الدالات الكيميائية الحياتية والعوامل المخطرة في احتشاء العضلة القلبية الحادة

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من قبل

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بكالوريوس طب وجراحة عامة

(١٤٢٧) (٢٠٠٦)

Biochemical Markers And Risk Factors In Acute Myocardial Infarction

A Thesis

Submitted to the College of Medicine, University of Babylon in partial fulfillment of the Requirement for the Master degree in Clinical Biochemistry

By
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١٤٢٧ ٢٠٠٦

بسم الله الرحمن الرحيم

" وُيسأَلونَكَ عنِ الرُوحِ قلِ الرُوحُ منِ أَمرِ ربيِ وَمَا أُوتيتم منِ العلمِ أَلاَ قَليلاً "

صدق اللّه العلي العظيم

سورة الإسراء" الآية ٨٥"

Dedication

To

my country

my parents ,

dear wife,

close friends

and

my son

Acknowledgment

I would like to express my sincere gratitude and whole hearted appreciation to Prof. Dr. Mufeed J Ewadh ,Ph.D of biochemistry (President of Karbala university) , my supervisor , for his

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I am thankful to all staff at the medical biochemistry department in the College of medicine Babylon university , cardiac care unite and laboratory unit in AL –Hussein general hospital in Karbala

I

We certify that this thesis was prepared under our supervision at the college of medicine, Babylon university , as partial fulfillment of the requirement for the Master Degree of Science (M. Sc.)in Clinical Biochemistry.

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In view of the avaible recommendation , I forward this thesis for debate by the examining committee .

Signature

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Head of Biochemistry Department
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We, the Examining Committee, after reading this thesis and examining, the student in its content, find it adequate as a thesis for degree of Master of Science in Clinical Biochemistry.

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Approved for the College of Council

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Dean of the College of Medicine

Abstract

This study was conducted in AL-Hussein general hospital in Karbala city during the period from (September ٢٠٠٤) to (May ٢٠٠٥). To assess total creatine kinase activity and creatine kinase-MB activity in the acute myocardial infarction and to get the true diagnosis of acute myocardial infarction, we depended on the relative index which equal (creatine kinase - MB / total creatine kinase) ١٠٠٪ which has high sensitivity and specificity for acute myocardial infarction.

This study included ١٠٠ patients ٧٧ were males and ٢٣ were females with their mean age (٥٨±١٩ years).

The patients diagnosis of having acute myocardial infarction is based on the World Health Organization (WHO) which required two of the following:-

١-Chest pain, heaviness or discomfort. Which lasted more than ٣٠ minutes.

٢-Typical ECG changes.

٣-Serum cardiac biochemical markers elevation (total creatine kinase activity and creatine kinase- MB and glutamate oxaloacetate transaminase GOT).The diagnosis was done by a consultant physician.

The control groups consist of ٤٥ subjects. They were chosen from medical staff and relatives who were free from signs and symptoms of coronary heart disease ٣٨ were males and ٧ were females, with their mean age (٥٦±١١ years old).

Blood samples were taken from the patients ٢٤ hours after attack and urine samples were collected from the patients in the ٣rd day after attack.

Blood and urine samples were gathered from the control groups for comparison.

II

The study shows the following results:-

١- Total creatine kinase in patients found to be significantly very high activity compared with control group (P<٠.٠٠١), A male patient has non significant higher activity compared with female patient (P>٠.٠٥).
٢- Creatine kinase-MB in patients found to be significant very high activity compared with control group (P<٠.٠٠١), Male patient has non significant higher activity compared with female patient (P>٠.٠٥).
٣- Relative index in patients found to be significant very high percentage compared with control group (P<٠.٠٠١), male patient has non significant higher percentage compared with female patient (P>٠.٠٥).
٤- Microalbuminurea in patients found to be significant higher concentration compared with control group

(P<٠.٠٥), Female patient has non significant higher concentration compared with male patient (P>٠.٠٥).

٥- Serum albumin in patients found to be significant lower concentration compared with control group (P<٠.٠٥), no significant difference serum albumin concentration in male and female patient (P>٠.٠٥).

٦- Serum uric acid in patients found to be significant higher concentration compared with control group (P<٠.٠٥), male patient has non significant higher concentration compared with female patient (P>٠.٠٥).

٧- From the data sheet we found that the following factors regarded as risk factors for acute myocardial infarction(smoking in male, hypertension in female and hyperlipidemia in male)

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Conclusions

● AMI diagnosis can not be based on the total CK only because of high negative and positive predictive value as the increment of total CK is not more than ٢ to ٣ folds in small infarction and in the patients with low muscle mass ,and it increase in many other situations .

● CK-MB isoenzyme found to be more sensitive and specific indicator for AMI.

● Relative index is highly sensitive and specific indicator for diagnosis of AMI .

● Microalbuminurea is highly correlated with development of atherosclerosis and associated with lipid profiles abnormalities .

●Our finding show there is significant difference in serum albumin concentration between patient with AMI and healthy subjects .

● Elevated serum uric acid may act as a marker of underlying tissue ischemia.

Recommendations

● The relative index is the corner stone in the diagnosis of AMI as we go to depend on it when clinical examination and ECG findings do not give clue about diagnosis of AMI .

●Any case present in the emergency department with typical chest pain and do not have definitive diagnosis of AMI ,should keep for observation for at least ٢٤hours , then send blood sample for total CK ,CK-MB as soon as possible .

●To get more accurate diagnosis of AMI ,serial blood samples ٠,٣,٦,٩,١٢,٢٤,and ٤٨ hours after attack of chest pain should be taken for CK-MB isoenzyme activity measurements in association with other biochemical parameters or cardiac markers .

●In diagnosed case of AMI ,the mortality should evaluate via biochemical factors (serum lipid profile, serum uric acid concentration , serum albumin concentration, and urinary albumin execration)

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Abbreviations

- AMI……Acute myocardial infarction
- ECG……Electrocardiograph.
- US……United state.
- BP……Blood pressure.
- ESR……Erythrocyte sedimentation rate .
- ED……Emergency department
- CK ……..Creatine kinase.

●CK-MB…….Creatine kinase-MB.

●LDH……..Lactate dehydrogenase .

●GOT …….Glutamate oxaloacetate transaminase

●CK-MM…… Creatine kinase-MM.

●RI…….. Relative index.

●ng/ml……..nano gram/ milliliter .

●U/L……..International unit /liter.

●COP…….Colloid osmotic pressure.

●MA……..Microalbuminurea .

●SLE……..Systemic lupus erythromatosus.

● RIA…….Radio immuno assay.

●ACR ……Albumin to creatinine ratio .

●HDL…….High density lipoprotein .

●LDL …….Low density lipoprotein .

●TG……Triglyceride.

●HT……Hypertension.

●WHO……World Health Organization.

●CCU……..Cardiac care unit.

●HCL ……..Hydrochloric acid .

IV

●NBT……Nitro blue tetrazolium.

●A……Absorbance.

●BCG……..Bromocresol green .

●IHD……Ischemic heart disease .

●ACS……..Acute coronary syndrome.

●CVS……Cardiovascular system .

●NO ……..Nitric oxide .

●ATP……Adenosine-٥- triphosphate

●ADP……Adenosine-٥- diphosphate

●AMP …….. Adenosine-٥- monophosphate

●IMP…… Inosine-٥- monophosphate

●XMP…… Xanthosine-٥- monophosphate

●GMP…… Guanosine -٥-monophosphate

●CO ……. Cholesterol oxidase

●CE ……. Cholesterol esterase

●No. of pt. …… Number of patient

V

١-١ Definition

Acute myocardial infarction (AMI) is defined as the death or necrosis of myocardial cells. It is a diagnosis at the end of the spectrum of myocardial ischemia or acute coronary syndromes (ACS). Myocardial infarction occurs when myocardial ischemia exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms that are

designed to maintain normal operating function and hemostasis. Ischemia at this critical threshold level for an extended period results in irreversible myocardial cell damage or death [1].

Critical myocardial ischemia may occur as a result of increased myocardial metabolic demand and/or decreased delivery of oxygen and nutrients to the myocardium via the coronary circulation. An interruption in the supply of myocardial oxygen and nutrients occurs when a thrombus is superimposed on an ulcerated or unstable atherosclerotic plaque and results in coronary occlusion. A high-grade (> ٧٥٪) fixed coronary artery stenosis due to atherosclerosis or a dynamic stenosis associated with coronary vasospasm can also limit the supply of oxygen and nutrients and precipitate an AMI. Conditions associated with increased myocardial metabolic demand include extremes of physical exertion, severe hypertension (including forms of hypertrophic obstructive cardiomyopathy), and severe aortic valve stenosis. Other cardiac valvular pathologies and low cardiac output states associated with a decreased aortic diastolic pressure, which is the prime component of coronary perfusion pressure, can also precipitate AMI [2].

