



**University Of Khartoum**  
**Faculty Of Medicine**  
**Postgraduate Medicine Studies Board**

**DIABETES MILLUTES AS RISK FACTOR  
FOR MYOCARDIAL INFARCTION**

By

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*A thesis submitted in partial fulfillment for the requirements  
of the Degree of clinical M.D in internal medicine,  
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قال تعالى :

( وقل ربي زدني علماً )

صدق الله العظيم

# Dedication

**To my Father**

To my Mother

To my Sister and brother

To my Friends

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# ABSTRACT

This is cross-sectional descriptive study conducted on patient with myocardial infarction period April – October 2003 in the CCU in Alshaab and Omdurman teaching hospitals to investigate diabetes as a risk factor.

Two-hundred patient were included in this study, 47% were diabetic, 44% of them had high level of FBS and 43% with high level of 2 hours post prandial.

In addition there was coexisting other risk factors such as hypertension 33% hypercholesterolemia 22%, hypertriglyceridaemia 23% and smoking 49%. In hypertensive patients the systolic blood pressure was more than 160mmHg in 42.2% while diastolic blood pressure were more than 110mmHg in 15.2%. Also this study showed that MI is more common in male 67% than female 33%.

This study concluded that diabetes is major risk factor for myocardial infarction in Sudanese patient.

2003

200

%47

%22

-%33

%49.1

%42.2

160

%15.2

110

## ABBREVIATIONS

<b>AMI</b>	Acute Myocardial Infraction
<b>CAC</b>	Coronary Artery Disease
<b>CCU</b>	Coronary Care Unit
<b>CDC</b>	Centre for Disease Control
<b>CHD</b>	Coronary Heart Disease
<b>CVD</b>	Cardiovascular Disease
<b>DCCT</b>	Diabetes Control and complication Trial
<b>HBA</b>	Hemoglobin A
<b>HBAc1</b>	Hemoglobin Ac1
<b>HDL</b>	High Density Lipoprotein
<b>LDL</b>	Low Density Lipoprotein
<b>MI</b>	Myocardial Infarction
<b>Mo</b>	Month
<b>S.O.B</b>	Shortness of Breath
<b>UKPDS</b>	United Kingdom Prospective Diabetes Study
<b>VLDL</b>	Very Low Density Lipoprotein

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## INTRODUCTION & LITERATURE REVIEW

Acute myocardial infarction (AMI) is the rapid development of myocardial necrosis caused by a critical imbalance between the oxygen supply and demand of the myocardium. This usually results from plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium<sup>(1)</sup>.

The most common cause of acute myocardial infarction is narrowing of the epicardial blood vessels due to atheromatous plaques. Plaque rupture with subsequent exposure of the basement membrane results in platelet aggregation, thrombus formation, fibrin accumulation, hemorrhage into the plaque, and varying degrees of vasospasm. This can result in partial or complete occlusion of the vessel and subsequent myocardial ischemia. Total occlusion of the vessel for more than 4-6 hours result in irreversible myocardial necrosis, but reperfusion within this period can salvage the myocardium and reduce morbidity and mortality. Most of the damage occurs in the first 2-3 hours. Restoration of flow within the first 4-5 hours is associated with salvage of the heart muscle, but the salvage is greater if flow is restored in the first 1-2 hours.

A major determinant of death and illness is the size of the infarct.

Increasing the oxygen supply to the involved site of blockage by coronary reperfusion (angioplasty, stent, and atherectomy) is more effective in salvaging the myocardium than decreasing oxygen demand<sup>(1)</sup>.

Diabetes is well recognized as independent risk factor for cardiovascular disease in men and women CVD is up to four times more common in people with diabetes than those without and 50% of diabetic people have evidence of CVD at the time of their diagnosis. In addition, the risk of myocardial infarction and death from coronary disease is the same for diabetic people without history of MI as for nondiabetic people with history of MI. Moreover, post infarction mortality is significantly higher in people with diabetes than in those with out. It is estimated that between 75% and 80% of diabetes related death is attributed to macrovascular complication of the disease, primarily CVD cerebrovascular disease and peripheral vascular disease<sup>(2)</sup>.

Prevalence of diabetes varies to some degree by sex and ethnicity. Among people who are 20 years of age or older, diabetes occur somewhat more commonly in white men than in white women (4.7% of woman 9.7% of man).

Remarkably, the mortality rate among African- American men and women is at least twice that of whites.<sup>(2)</sup> Asian has very high incidence of

Diabetes and I.H.D. The pathogenesis of CVD associated with diabetes is not yet fully understood. However, because atherosclerotic macrovascular complications occur at an earlier age and with greater severity in people with diabetes, it is likely that its pathogenesis is directly influenced by the diabetic state <sup>(2)</sup>.

Long-term exposure to elevated glucose levels alone can contribute to the endothelial cell dysfunction observed in diabetes. Increasing evidence suggests that endothelial dysfunction may play a central role in development of atherosclerosis. Endothelial dysfunction is characterized by inhibited vasodilatation increased vascular smooth muscle proliferation, increased thrombogenesis, and proatherogenic cellular processes. Abnormal endothelium dependent vasodilatation also occurs in the microcirculation of diabetic patients, where it may contribute to ischemia and its sequelae. In addition to accelerated atherosclerosis, endothelial dysfunction has been linked with increased thrombosis, hypertension, and dyslipidemia, all of which contribute to pathogenesis of vascular disease in diabetes <sup>(2)</sup>.

Hyperglycemia might contribute to atherosclerosis in type 2 diabetes in a number of other ways. For example, hyperglycemia causes glycosylation of proteins in a process that induces cross-linking of collagen and other extra cellular matrix proteins in the arterial wall <sup>(2)</sup>.

The end products of glycation modify low-density lipoprotein (L.D.L) cholesterol, prolonging its half-life and producing changes in the artery rendering it more susceptible to atherosclerosis. Among other proposed biochemical pathway in the pathogenesis of diabetic macro vascular disease is glucose induced activation of protein kinase C isoforms and increased intracellular oxidative stress <sup>(2)</sup>.

Hyperglycemia is a well-established independent risk factor for CVD, and intensive treatment of hyperglycemia has been shown to prevent or slow the progression of long-term micro vascular complications of type 2 diabetes.

According to the Center for Disease Control and Prevention [CDC], 97% of adults with diabetes have one or more lipid abnormalities. The central characteristic dyslipidaemia in-patient with type 2 diabetes is an elevated triglyceride level, particularly triglyceride-rich VLDL levels and decreased HDL cholesterol levels. In diabetic patients, the concentration of LDL cholesterol is usually not significantly different from that seen in nondiabetic individuals. However, patients with type 2 diabetes typically have a preponderance of smaller, denser, oxidized LDL particles, which may increase atherogenicity, even if the absolute concentration of LDL cholesterol is not elevated <sup>(2)</sup>.

Most recently, results of the Strong Heart Study indicate that LDL cholesterol is an independent predictor of CVD with diabetes, along with

age, albuminuria, fibrinogen, HDL cholesterol (inverse predictor), and percent body fat (inverse predictor). Starting with LDL levels as low as 70mg/dl, every 10mg/dl increase in LDL cholesterol was associated with a 12% increase in risk of CVD. This finding is supported by results of prospective, long-term clinical trials in which reduction of LDL levels was associated with a significantly reduced risk of cardiovascular events in both diabetic and nondiabetic participants <sup>(2)</sup>.

In addition to lipid abnormalities and hyperglycemia, which are independently atherogenic, hypertension is also known to be a major risk factor for CVD in all populations. Although a causal connection between insulin resistance and hypertension has been debated, the evidence to support this possibility is increasing. Together, hypertension and overt diabetes substantially and synergistically increase the risk of CVD, as well as of microvascular complication.

