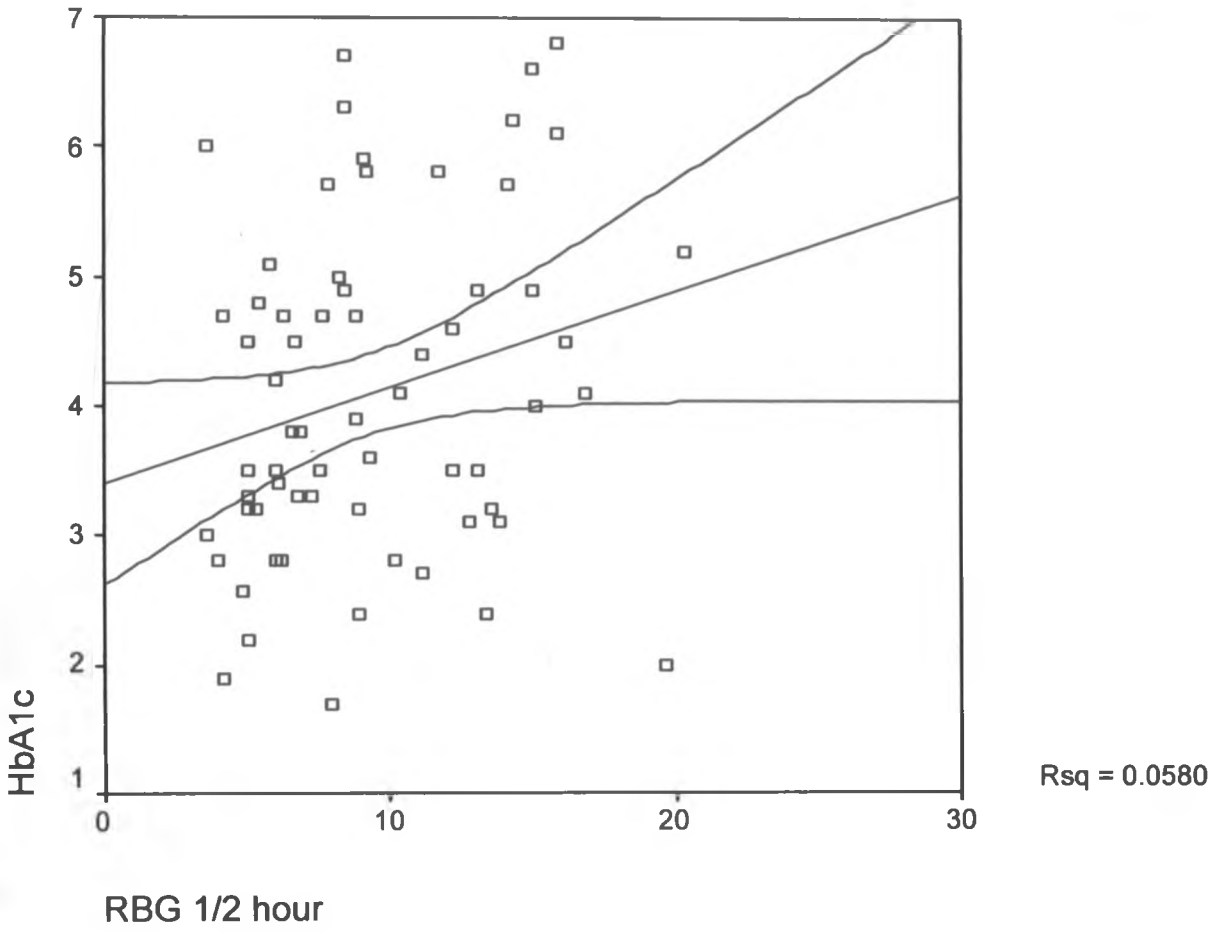


Figure 15 – Scatter diagram of HbA1c in relation to random blood sugar at ½ hour

Regarding HbA1c and random blood sugar at ½ hour, there was a statistically significant correlation between the two ($r = 0.265$, $p = 0.033$)

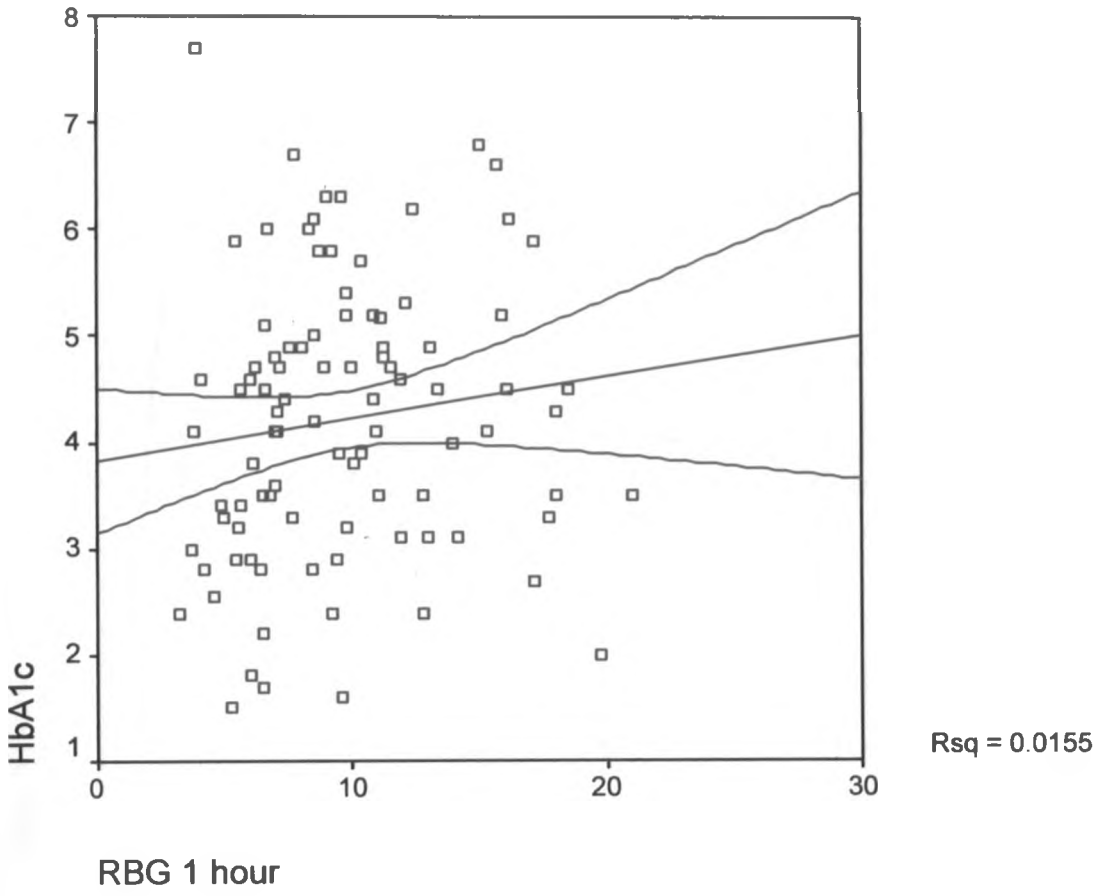


Figure 16 – Scatter diagram of HbA1c in relation to random blood sugar at 1 hour

With regard to HbA1c and random blood sugar at 1 hour, there was statistically significant correlation ($r = 0.213$, $p = 0.039$).