Myocardial infarction can be subcategorized on the basis of anatomic, morphologic, and diagnostic clinical information. From an anatomic or morphologic standpoint, the two types of AMI are transmural and nontransmural. A transmural AMI is characterized by ischemic necrosis of the full thickness of the affected muscle segment(s), extending from the endocardium through the myocardium to the epicardium. A nontransmural AMI is defined as an area of ischemic necrosis that does not extend through the full thickness of myocardial wall segment(s). In a nontransmural AMI, the area of ischemic necrosis is limited to either the endocardium or the endocardium and myocardium. The endocardial and subendocardial zones of the myocardial wall segment are the least perfused regions of the heart and are most vulnerable to conditions of ischemia. An older

subclassification of AMI, based on clinical diagnostic criteria, is determined by the presence or absence of Q wave on an electrocardiogram (ECG). However, the presence or absence of Q wave does not distinguish a transmural from anon-transmural AMI as determined by pathology[٣] .

A more common clinical diagnostic classification scheme is based on ECG findings as a means of distinguishing between two types of AMI—one that is marked by ST- segment elevation and one that is without ST-segment elevation(subendocardial infarction). The distinction between an ST-segment elevation AMI and a non-ST- segment elevation AMI also does not distinguish a transmural from a non-transmural AMI. The presence of Q waves or ST-segment elevation in ECG is associated with higher early mortality and morbidity; however, the absence of these two findings does not confer better long-term mortality and morbidity [٤] .

١-٢ PREVALENCE

Myocardial infarction is the leading cause of death in the United States (US) as well as in most industrialized nations throughout the world. Approximately ٨٠٠,٠٠٠ people in the US are affected and in spite of a better awareness of presenting symptoms, ٢٥٠,٠٠٠ die prior to presentation to a hospital. The survival rate for US patients hospitalized with AMI is approximately ٩٠٪ to ٩٥٪. This represents a significant improvement in survival and is related to improvements in emergency medical response and treatment strategies[١].

In Iraq ,some studies concerned with AMI provide some data and give an idea about this , In one study , the researcher

finds that AMI is the second leading cause of death [٦] .Some statistics in Karbala city obtained from the cardiac care unite (CCU) show that ١٨٠٠ patients per year admitted to the hospital are suffering from ACS(these data obtained directly from statistics of the CCU in AL Hussein general hospital).

In general, AMI can occur at any age, but its incidence rises with increasing age. The actual incidence is dependent upon predisposing risk factors for atherosclerosis, which are discussed below. Approximately ٥٠٪ of all AMI in the US occur in people younger than ٦٥ years of age. However, in the future, as demographics shift and the mean age of the population increases, a larger percentage of patients presenting with AMI will be older than ٦٥ years[٥].

١-٣ PATHOPHYSIOLOGY

١-٣-١ Mechanisms of Occlusion:-

The most common etiology of AMI is a thrombus superimposed on a ruptured or unstable atherosclerotic plaque . Most AMI are caused by a disruption in the vascular endothelium associated with an unstable atherosclerotic plaque that stimulates the formation of an intracoronary thrombus, which results in coronary artery blood flow occlusion. If such an occlusion persists long enough (٢٠ to ٤٠ minutes), irreversible myocardial cell damage and cell death will occur[٧].

The development of atherosclerotic plaque occurs over a period of years to decades. The initial vascular lesion leading to the development of atherosclerotic plaque is not known with certainty. The two primary characteristics of the clinically symptomatic atherosclerotic plaque are a fibromuscular cap and an underlying lipid-rich core. Plaque erosion may occur due to the actions of metalloproteases and the release of other collagenases and proteases in the plaque, which result in

thinning of the overlying fibromuscular cap. The action of proteases, in addition to hemodynamic forces applied to the arterial segment, can lead to a disruption of the endothelium and fissuring or rupture of the fibromuscular cap. The degree of disruption of the overlying endothelium can range from minor erosion to extensive fissuring that results in an ulceration of the plaque. The loss of structural stability of a plaque often occurs at the juncture of the fibromuscular cap and the vessel wall—a site otherwise known as the plaque's "shoulder region." Any amount of disruption of the endothelial surface can cause the formation of thrombus via platelet-mediated activation of the coagulation cascade. If a thrombus is large enough to completely occlude coronary blood flow for a sufficient time period, AMI can result[٥].

١-٣-٢ Mechanisms of Myocardial Damage:-

The severity of an AMI is dependent on three factors: the level of the occlusion in the coronary artery, the length of time of the occlusion, and the presence or absence of collateral circulation. Generally speaking, the more proximal coronary occlusion, the more extensive amount of myocardium at risk of necrosis. The larger AMI, the greater chance of death due to a mechanical complication or pump failure. The longer period of vessel occlusion, the greater the chances of irreversible myocardial damage distal to the occlusion[٨].

The death of myocardial cells first occurs in the area of myocardial wall that most distal to the arterial blood supply, the endocardium. As the duration of the occlusion increases, the area of myocardial cell death enlarges, extending from the endocardium to the myocardium and ultimately to the epicardium. The area of myocardial cell death then spreads laterally to areas of watershed or collateral perfusion. Generally, after ٦ to ٨ hours period of coronary occlusion, most of the distal myocardium has died. The extent of myocardial cell

death defines the magnitude of the AMI. If blood flow can be restored to the myocardium, more heart muscle can be saved from irreversible damage or death[٤].

١-٤ Risk Factors:

The major six risk factors have been identified with the development of atherosclerotic coronary artery disease and AMI . The presence of any risk is associated with doubling the relative risk of developing atherosclerotic coronary artery disease. Risk factors for myocardial infarction parallel those for atherosclerosis which include Hyperlipidemia (hypercholesterolemia , hypertriglyceridemia, increased concentration of LDL cholesterol and decrease concentration of HDL cholesterol) , diabetes mellitus , hypertension, truncal obesity ,male gender and smoking. Within the coronary vasculature the progression of stable atherosclerotic plague into vulnerable and ultimately unstable lesion, leading to a cascade of events illuminating in the clinical presentation of unstable angina or AMI[٩].

Most if not all risk factors that are related to atherosclerosis and cardiovascular morbidity and mortality , including traditional and non traditional risk factors , were also found to be associated with endothelial dysfunction. Endothelial dysfunction is systemic disorder and a critical element in the pathogenesis of atherosclerosis and its complication[١٠].

١.٤.١ Hyperlipidemia

Hyperlipidemia is an important risk factor for the development and progression of atherosclerosis and premature coronary heart disease . And the atherosclerosis is a progressive disease characterized by the accumulation of lipid, fibrous material and minerals in the arterial wall leading to narrowing the lumen of arteries. Thrombosis is a complication of atherosclerosis and hyperlipidemia is an important reversible

risk factor to develop acute thrombotic complication of atherosclerosis like myocardial infarction[١١].

Hyperlipidemia appears to be a key early event in a number of cardiovascular diseases including atherosclerosis [١٢][١٣].

١.٤.٢ *Diabetes mellitus*

Hyperglycemia contributes to interaction between endothelial function producing abnormal response to acetylcholine and increasing production of thromboxane, prostaglandin and increasing intracellular calcium ion ,all of which contribute to the release of endothelial vasoconstricting agents. The conversion of glucose, to sorbitol via aldose reductase, produces fructose sorbitol that enhances cell damage by augmenting cell swelling and endothelium derived aldose reductase contributes to highly abnormal cellular functioning and oxidative stress . Also hyperglycemia accelerates the generation of free radical mediated LDL oxidation [١٤]. Oxidized LDL is cytotoxic to endothelium , it impairs endothelium dependent vasodilatation by inactivating nitric oxide (NO) and causes endothelial disruption . The propensity for clotting is increased in patients with diabetes in which the level of plasminogen activator inhibitor which suppress fibrinolysis is elevated in serum of diabetic patient and elevated levels are associated with an increased risk for AMI [١٥].

