THE PREVALENCE OF DYSGLYCAEMIA IN ACUTE CORONARY SYNDROMES: CAN THE EMERGENCY DEPARTMENT CONTRIBUTE IN IDENTIFYING THOSE AT HIGH RISK OF CORONARY ARTERY DISEASE?

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M. Med in Emergency Medicine

By

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To my husband, Michael, for his unfailing support and understanding, and my father, who encouraged me to embark on this career

STATEMENT OF DECLARATION

I declare that this dissertation is my own unaided work submitted in partial fulfillment for the degree M Med in the Department of Emergency Medicine, University of Cape Town. It has not been submitted before for any degree or examination at any other educational institution.

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Yolandé Smit August 2007

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SUMMARY

1. Introduction

Cardiovascular disease is second only to HIV/AIDS as a cause of death in South Africa and diabetes mellitus - a major cardiovascular risk factor - is considered one of the leading non-communicable causes of years-of-life-lost in both males and females. Other Coronary Artery Disease (CAD) risk factors (including visceral obesity, hypertriglyceridemia, low HDL-cholesterol and hypertension) are also more prevalent in this subset of patients. It has been predicted that the prevalence of insulin resistance spectrum of diseases will increase by more than 120% in African countries by 2010, and these estimates are rising.

2. Objective

To assess the prevalence of dysglycaemia, dyslipidaemia and other metabolic risk factors in patients presenting to the Emergency Department of Karl Bremer Hospital (an urban secondary level hospital in the Western Cape) with an acute coronary syndrome (ACS).

3. Methods

We performed a cross-sectional observational, descriptive study on 214 consecutive patients with the complaint of chest pain who were subsequently diagnosed as having an ACS. The following data was collected: demographics, anthropometry, 75g modified oral glucose tolerance test, fasting LDL-cholesterol, HDL-cholesterol and triglycerides.

Patients were stratified according to a clinical picture, the presence or absence of an enzyme leak and ECG changes, as having a coronary event with ST elevation, high risk

angina with enzyme leak, high risk angina with ST depression or low risk angina with no enzyme leak and no ECG changes. The Modified 1997 ADA Criteria were used to categorize dysglycaemia. The fasting lipogram included total cholesterol, LDL-C, HDL-C and triglycerides. Values were regarded as abnormal if triglycerides $\geq$ 1.7 mmol/l, HDL – C $\leq$ 1 mmol/l in men and $\leq$ 1.3 mmol/l in women, LDL- C > 3 mmol/l.

4. Results

Chest pain due to ACS was a common presentation to the ED, with a similar prevalence in the Coloured (11.6%) and White (14.9%) populations. However, despite the large proportion of black patients assessed (n=623), ACS still seems to be uncommon in this population (1.4%). Sixty five percent of patients were dysglycaemic (126) and 35% normoglycaemic (68). Dysglycaemia was common in males (62.9%) and females (67%), p=0.55. Patients with normal glucose tolerance (NGT) were more likely to have low risk unstable angina (UAP) in comparison to both their prediabetic and diabetic counterparts ($p < 0.01$) and less likely to develop complications ($p = 0.04$). Central obesity was present in 58.6% (123) of patients and more common in the dysglycaemic (80, 65.6%) than in the normoglycaemic group (32, 47.1%, $p = 0.01$) and more commonly associated with females (84, 79.3%) than males (39, 37.5%, $p < 0.01$). Two thirds of the subjects (135, 67.2%) had an increased body mass index (BMI) (defined as a BMI $\geq$ 25), with a similar prevalence in the normoglycaemic (42, 62.7%) and dysglycaemic (85, 73.3%) groups ($p = 0.13$). There was no relationship to sex, with 70 (70%) females and 65 (64%) males having an increased BMI (p=0.39). The most common lipid abnormality seen in patients with ACS was that of a low HDL-C (160, 82.9%). The prevalence of a low HDL

was more common in the prediabetic (44, 86.3%) and diabetic (61, 91%) groups than in those with NGT (47, 73.4%), p = 0.02, whereas there was a similar prevalence of high LDL in the NGT (45, 72.5%), prediabetic (34, 68.0%) and diabetic (40, 63.5%) groups (p = 0.5). More than two thirds of coloured patients (45, 70.3%) met the ATP III criteria for the metabolic syndrome, as did 58.7% (71) of whites (p = 0.12). The metabolic syndrome was more common in females (76, 76.8%) than males (48, 50%), p < 0.01, and appeared to be more common in coloured females (n=26, 86.7%) than white females (43, 70.5%), p=0.09, putting coloured females more at risk of developing metabolic syndrome than their white counterparts (risk ratio 2.1, 95% CI 0.81 – 5.29).

5. Conclusion

Chest pain due to an ACS constitutes a large proportion of patients seen in the ED, and affects both Coloureds and Whites to the same extent. In contrast, we found ACS to be uncommon in Blacks (despite predictions of a potential epidemic in this population group).

Dysglycaemia, dyslipidaemia and central obesity are common in subjects presenting to the ED with ACS. This is a prime opportunity for early detection of cardio-metabolic risk factors, and pleads for early intervention, or even preventable intervention in this group.

CHAPTER 1

INTRODUCTION

Cardiovascular disease is second only to HIV/AIDS as a cause of death in South Africa, and diabetes mellitus - a major cardiovascular risk factor - is considered to be one of the leading non-communicable causes of years-of-life-lost in both males and females.[1] The most common cause of death in these patients is macrovascular disease, with coronary artery disease (CAD) accounting for up to 75% of all deaths.[2] Not only do patients with diabetes have a higher incidence of CAD, but they also have a significantly worse outcome and higher mortality rates than their non-diabetic peers, both in the acute phase and during long-term follow-up[3].

Diabetes is traditionally defined according to glucose thresholds primarily determined by values where the prevalence of microvascular complications of hyperglycaemia starts to increase. Even though macrovascular disease is a major cause of death in patients with type 2 diabetes and impaired glucose tolerance, it has not been considered in the classification. It may well be that the glucose threshold at which cardiovascular disease develops is set at lower levels than that for diabetes: this category is now recognized as impaired glucose tolerance. It is not surprising that recent evidence shows that increased mortality is not only associated with diabetic patients but that even asymptomatic abnormalities of glucose metabolism more than double mortality and the risk for myocardial infarction and stroke [4,5] . It is biologically plausible that there is no single absolute value which separates normality from abnormality and vascular risk is increased in those individuals with higher glucose levels even if their levels fall within the range conventionally considered "normal".

Other CAD risk factors (including visceral obesity, hypertriglyceridemia, low HDL-cholesterol and hypertension) are also more prevalent in this subset of patients; this contributes to the increased risk but is not sufficient to totally explain it.[5] These are all factors that tend to be higher or more common in hyperglycaemic patients compared with normoglycaemic patients.[6]

It is now commonly accepted that type 2 diabetes is only the tip of an iceberg, the end result of a complex disease process characterized by insulin resistance. The presence of insulin resistance is observed many years before the onset of dysglycaemia and later frank hyperglycaemia diagnostic of type 2 diabetes. In most cases this dysglycaemia has been present for years before the diagnosis of type 2 diabetes is formally made. During this early period, a clustering of metabolic risk factors are already present, even before the onset of dysglycaemia. Insulin resistance (the result of genetic susceptibility and aggravated by environmental factors) causes impairment in glucose metabolism leading to decreased peripheral glucose uptake and unsuppressed glucose production by the liver, which, in time, leads to hyperglycaemia. Initially the pancreas is able to compensate by increasing insulin production as an attempt to maintain euglycaemia. Eventually ß-cell failure develops with resultant dysglycaemia, initially manifest as impaired glucose tolerance or impaired fasting glucose, and later progressing to type 2 diabetes. By the time the diagnosis of type 2 diabetes is made, 50% of ß-cell function has already been lost. Similarly, by the time the diagnosis of diabetes is made, macrovascular disease is already well established.[7] The United Kingdom Prospective Diabetes Study estimates that this period from insulin resistance to dysglycaemia may exceed 10 years.[8] Therefore it can be assumed that by the time that type 2 diabetes is diagnosed, macrovascular disease

is already well established and accordingly type 2 diabetes is considered to be a coronary equivalent and managed as such with secondary coronary prevention. It therefore is not surprising that insulin resistance per se is recognized as an independent risk factor for cardiovascular disease[9] and that impaired fasting glucose and impaired glucose tolerance are both recognized risk factors for future diabetes and cardiovascular disease.

A dramatic increase, indeed an epidemic, is predicted for type 2 diabetes including a variety of its dysglycaemic and phenotypic forerunners such as the Dysmetabolic Syndrome (Syndrome X, Insulin Resistance Syndrome, Metabolic Syndrome).[10] To highlight the association between the dysglycaemia and central obesity this condition has been referred to as diabesity.[11] In the USA the increase of these dysglycaemic syndromes will exceed 60% but the major burden of this disease complex will be seen in developing countries such as South Africa. It has been predicted that the prevalence of insulin resistance spectrum of diseases will increase by more than 120% in African countries by the Year 2010, and these estimates seems to be rising[12]. The prevalence of type 2 diabetes and impaired glucose tolerance has increased dramatically in several ethnic groups whose lifestyle has become 'westernized' in the last few decades.[13,14] The most striking features in these groups (and of most patients who develop type 2 diabetes) are increased weight gain and decreased physical activity, each of which increases the risk of diabetes. Some of our population groups in South Africa, such as the Indian population, already have a high incidence of type 2 diabetes; the effect of this is seen in their high prevalence of atherosclerotic vascular disease.

In other areas where the incidence of type 2 diabetes is low, a high prevalence of impaired glucose tolerance (IGT) has been recorded and perhaps this is a sign that the

dysglycaemic epidemic has already taken hold. This would indicate that we can expect a rise in type 2 diabetes in the future.[15,16] This has been attributed to urbanisation, physical inactivity and obesity which have been identified as important risk factors.