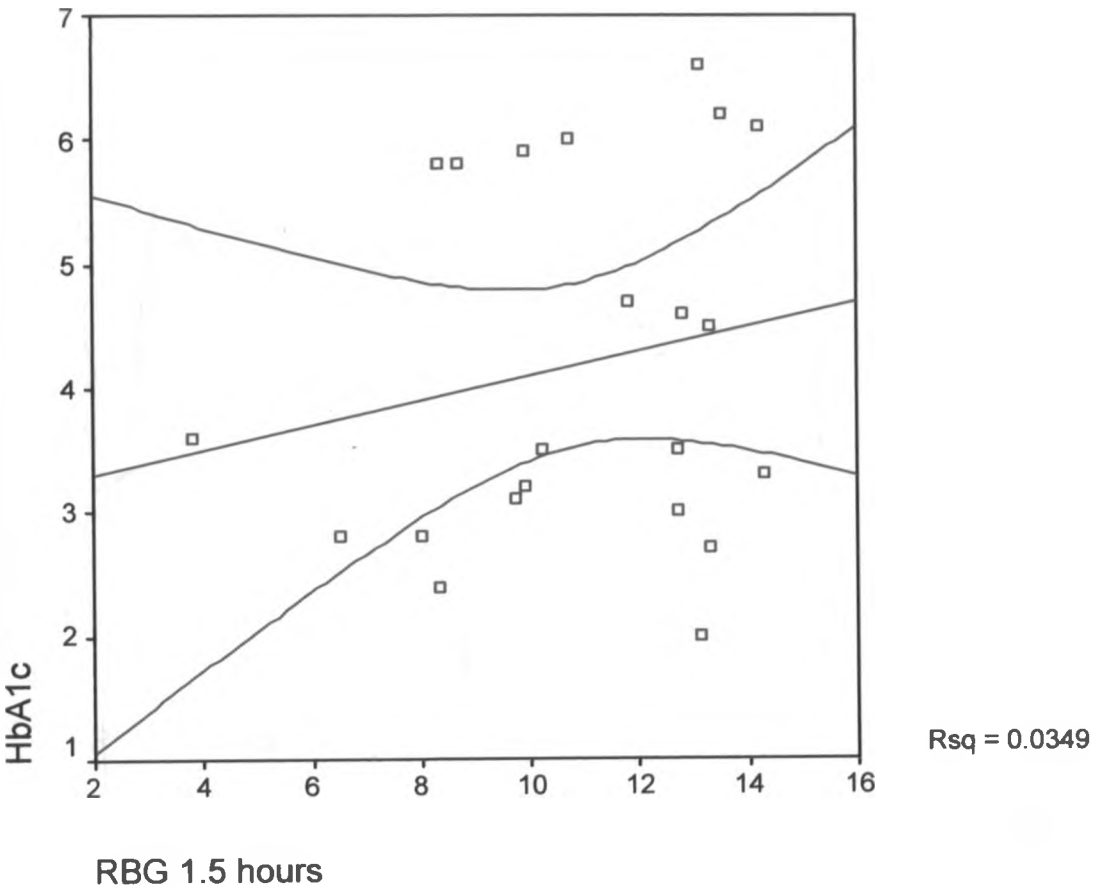


Figure 17 – Scatter diagram of HbA1c in relation to random blood sugar at 1.5 hours

Regarding HbA1c and random blood sugar at 1.5 hours, there was no statistically significant correlation ($r = 0.246$, $p = 0.269$).

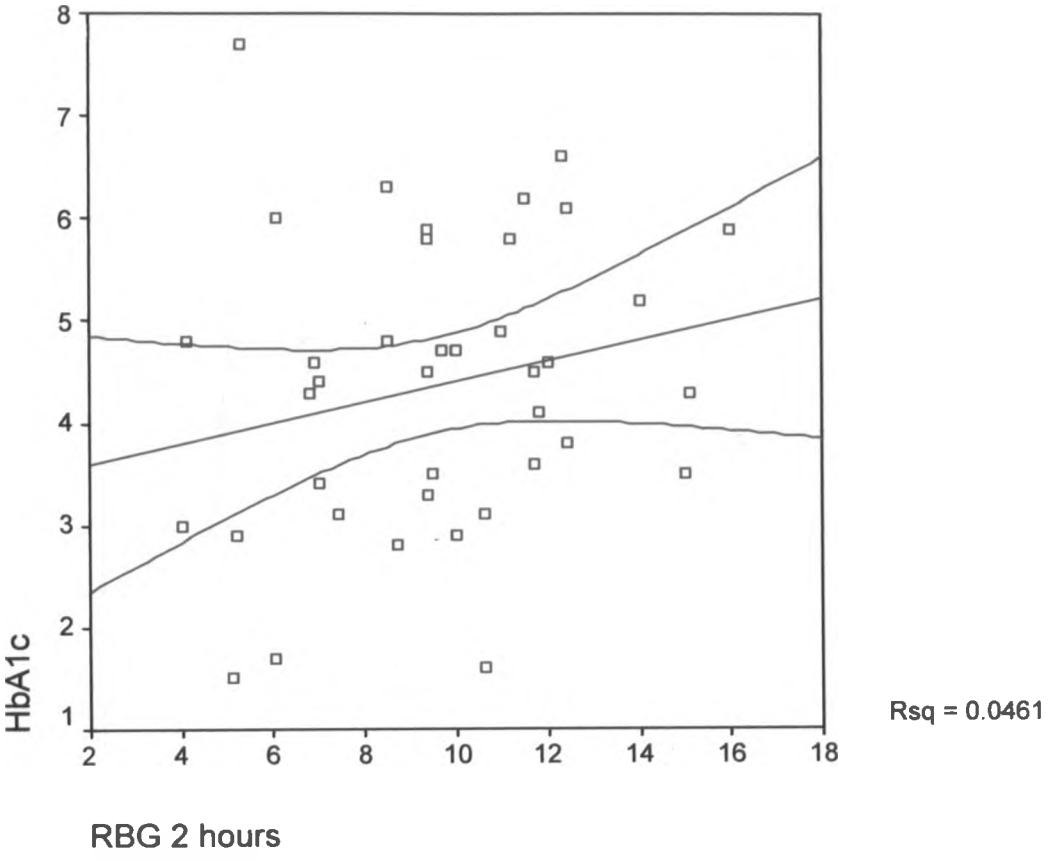


Figure 18 – Relationships of random blood sugar at 2 hours intra-operative with HbA1c

With regard to HbA1c and random blood sugar at 2 hours, there was no statistically significant correlation ($r = 0.235$, $p = 0.151$).