In addition to being at risk of microvascular disease, patients with diabetes are at very high risk of macrovascular disease, particularly CVD. Because diabetic patients without previous MI have as high a risk of MI as nondiabetic patients with previous MI, all diabetic patients should be treated aggressively for the prevention of CVD<sup>(2)</sup>.

Cardiovascular complications (e.g. Coronary artery disease [CAD], stroke, peripheral vascular disease, cardiomyopathy, congestive heart

failure) are the leading cause of morbidity and mortality related to diabetes mellitus.

Complications of atherosclerosis are responsible for about 80% of deaths in diabetic patients and 75% of hospitalizations for diabetic complications. In a 7 year study conducted in Finland, the absolute risk for major Cardiovascular events in patients who had type 2 diabetes with out known cardiovascular disease was 20.2% compared with 18.8% in matched non diabetic patients who had established cardiovascular disease. Even before the development of hyperglycemia, persons with impaired glucose tolerance have an elevated risk of macrovascular disease.

Fifty percent of patients have evidence of cardiovascular disease at the time of diagnosis of type2 diabetes <sup>(7)</sup>.

Although mortality due to cardiovascular disease has continued to decline in non-diabetic population in the past 25 years, it has remained steady or has increased in the diabetic population. Persons with diabetes also have higher risk of death before and after infarction as well as an increased incidence of congestive heart failure. As the number of diabetic patient's increase, so too does the implication on public health <sup>(7)</sup>.

In north Sweden in Monica area, a study was done to investigate diabetes as risk factor for acute myocardial infarction from population perspective in region with high cardiovascular disease risk. All patients with acute

myocardial infarction aged 35-64 years were included in a total of 3031 patients between 1984 and 1993. The results showed that the prevalence in diabetes was 5% in men and 4.4% in women. The relative (RR) risk in diabetic men was 2.9%, 95% confidence interval <sup>(1)</sup> 2.6-3.4, and in diabetic women, RR 5.0, CI 3.9-6.3. The risk for re-infarction was about twice as large in patients with diabetes as with patients without diabetes. In both sexes the over all 28 day case fatality (CF) was significantly higher in diabetic compared to non-diabetic subjects. When compared to non-diabetic population, the overall mortality from myocardial infarction in the diabetic population was 4 times higher among men and seven times higher among women. The population attributable risk [PAR], a crude estimate of all acute myocardial infarctions ascribed to diabetes, was 11% in men and 17% in women. The study concluded that diabetes increases the risk for A.M.I, attack rate, incidence, case fatality, recurrence and mortality and is an important contributor to all AMIs in middle aged people <sup>(3)</sup>.

Diabetes can be considered a vascular disease because it causes both microvascular complications (e.g.: Nephropathy, retinopathy) and macrovascular complications. Tight glycemic control has been shown to prevent long term microvascular complication in patients with type 1 diabetes in the Diabetes Control and Complication Trial (DCCT) and in those with type 2 diabetes in the United kingdom Prospective Diabetes

Study (UKPDS). However, glycemic control did not reduce the incidence of cardiovascular events in either study.

This result in the DCCT may have been due, in part, to the young age of the subjects and the short duration of the study. Nevertheless, early recognition of major risk factors for cardiovascular disease in addition to hyperglycemia should be emphasized in the primary care setting <sup>(7)</sup>.

The American Association now recognized diabetes as a major cardiovascular risk factor. The other major cardiovascular risk factors (Smoking, dyslipidaemia, and hypertension act) as independent contributors to cardiovascular disease in diabetic patients. The vascular affects of smoking have been well documented <sup>(7)</sup>.

### **Risk factors in Diabetes for MI:**

#### **Hyperglycemia:**

Results from the DCCT and the UKPDS showed that <sup>(7)</sup> intensive glycemic control (i.e. hemoglobin A1c [Hb A1c <7%]) significantly reduced the risk of microvascular events. In contrast, epidemiological studies have shown a clear association between glucose intolerance and coronary artery disease, as well as a direct relationship between elevated HBA1c values and risk of CAD. A large-scale meta-regression analysis involving 95,783 diabetic patients (94% men) during a 12.4-year period showed that nondiabetic level of fasting and postprandial hyperglycemia appeared to be associated with cardiovascular disease <sup>(7)</sup>.

The diagnostic parameter (e.g. Fasting glucose <126mg/dl and treatment goals (e.g. Hb A1c <7%) in diabetes have been selected to prevent microvascular complications and, thus, may not be adequate to prevent macrovascular disease.

Prevention of cardiovascular disease may require glycemic control to "normal" levels (i.e., Hb A1c < 6%) or a longer period of time as well as control of postprandial blood glucose levels <sup>(7)</sup>.

In the UKPOS, treatment of hyperglycemia with insulin, sulfonylureas, or metformin hydrochloride provided comparable reduction in microvascular complications in relation to reduction in HbA1c values. Only intensive treatment with metformin as first line therapy of a subset of obese patients achieved a positive effect on rates of macrovascular events. Intensive treatment with insulin or sulfonylureas (with raise insulin levels) did not increase the rate of myocardial infarction, thus, even though hyperinsulinemia is a risk factor for cardiovascular disease, treatment with this agent did not increase the risk of cardiovascular mortality. The thiazolidinediones may offer additional benefits by directly improving insulin sensitivity as well as glycemic control before its withdrawal from the market; troglitazone (Rezulin) was shown to have reduced intima-media wall thickness in carotid arteries independent of glycemic control <sup>(7)</sup>.

Under current standards, treatment of hyperglycemia alone clearly does not prevent macrovascular disease in patients with type 2 diabetes, although the impact of glycemic control on other variable (e.g. Dyslipidaemia with improvement in VLDL triglyceride level) can not be ignored, assessment of all risk factors and aggressive treatment to achieve goal are critical to reduce cardiovascular risk in diabetic patients<sup>(7)</sup>.

**Dyslipidaemia:**

Result from the study, which was done in China Medical (4) University, to assess the risk factor of myocardial infarction and polymorphism gene Apolipoprotein (APOE) genotype among MI patients and their siblings showed the medians of total cholesterol, (TC), triglyceride (TG), low density lipoprotein-c (LDL-C), in MI group and sibling group were higher than those in the control group with statistical significance. Body mass index (BMI) 25Kg/m, cigarette > 10/dl TC>5.2 mmol/L, TG >2.26mmol/L, LDL-C>3.4mmol/L, TC/HDL-C>5mmol/L and fasting blood glucose (FBG)>5.6mmol/L were risk factor for MI, HDL -c> 9mmol/L were a protective factor for MI. Among the here genotypes of APOE, E3/3 was the commonest one. However, no significant difference was found in the distribution frequencies of these 3 genotypes, levels of serum lipid and lipoprotein, and Tc/HDL-c. Among the patients the number of allele E4 carrier was nearly twice the number of the non-allele E4carrier. The conclusion is that dyslipidaemia is an important risk factor

for MI, and polymorphism of APOE may be an indirect risk factor of coronary heart disease genetically. Addition to that, serum total cholesterol remains an important risk factor for myocardial infarction in men and women aged 70 years and older, whilst HDL cholesterol at older age remains important in women only <sup>(4)</sup>.

The Scandinavian Simvastatin Survival Study (4s) showed 42% reduction in coronary heart disease events in diabetic patients with known high low density lipoprotein-c (LDL-C) levels with simvastatin therapy (mean also dose 27mg/d with LDL-c reduction approximately 35%. Less degree reduction have been shown in other secondary prevention studies in patients treated with pravastatin with mild to moderate elevation at baseline.

The diabetic subgroup in the Veterans Administration High Density Lipoprotein (HDL) Intervention Trial (V A-HIT) showed approximately 22% reduction events in patients with diabetes and known CHD when HDL -C was increased by approximately 6% by gemfibrozil.