Marked regional differences exist for the incidence of CAD and are for the most part based on ethnic differences. It is well known that type 2 diabetes and CAD are common amongst the Indian population from KwaZulu Natal. It has also long been known that type 2 diabetes and IGT together with obesity, dyslipidaemia (with a low HDL-cholesterol and hypertriglyceridemia) and hypertension play an important role in the genesis of acute myocardial infarctions.[17] Other studies have demonstrated that abnormal glucose tolerance is an importance cardiovascular risk factor in elderly Indian women together with hypertension and dyslipidaemia.[18] A high rate of progression from IGT to frank type 2 diabetes in the Indian population has been observed and commented on[19] but whether this is a recent or continuing tendency remains to be seen. Data from a 10-year study showed that the Indian population had a high prevalence of type 2 diabetes. In addition, a high proportion of those with IGT progressed to diabetes during the period of observation, with the 2-hour post-load glucose at baseline, obesity and a high body mass index (BMI) being significant predictors of the conversion to diabetes.[20]

Survivors of an AMI in the Indian population have been shown to have a high incidence of dyslipidaemia, particularly high triglycerides and a low HDL-cholesterol which show a significant correlation with hypertension and obesity.[21] This profile, highly suggestive of insulin resistance, has been noted by other researchers to be, like smoking, strongly associated with ischaemic heart disease in this Indian population,[22] and very prevalent in young survivors of an AMI two decades ago, in whom there was also a strong family

history of type 2 diabetes.[23] More recent data confirm these associations in the Indian population of KwaZuluNatal.[24]

All the data from the South African Indian population point to an ethnic group which displays a severe insulin resistant phenotype and who consequently have a high incidence of CAD. There are suspicions that the incidence of this insulin resistant phenotype is getting worse and this is a further indication of the predicted epidemic of diabesity. It may be that there are other ethnic groups in other geographical areas that are also prone to display an insulin resistant phenotype when exposed to an adverse diet and environment. There are some indications that the population of the Western Cape Province, for various reasons, may also be particularly prone to develop CAD.

In the Western Cape, the high prevalence of cardiovascular risk factors amongst the Coloured population has been documented.[25-27] In addition, the suboptimal management of these risk factors has been noted[25] and the similar poor management of hypertension has been singled out as showing room for marked improvement.[28,29] A higher incidence of CAD in the White than in other populations has been shown, whereas cerebrovascular disease predominated in the Coloured and Black populations.[25,30] In the Black population urbanisation has been shown to be associated with unhealthier lifestyles and an increased risk for chronic diseases of lifestyle. Elsewhere central obesity has been associated with an increase in non-communicable diseases and there is no reason to believe this will not be so in the Black population of the Western Cape.[31] Other cardiovascular risk factors demonstrated to be associated with urbanisation are hypertension,[32] type 2 diabetes[33] (which showed an increase over previous estimates) and obesity. The less than optimal management of diabetes has also been highlighted.[34,35] Conditions are such that an

increase in the prevalence of CAD in the Black population of the Western Cape is favoured, supporting widespread anecdotal data which points to an increase in CAD in this ethnic group, particularly amongst type 2 diabetics. There is as yet no evidence that this suggested epidemic has occurred or is even starting to develop. Thus far it is all anecdotal.

In support of anecdotal observations, the above data indicate that the population of the Western Cape, and in particular the Coloured population, is an insulin resistant population. Unpublished data from the Karl Bremer Hospital (KBH) shows that the admission profile at the hospital has changed from one where communicable diseases predominated to a present profile where chest pain due to acute coronary syndromes is the commonest single symptom seen in the medical Emergency Department. It is also the general impression that many more patients are being seen at the hospital who display a very typical dysmetabolic phenotype and that the presence of dysglycaemia has increased dramatically over the past four years. This is all interpreted as suggesting that the diabesity epidemic is not waiting to happen but has already started and is well on the way to causing a dramatic increase in acute coronary syndromes in the Western Cape. It is therefore evident that data regarding the profile of patients admitted for the management of acute coronary syndrome will be important to manage an envisaged increase in this condition, and the associated increase in a general insulin resistant phenotype in the population of the Western Cape. We therefore undertook a study at KBH to investigate this.

CHAPTER 2

STUDY DESIGN AND METHODS

2.1. AIMS

Primary aims

i. To assess the prevalence of dysglycaemia in patients admitted with ACS in the KBH population.

Secondary aims

i. To determine the cardio-metabolic profile of patients admitted with ACS.

ii. To determine the level of glycaemic control in patients previously diagnosed with diabetes.

2.2. METHODOLOGY

A. PATIENTS

We performed a cross-sectional observational, descriptive study on consecutive patients presenting to the Emergency Department (ED) of KBH (an urban secondary level hospital in the Western Cape) with the complaint of chest pain who were subsequently diagnosed as having an ACS. Data were collected during the period 26 May 2004 to 4 September 2004.

There was no comparison with any other groups. The population presenting to KBH are resident in the drainage area of KBH which encompasses the municipal area of Durbanville, Brackenfell, Kuilsriver and Khayelitsha. The population consists of White, Coloured and Black patients with varying levels of income.

The collection of data including risk factor history, clinical stratification of ACS, ECG measurement and blood collection was performed by the medical officers working in the ED, using a standardised tick list. Anthropometric measurements and vital signs were obtained by the nursing staff. The following Inclusion and Exclusion criteria defined the population whose data was collected:

Inclusion Criteria

1. All patients presenting with chest pain and subsequently admitted with the diagnosis of acute coronary syndrome, defined as:
    a. Unstable angina
        i. Low risk
            - no ECG changes and no positive biomarkers
        ii. High risk
            - with ECG changes and no positive biomarkers, or
            - positive biomarkers with or without ECG changes (NSTEMI)
    b. Myocardial infarction
        i. ST-elevation
        ii. New left bundle branch block (LBBB)
2. Men and women aged 18 years and older
3. Provision of signed and dated informed consent prior to any study procedures

Exclusion Criteria

1. Patients with chest pain but who were not initially diagnosed on admission to have an ACS
2. Patients who declined the glucose tolerance test
3. Patients who were too unstable, in the opinion of the investigator

Standard clinical practice was followed in all patients admitted with ACS.

B. MEASUREMENTS

The following measures were obtained:

1 Demographic data

1.1 Age

1.2 Sex

1.3 Race

2 Risk factor history

2.1 Family history of premature coronary artery disease (CAD)

2.2 Family history of type 2 diabetes

2.3 Family history of dyslipidaemia

2.4 Personal history of CAD

- Stable angina
- Previous unstable angina
- Previous acute myocardial infarction
- Previous CABG

- Previous percutaneous intervention (PCI)

2.5 History of other vascular disease

- Peripheral vascular disease
- Cerebrovascular disease (previous stroke, previous transient ischaemic event)

2.6 Smoking history

2.7 Presence of hypertension

2.8 Presence of type 2 diabetes

2.9 Presence of dyslipidaemia

3 Vital signs and anthropometric measurements

3.1 Blood pressure in mmHg

3.2 Pulse

3.3 Height in cm

3.4 Weight in kg

3.5 Abdominal circumference in cm

3.6 Hip circumference in cm

4 ECG

Ischaemic changes were diagnosed on ECG if:

4.1 T wave inversion > 3 mm

4.2 ST depression > 1mm

4.3 Transient ST elevation > 1mm (<30 min)

4.4 Persistent ST elevation > 1mm (>30 min)

4.5 New LBBB

5 Clinical stratification

Acute coronary syndrome was diagnosed, according to the South African Guidelines, as either unstable angina, NSTEMI or STEMI. Unstable angina was accordingly diagnosed as a clinical state with change in pattern of anginal pain, including new onset symptoms, increase in frequency or intensity of angina, chest pain at rest and post-infarct angina. The acute coronary syndromes were clinically stratified as:

- Low risk unstable angina: where there is no ECG changes and no cardiac enzyme leak
- High risk unstable angina: where there is either ECG changes with no enzyme leak, or an enzyme leak with or without ECG changes (NSTEMI), excluding ST elevation or new LBBB
- Myocardial infarction: either ST elevation or new LBBB

6 Bloods

Blood was sent away for analysis for the following on a *routine basis* in patients diagnosed to have an ACS:

6.1 Formal laboratory haemoglobin (Hb) measurement

6.2 Creatinine

6.3 Cardiac enzymes (CK and CK-MB) 6 hours or more after onset of the index pain for:

- Initial estimation
- Follow up estimation in the case of recurrence of chest pain

6.4 Random blood glucose testing on admission (bedside)

Blood was also collected for *study purposes*:

6.5 Modified 2 hour oral glucose tolerance test (OGTT)

A modified 75g glucose tolerance test was performed on all patients prior to discharge to identify dysglycaemia. The following blood samples were obtained:

- 10 hour fasting glucose level and
- 2 hour post load glucose levels

The ***Modified 1997 ADA Criteria*** were used to categorize dysglycaemia.

Table 1: Modified 1997 ADA Criteria

	Fasting	**2 hr post glucose**
NGT	< 5.6	< 7.8
IFG	5.6 - 6.9	-
IGT	-	7.8 - 11.0
DM	≥ 7	≥11.1

NGT = normal glucose tolerance, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, DM = diabetes mellitus

6.6 Fasting lipogram incorporating total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. Values were regarded as abnormal if:

- Triglycerides ≥ 1.7 mmol/l
- HDL – cholesterol ≤ 1 mmol/l in men and ≤ 1.3 mmol/l in women
- LDL cholesterol > 3 mmol/l

LDL- cholesterol was calculated by the following formula, provided that the total triglycerides did not exceed 4 mmol/l:

LDL-cholesterol = T-cholesterol - [Triglycerides/2.18 + HDL]

6.7 HbA_1c

All bloods collected were measured by conventional laboratory methods.

2.3. STATISTICAL ANALYSIS

Data were captured into a Microsoft Excel© database. All statistical analyses were performed using the statistical software Stata version 8©. The chi-square test was used for all categorical data. The Wilcoxon rank sum and Kruskal-Wallis tests were used for all non-parametric variables. Data are presented as medians and range as the data were skewed. Measures of association was performed by calculating risk ratios. A p-value of 0.05 or less was regarded as statistically significant.