١.٤.٣ Hypertension

Hypertension induces endothelial dysfunction by reducing NO, this may be related to increase calcium ion by either reduced NO synthetase or excess production of oxygen derived from free radicals which inhibit NO production [١٦]. Hypertension is a risk factor for coronary thrombosis and death in cardiac patients mediated in part by endothelial damage or dysfunction and increased thrombogenecity [١٧].

١.٤.٤ Smoking

The atherosclerosis and cigarette smoking are associated with dysfunction of the endothelium and in particular appear to impair the acute local endogenous fibrinolytic activity [١٨]. Smoking also increases platelets aggregation and contribute to the occlusive of arteries . Cigarette smoking also causes inhibition of substance induced tissue - plasminogen activator release in vivo in humans. This provides an important mechanism where by endothelial dysfunction may increase the risk of atherothrombosis through a reduction in the acute fibrinolytic capacity[١٩].

١.٤.٥ Male gender

The incidence of atherosclerosis and myocardial infarction in men higher than women in all age groups, this gender differences in myocardial infarction incidence however narrows with advanced age [٢٠].

١.٤.٦ Family history

Family history of coronary artery disease increases the risk of atherosclerosis and myocardial infarction in individuals and the etiology of familial coronary events is multi factorial and included other elements such as genetic component and acquired general health practice e.g. smoking and high fat diet [٢٠] .

١-٥ Diagnosis

١-٥-١ Signs and symptoms

AMI may have unique presentations in individual patients. The degree of symptoms ranges from non at all to sudden cardiac death. An asymptomatic AMI is not necessarily less severe than a symptomatic event, but patients who experience asymptomatic AMI are more likely to be diabetic. Despite the diversity of presenting symptoms of AMI, there are some characteristic symptoms **(Table ١-١)**:

Table(١-١) Signs and Symptoms of acute myocardial infarction

• Chest pain described as a pressure sensation, fullness, or squeezing in the midportion of the thorax • Radiation of chest pain into the jaw/teeth, shoulder, arm, and/or back • Associated dyspnea or shortness of breath • Associated epigastric discomfort with or without nausea and vomiting • Associated diaphoresis or sweating • Syncope or near-syncope without other cause • Impairment of cognitive function without other cause

AMI may occur at any time of the day, but most appear to be clustered around the early hours of the morning and/or are associated with demanding physical activity. Approximately ٥٠٪ of patients have some warning symptoms (angina pectoris or an angina equivalent) prior to the infarct [١]. The diagnosis of AMI is usually predicated on the WHO criteria chest pain , ECG changes and increase in biochemical markers of myocardial injury. About half of the patients with typical symptoms (chest pain)do not have AMI[٢١].

١-٥-٢ Silent AMI

Some patients, especially those with diabetes mellitus , hypertension , stroke and elderly patients may have no clinical history or physical findings, or a confusing clinical picture. For these patients, serum cardiac markers may be the only diagnostic clue for an AMI[٨].

١-٥-٣ *Age*

AMI occurs most frequently in persons older than ٤٥ years.

Certain subpopulations younger than ٤٥ years are at risk, particularly cocaine users, insulin –dependent diabetics, patients with hypercholesterolemia, and those with a positive family history for early coronary disease. A positive family

history includes any first-degree male relative aged ٤٥ years or younger or any first-degree female relative aged ٥٥ years or younger who experienced a myocardial infarction[٣].

١-٥-٤ Complete blood count

Leukocytosis may be observed within several hours after an AMI. It peaks in ٢-٤ days, and than levels filled within the reference range during ١ week.

Complete blood film may be useful if anemia is presented which regarded as a precipitant factor . Transfusion with packed red supplemental oxygen may be the only treatment in cases where anemia is only co precipitant.

Erythrocyte sedimentation rate (ESR) rises above reference range values within ٣ days and its elevation continued for several weeks[٢].

١-٥-٥ Electrocardiogram

An ECG should be obtained as soon as possible after presentation to the emergency department(ED). Approximately one half of patients have diagnostic changes on their initial ECG (i.e. ECG is specific for AMI but lack sensitivity). An ECG should be performed on any patient who is older than ٤٥ years and is experience new epigastric pain or nausea.

An ECG is a rapid, low-risk cost measure .Result indicating high probability of AMI are ST segment elevation greater than ١ mm in contiguous leads and new Q wave, results indicting

intermediate probability of AMI are ST segment depression or T wave inversion ,and ST segment ,T wave abnormalities that are know to be old AMI ,and results indicating low probability of AMI are normal finding on ECG ,however normal finding on ECG do not excluded probability of AMI.

Localization of AMI based on distribution of ECG abnormalities is as follows

١- Inferior wall – lead II,III,AVF.
٢- Lateral wall- lead I,AVL,$V_{٤}$-$V_{٦}$
٣- Antroseptal- $V_{١}$-$V_{٣}$.
٤- Antrolateral $V_{١}$-$V_{٦}$.
٥- Right ventricular – $V_{٤}$,$V_{٥}$.
٦-Posterior wall –R/S ratio >١ in $V_{١}$ and $V_{٢}$,T wave changes (i.e. up right)in $V_{١}$[٨].

١-٦ Markers of Cardiac Damage

The diagnosis of an acute myocardial infarction (AMI) has traditionally relied upon the combination of chest pain, ECG changes manifestations and elevations in serum markers of cardiac injury[٢٢]. However, there is considerable variability in the pattern of presentation of AMI with respect to these three elements, as exemplified by the following statistics; ST segment elevation and Q waves on the ECG, two features that are highly indicative of AMI are seen in only about half of AMI cases on presentation, Approximately one third of patients with AMI do not present with typical chest pain, No diagnostic ECG is recorded in approximately half of patients presenting to emergency departments with chest pain suggestive of AMI who ultimately are shown to have an AMI[٢٢].

Among patients admitted to the hospital with a chest syndrome, fewer than ٢٠ percent are subsequently diagnosed as having an AMI. Therefore, in the majority of patients, clinicians must obtain serum cardiac marker measurements at periodic intervals to either establish diagnosis or be useful for a rough quantization of the size of infarction. The availability of new serum cardiac markers with markedly enhanced sensitivity for myocardial damage enables clinicians to diagnose AMI in about an additional one third of patients who would not have fulfilled[٢٣].

As myocytes become necrotic, the integrity of the sarcolemmal membrane is compromised and intracellular macromolecules (serum cardiac markers) begin to diffuse into the cardiac interstitial and ultimately into the microvasculature and lymphatic in the region of the infarction [٢٤]. The rate of

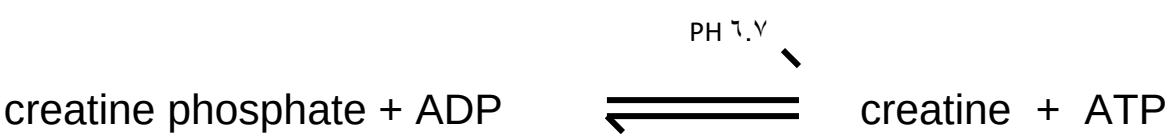
appearance of these macromolecules in the peripheral circulation depends on several factors, including intracellular location, molecular weight, local blood and lymphatic flow, and the rate of elimination from the blood . Time course of serum markers of AMI are listed in table (١-٢) below [٢٥].

Table (١-٢) : Time course of serum markers of AMI[٢٦]

Test	Onset	Peak	Duration
Total CK ,CK-MB	٣-١٢ hours	١٨-٢٤ hours	٣٦-٤٨ hours
Troponins	٣-١٢ hours	١٨-٢٤ hours	Up to ١٠ days
Myoglobin	١-٤ hours	٦-٧ hours	٢٤ hours
Total LDH	٦-١٢ hours	٢٤-٤٨ hours	٦ to ٨ days
GOT	٦-١٢ hours	٢٠ – ٣٠ hours	٢ to ٦ days

١-٦-١ *Creatine kinase (CK)*

Creatine kinase (CK) enzyme is dimeric enzyme composed of M and B polypeptide chains [٢٧] . and exist in three forms : MM, MB, and BB. The molecular weight of the M and B subunits range from ٣٩ to ٤٢ kDa. These isoenzymes reside in the cytosol and facilitate the egress of high energy phosphates into and out of mitochondria by catalyse the conversion creatine phosphate to the creatine with liberation of highly energy compound ATP at the PH ٦.٧ as show in the following equation:



In addition, there is a mitochondrial form of CK located in the mitochondria has clinical significantly in malignancy and sever ill patient [٢٨]. And there is type of CK what called macro CK contained immunoglobulin appear in the reign between CK-MM and CK-MB in the electrophoresis [٢٨].