### **Hypertension:**

Hypertension and diabetes are both independent risk factors for cardiovascular disease. When they coexist, they are synergistic in this effect. Hypertension in the diabetic patient markedly heightens the risk of end stage renal disease, coronary artery disease, stroke peripheral vascular disease, and diabetic retinopathy<sup>(6)</sup>.

Importantly, control of blood glucose alone is not enough to optimally reduce the incidence of diabetes-related mortality or myocardial infarction in the hypertensive diabetic patient treatment of coexistent hypertension is also essential. Indeed, drug therapy is recommended for any diabetic patient whose blood pressure is higher than 130/85mmHg<sup>(6)</sup>. Hypertension increases the risk of coronary heart disease, left ventricular hypertrophy, congestive heart failure, and peripheral vascular disease in patients with diabetes. Prospective trials in hypertensive patients with type 2 diabetes have shown that blood pressure control is an extremely effective and important prevention therapy, regardless of class of medication used<sup>(7)</sup>.

Between 1976 and 1991, morbidity and mortality from hypertension declined significantly because of increased awareness, more consistent treatment, and better control. Unfortunately, that trend has been reversed since 1991. The most recent figures of the national health and nutrition education survey (NHANES III, phase 2) showed that awareness, treatment, and control of hypertension have declined<sup>(5)</sup>.

According to the National High Blood Pressure Education Program working group report on hypertension in diabetes, hypertension is twice as common in people who have diabetes as in those who do not. The problem is particularly pervasive among women and specific ethnic groups. Almost twice as many African Americans as whites and three

times Mexican Americans as non-Hispanic whites have coexistent diabetes and hypertension <sup>(5)</sup>.

Although hypertension occurs more often in patients with type 1 than with type 2 diabetes mellitus, after adjustment for age, the prevalence of hypertension in type 2 diabetic patients increases with age. About 90% of patients who have a dual diagnosis of diabetes and hypertension have type 2 diabetes <sup>(5)</sup>.

Consequently, patients with type 2 diabetes represent the majority of hypertensive patients <sup>(5)</sup>.

**Pathophysiology:**

The diabetic patients have increased vascular reactivity to various vasoconstrictors and increased total exchangeable body sodium as sub group of patients are "salt-sensitive", which mean they have heightened vasoconstrictive response to a given sodium load. These patients have poor prognosis with respect to cardiovascular events.

Hyperinsulinemia and insulin resistance can contribute to hypertension, as can hyperlipidaemia and coagulation abnormalities. A strong family history of diabetes and essential hypertension appears to identify type 1 diabetic patients in whom renal disease and hypertension are likely to develop <sup>(5)</sup>.

Cardiovascular disease risk in patients with hypertension alone is a multifactorial problem complicated by the presence or absence of

diabetes, as well as other risk factors (e.g. Smoking, dyslipidaemia, age > 60 years, male sex, being postmenopausal family history of cardiovascular disease)<sup>(5)</sup>.

The Joint National Committee (JNC VI) report empirically classifies hypertensive patients into one of three risk groups, based on these components of cardiovascular risk (table1-1) <sup>(5)</sup>.

**Table (1-1): Risk stratification and treatment of hypertension**

<b>Blood pressure (mmHg)</b>	<b>Risk group A</b>	<b>Risk group B</b>	<b>Risk group C</b>
High normal (130-139/85-89)	Life style modification	Life style modification	Drug therapy
Stage 1 (140- 159/90-99)	Life style modification up to (12 mo)	Life style modification (up to 6 mo)	Drug therapy
Stage 2 and 3 > 160 > 100	Drug therapy	Drug therapy	Drug therapy

The JNCVI classification depends on the presence or absence of target organ damage or clinical cardiovascular disease (e.g. Left ventricular hypertrophy, previous coronary revascularization, and heart failure). Risk group A comprises patients who do not have any other risk factor or target organ damage or clinical cardiovascular disease <sup>(5)</sup>.

Risk B includes patients with at least one risk factor (excluding diabetes) but without target organ damage or clinical cardiovascular disease.

Risk group c comprises patients with target organ damage or clinical cardiovascular disease, with or without other risk factors. This group includes all patients with diabetes, regardless of the presence or absence of other risk factors or of target organ damage or clinical cardiovascular disease.

Drug therapy is the recommended strategy for any diabetic patient in any stage of hypertension.

Because of the variability in blood pressure and the propensity for autonomic dysfunction and orthostatic hypotension in patients with diabetes, blood pressure should be measured in the supine, sitting, and standing positions. Ambulatory monitoring may also be useful <sup>(5)</sup>.

The JNCVI classifies optimal blood pressure for cardiovascular risk to be at or below 120/80 mm Hg in adults aged 18 years or older. Normal blood pressure is classified as at or below 130/85 mm Hg, and data from clinical trials indicate that this is a realistic goal for patients with diabetes.

Moreover, the data also indicate that diabetic patients benefit more than the population at large from a decrease in blood pressure <sup>(5)</sup>.

Results from the Hypertension Optimal Treatment (HOT) study showed that the risk of major cardiovascular events in the patient population as a whole was not affected by lowering the diastolic blood pressure, while a

51% reduction in study events was seen in diabetic patients who were randomly assigned to a target diastolic blood pressure group with a goal at below 80 mm Hg <sup>(5)</sup>.

United Kingdom Prospective Diabetes Study (UKPDS) involving hypertensive patients with type2 diabetes, 758 patients were assigned to tight control of blood pressure and 390 patients to less tight control. Blood pressure was significantly lower in the group assigned tight control (144/82mm Hg), compared with the other group (154/87 mmHg).

Even though the difference in diastolic blood pressure between the two groups was only 5mmHg, tight control resulted in significantly greater reduction in risk of diabetes related end points, including deaths from diabetes and strokes and development of microvascular complications, than did less tight control. Although reducing diastolic blood pressure is clearly important, a recent study of elderly, type 2 diabetes patients with isolated systolic hypertension (systolic blood pressure  $\geq 160$ mmHg, diastolic pressure  $\leq 90$ mmHg) also indicated that reduction of systolic blood pressure reduce relative and absolute risk of cardiovascular events. In fact, anti-hypertensive therapy to lower systolic pressure was associated with reduced relative and absolute risks of nonfatal and fatal cardiovascular events (both coronary and cerebral) in diabetic as well as non-diabetic patients, compared with placebo-treated patients. Further more, the reduction in absolute risk was consistently greater for the

treated hypertensive diabetic patients than for treated nondiabetic patients<sup>(7)</sup>.

The Hypertension Optimal Treatment Trial evaluated the effect of calcium channel blocking agent on hypertensive patients (8% of who were diabetic).

Significant reduction in major cardiovascular events (prevention of 1.5 myocardial infarction per 1.000 patients treated for 1 year and 2.5 myocardial infarction per 1.000 patients -years in diabetic patients) was seen when diastolic blood pressure was reduced to a mean of 82.6-mm Hg. In study of isolated systolic hypertension in patients with type 2 diabetes in Europe (s-E trial), risk reduction in cardiovascular end points ranged from 35% to 76% in the diabetic patients, and no excess risk of major cardiovascular events was seen in the diabetic group compared with the nondiabetic group<sup>(7)</sup>.

In the Heart Outcomes Prevention Evaluation study, Angiotensin converting enzyme (ACE) inhibitors have potential renal protective effect and a macrovascular benefit in addition to effect on blood pressure. However, ACE inhibitors may worsen renal function in-patients with bilateral renal artery stenosis and may cause hyper- kalemia, conditions for which patients with type 2 diabetes at increased risk. Use of thiazide diuretics and beta-blockers in diabetic patients has been controversial, because these agents can cause worsening in lipid or glucose control as

well as blunting of hypoglycemic symptoms. However, risk of such effects need not preclude use of beta-blockers in diabetic patients who have myocardial infarction <sup>(7)</sup>.