In the patients in whom insulin was used intra-operatively, the mean total insulin used was 6.7 units, the median being 4 units and mode of 10. The standard deviation was 6.78905.

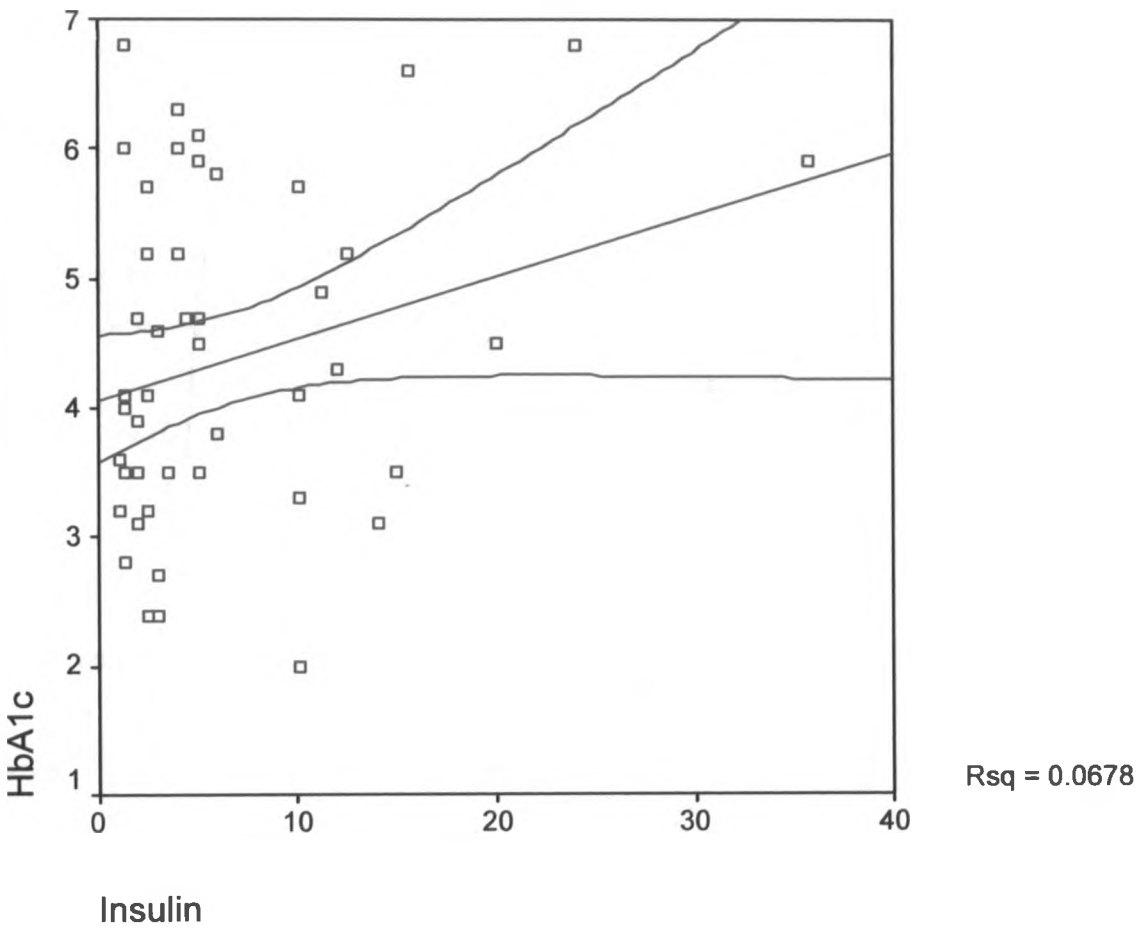


Figure 19 – Scatter diagram of HbA1c in relation to total amount of insulin used

With regard to HbA1c and total amount of insulin used intra-operatively, there was no statistically significant correlation ($r = 0.227$, $p = 0.116$).

84 patients underwent surgery under general anaesthesia, whereas 29 patients had surgery under regional anaesthesia. The duration of surgery for patients who underwent surgery under regional anaesthesia was less than 1 hour (51.55 minutes) and the mean blood sugar was 8.83 mmol/l, whereas for patients who had surgery under general anaesthesia, the duration of surgery was longer (1 hour 26 minutes) and the mean blood sugar was higher (9.13 mmol/l). The relation between the duration of surgery and the type of anaesthesia was statistically significant ($p = 0.003$), however, there was no statistically significant correlation between the type of anaesthesia and the mean blood sugar ($p = 0.660$) [table 1].

Type of Anaesthesia	Number	Mean blood sugar	Duration of surgery
Regional	29	8.83 mmol/l	51.55 minutes
General anaesthesia	84	9.13 mmol/l	85.54 minutes (1 h 26 min)

Table 1 – Relationship between mean blood sugar, type of anaesthesia and duration of surgery

Of the patients who had surgery under regional anaesthesia, 20 had subarachnoid anaesthesia, 8 had peribulbar blocks, and 1 had local infiltration.

The patients who had a surgical diagnosis that was a complication of diabetes, had mean blood sugar of 10.01 mmol/l and a mean HbA1c of 4.4 %, whereas those patients whose diagnoses were not as a result of their diabetic condition had a lower mean blood sugar of 8.15 mmol/l and a mean HbA1c of 3.95%. The relationship between surgical diagnosis, and mean blood sugar was statistically significant ($p = 0.002$); however, the relationship between mean HbA1c and surgical diagnosis was not statistically significant ($p = 0.07$) [table 2].