١-٦-١-١ *Distribution of CK :*

CK isoenzyme activity is distributed in a number of tissues[٢٩].The CK-MB fraction on a percentage basis is generally confined to heart tissue. However, sensitive radioimmunoassays are able to detect small amounts of B subunit in skeletal muscle. Although this represents only a small proportion of CK within that tissue, some muscles have been reported to contain up to ١٠ percent of B chain protein [٣٠]. Most muscles have much more CK per gram than heart tissue [٣١]. As a result, despite containing only a small percent of B chain protein, substantial skeletal muscle breakdown can lead to absolute increases in CK-MM in the plasma[٣٢].

Another potential complicating factor is that, in response to organ damage, such as increased regeneration of skeletal muscle fibers, there is re-expression of proteins that existed during ontogeny, resulting in increased production of more B chain CK protein [٣٣] [٣٤]. Thus, precisely timed biopsies after vigorous exercise (such as a marathon) [٣٥] or in individuals with skeletal muscles damage have demonstrated very substantial increases in the amount of CK-MM relative to total CK. Percentages

as high as ٥٠ percent have been reported in patient with chronic myopathies such as dermatomyosites and poliomyelitis [٣٦].

١-٦-١-٢ *Metabolism*

A large percentage of the CK that is released is degraded locally or in lymph [٣٧]. This local process is truncated by reestablishment of blood flow, which increases the rapidity and magnitude of egress of CK into plasma [٣٨].

١-٦-١-٣ *Isoforms of CK isoenzymes*

Isoforms of the CK isoenzymes occur because there are basic amino acids at the carboxy terminal ends of both the M and B chains . In tissue, virtually ١٠٠ percent of these chains have intact terminal lysine residues. When CK release into plasma, carboxypeptidase N cleaves these terminal lysines, resulting in the development of additional isoforms [٣٩].

Loss of basic amino acids leads to a difference in charge, permitting the isoforms to be separated and labeled according to migration toward the end [٤٠] [٤١]. The situation for MB only two isoforms were originally distinguished by rapid electrophoresis; they represent the tissue form (lysine positive M chain CK-MB٢) and the plasma form (lysine negative M chain CK-MB١).And about CK-MM, four potential isoforms exist, only three are actually relevant in vivo, (one M chain positive lysine and anther M chain positive lysine, the tissue form CK-MM٣), (one M chain negative lysine and anther M chain positive lysine

CK-MM٢) and (one M chain negative lysine and anther M chain negative lysine, the plasma form CK-MB١) [٤٢] [٤٣] [٤٢].

١-٦-١-٤ *Total CK measurements for the detection of cardiac damage*

Since CK is widely distributed in tissues, elevations in total serum CK lack specificity for cardiac damage, which improves with measurement of the MB fraction [٢٩]. Increases in total CK usually begin four to six hours after the onset of AMI, but at least ١٢ hours time is required to detect elevations in all patients who will show high serum CK [٤٣] (see table ١-٢). Most patients have a typical rising and falling pattern of activity. Peak activity is seen at ١٨ to ٢٤ hours with a return to baseline levels by ٣٦ to ٤٨ hours. Although elevation of the serum CK is a sensitive enzymatic detector of AMI that is routinely available in most hospitals [٤٤], important draw backs include false-positive results in patients with muscle disease, alcohol intoxication, diabetes mellitus, skeletal muscle trauma, vigorous exercise, convulsions, intramuscular injections, thoracic outlet syndrome, and pulmonary embolism [٤٥].

١-٦-٢ *CK-MB fraction*

CK-MB has high specificity for cardiac tissue and was the preferred marker of cardiac injury for many years [٢٤]. As with total CK, CK-MB typically begins to rise four to six hours after the onset of infarction but is not elevated in all patients until about ١٢ hours [٣١]. As a result, serial testing is performed after

four or more hours if the initial values are indeterminate, the ECG is not diagnostic, and clinical suspicion remains high [٤٦].

An elevated serum CK-MB is relatively specific for myocardial injury, particularly in patients with ischemic symptoms when skeletal muscle damage is not present. These elevations return to baseline within ٣٦ to ٤٨ hours compared with durations as long as ١٠ days seen with troponins (see table ١-٢). This means that CK-MB, unlike troponins, cannot be used for-the late diagnosis of an AMl but can be used to suggest infarct extension if levels rise again after declining. Earlier CK-MB assay methods that were in common use included radioimmunoassay and agarose gel electrophoresis techniques; these have now been largely supplanted by highly sensitive and specific enzyme immunoassays that use monoclonal antibodies directed against CK-MB [٤٧].

CK-MB generally comprises a lower fraction of total CK in skeletal muscle than in the heart ; as a result, percentage criteria (from ٢.٥ to ٥ percent) have been proposed to distinguish skeletal muscle. They may improve specificity and sensitivity in patients who have both skeletal and cardiac injury [٤٧][٤٨], but may be falsely positive in patients with chronic skeletal muscle disease [٤٩] [٥٠]. High percentages (up to ٥٠ percent) can occur with chronic skeletal muscle injury, such as dermatomyositis and polymyositis, due to increased production of B chain CK protein [٣٢][٣٤].

Prolonged increases in CK-MB can occur in cardiogenic shock; in this setting, however, the diagnosis is rarely in doubt . For reasons that are not understood, CK-MB levels appear to be rise in myocarditis[٣٦].

١-٦-٢-١ *Use in prognosis*

There is a direct relationship between infarct size, as reflected by, total CK and/or CK-MB, and prognosis. This relationship has been known for more than ٢٠ years and was reaffirmed in the cohort of ٨٢٥٠ patients in the PURSUIT trial in which mortality was related to the presence of an elevated serum CK-MB and the degree of elevation .The ٣٠ day and six month mortality was ١.٨ and ٤ percent, respectively when peak CK-MB levels were normal; these patients were considered to have unstable angina(٥١).

Mortality increased progressively to ٨.٣ and ١١ percent at ٣٠ days and six months when peak CK-MB levels were more than ١٠ times normal(٥٢).

١-٦-٢-٢ *CK and coronary reperfusion*

The time to peak CK levels and the slope of CK-MB release can be used to assess whether reperfusion has occurred after thrombolysis therapy (٥٣). Coronary reperfusion is associated with increases in the rate and amount of washout of CK relative to the amount depleted from the myocardium. This concept is known as the release ratio (٥٤). When enzyme is washed out early due to restoration of blood flow, the percentage of CK that is found in the plasma relative to that depleted from heart can be as high as twice what occurs under normal circumstances (٣٧). The more rapid egress of CK into plasma with reperfusion results in higher and earlier peak values. A time to peak of less than four hours is good evidence of recanalization, while a peak concentration occurring later than ١٦ hours is good evidence of persistent occlusion.

Unfortunately, ٨٠ to ٩٠ percent of patients have peak values between ٤ and ١٦ hours which provide little or no discriminative value. As a result, the release ratio is not often used [٥٥].

١-٦-٢-٣ *Infarct extension*

Since CK levels return to baseline one to two days after infarction, re-sampling can be used to detect infarct extension. New elevations that occur after normalization are indicative of recurrent injury, again with the caveats in regard to sensitivity and specificity indicated above [٥٥].

١-٧ *Relative index*

In attempt to confer more cardiac specificity to CK-MB, a relative index is used and calculated according to the following equation :-

Relative index (RI)=(CK-MB / total CK) ١٠٠٪

For mass assay relative index value exceeding ٢.٥٪ is associated with myocardial sources of CK-MB, and for activity assay relative index varies but it usually in the range above ٥٪ is associated with myocardial sources of CK-MB as shown in the following tables(١ –٣)

(٢٤).

Table (١-٣) Relative index in AMI by CK-MB Mass assay

Mass assay		
Interpretation	CK-MB ng/ml	RI %
AMI excluded	<٤	<٢
AMI probable	٤-٥	٢-٢.٥
AMI ensured	> ٥	>٢.٥

Table (١-٤) Relative index in AMI by CK-MB activity assay(٢٤)

Activity assay		
Interpretation	CK-MB U/L	RI %
AMI excluded	<١٩	< ٠-٤
AMI probable	١٩-٢٠	٤ - ٥
AMI ensured	>٢٠	> ٥

١-٨ ***Albumin***

Albumin is the most abundant plasma protein from the mid-gestation until death, accounting for approximately one-half of the plasma protein mass. Albumin has a single polypeptide chain of ٥٨٠ amino acid and it is relatively small protein (molecular mass ٦٦.٣ kDa) [٥٦].