The American Diabetes Association and the Sixth Report of the Joint National Committee recommended a target blood pressure of less than 130 /85 mm Hg where the National kidney Foundation urges a more aggressive treatment goal of 130/80 mmHg.

Independent of the agent used, aggressive blood pressure control should be a high patients priority in diabetic <sup>(7)</sup>.

**Table (1-2): Lipoprotein risk adult patients levels and treatment goals in with diabetes:**

	<b>Low Risk Level, mg/dl (mmol/L)</b>	<b>Optiml level, mg/dl (mmol/L)</b>	<b>Border line</b>	<b>High</b>
Lipoprotein				
LDL cholesterol	100	< 100 (2.60)	< 100-129 (2.60-334)	130 (3.35)
HDL cholesterol	>45	>45 (1.15)	33-45 (0.85-1.15)	<35 (0.90)
Triglycerides	<200	<200 (2.26)	200-399 (2.26-450)	400 (4.52)

Lifestyle
Social history
Family history
Physical activity
Serum lipids and lipoprotein levels
Cigarette smoking
Diet, nutrition, alcohol ingestion
Physical examination (renal status, cardiovascular disease, retinopathy)
Blood pressure
Glycemic status
Comorbid diseases

**(8) Adapted with permission from Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al.**

Diabetes and cardiovascular disease:

A statement for healthcare professional's from the American Heart Association.

Circulation 1999;

100: 1134-46 (Published erratum appears in circulation 2000; 101: 1629-31).

**Smoking:**

The link between smoking and heart disease has been well described in population all over the world. Twenty five Years follow up of Seven COUNTRIES study, (16 cohorts of men aged 40 to 59 at enrolment in the USA, Finland, the Netherlands, Italy, Croatia, Serbia, Greece and Japan), reported a dose- dependent increase in risk of death. After 25 years, 57.7% of parsons smoking 30 cigarettes per day had died compared to only 36.3% of non -smoking. Additional long-term data came from a 40 year follow up to British physicians which noted that excess mortality from cardiovascular disease was two times higher among smokers compared to non- smokers but that ratio was even more extreme during middle age<sup>(9)</sup>. The data for men and women differ somewhat but recent work underlines the importance of smoking as a cause of myocardial infarction in both men and women.

As an example, in a Norwegian study, rates of myocardial infraction were 4.6 times in men than in women but rates among women who smoked were six times higher than non-smokers and rates among men, three times higher than among nonsmokers. Danish investigators concluded that women may be more sensitive to tobacco as risk of myocardial infarction as both current smoking and total tobacco exposure were consistently higher in women than men, and higher for both groups regarding myocardial infraction rates among non-smokers<sup>(9)</sup>.

While there are certain genetic conditions that cause atherosclerosis, studies of twin pairs in which one smokes and other does not demonstrate that smoking can increase the size of plaques in the carotid arteries by over three fold. A larger plaque means the vessel is narrower, thus increasing risk of stroke, in the case of the carotid arteries, or ischemic heart disease in case of coronary arteries <sup>(9)</sup>.

In an increasing number of health systems, patients are offered expensive therapies such as coronary bypass surgery or angioplasty in an effort to open or bypass vessels that have become so narrow that they are unable to supply sufficient oxygen to the heart. American data report that after an average four and a half years of follow-up, people who continued to smoke after angioplasty had a 76% increased risk of death compared to non-smokers and a 44% higher risk of death compared to those who quit smoking<sup>(9)</sup>.

Moreover, risks of myocardial infarction were similar in non-smokers and those who were successful in quitting smoking after surgery <sup>(9)</sup>.

### **Smoking and Diabetes:**

As documented in the American Diabetes Association's technical review "Smoking and Diabetes" [1], a large body of evidence from epidemiological, case-control, and cohort studies provides convincing documentation of the causal link between cigarette smoking and health risks. Cigarette smoking is the leading avoidable cause of mortality in the

U.S., accounting for [sim] 434,000 deaths each year. Cigarette smoking accounts for one out of every five deaths in the U.S. and is the most important modifiable cause of premature death. Cigarettes provide the delivery system for nicotine, an addictive substance related to various pharmacological, biochemical, and psychological processes that interact to support a compulsive pattern of drug use<sup>(20)</sup>.

Much of the prior work documenting the impact of smoking on health did not discuss separately results on subsets of individuals with diabetes, suggesting the identified risks are at least equivalent to those found in the general population. Other studies of individuals with diabetes consistently found a heightened risk of morbidity and premature death associated with the development of macrovascular complications among smokers. The cardiovascular burden of diabetes, especially in combination with smoking, has not been effectively communicated to both people with diabetes and health care providers. Smoking is also related to the premature development of microvascular complications of diabetes and may have a role in the development of type 2-diabetes.

General smoking prevalence has decreased over the past 10 years because of extensive public health efforts, which include making the population aware of the health hazards of active and passive smoking, implementation of smoking cessation interventions, and policy changes. However, 26-28% of American adults continue to smoke, with variations

reported by ethnic and sociodemographic groups. These figures mirror the prevalence of tobacco use among individuals with diabetes. It appears adolescents may initiate smoking after being diagnosed with diabetes and that the prevalence of tobacco use decreases with disease duration.

Effectiveness of smoking cessation counseling: Smoking cessation is one of the few interventions that can safely and cost-effectively be recommended for all patients and has been identified as a gold standard against which other preventive behaviors should be evaluated. A number of large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of certain forms of provider and behavioral counseling in changing smoking behavior of primary care and hospitalized patients. This work, combined with the more limited studies specific to individuals with diabetes, suggests that smoking cessation counseling is effective in reducing tobacco use in this high-risk group <sup>(20)</sup>.

Although many large-scale well-controlled outcome studies have included patients with diabetes, seldom have results been reported separately for diabetes versus other participants. Special issues that affect successful abstinence have been identified in these studies and include weight management and depression.

Post cessation weight gain may be an impediment to smoking cessation, especially among women or other people concerned with weight management. The presence of comorbid psychiatric conditions such as

depression is associated with prevalence of smoking and heightened relapse after quitting. Though not reported separately, these issues are expected to be at least equally relevant for diabetic patients as for general patients<sup>(20)</sup>.

**Relation of cigarette smoking to myocardial infarction in young women:**

To examine the relation between myocardial infarction and cigarette smoking in young women, the smoking habits of women under the age of 50 who had survived a recent myocardial infarction were investigated. They had not been using oral contraceptives, and other identifiable risk factors were excluded. Among 55 such women and 220 control matched for age and area of residence, the proportions of cigarette smokers were 89% and 55% respectively (P less than 0.001). A dose-response relation was evident; among women 35 or more cigarettes per day the rate of myocardial infarction was estimated to be some 2 folds higher than among those who had never smoked. This study demonstrates that cigarette smoking is a factor for myocardial infarction in young women who are otherwise apparently healthy<sup>(10)</sup>.

**Secondary prevention:**

This prospective study on one hundred and nineteen cigarette smokers (90men, 29 women) who survived their first myocardial infarction for one month were followed for five years or until their death if earlier. The

age corrected mortality rate of men who continued to smoke cigarettes was 2.2 times the age corrected mortality rate of those who stopped smoking after their infarct. The women who continued to smoke had 2.4 times the age corrected mortality of those who stopped smoking. The age corrected mortality rates for the combined group of men and women show that those who stopped smoking after their infraction have 55% of the mortality of those who continued to smoke (P less than 0.05). These results suggest that smoking is not merely "risk factor" for myocardial infarction but is also a causal factor whose effects can be avoided by both men and women after an initial myocardial infraction <sup>(11)</sup>.