2.4. ETHICAL APPROVAL

The Ethics Committee of Karl Bremer Hospital as well as the Research Ethics Committee of the University of Cape Town granted approval for the study.

CHAPTER 3

RESULTS

The ED evaluated 2131 medical emergencies (excluding triage, minor complaints, surgical and gynaecological conditions) during the period 26 May to 4 September 2004. Of the 2131, 951 (45%) were male and 1180 (55%) were female. Acute coronary syndromes were responsible for 10% (n=214) of ED visits.

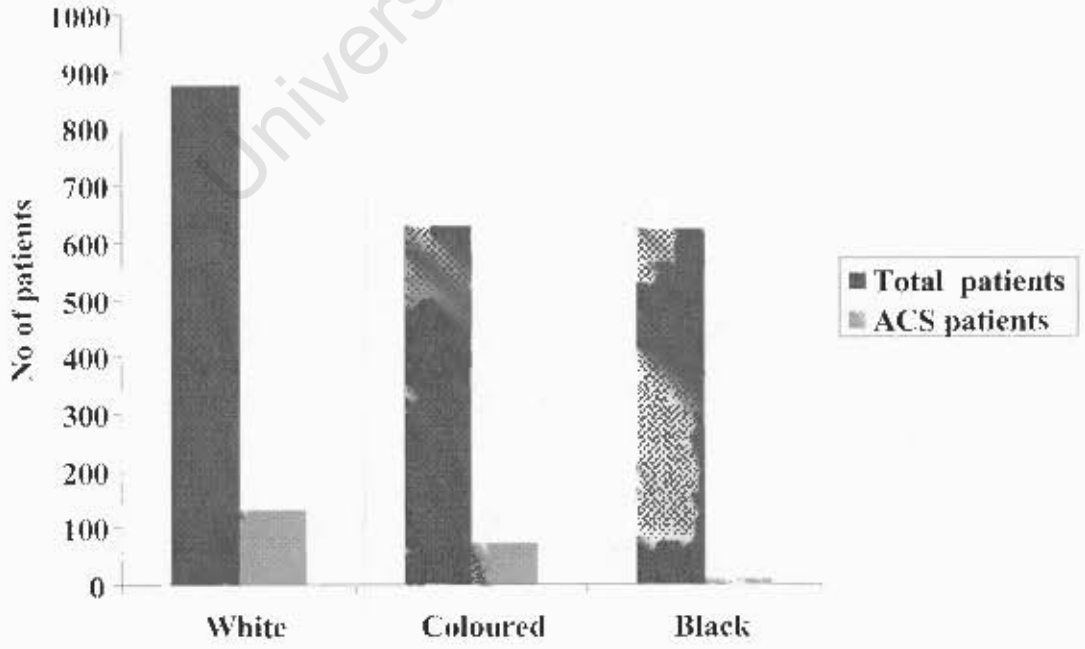
3.1. Demographic Data

The majority of patients diagnosed with ACS were White (n=131, 61.2%), followed by the Coloured (73, 34.1%) and Black (9, 4.2%) population. Patients of other ethnicity constituted only 0.5% (1). There were equal numbers of males (107) and females (107), reflecting a slightly higher prevalence of ACS in males (11.3%) than in females (9.1%). The median age of patients with ACS was 62 years (range 24 – 97), with the median age of females significantly higher than males (68 and 57 years respectively, $p < 0.01$). There was no statistically significant difference in the median age of the two main ethnic groups: Whites (63 years) and Coloureds (59 years) ($p = 0.15$). Demographic details of patients evaluated are presented in table 2 and figure 1.

Table 2: Demographic characteristics of patients evaluated in the ED

	Total patients n=2131	ACS patients n=214
Age (median, range)(years)	44 (18 - 97)	62 (24 - 97)
Ethnicity		
White	877	131
Coloured	629	73
Black	623	9
Other	2	1
Gender		
Male	951	107
Female	1180	107

Figure 1: Ethnic distribution in patients seen in ED and those with ACS



3.2. Clinical Findings

At least one risk factor for cardiovascular disease (on history) was present in 203 patients (94.9%). Hypertension was the most common risk factor, followed by known CAD and a family history of CAD, cigarette smoking (current), type 2 diabetes, a family history of type 2 diabetes, high cholesterol, peripheral vascular disease and stroke (table 3). Two or more cardiovascular risk factors were present in 158 patients (73.8%), 3 or more in 103 patients (48.1%), 4 or more in 50 patients (23.4%), 5 or more in 19 patients (8.9%) and 4 patients (1.9%) had 6 risk factors. In total, 73 patients (34.1%) were diagnosed with low risk unstable angina, 76 (35.5%) with high risk unstable angina, 31 (14.5%) with NSTEMI and 34 (15.9%) with STEMI. In-hospital complications occurred in 85 patients (39.7%). Congestive heart failure was the most common complication. A small subset of patients were referred to a tertiary hospital for invasive intervention and an even smaller group died (table 4).

Table 3: Risk factors for CAD on history

Risk Factor	Number patients	Percentage
Hypertension	143	66.8
Known CAD	113	52.8
Family history of CAD	71	33.2
Smoking history	64	29.9
Diabetes Mellitus	52	24.3
Family history of DM	51	23.8
High Cholesterol	34	15.9
Peripheral vascular disease	32	14.9
Cerebrovascular disease	25	11.7

Table 4: In-hospital complications

Complication	Number patients	Percentage
None	129	60.3
Congestive heart failure	75	35.1
Recurrent angina	6	2.8
Referred	13	6.1
Death	7	3.3

3.3. Oral glucose tolerance

The glycaemic profile was determined and compared in 194 of the 214 patients admitted with ACS. It was not done in 20 patients due to unwillingness (n=10), death (n=3) or transfer to a tertiary institute for further intervention (n=7).

Glucose categories A modified oral glucose tolerance test was performed at discharge on all patients admitted with an ACS and not already known to have diabetes (142). Taking the known diabetics into account, patients were then divided into those with a normal glucose tolerance (68, 35.1%) and those with dysglycaemia (126, 64.9%). Subjects who had a prior history of diabetes were classified as having previously diagnosed diabetes. Other subjects were classified according to the modified 1997 ADA criteria, as having a normal glucose tolerance, an isolated impaired fasting glucose, an isolated impaired glucose tolerance, both impaired fasting glucose and impaired glucose tolerance (the latter three categories also known as prediabetes) or diabetes. Patients with diabetes were subdivided into those already known to have diabetes and those with newly diagnosed diabetes. Classification of glucose abnormalities according to the 1997 modified ADA criteria are tabulated in table 5. The prevalence of glucose abnormalities

were determined with the fasting plasma glucose (FPG) test alone and then compared to the prevalence of dysglycaemia when adding the 2 hr post–load glucose (PG) value (table 6).

Table 5: Prevalence of glucose abnormalities according to 1997 modified ADA criteria

Glucose category		n	%
Normal (35.1%)	*NGT*	68	35.1
Prediabetes (26.8%)	*Isolated IFG*	13	6.7
	Isolated IGT	23	11.9
	IFG and IGT	16	8.3
Diabetes (38.1%)	*New*	22	11.3
	Old	52	26.8

NGT = normal glucose tolerance, IFG = impaired fasting glucose, IGT = impaired glucose tolerance

Table 6: Number of patients recruited with FPG, 2 hr PG and the total of glucose abnormalities

	FPG	2 hr PG	Both
NGT	100	58	68
IGT	29	39	52
DM	13	18	22

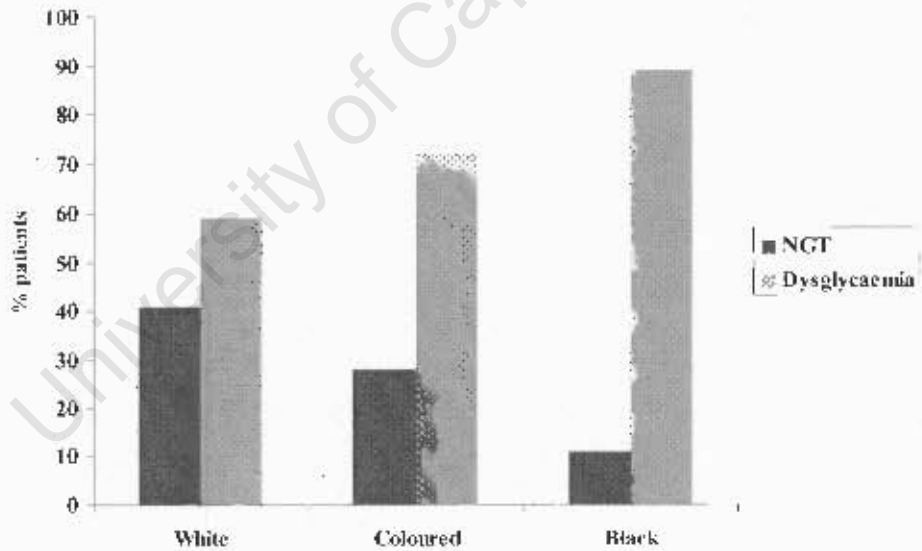
NGT = normal glucose tolerance, IGT = impaired glucose tolerance, DM = diabetes

FPG = fasting plasma glucose, 2 hr PG = 2hr post-load glucose

Recruiting diabetic patients by either criterion alone or their combination, 40.1% (9) met both, 18.2% (4) met the fasting criteria alone and 40.9% (9) met the 2 hr post load criterion alone. Similarly, recruiting patients with impaired glucose tolerance by either criterion alone or their combination, 30.8% (16) met both, 25% (13) met the fasting criteria only and 44.2% (23) met the 2 hr post-load criterion alone.