Albumin is synthesized primarily by hepatic parenchymal cells except in early fetal life, when it is synthesized largely by the yolk sac [٥٧]. The synthetic rate is controlled primarily by colloidal osmotic pressure (COP) and secondarily by protein intake, and the normal plasma half-life of albumin is١٥ to ١٩ days [٥٦]. The primary function of albumin is generally considered to be the maintenance of COP in both vascular and extra vascular spaces. Also the presence of many surfaced charged groups plus many specific binding sites, both ionic and hydrophobic, give albumin the ability to bind and transport a large number of compounds. These include free fatty acids , phospholipids , metal ions , amino acids , drugs , hormones, bilirubin, and many others [٥٨].

١-٨-١ Microalbuminuria

Microalbuminuria (MA) is defined as elevated albumin excretion in urine more than ٣٠ mg/day and of below ٣٠٠ mg/day. These values less than the value detected by the urine dipstick testing for the protein which become positive until protein excretion in the urine exceed ٥٠٠ mg/day which is considered as overt proteinuria. MA was less than detected by routine urine dipstick testing for proteinuria thus; the routine urine dipstick is insensitive marker for MA[٥٩].

The patient with MA will not notice any sings of protein in urine unless enlarged amount of protein (i.e. more than several grams/٢٤ hr) excreted in the urine, in this case the urine become frothy because the protein lowers the surface tension of the urine & permit stable forms to form . Significant MA by above definition may be found in the patients with very early stage of diabetic nephropathy, controlled, poorly controlled or sever untreated hypertension ,and SLE [٥٩].

١-٨-١-١ Measurement Techniques for urinary albumin

Urinary albumin excretion is routinely measured in the identification and management of renal diseases. A variety of methods are available to quantify total urine protein, irrespective of the type of protein. The simplest and most widely used methods are semiquantitative tests done on random urine samples. That involves either precipitation of albumin by acid (trichloroacidic acid) or albumin induced color changes of an indicator dye on a dipstick[٦٠].

Although these tests are extremely useful in screening for microalbuminuria , they detect an abnormal concentration for the total urine albumin , not an abnormal excretion rate. Therefore, they might be positive in patients with low urine volume even if the excretion rate is normal, and they may be negative in patients with high urine volume even if the elevation rate is high [٦١] .

For more definitive evaluation and management of patients with microalbuminuria, quantitative albumin analysis of ٢٤ hour urine collection or quantitative albumin analysis of early

morning urine collection or calculation of the random urinary albumin to creatinine ratio(ACR) in which the urinary creatinine use as corrective factor for variable urinary albumin concentration[٥٩].

A number of different methods are available which are semiautomated and two dimensional electrophoresis systems, which employ ultrathingels combined with silver staining allow the detection of a host of specific urinary proteins on a routine basis. These techniques also improve the characterization of urinary proteins with molecular weight less than ٧٠.٠٠٠ Dalton[٦١].

The group at Guy's hospital London, in ١٩٦٣, coined the term microalbuminurea; as they developed the first radioimmunoassay (RIA) for detection of albumin in low concentrations in urine. Since then a great number of RIA or chemicoimmunoassays have been developed[٦٢].

Measurement of total protein and immunoglobulin G excretion have also been used in the evaluation of kidney function in diabetic patients, but the predictive value of these measurements is unknown. Therefore, measurement of urinary albumin excretion by sensitive methods remains a key factor[٦١].

١-٨-١-٢ Types of measurement of MA

While ٢٤hours urine collection was golden standard for the detection of MA several recent studies have shown strong correlations between random spot morning urine sample and ٢٤ hours urine collection. A spot morning urine may be collected from the patient with MA by the measurement of both

albumin and creatinine in the urine. The reason for measuring both albumin and creatinine is that measuring the albumin concentration alone can give result of albumin concentration but not the rate of albumin concentration, that is influenced by urinary albumin value above ٣٠ mg/day therefore MA present. Dehydration, fever, exercises, heart failure are among the factors that can cause transient MA, and use of albumin to creatinine ratio is recommended for the screening of the patient with MA[٦١] .

MA should be checked annually in every one ,and every six months to one year in those started on anti-hypertensive therapy[٦٢].

MA is usually detected by using dipstick analyses, however recent studies documented the inaccuracies of this method which give high false and negative results when compared with golden standard of ٢٤ hours urine measurement. On alterative method is the spot urine sample which has certain advantage as it is easily available, non expensive and reproducible, the best method to diagnose MA in spot urine sample is still matter of discussion, it is remained unclear whether MA measurement alone is sufficient screening method or calculation of urinary albumin to creatinine ratio is required to detect MA [٦٣].

It is recommended that ٣٠ mg/ ٢٤ hours of albumin in spot urine sample show the highest diagnostic performance, (i.e. the value with high specificity and sensitivity), although this result was not significantly different from the direct albumin to creatinine ratio measurement, however a positive result of urinary albumin to creatinine ratio and early morning random urinary albumin measurement a lone should be confirmed by ٢٤ hours urine collection . Urine sampling of albumin

measurement, so ٢٤ hours urinary albumin collection is the more convenient screening method in daily clinical practice [٦٤].

١-٨-١-٣ Pathphysiological mechanism of MA in AMI

The pathophyiological mechanism of MA in AMI is still poorly understood, but MA has been suggested as a marker of endothelial dysfunction of hyperpermeability to the macromolecules which occur early in atheroneogenesis and this is explained by increasing transvascular albumin transport which is associated with an increased transport of proportion into the arterial wall ,and therefore speculated that MA might be a marker of increased susceptibility to the atherogenic effect of other risk factors [٦٥].

The other association of MA with AMI is due to the systemic increase in the vascular permeability including the renal vessel as part of early acute inflammatory process that is associated with AMI.

The patient with AMI and previously had congestive heart failure was markedly associated with MA and this due to elevated glomular capillary pressure which is present in congestive heart failure, facilitates the transglomular passage of albumin and this is due to the increase of activity of rennin-angiotensine system[٦٦] .

In addition the high level of arterial natriuretic peptide also contribute to the renal escape of albumin in the heart failure by increasing capillary permeability MA in AMI represented early generalized vascular endothelial damage . It is also clear that several factors such as an increase in body weight, male gender, high triglyceride level, high cholesterol level, low HDL cholesterol level are associated with MA in AMI[٦٧].

MA is a consequence of inflammatory reaction that occur in AMI and involve the renal vascular-system. The systemic

release of thromboxane and leukotrains have been reported in patients with severe unstable angina and AMI ,further more, the increase in plasma C- reactive protein and serum myeloid A which have recently been documented in the patient with unstable angina and AMI, point to the existence of an inflammatory component in clinical conditions[٦٨] .

١-٨-١-٤ The course of urinary albumin during AMI

Urinary albumin excretion was markedly increased in the acute phase of AMI, slight to moderate increase in the urinary albumin concentration usually measured on the first ٣ days after attack of AMI and after these ,initially raised. urinary albumin progressively fail toward normal value during weeks after attack of AMI[٦٩] .

١-٨-١-٥ MA and AMI

MA is generally regarded as a risk indicator rather than risk factor and some regarded as risk factor for cardiovascular disease (coronary heart disease and hypertension), urinary albumin exertion increase during AMI [٧٠].

Several studies show that MA significantly is higher in the patients with the AMI compared with healthy persons. MA is not specific only for diabetic nephropathy and renal disease but it may also be associated with AMI in its early stage, poorly controlled hypertension, some plasma lipid abnormalities (high triglyceride and low HDL- cholesterol) and several immune disorders[٦٦].

Any degree of MA is a risk factor for cardiovascular disease including AMI in individuals with or without diabetes mellitus[٧٢] .

MA is associated with several risk factors for atherosclerosis including high total cholesterol, high triglyceride(TG), low HDL-cholesterol (i.e. high TG, low HDL- cholesterol are statistically correlated to the hypertension , MA in AMI) [٦٥]

However, recent report indicates that the presence of MA may be a marker of cardiovascular disease, hypertensive left ventricular hypertrophy and peripheral arterial obstructive disease. The patients of AMI with MA have stronger predictor of an increased mortality and morbidity rate or for one year mortality and might be associated with an increased ٤ years risk of death among patients of AMI [٧٣] .