**Effect of smoking cessation on mortality after myocardial infarction:**

**Meta-analysis of cohort studies:**

Result of several cohort studies suggests that smoking cessation after myocardial infarction is associated with a significant decrease in mortality <sup>(12)</sup>.

**Oral contraceptives and myocardial infarction:**

Shortly after oral contraceptives become widely available, a 1963 report identified them as a risk factor for myocardial infarction. Subsequent studies showed that women who took oral contraceptives and were heavy smokers were at 30 times greater risk for myocardial infarction than were women with neither risk factor. Partly in response to these adverse effects, oral contraceptives with lower doses of estrogen and varying

types of progestogens were developed. These newer contraceptives, containing second generation (mainly levonorgestrel) appeared to be an improvement over the earlier ones, but risks of arterial disease and myocardial infarction remained <sup>(13)</sup>.

Oral contraceptive containing third generation progestogens (gestodene or desogestrel) has recently been marketed. There is conflicting evidence regarding the cardiovascular risks of these newer agents. Some studies showed no significant difference in the myocardial infarction between women reporting prior use of second-generation oral contraceptives and those reporting use of third generation products.

Smoking remains the most important risk factor for myocardial infarction in women aged 18 to 49. Tanis and colleagues whom conduct a case - control study using the knowledge that third generation products are widely used in the netherlands, found that women who did not take oral contraceptives but who smoked had an adjusted risk for myocardial infarction of 7.9 (9504.9-12.9) compared with women who did not smoke<sup>(13)</sup>.

### **Control and prevention:**

Despite the findings of Tanis and his colleagues, the overall evidence makes it unclear whether third-generation oral contraceptives pose less of a risk for myocardial infarction than their second-generation counterparts. However, whatever the patient's choice, she should be advised that the

risk of myocardial infarction increases with age, that smoking remains a very strong risk factor, and that smoking and taking oral contraceptives may put them at very high risk. As with patients of any age demonstrable gains in risk reduction are possible by paying attention to treating hypertension and lowering elevated cholesterol levels <sup>(3)</sup>.

## OBJECTIVE

It has been observed that diabetes mellitus is very common in Sudanese patients presenting with acute myocardial infarction.

This study was carried out to investigate the frequency of diabetes as a risk factor for myocardial infarction in Sudanese patients compared to some other countries and to look into the status of glycaemic control by such patients.

## PATIENTS AND METHODS

### **Study design and area:**

A descriptive cross-sectional study conducted on all patients with myocardial infarction in the CCU in Alshaab and Omdurman Teaching Hospitals.

### **Study period:**

During the period, first April – October 2003.

### **Study population:**

This study was conducted on 200 patients who were admitted to the CCU with myocardial infarction, and studied by the author herself.

### **Methodology:**

A questionnaire consisting of age, sex, duration of diabetes, type of medication, other risk factors – presenting symptoms, physical examination was designed, and investigation including, ECG, cardiac enzymes, lipid profile, Fasting Blood Sugar (F.B.S), 2 hours post prandial (2hpp) [Normal <140, 4mg/dl], chest x-ray, echocardiography, blood urea and electrolyte were all done.

### **Data analyses:**

Computer using SPSS (Statistical Package for Social Sciences) analyzed the data.

## RESULTS

This study was conducted on 200 patients with myocardial infarction to investigate diabetes as a risk factor. Ninety-four patients (47%) were diabetic as shown in (**Table 1**).

The age distribution of the patients ranged between (30-85) (**Table 2**) with minimum of 32 and maximum of 80 years.

Male : female distribution, is 67% : 33% respectively (**Figure 1**).

**Figure (2)** shows medications, dietary control, oral hypoglycemic agent, and insulin therapy.

The risk factors are shown in (**Tables 3, 4, 5 & 6**), with frequency of smoking in 49% of patients, and a duration of more than 10 years in 65.3% of them. Hypertension occurred in 33% with a duration of more than 10 years in 48.5%, hypertriglyceridaemia in 23% and hypercholestraemia in 22%. High-density lipoprotein was low in one-percent only (**Table 7**), while low density lipoprotein was found in 10%, as shown in (**Table 8**). Alcohol consumption in 24%, with duration of more than 10 years (62%).

Distribution of presenting symptoms and signs, 85% presented with chest pain, 69% with sweating, 46% with palpitation, 20% with signs of heart failure, 8% with syncope and 2% with signs of hyperlipidaemia (**Figure 3 & 4**).

ECG showed 94% of patients had evidence of acute MI, 7% had arrhythmia and 9% had other abnormal finding (**Figure 5**).

Cardiac enzyme was abnormally high. CPK was high in 82%, LDH in 82%, and SGOT in 73% (**Figure 6**).

Abnormal chest x-ray was found in 37% while echo was found to be abnormal in 98%.

Fasting blood glucose was high in 44% where postprandial was high in 43% (normal values 126mg/dl, 140.4mg/dl respectively).

The blood urea was high in 14%. The systolic blood pressure was high in 42.2% of patients (> 160 mmHg) and the diastolic pressure was high in 15.2% (110 mmHg).

**Table (1):**

**Showing frequency of diabetes among the study group**

<b>Case distribution</b>	<b>No.</b>	<b>%</b>
Not diabetic	106	53.0
Diabetic	94	47.0
Total	200	100.0

**Table (2):**

**Showing age distribution**

<b>Age group</b>	<b>No.</b>	<b>%</b>
30 – 39 years	8	4.0
40 – 49 years	34	17.0
50 – 59 years	50	25.0
60 – 69 years	68	34.0
70 – 79 years	32	16.0
80 – 89 years	8	4.0
Total	200	100.0

**Table (3):**

**Other risk factor (Hypertension)**

<b>Hypertensive</b>	<b>No.</b>	<b>%</b>
Yes	66	33.0
No	134	67.0
Total	200	100.0

**Table (4):**

**Other risk factor (Smoking)**

<b>Smoker</b>	<b>No.</b>	<b>%</b>
Yes	98	49.0
No	102	51.0
Total	200	100.0

**Table (5):**

**Investigation (Triglyceride)**

<b>Triglyceride</b>	<b>No.</b>	<b>%</b>
Normal	154	77.0
Abnormal	46	23.0
Total	200	100.0

**Table (6):**

**Investigation (Cholesterol)**

<b>Cholesterol</b>	<b>No.</b>	<b>%</b>
Normal	156	78.0
Abnormal	44	22.0
Total	200	100.0

**Table (7):**

**Investigation (LDL)**

<b>LDL</b>	<b>No.</b>	<b>%</b>
Normal	180	90.0
Abnormal	20	10.0
Total	200	100.0

**Table (8):**

**Investigation (HDL)**

<b>HDL</b>	<b>No.</b>	<b>%</b>
Normal	198	99.0
Abnormal	2	1.0
Total	200	100.0

**Table (9):**

**Range of systolic blood pressure (mm/hg)**

<b>Blood pressure</b>	<b>No.</b>	<b>%</b>
80 – 89	4	2.0
90 – 99	20	10.0
100 – 109	12	6.0
110 – 119	42	21.0
120 – 129	24	12.0
130 – 139	30	15.0
140 – 149	28	14.0
150 – 159	12	6.0
160 – 169	6	3.0
170 – 179	6	3.0
180 – 189	10	5.0
200 – 209	2	1.0
240 – 249	2	1.0
Irricordable	2	1.0
Total	200	100.0