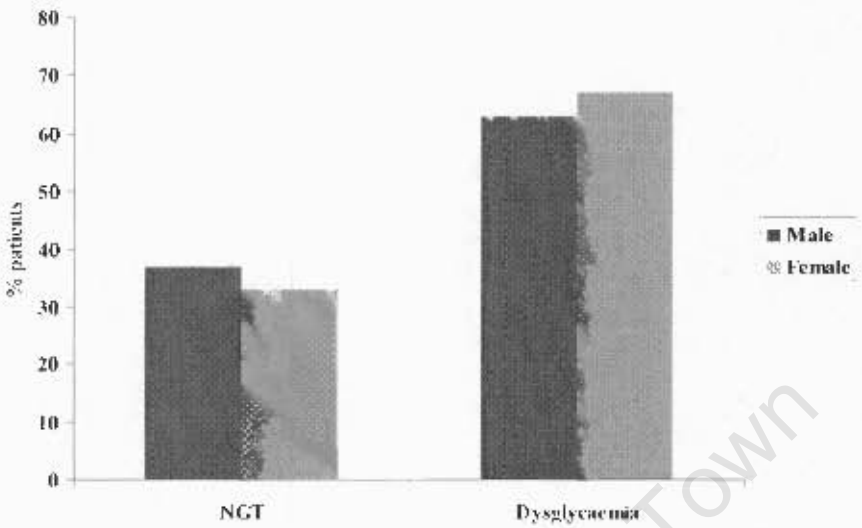
Demographics Dysglycaemia was more common in Coloureds (72.3% of all Coloureds) than Whites (58.8%), however, this did not reach statistical significance (p=0.07). The majority of Blacks (88.9%) and all Indians had dysglycaemia but these latter two groups were too small to be statistically significant (figure 2).

Figure 2: Distribution of dysglycaemia by ethnicity



Dysglycaemia was common in both males (62.9% of all males) and females (67%), p=0.55 (figure 3). The median age of patients with dysglycaemia (65 years, range 38-97) was significantly higher than those with NGT (56 years, range 24-90) (p = 0.03).

Figure 3: Distribution of dysglycaemia by gender

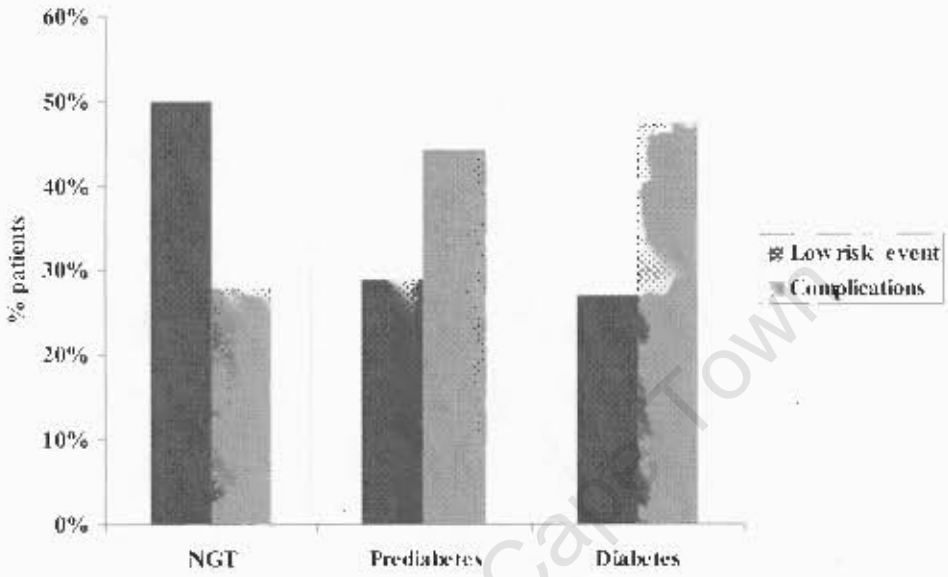


Clinical A history of a previous ischaemic event was present in 46.2% of prediabetics and 59.1% of new diabetics. Patients with NGT were more likely to have low risk UAP in comparison to both their prediabetic and diabetic counterparts ($p < 0.01$) (table 7, figure 4) and less likely to develop complications ($p = 0.04$). Mortality was highest in diabetics (3, 4.1%), compared to prediabetics (1, 1.9%) and NGT (1, 1.5%) but this was not statistically significant ($p = 0.58$).

Table 7: A comparison of low risk coronary events and complications in the different glucose categories

	NGT	Prediabetes	Diabetes
Low risk event	34 (50%)	15 (28.9%)	20 (27%)
Complications	19 (27.9%)	23 (44.2%)	35 (47.3%)

Figure 4. A comparison of low risk coronary events and complications in the different glucose categories



3.4. Random glucose on admission

A random glucose was determined in patients whose glycaemic profiles were known (as determined with an OGTT on discharge or known history of diabetes). The median random glucose value was 6.6 mmol/l (3.3 – 44.3 mmol/l). A random glucose level ≥ 11.1 mmol/l, diagnostic of diabetes, was found in 23 patients of which 16 patients were already known with diabetes and 3 patients were later diagnosed with diabetes by OGTT. A random glucose level ≥ 8 (a random cut-off value for dysglycaemia) was found in 5 patients with NGT (7.6%), 12 patients with IGT (23.5%), 31 patients with known diabetes (59.6%) and 10 patients with newly diagnosed diabetes (47.6%). The median random glucose in patients with a low risk coronary event was significantly lower than those with a high risk coronary event (5.8 mmol/l and 7.1 mmol/l respectively, $p < 0.01$).

Similarly, the median random glucose level in patients who developed complications was significantly higher than those who did not (7.65 mmol/l vs 5.8 mmol/, $p < 0.01$).

3.5. Hb1Ac

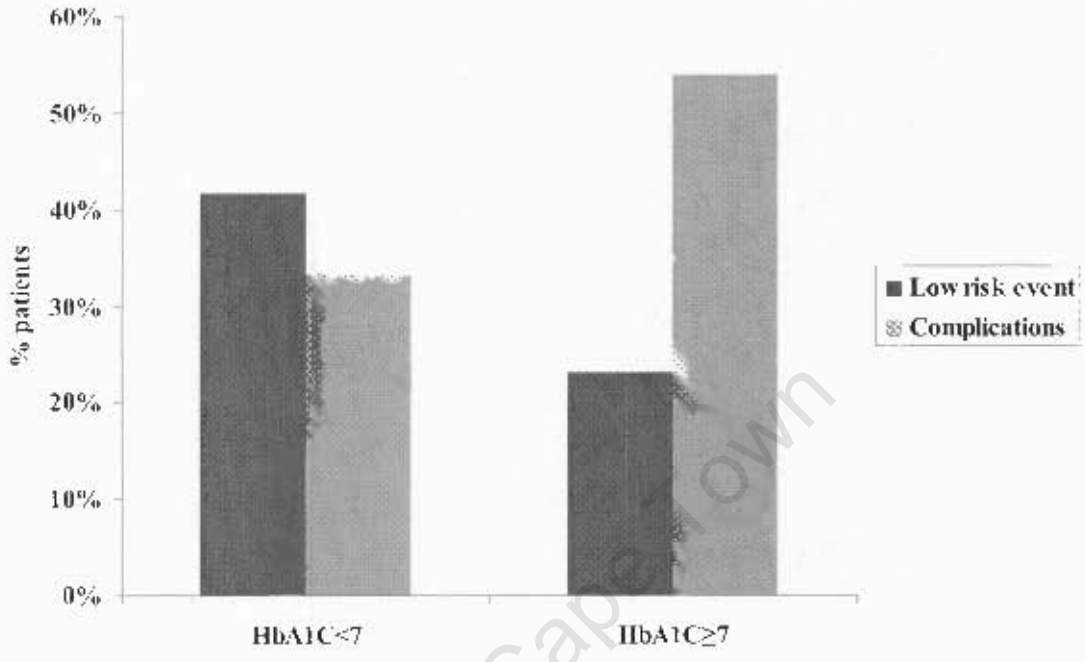
An Hb1Ac was performed on 179 of the 194 patients whose glycaemic profile were determined. A collection or laboratory error was responsible for missing data in 15 patients. The median Hb1Ac was less in those with NGT than in the prediabetics ($p < 0.01$) as well as in prediabetics compared to diabetics ($p < 0.01$). The median HbA1c was also significantly higher in known diabetics than in new diabetics ($p < 0.01$). There was no difference in the median HbA1c between patients with low and high risk coronary events and in those who developed complications and those who did not ($p=0.59$ and p 0.05 respectively). See table 8.

Table 8: Association between median HbA1c and glycaemic profile, coronary events and complications

	Median HbA1C %	Range
Glycaemic Profile		
NGT	5.2	4.4 - 6.0
Prediabetics	5.4	4.5 - 6.9
Diabetics	6.6	4.6 - 12.5
Old	7.1	4.9 - 12.5
New	5.9	4.6 - 9.9
Coronary event		
Low risk	5.5	4.5 - 12.5
High risk	5.5	4.4 12.5
ECG changes	5.4	4.4 - 12.5
NSTEMI	5.6	4.7 - 12.0
STEMI	5.5	4.5 - 8.8
Complications		
Yes	5.6	4.4 - 12.5
No	5.4	4.4 - 12.5

A glycaemic target of Hb1AC < 7 (as suggested by the American Diabetes Association) was found in 48% of patients known to have diabetes. Known diabetics with a Hb1AC < 7 were more likely to have a low risk coronary event (10, 41.7%) and less likely to develop complications (8, 33.3%) in comparison to their diabetic counterparts with a Hb1AC ≥ 7, who were less likely to have a low risk coronary event (6, 23.1%, p=0.16) and more likely to develop complications (14, 53.9%, p=0.14) but this did not meet statistical significance. See figure 5.