Relationship of diagnosis to diabetes	Number of patients	Mean HbA1c	Mean blood sugar
Related to diabetes	55	4.40 %	10.01 mmol/l
Unrelated to diabetes	58	3.95 %	8.15 mmol/l

Table 2 – Mean intra-operative blood sugar and mean HbA1c in relation to diabetic related, and non-diabetic related surgical diagnosis

Immediate post-operative events were used to determine outcome of the diabetic patients following anaesthesia. These events included haemodynamics : bradycardia, hypotension, respiratory distress; easy or poor reversal from anaesthesia, admission to the intensive care unit and death. A relationship between these events and HbA1c was sought.

No patients had bradycardia (pulse rate < 50).

The criteria that were used to determine whether reversal was good or poor were: the rate of respiration, whether respiration was shallow or regular and deep, ability to raise the head and calm patient who was able to obey commands.

16.8% of patients had respiratory distress (respiratory rate >20) immediately post-operatively, but none of these patients had a HbA1c of > 6.4%. There was no statistical significance between HbA1c and respiratory distress ($X^2 = 1.057$, $p = 0.304$) [table 3].

Table 3 – Cross tabulation of respiratory distress and HbA1c

			Respiratory Distress		
			No	Yes	Total
HbA1c	<6.4	Count	89	19	108
		% within Respiratory Distress	94.7%	100.0%	95.6%
	6.4 and over	Count	5	0	5
		% within Respiratory Distress	5.3%	.0%	4.4%
Total		Count	94	19	113
		% within Respiratory Distress	100.0%	100.0%	100.0%

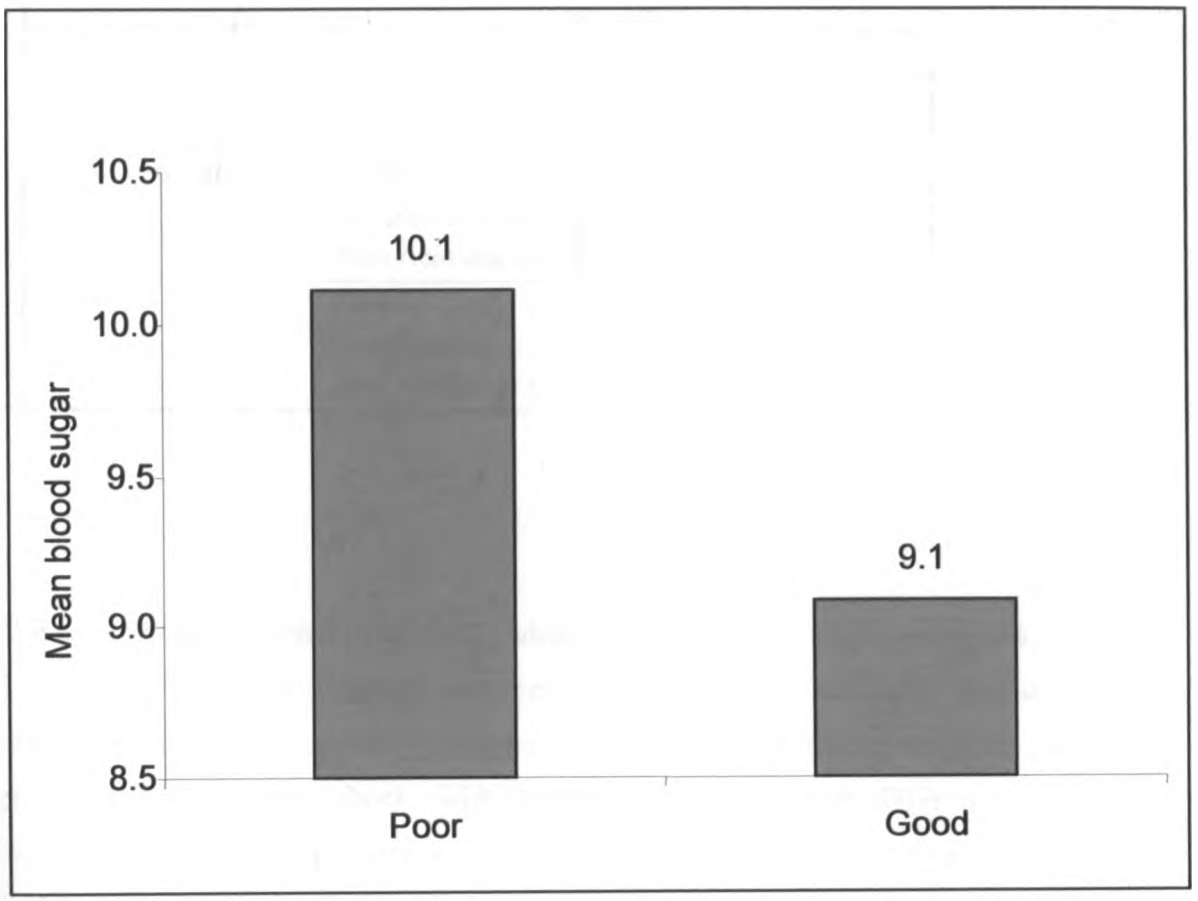
6.2% of patients had hypotension in the immediate post-operative period, of whom only 1 patient had HbA1c > 6.4%. There was no statistically significant correlation between HbA1c and hypotension ($p = 0.190$) [table 4].

	Hypotension		
	No	Yes	Total
HbA1c < 6.4 %	102	6	108
HBA1c 6.4% and over	4	1	5
Total	106	7	113

Table 4 – Cross tabulation of hypotension and HbA1c ($X^2 = 1.716$, $p = 0.190$)

6.2% of patients reversed poorly from anaesthesia, whereas 93.8% had a good reversal from anaesthesia.

Figure 20 – Mean blood sugar and reversal from anaesthesia



The mean blood sugar of the patients who reversed poorly from anaesthesia was 10.1 mmol/l compared to 9.1 mmol/l in the good reversal group, and this was not statistically significant ($p = 0.476$).

Of the patients who reversed poorly, only 1 (14.3%) had a HbA1c of more than 6.4% . There was no statistical significance between HbA1c and reversal from anaesthesia (X^2 = 1.716, p = 0.190) [table 5].

Table 5 – Cross tabulation of reversal from anaethesia and HbA1c

			Reversal from Anaesthesia		
			poor	good	Total
HbA1c	<6.4	Count	6	102	108
		% within Reversal from Anaesthesia	85.7%	96.2%	95.6%
	6.4 and over	Count	1	4	5
		% within Reversal from Anaesthesia	14.3%	3.8%	4.4%
Total		Count	7	106	113
		% within Reversal from Anaesthesia	100.0%	100.0%	100.0%

The patients who reversed poorly were admitted to the intensive care unit (4.4%).