**Table (10):**

**Range of diastolic blood pressure (mm/hg)**

<b>Blood pressure</b>	<b>No.</b>	<b>%</b>
60 – 69	34	17.0
70 – 79	36	18.0
80 – 89	56	28.0
90 – 99	50	25.0
100 – 109	12	6.0
110 – 119	2	1.0
120 – 129	4	2.0
130 – 139	2	1.0
140 – 149	2	1.0
Irricordable	2	1.0
Total	200	100.0

**Table (11):**

**Showing the levels of LDL in studied population**

<b>LDL mg/dl</b>	<b>No.</b>	<b>%</b>
400 – 499	7	35.0
500	13	65.0



Figure 1: Male : Female distribution

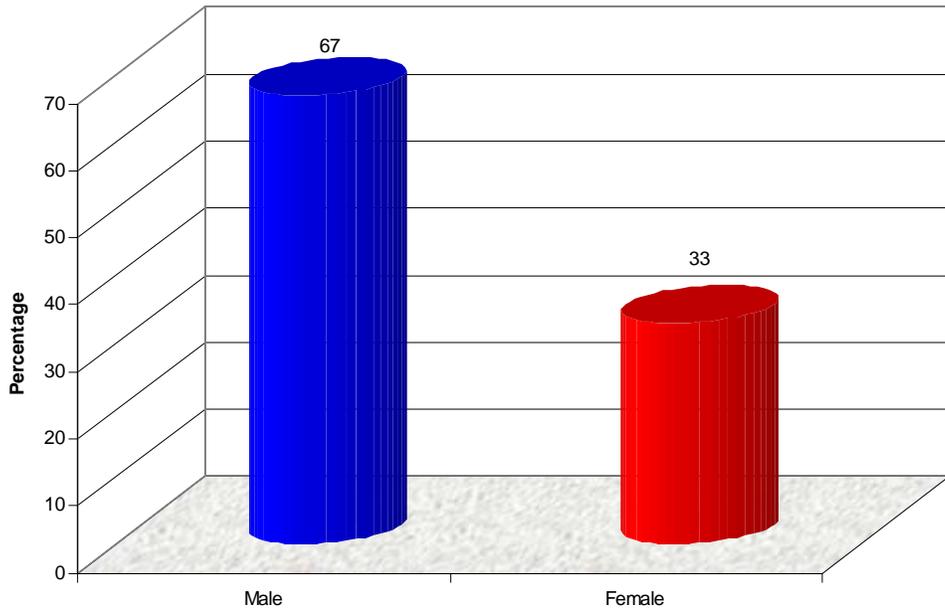


Figure 2: Type of medications

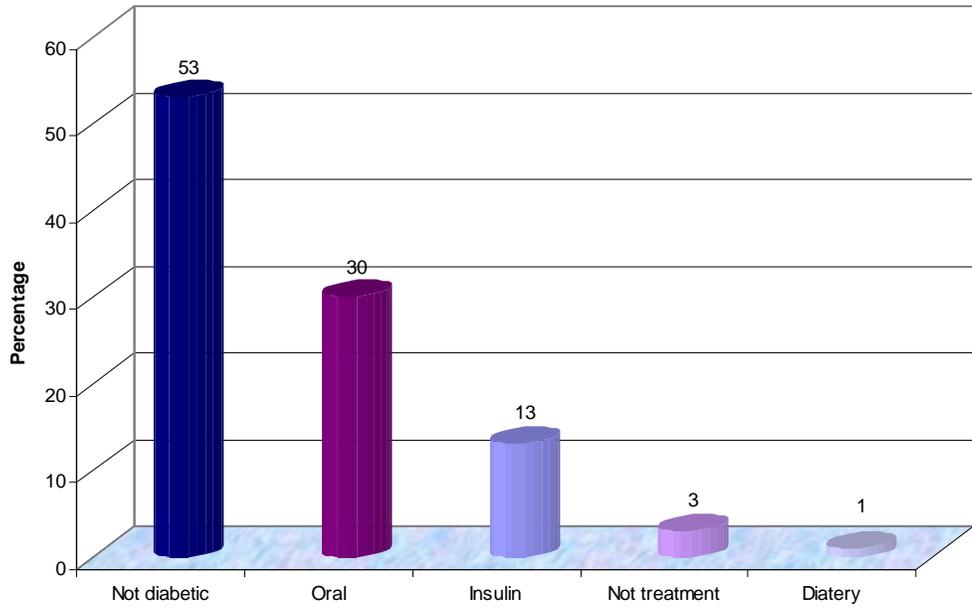


Figure 3: Presenting symptoms

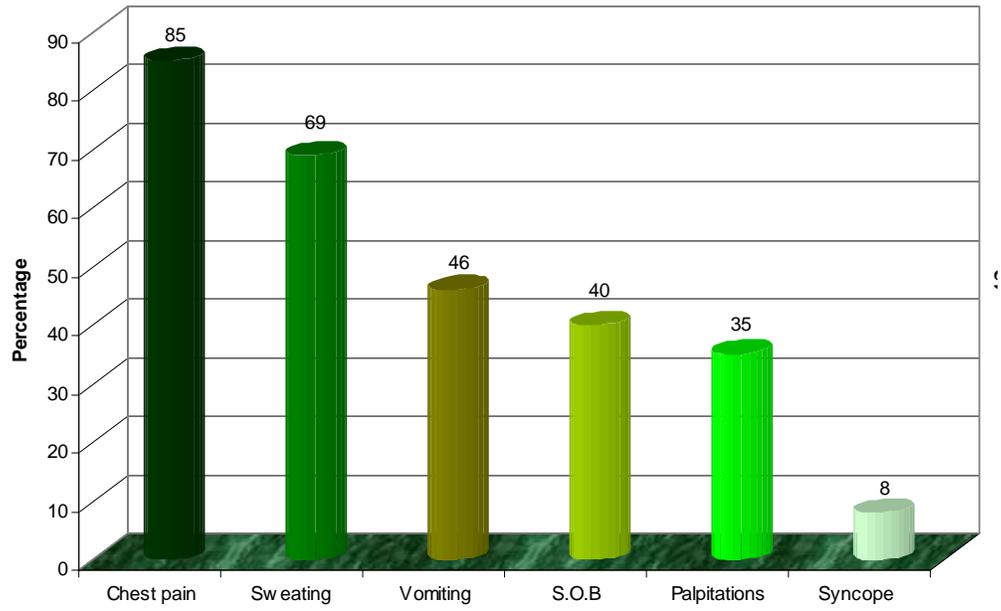


Figure 4: Clinical signs

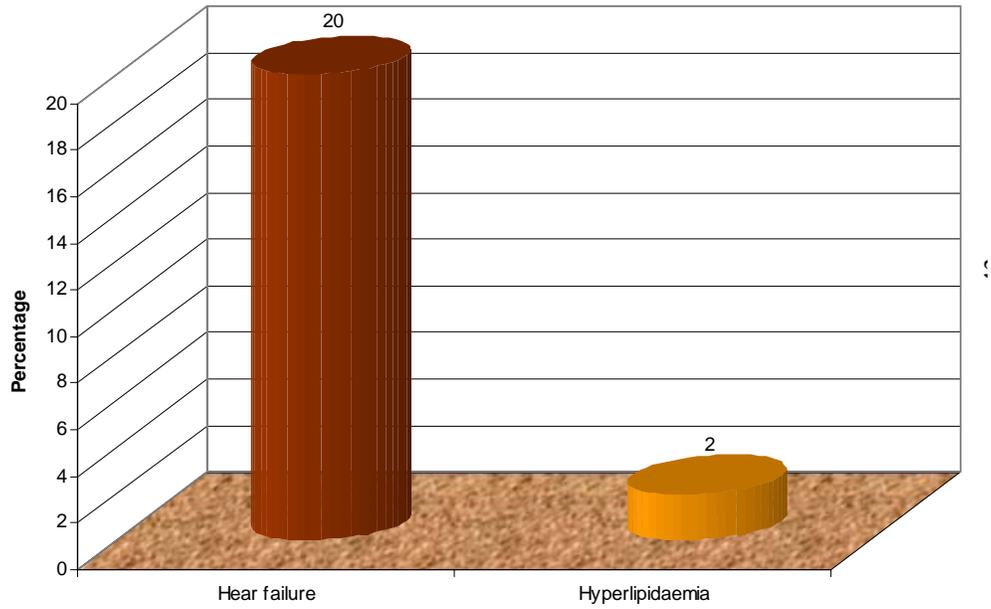


Figure 6: Abnormal findings enzymes

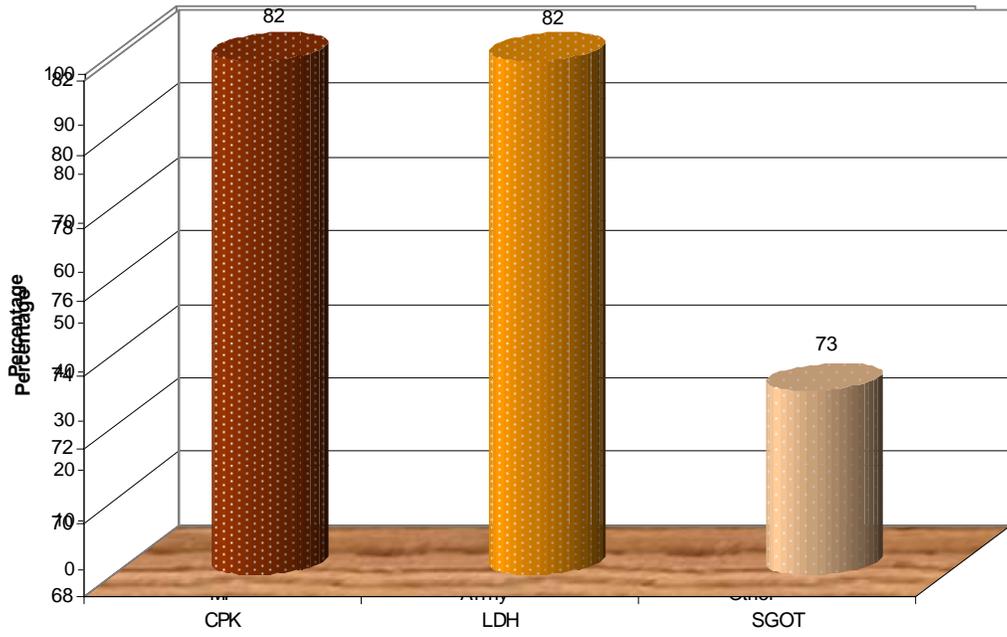


Figure 7: Investigation (FBS)

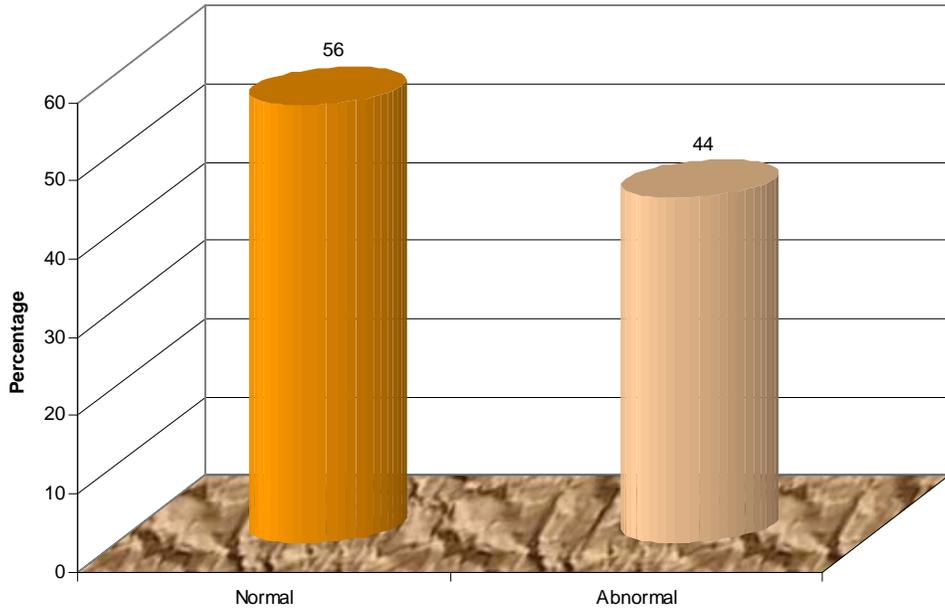
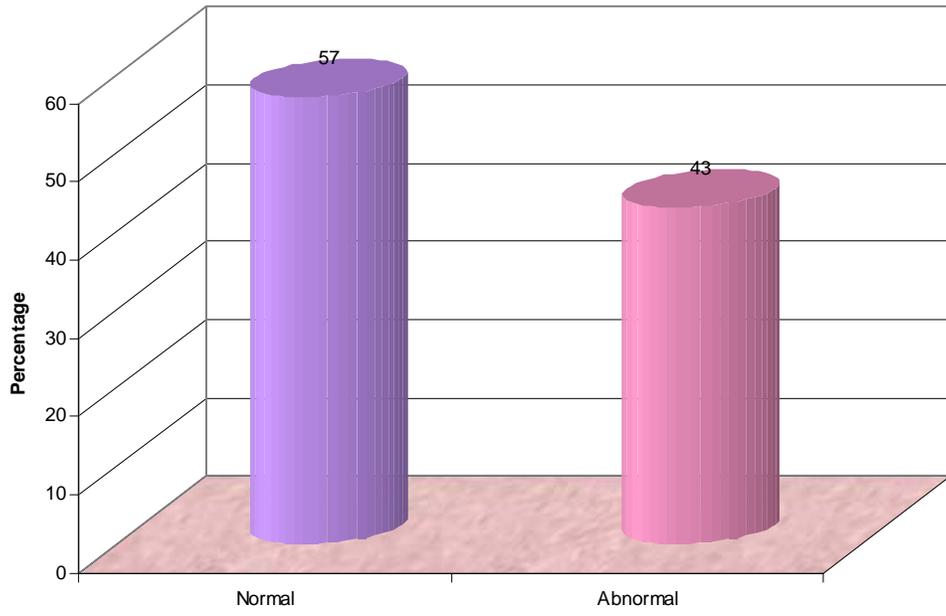


Figure 8: Investigation (Postprandial)

















## DISCUSSION

This descriptive cross-sectional study was carried out to investigate diabetes as a risk factor for myocardial infarction in Sudanese patients.

A total of 200 patients were investigated, 47% of patients were found to be diabetic. This is the highest figure in comparison with other risk factors apart from smoking, which accounted for 49% of patients, while hypertension represented 33%, hypertriglyceridaemia 23%, and hypercholesteraemia 22%.

This figure of 47% is high even in comparison to other studies, which were done elsewhere to investigate diabetes as a risk factor for myocardial infarction. In north Sweden in the Monica area such a study was done from a population studied in a region with high cardiovascular disease. The population attributable risk (PAR), a crude estimate of all acute myocardial infarction ascribed to diabetes, was 11% in men and 17% in women, a total of twenty-eight percent<sup>(3)</sup>.

In EUROASPIRE I and II surveys patients with CHD aged 70 years or younger were interviewed and examined at least 6 months after

hospitalization for a revascularization procedure or acute myocardial or ischaemia.

In EUROASPIRE I and II 18% and 20% of CHD patients respectively had been previously diagnosed with diabetes. Fasting glucose screening raised the prevalence of diabetes in EUROASPIRE II to 28%.