Figure 5: Association between HbA1C, low risk coronary events and complications



3.6. Anthropometry

Two thirds of the subjects (135, 67.2%) had an increased body mass index (BMI) (defined as a BMI ≥ 25), with a similar prevalence in the normoglycaemic (42, 62.7%) and dysglycaemic (85, 73.3%) groups (p – 0.13). There was no relationship to sex, with 70 (70%) females and 65 (64%) males having an increased BMI (p=0.39). However, significantly more females (43, 43.0%) than males (24, 23.8%), were classified as obese (defined as a BMI ≥ 30) (p < 0.01). See figure 6. Central obesity (described as an abdominal circumference ≥ 88 cm in females and ≥ 102 cm in males) was present in 58.6% (123) of patients but more common in the dysglycaemic (80, 65.6%) than in the normoglycaemic group (32, 47.1%, p – 0.01) and more commonly associated with females (84, 79.3%) than males (39, 37.5%, p < 0.01). See figure 7.

Figure 6: Prevalence of ↑ BMI by gender

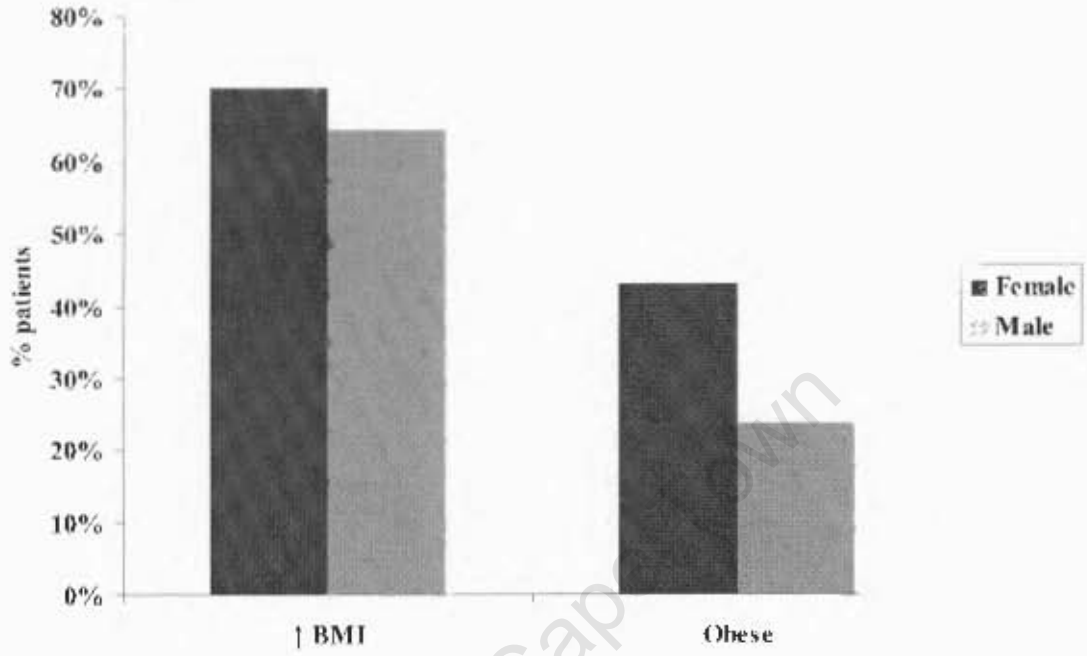
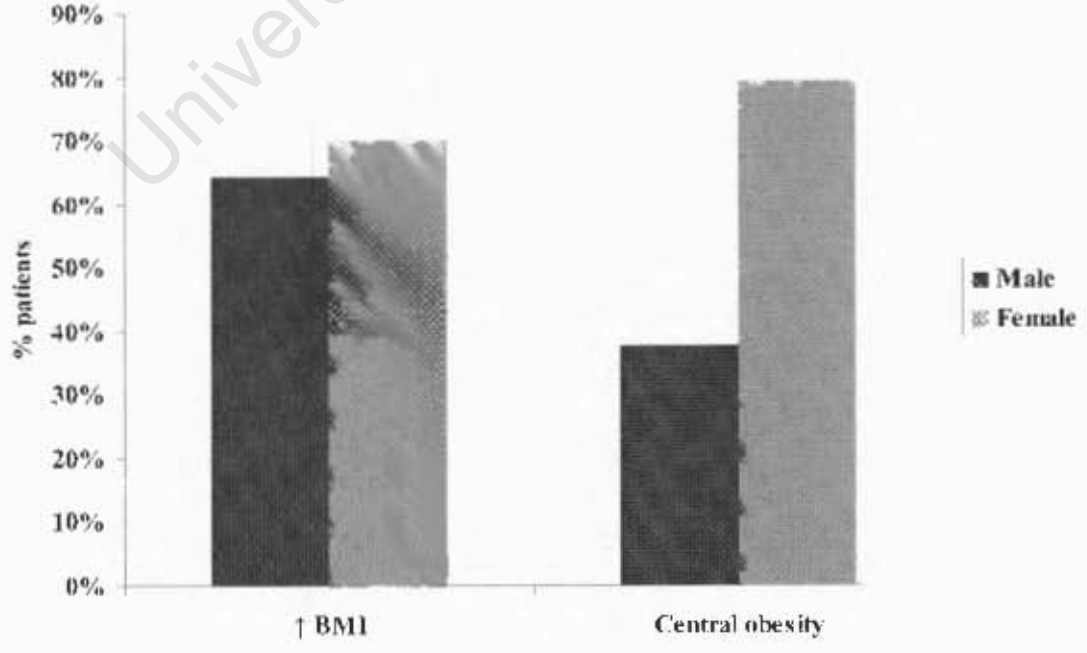


Figure 7: Prevalence of ↑ BMI and central obesity by gender



3.7. Lipid profile

The most common lipid abnormality seen in patients with ACS was that of a low HDL-C. The prevalence of different lipid abnormalities is detailed in table 9. The prevalence of a low HDL-C was less common in those with a normal glucose tolerance compared to the prediabetics as well as diabetics. A similar trend was seen with increased triglycerides, and the combination of low HDL-C and high triglycerides (the so-called insulin resistant dyslipidaemia). A high LDL-C, however, was common in all 3 glucose categories. See table 10 and figure 8.

There was no significant difference between the lipid profiles of the different ethnic groups or between males and females within the same ethnic groups. See table 11.

Table 9: Prevalence of different lipid abnormalities

Lipid Abnormality	Prevalence	
	n	%
↓ *HDL*	160	82.9
↑ *LDL*	127	68.3
↑ *TG*	70	36.3
↓ *HDL* & ↑ *TG*	66	34.2

Table 10: Prevalence of lipid abnormalities in the different glucose categories

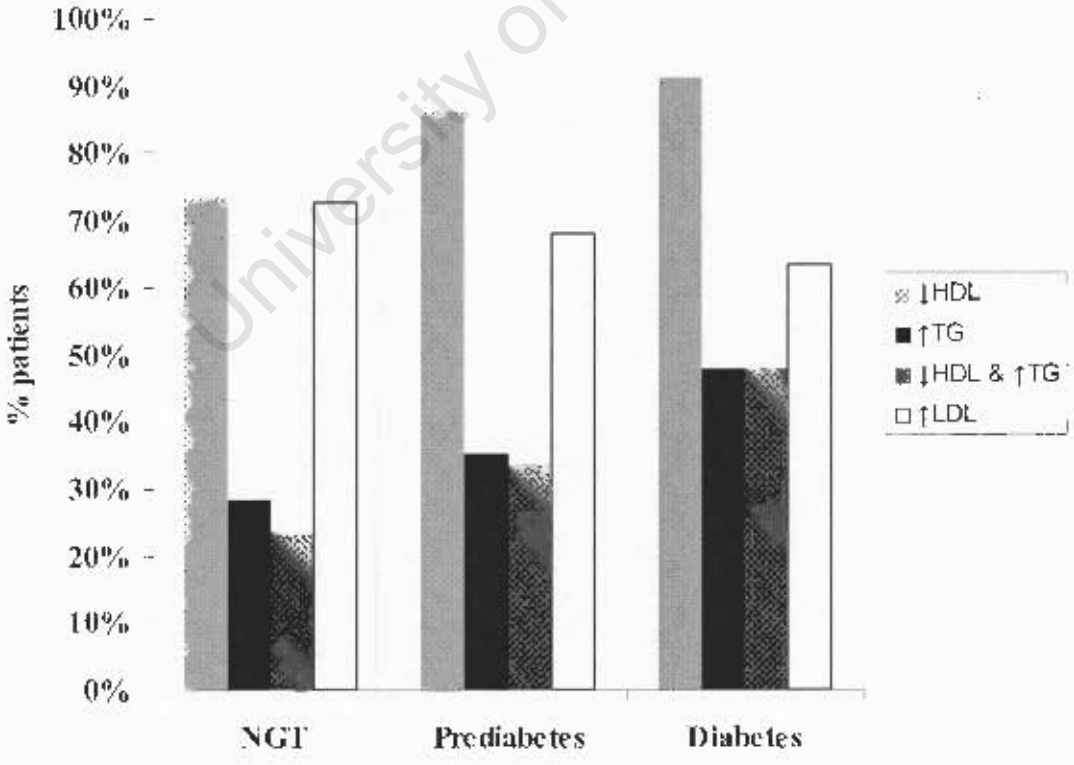
	Glucose Category						*p*
	NGT		*Prediabetes*		*Diabetes*		
↓ *HDL*	47	(73.4%)	44	(86.3%)	61	(91.0%)	0.02
↑ *TG*	18	(28.1%)	18	(35.3%)	32	(47.8%)	0.06
↓ *HDL* & ↑ *TG*	15	(23.4%)	17	(33.3%)	32	(47.8%)	0.01
↑ *LDL*	45	(72.6%)	34	(68.0%)	40	(63.5%)	0.50

Table 11: Prevalence of different lipid abnormalities by gender and ethnicity

	Males					Females				
	Coloured		*White*		*p*	*Coloured*		*White*		*p*
↓ *HDL*	31	(86.1%)	49	(83.1%)	0.14	27	(90.0%)	44	(75.0%)	0.11
↑ *TG*	16	(44.4%)	25	(42.4%)	0.67	8	(26.7%)	20	(34.5%)	0.46
↓ *HDL* & ↑ *TG*	15	(41.7%)	23	(38.9%)	0.35	8	(26.7%)	19	(32.8%)	0.18
↑ *LDL*	27	(75.0%)	43	(75.4%)	0.71	20	(71.4%)	31	(56.4%)	0.59

Data are number (%) unless otherwise indicated

Figure 8: Prevalence of lipid abnormalities in the different glucose categories



3.8. Metabolic Syndrome

Two thirds of patients admitted with ACS (124, 63.6%) fulfilled the diagnostic criteria for metabolic syndrome as stipulated by the ATP III.[36] The median age of patients with metabolic syndrome was 60.5 years (range 34-97). Males were younger than females (52 and 66 years respectively, $p < 0.01$). The highest prevalence was in the black patients (8, 88.9%) but this sample size was too small to be representative. More than two thirds of coloured patients (45, 70.3%) met the ATP III criteria for the metabolic syndrome, as did 58.7% (71) of whites ($p = 0.12$). The metabolic syndrome was more common in females (76, 76.8%,) than males (48, 50%), $p < 0.01$, and appeared to be more common in coloured females (n=26, 86.7%) than white females (43, 70.5%). p=0.09, putting coloured females more at risk of developing metabolic syndrome than their white counterparts (risk ratio 2.1, 95% CI 0.81 – 5.29). See figure 9. There seemed to be no difference in the prevalence of the clustering of metabolic risk factors in the different ethnic categories as outlined in table 12.