2 patients presented for surgery with peritonitis requiring laparotomy. One developed respiratory distress immediately post-operative requiring ventilatory support. The other patient developed septic shock with symptoms of hypotension, fever and respiratory distress requiring inotropic support, ventilatory support and antibiotic treatment.

One patient who had eclampsia, developed respiratory distress immediately following caesarean section and required ventilation in the intensive care unit. Another developed respiratory distress following elevation of depressed skull fractures.

There were no recorded deaths in the immediate post-operative period in the group of patients studied.

DISCUSSION

The prevalence of type 1 diabetes in sub Saharan Africa is 0.01%, however there are poor records on this. It was estimated that by 2003, there were about 40,000 patients with type 1 diabetes mellitus. The rest of the diabetic population is type 2 the prevalence being 2.4%, with numbers estimated at 7.1 million in 2003, to rise to 15 million in 2025.[52]

The study was carried out in Kenyatta National Hospital, a teaching and referral hospital in Kenya. The hospital receives 3500 patients with diabetes mellitus each year both out-patients and in-patients.[53]

The mean age of the study population was 51.76 years. This was almost similar to a mean of 52.2 years in the study by Raucoules-Aime[46] and was comparable to 65.6 and 62.75 years in other previous studies.[4,12] The median age was 53 years, whereas in the Dronge[54] study it was 71.3 years. The age range was 12 – 90 years compared to 25 – 75 years in the study by Raucoules-Aime[46] and 38 – 87 years in the study by Dronge.[54]
The selection of patients in this study was random, and their surgical diagnoses were varied hence the wide age range; this compares to the study by Raucoules-Aime[46] that included patients who presented for major or minor surgery; and the study by Dronge[54] that included patients who presented for non-cardiac surgery. The age ranges in these two studies were also wide. In the studies by McAlister[4] and Golden,[12] the patients were selected by their surgical diagnosis: the patients were presenting for coronary artery bypass surgery. Coronary artery disease tends to occur in diabetics and the older population, a combination seen commonly in > 60 years in the Western world.
45% of patients were male, compared to 54% male patients in a study by Golden et al[12] and 71% in the study by Van den Berghe[49].
The mean duration of diabetes was 4.9 years and median duration of 2 years which was much lower than 12.7 years and 10 years respectively in the study by McAlister.[4]
The demographic variation reflects multiple factors including age of onset of diabetes, reasons for surgical intervention, affordability of health care facilities as well as the diverse established health care systems that vary in countries world wide.

Regarding the pre-operative diabetes treatment used, majority of patients (38.1%) were on insulin only whereas 23% were on oral hypoglycaemic treatment only. In the studies by Golden et al[12] and McAlister et al,[4] majority of patients were on oral hypoglycaemic treatment only compared to insulin treatment (45.1% and 50% on oral hypoglycaemic agents compared to 41.7% and 22% on insulin treatment respectively). 34.5% of patients were on diet only compared to a lower number, 20% in the McAlister[4] study and 11.7% in the Golden et al[12] study. The percentage of patients on insulin and oral hypoglycaemic treatment combined was lower in the 3 studies : 4.4% in this study, 8% in the study by McAlister[4] and 1.5 % in the study by Golden.[12] In this study, there was statistically significant variation of means of HbA1c within the diabetic treatment used. In the study by Dronge et al[54] on glycaemic control and post-operative infections, there was no comparison made between HbA1c and the type of diabetes treatment used pre-operatively. In that study though 59% of patients used oral hypoglycaemic agents, and 41% used insulin; the diabetic treatment did not have any impact on outcome following surgery.

The median HbA1c was 4.1% which was much lower than a median of 7.3% in the Dronge[54] study. In the study by Dronge[54] the HbA1c levels ranged from 4.6 – 15.1%. In this study, most of the diabetic patients had good glycaemic control as evidenced by the low levels of HbA1c ranging from 1.5 – 7.7%. Furthermore, the study did not selectively look at a particular group of diabetics. Also in the sequential sampling, quite a significant number of patients had diabetes for a period of less than 1 year, whereas in the Dronge[54] study, the objective was to study long standing diabetes, glycaemic control and surgical outcomes.

The findings of good glycaemic control in this study are unexpected considering the fact that some patients presented for surgery with conditions that were related to diabetes such as diabetic foot, retinopathy, diabetic ulcer, and septic wounds where HbA1c would be expected to be high, whereas other conditions were unrelated to diabetes such as fractures, tumors, and appendicitis. Even those patients presenting for emergency procedures, whose control was expected to be poor, had good control. In addition to this

unexpected finding, local studies carried out on ambulatory patients at the out-patient clinic found that 60.5% of patients had poor glycaemic control (HbA1c $\geq$ 8%).[53] This discrepancy may be explained with the fact that the patients in this study were randomly selected, all diabetic patients presenting for any type of surgery, emergency or elective were recruited. Another reason could be the difference in HbA1c assay methods. Since the tests were performed in one laboratory, there could be differences in assays within the same laboratory, probably observational. Differences in the reference ranges could also explain this discrepancy. Alternatively, because of cost-sharing policy, the patients presenting for surgery were able to afford care both for their diabetic condition, and surgical intervention. In addition, the patients who presented for elective surgery, had good glycaemic control due to adequate preparation pre-operatively through attendance and follow-up in the diabetic clinics. The patients who presented for emergency surgery, had their blood sugars controlled in the wards before they were brought to theatre. Furthermore, diabetes associated complications will occur despite the sugar control, good glycaemic control reduces the onset time, extent and severity of these complications. There is also a possibility that other factors contributed as co-morbidities and these were not identified in this study. Finally, no random study has been carried out in the outpatient department to determine the number of diabetic patients that have had surgery and their glycaemic profiles.

In the study by Bolli,[55] there was a close correlation between HbA1 and fasting plasma glucose, confirming that HbA1 reflects blood glucose levels in diabetics and is a good indicator of glycaemic control in patients with clinically overt diabetes. Results of this study support this; there was statistically significant correlation between HbA1c and random blood sugar at time of presentation for surgery, considered as time 0.

There was also a statistically significant correlation between HbA1c and random blood sugars at ½ and 1 hour intra-operatively. This correlation was lost at 1.5 and 2 hours probably due to the intra-operative treatment used including the glucose infusion alongside insulin, the amount of insulin used and the hormonal response to surgical stress. Another study by Derr et al[56] also had similar conclusions, after an analysis of the relationship between HbA1c and mean blood glucose of 256 subjects who self monitored

their blood glucose. A close correlation between HbA1c and mean blood glucose was found ($r = 0.62$, $p < 0.001$). Thus the mean of multiple blood glucose assays are a fair measure of HbA1c over the period.