A comparison of both studies showed that for diabetic and non-diabetic patients the prevalence of smoking had increased somewhat and that the prevalence of obesity had increased clearly. There was no improvement in blood pressure control, but cholesterol control had improved, mainly explained by the increased use of lipid-lowering drugs. These European surveys showed that a high risk factor status was more adverse in diabetic patient's<sup>(18)</sup>.

In Kuwait a study to compare the in hospital mortality after acute myocardial infarction (AMI) among diabetic versus non-diabetic patients was carried out.

19% of 149 patients were diabetic. History of diabetes mellitus (DM) was found to be significantly associated with in hospital mortality after AMI (odds ratio : 1.9, 95% CI : 1.2 – 3.0).

This study concluded that the risk of in hospital mortality after AMI is almost doubled among diabetic patient's<sup>(19)</sup>.

In Perth, Australia retrospective study was conducted to assess the relationship between clinical course after AMI and diabetes treatment. Short (28 days) and long-term survival and complication in diabetic and non-diabetic patients were compared, 12.9% were diabetic. Mortality at 28 days was 12 and 28.1% for non-diabetic and diabetic patients respectively<sup>(17)</sup>.

In Diabetes Control and Complication Trial and United Kingdom Prospective Diabetes Study, it was proved that tight glycaemic control prevent long term microvascular complications in patients with type I and type II diabetes<sup>(7)</sup>, so the high percentage of diabetes in our patients with myocardial infarction, might be contributed to poor glycaemic control. This is shown by the high fasting blood sugar in 93.62% pt, and the high two hours postprandial in 91.49%pt. Kumar and Clark<sup>(15)</sup> had mentioned that there is a progressive secretory failure of beta cells in type2 diabetes. The diabetes slowly worsens over years and those patients, who are initially adequately controlled with diet, or diet and tablet, will need gradual increases of their treatment over time. For most patients tablets will eventually fail to achieve adequate metabolic control and change to insulin treatment will become necessary. The most wide spread error in management at this stage is procrastination; the patient whose control is inadequate on oral therapy should start insulin without undue delay<sup>(15)</sup>. However in this study the majority of patients were on oral hypoglycemic

agent (63.8%), while only 27.1% were on insulin therapy. It is well known that ischemic heart disease is more common in type2 diabetes. Accordingly, this might be the cause of high percentage of cases of M.I in the studied population, or it might be due to wrong treatment with tablets instead of insulin, or due to poor patient's compliance or to the unwise follow up. Two third of this group were diabetic for more than ten years which increases the chance for long-term complications. 54% percent of the patients were over 60year of age.

It is reported that a graded relation ship has been demonstrated between the duration and degree of sustained hyperglycemia, however caused and at whatever age it develops, and the risk of vascular disease<sup>(16)</sup>.

This means, the longer the duration of diabetes the more is prone to long term complications due to diabetes and other coexisting risk factors e.g. hypertension and dyslipidaemia. Thus comparing our study for incidence of diabetes in cases of AMI with studies mentioned above shows that diabetes is very common among Sudanese patients presenting with M.I.

Screening of the studied population showed high levels of serum cholesterol (22%), triglyceride (23%), low-density lipoprotein (10%), while high-density lipoprotein was only present in one percent. Indeed these high levels were attributable at least partially, to uncontrolled

diabetes in the study group, which causes some degree of dyslipidaemia. In addition, the great majority of patients were not on anti-dyslipidaemic therapy. Anti-dyslipidaemic drugs leads to reduction in coronary heart disease. This was proved in diabetic patients in the Scandinavian Simvastatin Survival Study (4S)<sup>(7)</sup>.

This dyslipidaemia possibly is related to dietary factor, because Sudanese peoples tend to consume meat, which is great source of exogenous fat.

The striking thing in this data was that the high-density lipoprotein was low in only one percent of patients, and it is unclear whether it was due to small studied population, laboratory errors or other unknown factors.

33% of patients in the study group were hypertensive: 42.4 % of them had systolic pressure of more than 160mmHg and 15.2 % had diastolic pressure more than 110mmHg at presentation reflecting uncontrolled severe hypertension. This might be due to poor compliance; also most patients tend to stop medication if they were informed that they have normal reading in follow up clinic. Also poor dietary measures were additional factor.

The coexistent hypertension in diabetes <sup>(7)</sup> markedly heightens the risk of coronary artery disease, so it is essential to treat high blood pressure. The prospective trials in hypertensive patients with type 2

diabetes have shown that blood pressure control is an extremely effective and important prevention therapy, regardless to class of medication. A result from Hypertension Optimal Treatment (HOT) study showed that the risk of major cardiovascular event in the patient population as whole was not affected by lowering the diastolic blood pressure, while 51% reduction was seen in diabetic patients who were randomly assigned to a target diastolic blood pressure group with a goal at below 80 mm Hg<sup>(5)</sup>.

## CONCLUSION

- This study concluded that diabetes is major risk factor for myocardial infarction, representing highest percentage among other risk factors.
- Tight glyceemic control in type 1 and type 2 diabetes prevents long-term microvascular complications.
- Dyslipidaemia should be detected early and treated aggressively, especially in diabetic patients.
- Optimal blood pressure control with accurate antihypertensive drugs will lead to average reduction in cardiovascular events in diabetic patient.

## RECOMMENDATIONS

- Good glycemic control is important to prevent myocardial infarction in diabetic patient.
- Optimal blood pressure control in diabetic patient will reduce the occurrence of myocardial infarction in diabetic patient.
- Detection of dyslipidaemia in diabetic patient and aggressive therapy will lead to average reduction in the percentage of diabetes as risk factor for MI.
- Diabetic patient should be encouraged to stop smoking.
- Diabetic patient should be advised to perform certain physical activities with ideal dietitian and nutritional program.
- Physical examination including renal status, cardiovascular disease and retinopathy should be carried out in every follow-up clinic.
- Accurate decisions concerning the type of medication whether to be oral or insulin therapy.
- Diabetic patient with positive family history of MI should be under especial concern.

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**Diabetes as Risk Factor for  
Myocardial Infarction in Sudanese  
*Questionnaire***

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Patient Name:

Age  Yr.

Gender: M  F

Tribe:

Residence:

Origin:

Occupation:

Duration of Diabetes:

Type of Medication: insulin  Oral

Other Risk Factors:

- Hypertension

Duration      ↓ 10       ↑ 10

- Smoking

Duration      ↓ 10       ↑ 10

- Hyperlipidemia

- Alcohol

Duration      ↓ 10       ↑ 10

Others

Symptoms :

- Chest Pain

-Palpitations

-Syncope

Examination:

- Pulse  Beats/ min

- BP  MMHg

- Sign of Heart Failure

- Sign of Hyperlipidemia

Investigations:

	Normal	Abnormal	
- ECG	<input type="checkbox"/>	<input type="checkbox"/>	MI Arr Oth
			<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

	Normal	High	
- Cardiac Enzymes	<input type="checkbox"/>	<input type="checkbox"/>	CPK LDH SGOT
			<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

-Triglyceride

-Cholesterol

-HDL

-VLDL

	Normal	Abnormal
- CXR	<input type="checkbox"/>	<input type="checkbox"/>
-ECHO	<input type="checkbox"/>	<input type="checkbox"/>
-FBS	<input type="checkbox"/>	<input type="checkbox"/>
-Post Prandial	<input type="checkbox"/>	<input type="checkbox"/>
-B.rea	<input type="checkbox"/>	<input type="checkbox"/>
-S.Creatinine	<input type="checkbox"/>	<input type="checkbox"/>
-K	<input type="checkbox"/>	<input type="checkbox"/>
-Na	<input type="checkbox"/>	<input type="checkbox"/>