Figure 9: Association between metabolic syndrome, gender and ethnicity

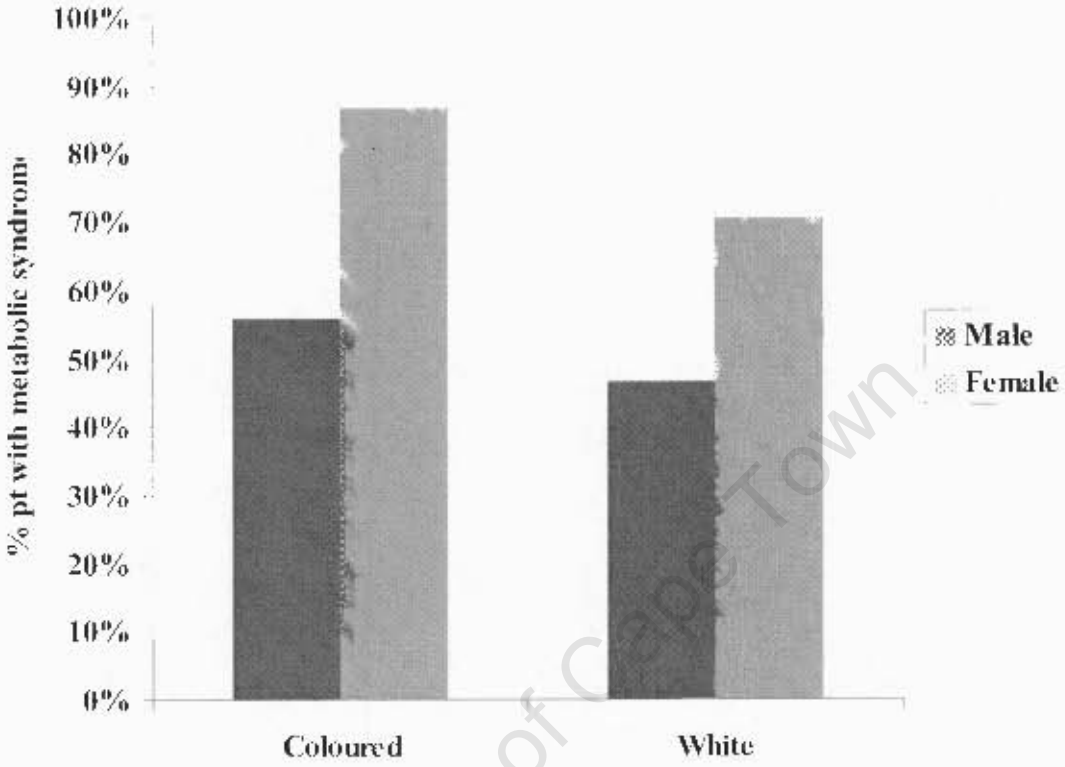


Table 12: Prevalence of the clustering of metabolic risk factors in the main ethnic categories

No risk factors	Ethnicity			
	Coloured		Whites	
0	0	(0)	3	(2.3)
1	9	(12.3)	22	(17.1)
2	19	(26.0)	34	(26.4)
3	25	(34.3)	33	(25.6)
4	11	(15.1)	23	(17.8)
5	9	(12.3)	14	(10.9)

Data are number (%) unless otherwise indicated

CHAPTER 4

DISCUSSION

Chest pain due to ACS was a common presentation to the ED, with a similar prevalence in the Coloured (11.6%) and White (14.9%) populations. However, despite the large proportion of black patients assessed in the ED (623), ACS still seems to be uncommon in this population (1.4%). It is commonly accepted that ACS affects males more than females: however, in our study population both males and females were affected to a similar extent (11.3% vs 9.1%). This may indicate that there was no bias in the study selection (which commonly occurs due to the atypical presentation of chest pain in females), or it may be an indicator that CAD has finally caught up in females.

4.1. Dysglycaemia

The importance of identifying not only people with asymptomatic diabetes but also those with IFG and IGT (prediabetes) can not be emphasized enough, as it is well documented that macrovascular disease is a major cause of death in all categories of glucose abnormalities, including those below diabetic levels. Not only do patients with established diabetes have an increased risk for cardiovascular disease, but also those with increased FPG and 2 hr blood glucose; these are also independent risk factors for all-cause and cardiovascular morbidity and mortality[17]. Increasing evidence suggests that, for diagnosis, the use of fasting plasma glucose levels alone will miss patients with a high risk of diabetes related morbidity and mortality.[18] Furthermore, the prevalence of undiagnosed diabetes and IGT will be under estimated to a large extent, especially in female and elderly populations, if fasting glucose alone is used.[5] Also, fasting glucose

measurements alone do not identify individuals at increased risk of death associated with hyperglycaemia.[4]

Currently there is no unique biological marker that can distinguish people with IFG, IGT or diabetes from people with normal glucose metabolism, thus the oral glucose tolerance test is recommended as the gold standard in identifying the different categories of glucose abnormalities. It also provides additional prognostic information and enables detection of individuals with impaired glucose tolerance, who have the greatest attributable risk of death.[4]

So far, mass screening for asymptomatic diabetes and IGT has not been recommended in the general population; however, targeting of groups at high risk of diabetes could be beneficial as these patients could benefit from early intervention.[39] Patients with CAD by definition can be considered at high risk and should thus be included in the subgroup of population in whom glycaemic testing must be performed. Benefits of screening include identifying those patients with undiagnosed diabetes (as up to 50% of patients with diabetes are undiagnosed as they remain asymptomatic for many years) as well as those at risk for diabetes (IFG and IGT). Early identification of the latter group leans to early intervention strategies to reduce or delay progress to diabetes[37] as well as an increased surveillance and treatment for other associated risk factors like hypertension, dyslipidaemia, obesity and smoking. Screening in CAD improves possibilities for prevention of cardiovascular complications.

We found a high prevalence of dysglycaemia (65%) in patients admitted with an acute coronary syndrome and it can be assumed that this condition is also prevalent at other hospitals serving the same population groups. These results are in agreement with several

recent reports.[40,42,43] Of the 126 patients diagnosed with dysglycaemia, 74 (58.7%) were newly diagnosed with a glucose abnormality and 52 (41.3%) were previously diagnosed with diabetes. It may well be that the true prevalence of dysglycaemia is higher in our population bearing in mind that an OGTT could not be performed in a small subset of patients due to serious cardiovascular related complications (eg death or referral to tertiary hospitals for revascularization).

In patients not previously diagnosed with diabetes, the prevalence of glucose abnormalities was determined with the fasting glucose test alone and then compared to the prevalence of dysglycaemia when adding the 2 hr post–load glucose value. By recruiting diabetic patients by either criterion alone or their combination, 40.1% (n=9) met both, 18.2% (n=4) met the fasting criteria alone and 40.9% (n=9) met the 2 hr post load criterion alone. Similarly, recruiting patients with impaired glucose tolerance by either criterion alone or their combination, 30.8% (n=16) met both, 25% (n=13) met the fasting criteria only and 44.2% (n=23) met the 2 hr post-load criterion alone. These findings suggest that a significant proportion of patients with prediabetes or diabetes would have been missed if a FPG alone was used as the sole screening procedure (even using the suggested lower cut-off value of 5.6 mmol/l for diagnosis of IFG and 7 mmol/l for the diagnosis of diabetes). These findings also agree with previous findings that although a FPG and 2 hr PG level sometimes identify the same individuals, often they may not coincide.[4] This has important implications for usual medical practice. An OGTT should become a more widely used tool in screening high-risk populations.

Patients with dysglycaemia were older (median age 65 years) than those with a normal glucose tolerance (median age 56 years) in our study cohort. This is not surprising as the

age specific prevalence of patients with diabetes and impaired glucose tolerance increases linearly with age up to the seventh to eight decades in both men and women.[43] A higher prevalence of dysglycaemia in females than males was suggested,[45] however, we found dysglycaemia to be as common in males (63%) as females (67%) in our study group. High diabetes rates have previously been reported in Coloureds compared to Whites and Blacks.[44] There was a trend to an increased prevalence of dysglycaemia in Coloureds (72.3%) compared to Whites (58.8%), but this did not reach statistical significance (p=0.07).

Typically, persons with IGT and asymptomatic diabetes and those at high risk of developing diabetes are unaware of their high risk status. Much attention has been directed at detecting undiagnosed diabetes as its increased risk for subsequent complications and mortality is well acknowledged[45]. Only recently, attention has turned to those with lesser degrees of glucometabolic abnormalities, who tend to share the same risk factors as those with type 2 diabetes. We found that 46% of prediabetics and 59% of new diabetics in our study population already experienced a previous ischaemic event. One would like to presume that this was a valuable opportunity missed to identify patients at high risk for developing cardiovascular disease and its complications. Earlier detection of impaired glucose tolerance and asymptomatic diabetes could lead to initiation of secondary preventive measures at an earlier stage.