The mean pre-operative blood sugar of 8.7 mmol/l was comparable to a mean of 8.4 mmol/l in the study by Raucoules-Aime.[57] The mean intra-operative blood sugar was 9.14 mmol/l depicting an optimal glycaemic control. There was suboptimal glycaemic control with mean blood sugar of 11.4 mmol/l in the McAlister[4] study on outcome of diabetic patients who underwent coronary artery bypass grafting. The study by Golden et al[12] on the development of infectious complications in diabetics who underwent coronary artery surgery, had an even higher mean of 12.7 mmol/l. The range of mean blood sugars was comparable for the two: 4 – 19 mmol/l in this study versus 6.7 – 19.5 mmol/l in the study by Golden.[12]

In this study, 68.1% of patients had blood sugar levels below 10 mmol/l compared to 85% of patients with blood sugar less than 11.1 mmol/l in the Furnary[41] study carried out over a period of 10 years on the development of deep sternal wound infections following open heart surgery on diabetic patients; and 11% in the study by Thomas[43] on diabetic patients who underwent renal transplant and the developed a rejection episode.

The mean total amount of insulin used intra-operatively in the patients who required insulin, was 6.7 units (4.8 units/hr) which was comparable to, though slightly higher than the total amount of insulin used for patient undergoing major surgery (3.0 units/hr) in the study by Raucoules-Aime.[46] Most of the patients who received insulin intra-operatively had been on insulin treatment prior to surgery, thus this may explain the high mean intra-operative insulin dose.

The mean duration of surgery was 77 minutes compared to 115 minutes in the study by Dronge.[54] The mean duration of surgery for patients who had general anaesthesia, was still lower (85.54 minutes), though it was higher than for patients who had local anaesthesia (51.55 minutes). The pre-operative estimated surgical time and type of surgery, though not included in the study, influenced to some extent the choice of

anaesthetic technique. The least surgical time for patient undergoing surgery under general anaesthesia was 20 minutes for curettage for endometrial hyperplasia, whereas the longest time was 6 hours for decompression for cord compression. The least surgical time for patient having surgery under regional anaesthesia, was 20 minutes for cryotherapy for glaucoma, while the surgery time was 2 hours for cryotherapy for retinal haemorrhage under regional anaesthesia.

The mean total amount of insulin used in patients who had general anaesthesia was 7 units compared to 5.8 units in patients who had regional anaesthesia.

Surgery and anaesthesia, in general elicits a neuroendocrine response resulting in hyperglycaemia and insulin intolerance. In the diabetic patient, the stress of surgery results in altered glucose homeostasis interfering with glycaemic control in the well controlled patient, and worsening hyperglycaemia in the poorly controlled patient, increasing the insulin requirements. Tight glycaemic control means maintaining blood glucose levels within a target range of 6.67 – 10 mmol/l during the peri-operative period. This is best achieved through use of insulin infusion, as this can be altered according to the blood glucose results.

In this study, various regimens were employed, depending on the anaesthetist's preferences. An algorithm could have been used to standardize the treatment, however this was not one of the objectives.

Patients who were on diet pre-operatively had the best glycaemic control and most of them did not require insulin intra-operatively probably due to an adequate pancreatic reserve. Most of the patients who were on insulin treatment pre-operatively, received insulin intra-operatively; while almost half of the patients who were on oral hypoglycaemic agent received insulin during surgery, and the other half did not receive insulin. The patients who were on combined oral hypoglycaemic agent and insulin had relatively poor pre-operative glycaemic control, and all except one received insulin intra-operatively. It is possible that these patients also required insulin due to reduced pancreatic reserve.

Reversal refers to antagonism of muscle relaxants through use of anticholinesterase agents such as neostigmine. Reversal is influenced by a number of factors including age, (elderly are more likely to reverse poorly than younger patients), use of narcotic agents or sedating agents, time between administration of last muscle relaxant dose and end of surgery, metabolic causes, idiosyncracy and even the primary presenting pathology unique to each patient. Diabetic mellitus may delay reversal from anaesthesia either due to hypoglycaemia, ketoacidosis, hyperosmolar coma, or autonomic effects such as hypotension. Majority of the patients in this study (93.8%) reversed well from anaesthesia. This could be due to the good glycaemic control observed in the patients in the study, or due to the fact that the diabetic patients may not have had diabetes for long (the duration of diabetes for 51.3% of the patients was < 1 year), hence the paucity of diabetes-related complications of serious magnitude.

14.3% of patients who reversed poorly had HbA1c > 6.4%. Findings from a previous study on poor outcome (mortality) showed that 82% mortality of diabetic men occurred with HbA1c between 5 and 6.9%.[29] Dronge[54] and colleagues examined relationship between glycaemic control through HbA1c and post-operative infections in diabetic patients who underwent major non-cardiac surgery in the Veterans Affairs Connecticut Healthcare System and the findings were that 12% of patients who had HbA1c < 7%, had infectious complications, whereas 20% of patients who had HbA1c ≥ 7% had infectious complications post-operatively, including pneumonia, wound infections, urinary tract infections, or sepsis. Thus good glycaemic control assessed by HbA1c, is associated with good outcome following surgery.

The mean blood glucose of the patients who reversed poorly was 10.1 mmol/l compared to 9.1 mmol/l in the patients who reversed well from anaesthesia. It can thus be concluded that patients with mean blood glucose of > 10.1 mmol/l are likely to experience immediate post-operative complications including poor reversal from anaesthesia, respiratory distress, hypotension and admission to the intensive care unit. These findings support conclusions from an earlier study by Golden[12] and associates, where diabetic patients who underwent coronary artery surgery developed short-term infectious complications at post-operative blood sugar > 11.5 mmol/l. The findings also

concur with results from the study by McAlister[4] where 27% of patients who had undergone coronary artery bypass grafting, and had mean blood glucose ≥ 12.5 mmol/l suffered adverse outcomes post-operatively including non-fatal stroke, septic complications and death. In another study by Van den Berghe,[49] of patients admitted to the surgical intensive care unit following surgery or multiple trauma, patients whose blood glucose levels were kept between 4.4 – 6.1 mmol/l with intensive insulin therapy had mortality of 4.6%, whereas those patients whose blood glucose were > 11.0 mmol/l and on conventional insulin therapy, had mortality of 8%, the causes of mortality being multiple organ failure with or without a septic focus, severe brain damage and acute cardiovascular collapse.