١-٨-٢ Serum albumin &AMI.

Albumin is plasma protein synthesized in the liver and its level fall about ٢٠٪ during inflammatory process. Albumin is inversely correlated with age, obesity and hypertension[٧٣], it is not clear whether low serum albumin level is non specific prognostic marker for AMI or whether it is part of the causal mechanism leading to AMI. Several epidemiological studies have reported an inverse association between serum albumin and ischemic heart disease[٧٤] ,and stroke, and some studies show low serum albumin was associated with ٥٠٪ increased risk of ischemic heart disease, in contrast observational studies did not find an association between serum albumin and ischemic heart disease. [٧٥]

Previous studies have suggested that lower concentration of serum albumin is associated with two fold increased risk of total cardiovascular mortality [٧٦]. However, with reports in U.S.A show that relative risk for coronary heart disease decrease with increase concentration of serum albumin in both men and women[٧٧], the role serum albumin concentration in etiology of ischemic heart disease do not have adequate explanation for such an association .However the association between serum albumin and ischemic heart disease was increase with increased serum total cholesterol [٧٨] .

Albumin has anti-oxidant properties and at low concentration less than physiological value can inhibit copper stimulate peroxidation and hemolysis accrue[٧٩] , it also inhibits production of free hydroxyl radicals from systems containing copper ions and H_2O_2 ,and is able scavenge proxy radicals[٨٠] , albumin also inhibit copper depended lipid peroxidation system

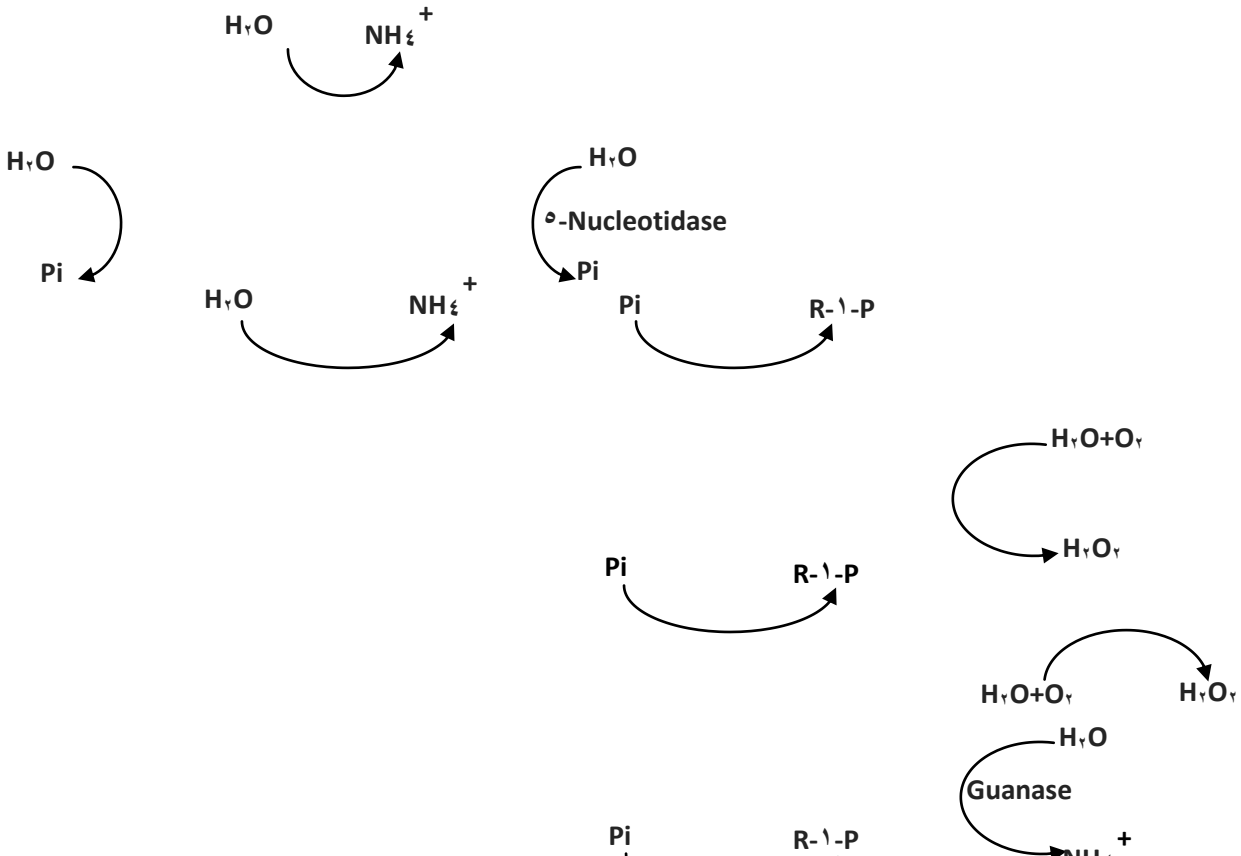
.LDL oxidation is one of early steps in atherosclerotic process ,serum albumin may inhibit endothelial apoptosis [٨١] .

It is unclear whether the prognostic value of low albumin reflect inflammation or if there is an independed effect of albumin, Reuben have shown that low serum albumin associated with increase mortality rate of ischemic heart disease without evidence of inflammation [٨٢].

١-٩ Uric acid

١-٩-١ Uric acid synthesis

Purines arise from metabolism of dietary and endogenous nucleic acids, and are degraded ultimately to uric acid in man, through the action of the enzyme xanthine oxidase . Uric acid is a weak acid (pKa ٥.٨), distributed throughout the extracellular fluid compartment as sodium urate, and cleared from the plasma by glomerular filtration Around ٩٠٪ of filtered uric acid is reabsorbed from the proximal renal tubule, while, active secretion into the distal tubule by an ATPase-depende mechanism contributes to overall clearance as show in the following figure . [٨٣]