It has been reported that patients with impaired glucose tolerance run an additional risk of increased cardiovascular morbidity and mortality compared with patients with a normal glucose tolerance; this excess cardiovascular risk is present even at lower blood glucose concentrations than those that cause microvascular complications.[46] In our study,

patients with dysglycaemia were more likely to present with a high risk coronary event (73%) and more likely to develop cardiovascular complications (75%) in comparison to their counterparts with a normal glucose (27% and 25% respectively).

4.2. HbA1c

Glycated haemoglobin (HbA1c) has never been recommended as a diagnostic test for diabetes, although its usefulness in the screening and diagnosis of diabetes has been widely debated.[46] It is insensitive in the low range, thus a normal HbA1c can not exclude the presence of diabetes or IGT[37] Another down fall is that it does not reveal information about post-prandial glucose levels: this information is useful in order to predict increased cardiovascular risk in patients with both normal and impaired glucose tolerance. Although there was a statistically significant difference in the median HbA1c in our study group between those with NGT, those with IGT and those with newly diagnosed diabetes, each value would still be interpreted as within normal limits. This suggests that HbA1c on its own is insensitive to determine those subset of patients with newly diagnosed dysglycaemia. The median HbA1c in patients with previously diagnosed diabetes was, as expected, significantly higher than all other groups and above the perceived 'normal' limit. In view of this, we would like to suggest that HbA1c determination is not essential in the acute management of ACS in patients not known with diabetes and is thus of minimal value in the ED.

HbA1c is however a useful measure of the efficacy of glucose lowering treatment in those known with diabetes, as it gives an integrated summary of blood glucose levels during the preceding 6-8weeks. There is convincing evidence that diabetic

microangiopathy can be reduced by tight glycaemic control. A recent randomized study has demonstrated that macrovascular morbidity and mortality in type 1 diabetes can also be effectively reduced with tight glycaemic control.[47] Whether this can be extrapolated to type 2 diabetes is yet to be determined. The reduction of HbA1c was by far the most important factor behind the reduction of CAD with a 21% reduction in each 1% decrease in HbA1c. Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) has clearly shown that each percent decline in HbA1c caused a 14% lower rate of myocardial infarction and fewer deaths from diabetes or any cause.[38] Various diabetes associations have advocated HbA1c targets <7%. Less than 50% of known diabetics in our study group reached this proposed glycaemic target, indicating the suboptimal management in this high risk group. Although there was a tendency for known diabetics with a HbA1c < 7 to have a low risk coronary event and they were less likely to develop complication, this did not reach statistical significance.

4.3. Random glucose on admission

Current practice in most smaller hospitals in the Western Cape is to determine a random glucose as a 'fifth' vital sign on admission of patients with ACS, mainly as a screening test to identify those with diabetes, disregarding those subset of patients falling into the category of impaired glucose tolerance. Not only is random glucose insensitive in diagnosing diabetes and thus unsuitable in this high risk population, but it is even less useful in diagnosing those with prediabetes. It also has a high risk of false positive and false negative results. It has been suggested however to have a significant increased sensitivity in diagnosing diabetes if the cut-off point is markedly reduced to 7.2mmol/l[48], but this still need to be validated. By lowering the cut-off point of random glucose to

8mmol/l in our study, we identified only 41 patients (59.4%) of patients later diagnosed with diabetes and 12 patients (23.5%) with IGT.

Although determining random glucose on admission to diagnose those with glucose abnormalities is not useful, there is strong evidence that high blood glucose at admission, independent on the state of premorbid glucose tolerance, predicts in-hospital and subsequent morbidity and mortality after an acute myocardial infarction in both diabetics and non-diabetics, the mechanism of which is not fully understood as yet.[49-52] Whether this can be extrapolated to the whole spectrum of ACS is unsure. It was clear from our findings though that those patients presenting with a high risk event had a significantly higher admission glucose (7.1mmol/l) than those with a low risk event (5.8 mmol/l), despite a similar HbA1c (5.5%), indicative of similar previous glucometabolic status in the two groups. Similarly, those patients that developed in-hospital complications had significantly higher admission glucose levels (7.7mmol/l) than those without complications (5.8mmol/l), but again there was little difference in the HBA1c between these two groups. Recent studies also suggest that reversal of stress hyperglycaemia at the time of myocardial infarction can improve the clinical outcome in these patients[52] and that the use of a glucose, insulin and potassium infusion may reduce short and long term cardiovascular morbidity and mortality in both diabetic and non-diabetic patients with acute myocardial infarctions although definitive proof of the latter is lacking and the practice has not gained universal approval.[53-55] Again, we do not know if this data can be extrapolated to all categories of ACS. If so, clinicians responsible for the management of these patients may not only have a responsibility to perform an OGTT on patients with ACS before discharge, but also need to determine the admission glucose and manage it

appropriately as this will have clear benefits in decreasing morbidity and mortality. It is important to stress that a single glucose measurement on admission alone does not suffice as even those people without diabetes might benefit from tight glucose control and should thus be preformed routinely throughout their hospital stay.

It has been suggested that patients who develop stress hyperglycaemia are likely to be dysglycaemic when not stressed.[40] Our findings suggest a similar result as 53 of the 58 patients (91.4%) with a random glucose of 8 or more were subsequently diagnosed with dysglycaemia on discharge, of which 31 patients were previously diagnosed with diabetes and 22 diagnosed with dysglycaemia on the OGTT.

Abnormal glucose tolerance is often clustered with other components of the metabolic syndrome (including visceral obesity, hypertriglyceridemia, low HDL, hyperinsulinemia and hypertension), each of which independently promote atherothrombosis. All are factors that tend to be higher or more common in hyperglycaemic patients compared with normoglycaemic patients.[6] Early identification of these metabolic abnormalities would enable initiation of potentially beneficial treatment contributing to an improved prognosis.[41] We can thus assume that interventions that reduce the risk of progression to diabetes are also likely to reduce CHD mortality in this group and could be of great potential benefit.[56]

4.4. Anthropometry

It is generally accepted that obesity, whether it is measured as an increased BMI or central obesity, carries a health risk because of its association with numerous metabolic complications such as cardiovascular disease, type 2 diabetes and dyslipidaemia.[57] Being overweight and obese is associated with insulin resistance and the syndrome's cluster of

metabolic disorders and subsequently all components of the metabolic syndrome are positively affected by weight loss.[58] Insulin resistance is considered to be the link between obesity and dysglycaemia. It is particularly the presence of visceral or central obesity which is one of the hallmarks of the disease. It has long been noted that complications commonly found in obese patients are more closely related to where the excess fat is rather than to excess fat per se.[59]

We found a high prevalence of overweight and obesity in our study population, whether measured as an increased BMI (67%) or central obesity (59%). Females had a significant higher tendency than males to be obese, regardless of whether increased BMI or abdominal circumference was determined.. Our study agrees with the findings of the Interheart Africa study[44] that overweight and obesity are as common in Coloureds as in Whites.

The prevalence of abdominal obesity has been shown to be more highly correlated with metabolic risk factors than is an elevated BMI.[60] These data can be extrapolated to our findings of a significant difference in the prevalence of central obesity between normoglycaemic (47%) and dysglycaemic (66%) groups (p=0.01), but no difference could be demonstrated in the prevalence of an increased BMI between the normoglycaemic (63%) and dysglycaemic (73%) groups (p=0.13). Further, central obesity was associated with more metabolic risk factors than an increased BMI (3 and 2 risk factors respectively).

4.5. Dyslipidaemia

Dyslipidaemia is a major risk factor for cardiovascular disease. Many patients with type 2 diabetes and metabolic syndrome typically demonstrate a characteristic dyslipidaemia

(also known as diabetic dyslipidaemia or atherogenic dyslipidaemia), which consists of moderate elevation in triglyceride levels, low HDL cholesterol values, and small dense LDL particles. This lipoprotein pattern is associated with insulin resistance and, importantly, is present long before the onset of diabetes. [61]

It was predicted long ago that the lipid abnormalities of the insulin resistance syndrome are likely to be the commonest form of dyslipidaemia seen in South Africa.[62] It is thus not surprising that we found that a low HDL-C was the most common lipid abnormality (83%), more so than an increased LDL (68%). Despite the predicted high prevalence of insulin resistant dyslipidaemia (low HDL-C and/or elevated triglycerides) in prediabetics (88%) and diabetics (91%) we also found a high prevalence of this form of dyslipidaemia in patients with a normal glucose tolerance (78%). We are tempted to assume that these patients are already on the insulin resistance path and that many more patients are destined to develop dysglycaemia in the near future.

In contrast to the increasing prevalence of the insulin resistant dyslipidaemia in the different glucose categories, the prevalence of a low LDL remained similar in all glucose categories. This is in agreement with previous reports.[63] However, in the UKPD study, LDL was the strongest independent predictor of CAD followed by HDL cholesterol, supporting current guidelines in which LDL lowering remains the primary lipid target.[59]

The Coloured population of the Western Cape has been shown to have a high prevalence of cardiovascular risk factors, particularly dyslipidaemia.[22,24] Our study confirmed this finding and also noted that dyslipidaemia disregards both gender and race with similar high prevalences in Whites and Coloureds as well as males and females.