It was not possible in this study to also outline whether patients who had regional anaesthetic techniques had any related poor neurological outcomes as a sequelae of the local anaesthetic agent in the presence of diabetes mellitus in comparison to non-diabetic patients. Studies otherwise have shown the presence of diabetic autonomic neuropathy may lead to poor tolerance of spinal anaesthesia-induced hypotension among patients with co-existing coronary artery, cerebrovascular or renovascular disease.[35]

CONCLUSION

Glycaemic control of patients pre-operatively was optimal as evidenced by the HbA1c and the pre-operative blood glucose levels. Patients managed on diet pre-operatively had the best control.

Good glycaemic control was achieved intra-operatively through use of insulin in patients who were on insulin, oral hypoglycaemic agent, and combined oral hypoglycaemic agent and insulin pre-operatively. Most of the patients who were on diet, did not require insulin intra-operatively.

Good glycaemic control, (mean blood sugar < 10 mmol/l) was not associated with immediate post-operative complications.

Pre-operative blood glucose and intra-operative blood glucose taken up to 1 hour intra-operatively, correlated well with HbA1c. Therefore, HbA1c could be used as a predictor of outcome of surgery of diabetic patients.

Post-operative complications experienced by the patients in this study included poor reversal from anaesthesia, respiratory distress, hypotension, and some were admitted to the intensive care unit.

RECOMMENDATIONS

Closer intra-operative monitoring of wide range diabetic patients needs to be done to outline other co-morbid factors that may be associated with poor outcomes.

A study of outcome of diabetic patients admitted to the intensive care unit following surgery is required regarding duration of stay in the ICU, level of glycaemia, causes of morbidity including post-operative infections, and incidence of mortality.

STUDY LIMITATIONS

This was a cross sectional study that included all forms of anaesthesia; regional and general anaesthesia, and it was not determined whether changes in intra-operative treatment would influence the relationship between glycaemic control and outcome following surgery. The study did not compare the type of anaesthesia and their influences outcome of surgery in the diabetic patient.

The co-morbidities that were associated with diabetes were not factored in the analysis in this study. Other factors that could influence outcome of surgery were not excluded, for instance, outcome of head injury, eclampsia, and peritonitis is likely to be poor whether the patient is diabetic or not.

An algorithm for insulin use intra-operatively was not used, thus insulin administration and dose was left at the discretion of the anaesthetist. It is therefore expected that since the patterns of glycaemic control intra-operatively were different, the outcome would be poor. However, glycaemic control was optimal, and the study being observational serves as an audit of existing practices peri-operatively.

The study did not look at the presence of diabetic autonomic neuropathy and its possible effects on general as well as regional anaesthesia.
Any neurological outcomes in the diabetic patients who had regional anaesthesia were not outlined in this study.

APPENDIX 1

INFORMED CONSENT FORM

I _____ agree to take part in this study explained to me by

_____ with all the risks and side effects that might occur.

My participation is out of my own will and not due to the benefits I may or may not gain from the study.

Participant's signature _____

I, the researcher, have explained fully to the participant about the study, its benefits and side effects, and have not with held any information regarding the study. I have also assured the participant of his or her confidentiality during the study, and in case he withdraws from the study.

Researcher's signature _____

APPENDIX 2

QUESTIONNAIRE

Name _____ Age ____ Sex ____

Duration of diabetes _____

Diabetes treatment used by patient

Diet only □ Insulin only □ Insulin and Oral hypoglycaemic agent □

Oral hypoglycaemic agent only □

Type of surgery_____

Emergency _____ Elective _____

HbA1c _____%

Type of anaesthesia : general _____ regional _____

Duration of surgery _____

Glucose measurements and insulin administered

Time ‡intraop	0 hr	½ hr	1 hr	1 ½ hr	2 hr	2 ½ hr	3 hr	3 ½ hr
Blood glucose								
Insulin dose + route								
Insulin infusion Fluid + dose of insulin								

Outcome at reversal

Haemodynamics

Blood pressure	Pulse rate	Temperature	Respiratory rate

Reversal from Anaesthesia

Good □ Poor □

Transfer from recovery ward

To general ward □ To Intensive Care Unit □ Death □

‡Intraop : intra-operative

KENYATTA NATIONALHOSPITAL
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Ref: KNH-ERC/01/3112 **Date: 3rd November 2005**

Dr. Jane K.Gwaro
Dept. of Surgery(Anaesthesia)
Faculty of Medicine
University of Nairobi

Dear Dr. Gwaro

RESEARCH PROPOSAL: "GLYCAEMIC CONTROL DURING SURGERY IN DIABETIC PATIENTS AT KENYATTA N.HOSPITAL" (P80/5/2005)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** revised version of your above cited research proposal for the period 3rd November 2005 – 2nd November 2006. You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M.Bhatt,Chairperson,KNH-ERC
The Deputy Director CS, KNH
The Dean,Faculty of Medicine,UON
The Chairman,Dept of Surgery(Anaesthesia) UON
The HOD, Medical Records, KNH
Supervisors: Dr T.M. Chokwe, Dept.of Medicine(Anaesthesia),UON
Dr. C.F. Otieno, Dept. of Medicine, UON

APPENDIX 4

HbA1c% liquidirect

Immunoassay for the Direct Photometric Determination of Glycohemoglobin A1c%

REF	10770	40 ml	Test Kit
	10776	4 x for 1 ml	Calibrator Set
	10775	4 x for 1 ml	Controls

IVD

Intended Use

For the quantitative determination in percent of hemoglobin A1c (HbA1c) in human blood. The determination of HbA1c is performed for the long term control in diabetes mellitus. HbA1c values provide an indication of the average glucose levels over the preceding 4-8 weeks. A high HbA1c value indicates poor glycemic control. HbA1c is normally expressed as percentage of the total Hb concentration: HbA1c%.
Recently the IFCC has recommended reference values for HbA1c to improve comparability between methods and laboratories.[5]

Method

This method utilises the linkage of antigen and antibody to directly determine the percentage of HbA1c in whole blood. Both total Hb and HbA1c bind competitively to specific latex particles, proportional to their concentration. Monoclonal antibodies (mouse) against HbA1c are cross-linked by anti-mouse antibodies (goat), and react specifically with HbA1c, resulting in an agglutination of the latex particles. The degree of agglutination depends on the amount of bound HbA1c. The increase of turbidity in the reaction mixture is measured photometrically. The HbA1c% value is extrapolated from a curve established with the calibrators.