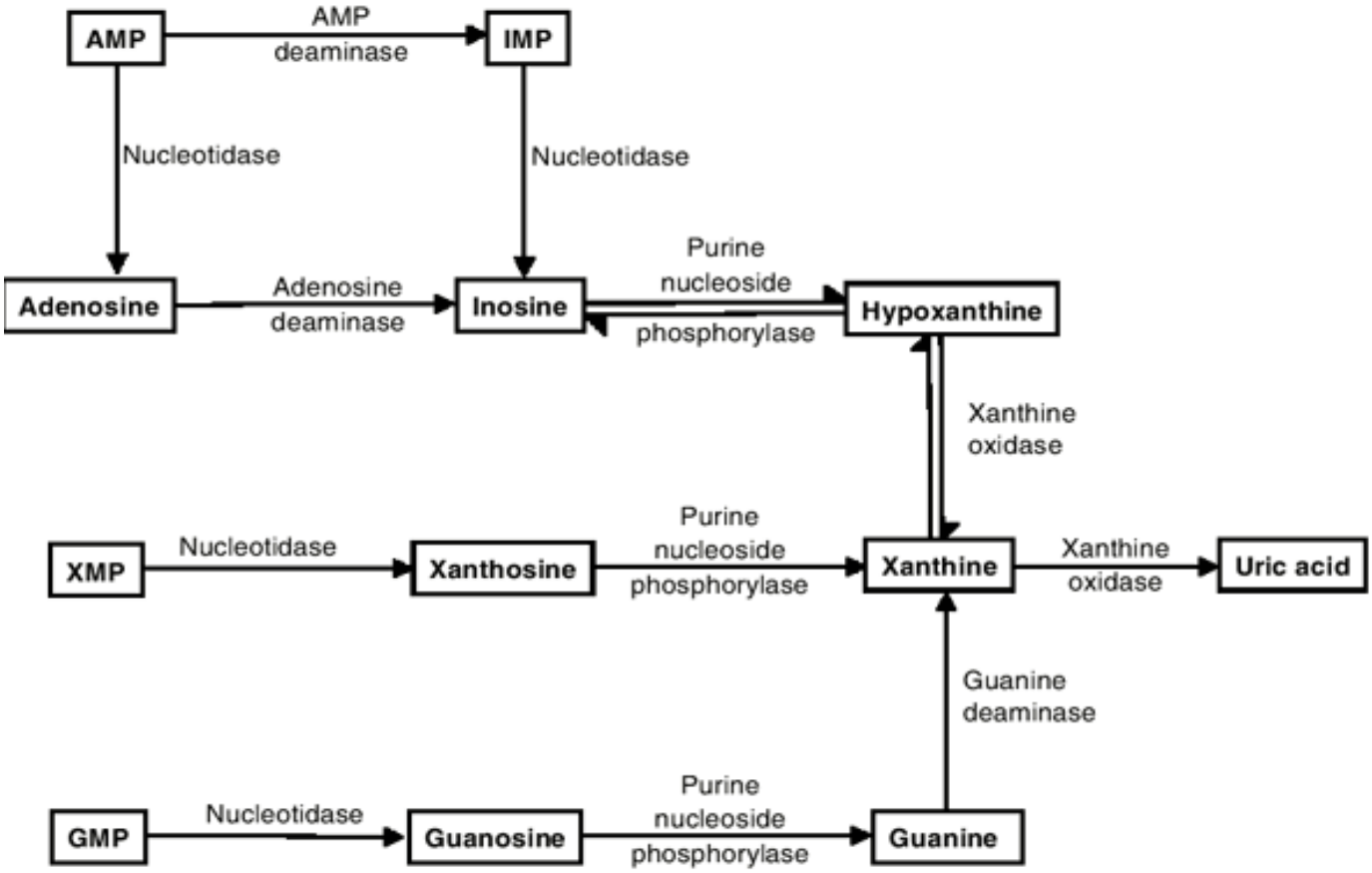


Figure (١-١) Uric acid synthesis

١-٩-٢ *Uric acid as a risk factor for cardiovascular disease*

An epidemiological link between elevated serum uric acid and an increased cardiovascular risk has been recognized for many years[٨٤].Observational studies show that serum uric acid concentrations are higher in patients with established coronary heart disease compared with healthy controls .Elevated serum uric acid concentrations are also found in healthy off spring of parents with coronary artery disease, indicating a possible causal relationship[٨٥]. However, hyperuricemia is also associated with possible confounding factors including elevated

serum triglyceride and cholesterol concentrations, blood glucose, fasting and post-carbohydrate plasma insulin concentrations, waist-hip ratio and body mass index [٨٦]. About one quarter of hypertensive patients have co-existent hyperuricemia and, interestingly, asymptomatic hyperuricemia predicts future development of hypertension, irrespective of renal function[٨٧].

١-٩-٣ Uric acid as a marker of subclinical ischemia

Adenosine is synthesized and released by cardiac and vascular myocytes. Binding to specific adenosine receptors causes relaxation of vascular smooth muscle and arteriolar vasodilatation[٨٨]. Adenosine makes a small contribution to normal resting vascular tone, since competitive antagonism at the adenosine receptor by methylxanthenes, such as theophylline, reduce blood flow response to ischemia in the forearm vascular bed [٨٩]. Under conditions of hypoxia and tissue ischemia, vascular adenosine synthesis and release are unregulated, causing significantly increased circulating concentrations [٩٠]. Cardiac and visceral ischemia promote generation of adenosine, which may serve as an important regulatory mechanism for restoring blood flow and limiting the ischemia[٩١] . Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by the endothelium to uric acid, which undergoes rapid efflux to the vascular lumen due to low intracellular PH and negative membrane potential [٩٢]. Xanthine

oxidase activity and uric acid synthesis are increased in vivo under ischemic conditions, and therefore elevated serum uric

acid may act as a marker of underlying tissue ischemia. In the human coronary circulation, hypoxia, caused by transient coronary artery occlusion, leads to an increase in the local circulating concentration of uric acid [٩٣]. Study of tourniquet-induced lower limb exsanguinations in patients undergoing surgery shows a fivefold increase in systemic vascular xanthine oxidase activity during reperfusion, and a significant elevation of serum uric acid, which persists for at least ٢ hours. These findings are also consistent with the inverse relation between baseline serum uric acid concentration and maximal lower limb blood flow in patients with cardiac failure, where higher concentrations could predict subclinical ischemia. In conclusion therefore, elevated serum uric acid may be a marker of local or systemic tissue ischemia and provides one possible explanation for a non-causal associative link between hyperuricemia and cardiovascular disease[٩٤].

١-١٠ Aim of the study

● How to get the definitive diagnosis of AMI by the specific biochemical cardiac markers(CK-MB isoenzyme) other than clinical examination and ECG ,which do not have high sensitivity and specificity compared with the former which have high sensitivity and specificity for the myocardial ischemia ,and by use relative index to know the increment of total CK or CK-MB isoenzyme due to the myocardial injury .

● AMI patients evaluated with traditional risk factors (smoking, diabetes mellitus, hypertension, Hyperlipidemia ,obesity ,age and male gender) and compared with non-traditional biochemical risk factors included microalbuminurea, hypoalbuminemia and hyperuricemia to plan type of treatment ,type of life habbit ,mortality and morbidity

٢-١ Materials

٢-١-١ *Subjects*

٢-١-١-١ *Patients*

This study was done in the department of medical biochemistry, college of medicine, Babylon University.

The collection of samples was conducted during the period from (September ٢٠٠٤) to (may ٢٠٠٥). Of ١٢٢ patients were taken from cardiac care unite (CCU) in AL-Hussein general hospital in Karbala . About ٢٢ patients were excluded from the study for having one or more of the following:-

-Renal diseases.

-Urinary tract infection.

-Diabetic nephropathy.

-Intramuscular injection for last ٢٤hours.

-Cardiac defibrillation.

-Liver diseases.

-Gout.

- Patients with thrombolysis therapy.

So ١٠٠ patients were left for study. Of ٧٧were males and ٢٣were females with male to female ratio (٣.٣ : ١) and age range from ٣١ to ٨٣ years.

The patient diagnosed as AMI for both sexes based on the World Health Organization (WHO) which required two of the following [٩٥].

١-Chest pain, heaviness or discomfort. Which lasted more than ٣٠ minutes, located to the retrosternal area radiated to left arm, neck, and jaw.

٢-Typical ECG changes involving ST segment elevation or depression, T- wave inversion, Q- wave development.

٣-Serum cardiac biochemical markers elevation (CK, CK-MB, Glutamate oxaloacetate transaminas GOT).

The first two criteria diagnosed by a consultant physician

٢-١-٢-٢ *Control*

The control groups consist of ٤٥ subjects. They were collected from medical staff and relatives who were free from signs and symptoms of coronary heart disease. ٣٨ were males and ٧ were females, with male to female ratio (٤.٥:١) and their age ranges from ٤٥ to ٧٢ years.

٢-١-٢ *Collection of Samples*

٢-١-٢-١ *Blood sample*

Ten milliliters of venous blood were drawn from each patient about ٢٤h after attack of AMI(i.e. attack of chest pain). Slow aspiration of the blood sample via the needle of syringe

to prevent hemolysis and from veins of cubital fossa and tourniquet apply ١٥cm above. All the samples were grossly hemolysed, were neglected and another sample was taken.

The samples were dropped into clean disposable tubes, left at the room temperature for ٣٠ minutes for clot formation and then centrifuged for ٢٠ minutes at ٥٠٠٠ run per minute. The serum was separated and divided into two parts ,The first part ١.٥ml of serum was kept in the eppendrof tube which is used for measuring total CK and CK-MB, and stored at -٢٠ Cº . The second part of serum ١ml was kept in the eppendrof tube and stored at ٢-٨ Cº which is used to measure serum albumin, uric acid and serum total cholesterol.

Similarly the blood samples were taken from the control group.

٢-١-٢-٢ ***Urine samples***

The urine samples were taken from patients in the CCU during ٢nd and ٣rd day after attack of AMI(i.e. attack of chest pain).

A ٢٠ ml of newly ٢٤-hours collected urine samples were

taken from urine bag for those who were catheterized or from ٢٤-hours urine container for those who were not catheterized

Similarly the urine samples were taken from the control group.