4.6. Metabolic syndrome

The clinical importance of the metabolic syndrome is related to its putative impact on cardiovascular morbidity and mortality. People with the metabolic syndrome have been shown to be at increased risk for cardiovascular disease and diabetes, as well as for death from cardiovascular disease and from all causes.[64-66] Once identified, early preventative measures are needed in these high risk people with the main focus on life style change and treatment of the individual components if the former fails.[67]

The prevalence of the metabolic syndrome is dependent on the definition used to diagnose it. Several definitions of the metabolic syndrome exist. Recently, the International Diabetes Federation consensus group redefined the metabolic syndrome in order to provide one practical definition that could be used in any country to identify people at high risk of cardiovascular disease and diabetes.[67] They used the ATP III components as background with two main changes: 1) central obesity, as assessed by waist circumference, is now a compulsory component to make the diagnosis of metabolic syndrome, and ethnic-specific waist circumference cut-offs have been incorporated into the definition, 2) FPG only, and not an OGTT, is still required to diagnose glucose abnormalities but it is now recognized that impaired glucose tolerance determined by a 2 hr PG is also acceptable in clinical practice and they strongly recommend an OGTT if FPG ≥ 5.6. (Clinicians and researchers are encouraged though to rather add the 2 hr PG as supplementary finding in order to retain the simplicity of the definition).

At the time of processing data for our study, we still used the ATP III criteria for the diagnosis of metabolic syndrome.

The components of the metabolic syndrome were frequently present in patients admitted with ACS at Karl Bremer Hospital. We found a large proportion of patients admitted with acute coronary syndrome to have metabolic syndrome (64%). As we only used the FPG to define glucose abnormalities, we can safely assume, that even more patients would have been diagnosed had we added those with IGT diagnosed with the OGTT. As mentioned, abnormal glucose tolerance is often clustered with other components of the metabolic syndrome. It is therefore not surprising that we found a higher prevalence of metabolic syndrome in patients with IGT (63.5%) and diabetes (82.4%) than those with NGT (37.3%). An increased clustering of metabolic risk factors was also noted as the glycaemic profile deteriorated from NGT to IGT to diabetes.

A similar prevalence of metabolic syndrome in males and females has been noted before.[68] However, we found a significantly higher prevalence in females (77%) than males (50%), $p<0.01$. It is possible that the gender prevalence may change when adjusted for age. Although we could not demonstrate a significant difference in the prevalence of metabolic syndrome between the two main ethnic groups (Coloured and White), it appears that coloured females were at higher risk than white females to have metabolic syndrome (risk ratio 2.1, 95% CI 0.81 – 5.29).

The metabolic syndrome is variously defined by different organisations and all definitions are to some extent arbitrary given the natural continuum of biological variables. Clinicians recognising this will pay attention to correcting abnormalities of each of the components of the syndrome.

CHAPTER 5

LIMITATIONS

Our study has several limitations. Firstly, the diagnosis of dysglycaemia was made during hospital stay where the effect of so-called stress-induced hyperglycaemia could influence the results. This longstanding concern and objection has been conclusively answered by Norhammer et al[40] who demonstrated a strong correlation between the 2 hr blood glucose values at discharge and at 3 months follow-up, indicating raised blood glucose levels are not only related to stress induced by the ischaemic event and this was confirmed in a later study[41] supporting evidence that abnormal glucose metabolism can be identified in the early phase of an acute coronary syndrome and therefore high risk individuals can be identified during their hospital stay, thereby permitting early initiation of appropriate preventive measures.

Secondly, laboratory data for certain study measures were not obtained in a small subset of patients due to inadequate collection or inability of the laboratory to process samples. This could possibly have influenced the results; although the numbers involved were small, the magnitude of this effect is unknown.

Thirdly, the overall mortality recorded was low at 3.3%. This may reflect several factors including incomplete follow-up, as the outcome of those patients transferred for further intervention is unknown.

Finally, there was no subsequent follow-up of patients admitted with ACS and therefore we can not comment on the short or long term outcome of patients in the different glucose categories. This is an area of concerns which requires further study.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1. CONCLUSION

Chest pain due to an acute coronary syndrome constitutes a large proportion of patients seen in the ED and affects both Coloureds and Whites to the same extent. This suggests that CAD is not only a disease of the higher income Whites. In contrast to the high prevalence of ACS in both Whites and Coloureds, we found ACS to be still uncommon in Blacks despite predictions of a potential epidemic in this population group.

In many smaller hospitals in the Western Cape, admission and management to discharge of patients with acute coronary syndrome is the responsibility of the Emergency Department as the chest pain unit forms an integral part of the acute admissions ward. It has been shown repeatedly that dysglycaemia occurs commonly in patients with ACS and is associated with several other metabolic risk factors: the population of the Western Cape is not excluded as indicated in our study. The high prevalence of dysglycaemia in patients with ACS and the poor management of those patients already diagnosed with diabetes implicate that urgent strategies should be devised to manage dysglycaemia and to prevent the consequences of the syndrome.

Surely, few clinical settings exist where the identification of this number dysglycaemic patients can be exceeded, and not to perform an OGTT during the convalescence of an acute coronary syndrome is a valuable opportunity missed.

6.2. RECOMMENDATIONS

Our study supports the following recommendations:

1. All patients admitted with an ACS should have screening for diabetes.

2. This screening is best done with an OGTT prior to discharge.
3. Associated metabolic risk factors should actively be searched for and managed accordingly: most of these can be measured with simple clinical parameters obtained in the ED.

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APPENDIX A

INFORMED CONSENT

We invite you to participate in a survey to establish what percentage of patients admitted to Karl Bremer Hospital with angina, suffers with the Insulin Resistance Syndrome. This condition is characterized by derangement of the sugar and cholesterol metabolism, abnormal blood pressure and resistance to the action of insulin in your body, leading to an increased risk of heart disease. If it appears during this survey that a high percentage of patients admitted with angina suffers from this condition, which seems to be increasing in our population, strategies can be devised to address this problem and reduce the risk of coronary events in the future.

What can you expect during this survey? Your doctor will perform a routine examination and an ECG will be done as usual. You will be weighed and we will measure your length as well as your hip and abdominal circumference. Blood will routinely be taken to identify if any underlying myocardial damage is present. During this venepuncture, additional blood will also be collected to check your bloodcount, lipid profile, your glucose control over the last few months, insulin levels and inflammatory markers. No extra venepunctures wil be performed on admission. A urine sample will also be collected to see if there are any proteins present in your urine. Routine care will be taken of you during your hospital stay. On your day of discharge we will ask you for an additional blood sample to check your fasting glucose and cholesterol. This means that you will be asked not to eat or drink anything from 22h00 the previous night, and blood will be taken early in the morning so that you can still have your breakfast. We will also provide you with a sugar drink (if you are not already diagnosed with diabetes) and

repeat the blood sample in 2 hrs. This enables us to see if you have diabetes, if not already diagnosed, or at risk for developing diabetes. If so, we will advise you regarding your future management.

If at any point during this survey you would like to discontinue your participation, you are free to do so and your care thereafter will not be affected.

I have read and understand the above information and would like to participate/ would not like to participate in the survey.

Patient:

Printed name Signature Date

Witness:

APPENDIX B

ADMISSION SHEET FOR ALL PATIENTS WITH SUSPECTED ACUTE CORONORY SYNDROME

Name:
File no:
DOB:
Gender:

ON ADMISSION

Risk Factor Profile: *Yes* *No*

- Known with CAD
  - Stable Angina
  - Unstable Angina
  - NSTEMI
  - STEMI
  - Previous PTCI/CABG
- Hx of other vascular diseases
  - Previous CVA
  - Peripheral vascular disease
- Smoking
  - Current
  - Previous
  - Never
- Presence of dysglycaemia
  - Previous dx of DM 2
  - Impaired glucose tolerance
  - Impaired fasting glucose
- Hypertension
- Dyslipidaemia

Family history of:

- Premarure CAD
- Type 2 Diabetes
- Dyslipidaemia

2. Current Medication *Yes* *No*

- Aspirin in last 7 days
- Lipid lowering drugs
- Other _____

3. Clinical Data

- Race
- BP ____/____
- Pulse _____
- Hb
- Abdominal circumference _____ cm
- Hip circumference cm
- Height _____cm
- Weight kg

4. ECG *Yes* *No*

- Normal
- ST depression >1mm
- T wave inversion > 3mm
- Transient ST elevation < 30 min
- Persistent ST elevation
- LBBB

5. Biomarkers *Yes* *No*

- Trop T +
- CK ↑
- CK-MB ↑

6. Urinalysis *Yes* *No*

- Presence of proteinuria
- Presence of microalbuminuria

7. Additional bloods *Yes* *No*

- FBC
- HsCRP
- Insulin & glucose
- Non- fasting lipogram
- HbIAC

8. Initial Diagnosis *Yes* *No*

- UAP with ST depression or
- T wave inversion
- UAP with normal ECG
- NSTEMI
- AMI (STEMI/LBBB)

9. Admission History (study related)

1 2 3 4 5 6 7 8 9 10

ON DISCHARGE

1. Any complications? *Yes* *No*

- Recurrent angina
- Refractory angina
- Hemodinamic instability
- Signs of pump failure
- + biomarkers (re-peated)
- Acute MI
- Referred to tertiary hospital
- Death

2. Special Investigations

- Fasting lipogram
  - Triglyceride
  - T-cholesterol _____
  - LDL
  - HDL _____
- Fasting glucose mmol/l
- 2 hr plasma glucose _____mmol/l

3. Discharge Diagnosis *Yes* *No*

- Unstable angina
  - Without ECG changes
  - With ECG change
- NSTEMI
- AMI (STEMI/LBBB)

PPENDIX C

APPENDIX C
ABBREVIATIONS

ACS	Acute coronary syndrome
ADA	American Diabetes Association
AMI	Acute myocardial infarction
ATP	Adult Treatment Panel
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence Interval
DM	Diabetes mellitus
ED	Emergency Department
HDL-C	High-density lipoprotein cholesterol
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
FPG	Fasting plasma glucose
KBH	Karl Bremer Hospital
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
NGT	Normal glucose tolerance
NSTEMI	Non-ST elevation myocardial infarction
OGTT	Oral glucose tolerance test
PCI	Percutaneous intervention
PG	Plasma glucose

STEMI	ST-elevation myocardial infarction
TG	Triglycerides
UAP	Unstable angina pectoris
UKPDS	United Kingdom Prospective Diabetes Study