Reagents

REF 10770

RGT1 1 x 30 ml Latex reagent

Latex	0.13 %
Glycine buffer	20 mmol/l

BUF 1 x 9.5 ml Buffer

Glycine buffer (pH 7.3)	80 mmol/l

AS 1 x 0.5 ml Antibodies

anti-human HbA1c (mouse, monoclonal)	0.05 mg/ml
anti-mouse IgG (goat, polyclonal)	0.08 mg/dl
Stabilisers	

LYS 2 x 100 ml Hemolysis reagent

Lysing reagent	
NaN3	0.05 %

REF 10776

CAL1...4 4 x for 1 ml Calibrators
Human blood (lyophilised)

Concentrations, traceable to the NGSP/DCCT are stated on the labels.

REF 10775

CBN 2 x for 1 ml Control blood normal

CBA 2 x for 1 ml Control blood abnormal
Human blood (lyophilised)

Concentrations are stated on the labels.

Reagent Preparation and Stability

RGT1 and LYS are ready to use.
Store reagents at 2...8°C. All reagents are stable to the expiration date stated on the labels.
RGT2 is prepared by pouring the entire contents of one vial AS into one vial BUF. Rinse vial AS with RGT2. Mix gently.
Reconstitute one vial CAL or CBN/A with exactly 1.0 ml dist. or deionised water. Shake gently for 10 min.
RGT1, LYS, RGT2, CAL and CBN/A are stable for 1 month after opening or preparation when stored at 2...8°C and tightly closed.

Specimen Collection and Preparation

Special preparation of the patient or fasting is unnecessary. Collect venous blood with EDTA using aseptic technique.
Stability: 1 week at 2...8°C.[7]

Hemolysis

Pipette into tubes	
LYS	1000 µl
Sample/CAL/CBN/A	20 µl
Mix, allow to stand for 5 min. or until complete hemolysis is evident. Use lysates for the assay. Stability: 10 days at 2...8°C	

Assay

Wavelength: 600 - 660 nm
Optical path: 1 cm
Temperature: 37°C

NEW

Pipetting Scheme

Mix RGT1 carefully prior to use to suspend the latex particles completely		
Pipette into cuvettes	Reagent blank (RB)	CAL or sample
RGT1	750 µl	750 µl
Hemolysate (Sample/CAL..)	—	20 µl
Mix and incubate for 5 min. at 37°C.		
RGT2	250 µl	250 µl
Mix, incubate for 5 min. at 37°C. Read absorbance of the sample (A_{sample}) and of CAL (A_{CAL}) against the reagent blank within 30 min.		

Keep ratio RGT1 : sample : RGT2 constant if total volume should be reduced.

Calculation

Calculate the absorbance difference ($\Delta A_{CAL} = A_{CAL} - A_{RB}$) of each calibrator and plot the values (y-axis) against the respective concentrations (x-axis). The concentration in the sample is interpolated from the calibration curve.
Conversion to the IFCC reference values:
HbA1c% (NGSP) = HbA1c% (IFCC) x 0.876 + 2.27
HbA1c% (IFCC) = HbA1c% (NGSP) x 1.142 - 2.60

Performance Characteristics

Linearity: The measure range is defined by the concentration range of the calibrators and may encompass 2.0 - 16.0% HbA1c.
Sensitivity: A ΔA = 0.073 absorbance change is approximately equivalent to 1.0% HbA1c.
Typical performance data can be found in the Verification Report, accessible via:
www.human.de/data/gb/vr/su-hba1c.pdf or
www.human-de.com/data/gb/vr/su-hba1c.pdf

Interferences

1. Bilirubin < 50 mg/dl, ascorbic acid < 50 mg/dl, triglycerides < 2000 mg/dl, carbamylated Hb < 7.5 mmol/l and acetylated Hb < 5.0 mmol/l and labile intermediates (Schiff base) do not interfere in this assay.[1]
2. Elevated levels of HbF may lead to underestimation of HbA1c.[4]

Recommended Values[5]

Less than 6% for a non-diabetic, less than 7% for glycemic control of a person with diabetes (NGSP[6]/DCCT[7]).
Each laboratory should establish its own recommended values. In using HbA1c to monitor diabetic patients, results should be interpreted individually. That is, the patient should be monitored against him or herself.

Quality Control

All control bloods with HbA1c% values determined by this method can be employed.
We recommend to use our human blood based controls REF 10775. If controls do not fall into the assayed range patient values from that run should not be reported. Repeat the run, making sure that all instructions are strictly followed.

Automation

Proposals to apply the reagents on analysers are available on request. Each laboratory has to validate the application in its own responsibility.

Note

CAL and CBN/A are derived from human material which has been tested with accepted methods and found non-reactive for HBsAg, anti-HCV and anti-HIV1/2 antibodies. As no test method can offer complete assurance, CAL and CBN/A should be handled as potentially infectious material.

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HemoCue Glucose 201+

The HemoCue Glucose 201+ is a system for the determination of the total amount of glucose in whole blood. The system consists of an analyser with specially designed cuvettes containing dried reagents. The system is factory calibrated according to a wet chemistry glucose dehydrogenase method using haemolysis and deproteinisation.
The analyser stores test results, QC tests, date and time for up to 600 results. The data can be printed directly via an external printer or downloaded to a PC. This portable, direct reading analyser should be used with HemoCue Glucose 201 Microcuvettes, available in vials or individually packaged.

Data	
Measuring range:	0-22.2 mmol/L (0-400 mg/dL)
Test time:	40-240 seconds
Test results:	mmol/L or mg/dL
Size:	w 85 mm / h 43 mm / d 160 mm
Weight:	350 g (batteries included)
Memory:	Stores up to 600 results
Power:	Four R6 or AA batteries or HemoCue AC/DC adapter

HemoCue Glucose 201 Microcuvettes Individually packaged

The individual packaging provides extra protection and increased stability for the microcuvette. It enables the user to withdraw from the refrigerator only as many cuvettes as are needed for the day, instead of a complete vial.
The disposable cuvette is made of plastic and comprises a body having a cavity which takes about 5 µL. The cuvette cavity contains reagents deposited on its inner walls and the blood sample is drawn into the cavity by capillary action and is spontaneously mixed with the reagents. Capillary, venous and arterial whole blood can be used. The cuvette is then placed in the HemoCue Glucose 201 or in the HemoCue Glucose 201+ in which the absorbance is measured and the glucose level calculated.

Data

Chemistry method:	A modified glucose dehydrogenase method
Stability:	Stored in refrigerator each individually packaged cuvette is stable until the expiry date. Stored at room temperature the individually packaged cuvette is stable for up to three days.
Package:	4 x 25 individually packaged cuvettes

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