٢-١-٣ ***Chemicals***

The chemicals and kits that were used in this study were of the highest purity and are listed in table below with their suppliers:-

Table (٢-١) Chemicals with their suppliers

	Chemicals	Suppliers
١-	Total CK kit	*Randox com. England*
٢-	CK-MB kit	*Linear com. Spain*
٣-	Albumin kit	*Linear com. Spain*
٤-	Uric acid kit	*Linear com. Spain*
٥-	Urine strips	*Linear com. Spain*
٦-	Urine strips for albumin	*Linear com. Spain*

٧-	Cholesterol kit	*Linear com. Spain*

٢-١-٤ ***Instruments***

All the instruments and tools which used in this study are listed in the table below :-

Table (٢-٢) Instruments and tools with their suppliers

١-	Different grade of automatic Pipette.	*Eppendrof, England.*
٢-	Water bath	*kottermann-laboratechnic,W-Germany*
٣-	Centrifuge	*Runne-Heidelberg.*
٤-	UV-visible spectrophotometer.	*Cecil ٧٥٠٠ England*
٥-	Spectrophotometer	*Apple ٣٠٣, Japan*
٦-	Stop watch	*China*
٧-	١٠ml disposable Syringes	*Medicaljet,Syria*

٨-	Eppendrof tube ١ ml for serum.	*China*
٩-	Centrifuge tube	*China*
١٠-	Disposable test tube	*China*

٢-٢ Methods

٢-٢-١ *Total CK*

Serum total CK was measured for patients as part of enzymatic changes occurring during AMI.

Principle of the test: - CK utilizes creatine phosphate and ADP as substrate to act as initial catalyst for a series of reaction resulting in the formation of NADPH as outlined in the coupled enzyme assay. The NADPH produced is proportional to CK activity and it is used to reduce into blue tetrazolium (NBT). In the presence of diaphorase to give the blue / violet color of diformazan which its absorption at ٥٦٠nm. A reaction stopped by the addition of HCI as show in the following equations .

Creatine Phosphate + ADP $\xrightarrow{CK\ Mg^{+٢}}$ Creatine + ATP

Glucose + ATP $\xrightarrow{HK\ Mg^{+2}}$ Glucose- ٦-P + ADP

Glucose- ٦-P +$NADP^+$ $\xrightarrow{G6P\text{-}DH}$ Gluconate-٦-P + NADPH + H^+

٢ H^+ + ٢ NADPH +NBT $\xrightarrow{Diaphorase}$ Diformazan + ٢ $NADP^+$

The procedure summarized in the following table :

	Sample	Standard	Reagent blank	Sample blank
Color reagent solution	٠.٥ml	٠.٥ml	٠.٥ml	٠.٥ml
Incubate for ٣ minutes at ٣٧ Cº				
Sample	٠.٠٥ml	٠.٠٥ml	٠.٠٥ml	-
Incubate for ١٠ minutes at ٣٧ Cº				
٠.١N HCl	٥ml	٥ml	٥ml	٥ml
Sample	-	-	-	٠.٠٥ml
Measures the absorbance at ٥٦٠nm				

CK activity(U/L)= (absorbance sample/ absorbance standard)× standard concentration

Normal value Male (٢٤ -١٩٠ U/L) Female (٢٤-١٧٠ U/L) [٩٦] .

٢-٢-٢ ***CK-MB***

CK-MB measurement was performed for the samples of patients who were diagnosed as AMI by clinical examination, ECG changes and elevation of serum CK, serum GOT to prove the true diagnosis of AMI.

The technique that involves the measurement of CK activity employed an antibody to the human CK-M monomer incorporated to the substrate which completely inhibits the activity the CK-MM and half of the CK-MB present in the samples.

The activity of the non-inhibited CK-B monomer which corresponds to the half of CK-MB concentration is then determined as total CK activity procedure monitored kinetically at ٣٤٠ nm .

Incubate the reagent and sample at ٣٧ C

The procedure summarized in the following table :

Working reagent	٢.٥ml
Sample or control	١٠ µ
Wait for ١٠ minutes and measured the absorbance at ٣٤٠ nm	
And than after ١٥minutes measured the absorbance at ٣٤٠ nm	
Δ A = absorbance (١٥) - absorbance (١٠)	

CK-MB activity (U/L)= ΔA×١٦٥٠

normal value of CK-MB activity (٢-٢٠ U/L) [٩٧] .

٢-٢-٣ *Urinary albumin*

The method of measuring urinary albumin was performed according to the method described by Asad in Mousel University in which urinary albumin was measured from ٢٤hours collected urine[٩٧] .

The principle of this method indicated that albumin binds selectively to the dye of bromocresol green(BCG) at PH ٤.٢ . The absorbance of blue/green complex at ٦٣٠nm proportional to the albumin concentration as show in the following equation .

BCG + Albumin $\xrightarrow{\text{PH ٤.٢}}$ BCG- albumin complex (blue/green)

The procedure summarized in the following table :

	Sample	Standard	Blank
BCG reagent	٢ml	٢ml	٢ml
Sample	١٠ µ	-	-
Standard	-	١٠ µ	-
Distal water	-	-	١٠ µ
Then wait for ٥ minutes , and measured absorbance at ٦٣٠ nm			

Albumin concentration (mg/day) = (absorbance sample/ absorbance standard) ×standard concentration (mg/dl)

Normal value=(less than ٣٠mg/day) [٩٨] .

٢-٢-٤ ***Serum albumin***

The principle of this method is that serum albumin binds selectivity to the dye of bromocresol green reagent BCG at PH ٤.٢ . The absorbance of the blue/green complex at ٦٣٠nm is proportional to the albumin concentration as show in the following equation .

BCG + Albumin $\xrightarrow{\text{PH } ٤.٢}$ BCG- albumin complex(blue/green)

The procedure summarized in the following table :

	Sample	Standard	Blank
BCG reagent	٢ml	٢ml	٢ml
Sample	١٠ µ	-	-
Standard	-	١٠ µ	-
Distal water	-	-	١٠ µ
Then wait for ٥ minutes , and measured absorbance at ٦٣٠ nm			

Serum albumin concentration = (absorbance sample/ absorbance standard)×standard concentration

Normal value of kit (٣.٨-٥.١g/dl) [٩٥] .

٢-٢-٥ ***Serum Uric acid***

The principle of the method is that uric acid oxidized by uricase to allantoin with the formation of hydrogen peroxide ($٢H_٢O_٢$) which is under the influence of peroxidase(POD),A mixture of ADPS(ethyl-N-sulphopropyl-m-anisidine)and٤-aminoantipyrine(٤-AA) is oxidized by hydrogen peroxide to form red quinoneimine compound proportional to uric acid concentration as shown in the following equations.

$$\text{Uric acid} + ٢H_٢O \xrightarrow{\text{uricase}} \text{Allantoin} + ٢H_٢O_٢$$

٤-aminoantipyrine + ADPS $\xrightarrow[POD]{H_2O_2}$ quinoneimine+ ٤H_2O

The procedure summarized in the following table :

	Sample	Standard	Blank
Working reagent	١ml	١ml	١ml
Sample	٢٥ µ	-	-
Standard	-	٢٥ µ	-
Distal water	-	-	٢٥ µ
Then wait for ٥ minutes , and measured absorbance at ٥٢٠ nm			

Serum uric acid concentration (mg/dl) = (absorbance sample/ absorbance standard)× standard concentration

Normal value Male= (٣.٥- ٧mg/dl) Female=(٣.٥ -٦ mg/dl) [٩٥] .

٢-٢-٦ ***Serum total cholesterol***

The principle of the method for the measurement of total cholesterol in serum involves the use of three enzymes: cholesterol esterase (CE), cholesterol oxidase (CO) and

peroxidase (POD) In the presence of the former the mixture of ADPS (ethyl-N-sulphopropyl-m-anisidine) and ٤-aminoantipyrine (٤-AA) are condensed by hydrogen peroxide to form a quinoneimine dye proportional to the concentration of cholesterol in the sample.

cholesterol esters $\xrightarrow{CE}$ cholesterol + Fatty acid

cholesterol + O_2 $\xrightarrow{CO}$ Cholestenone + H_2O_2

٤-aminoantipyrine + ADPS $\xrightarrow[POD]{H_2O_2}$ quinoneimine + ٤H_2O

The procedure summarized in the following table :

	Sample	Standard	Blank
Monoreagent	١ml	١ml	١ml
Sample	١٠ µ	-	-
Standard	-	١٠ µ	-
Distal water	-	-	١٠ µ
Then wait for ١٠ minutes , and measured absorbance at ٥٥٠ nm			

Total serum cholesterol mg /dl =(absorbance sample/ absorbance of standard) × concentration of standard . Normal value = (١٨٠- ٢٤٠mg/dl). [٩٥]

٢-٣ Biostatistics analysis

The biostatistics used in this study depended on (SPSS) and (Excel) programs and obtained an important significant statistical association were student T-test and chi-square .At the level of high significance (P value<٠.٠٥) and very high significant (P value<٠.٠٠١).

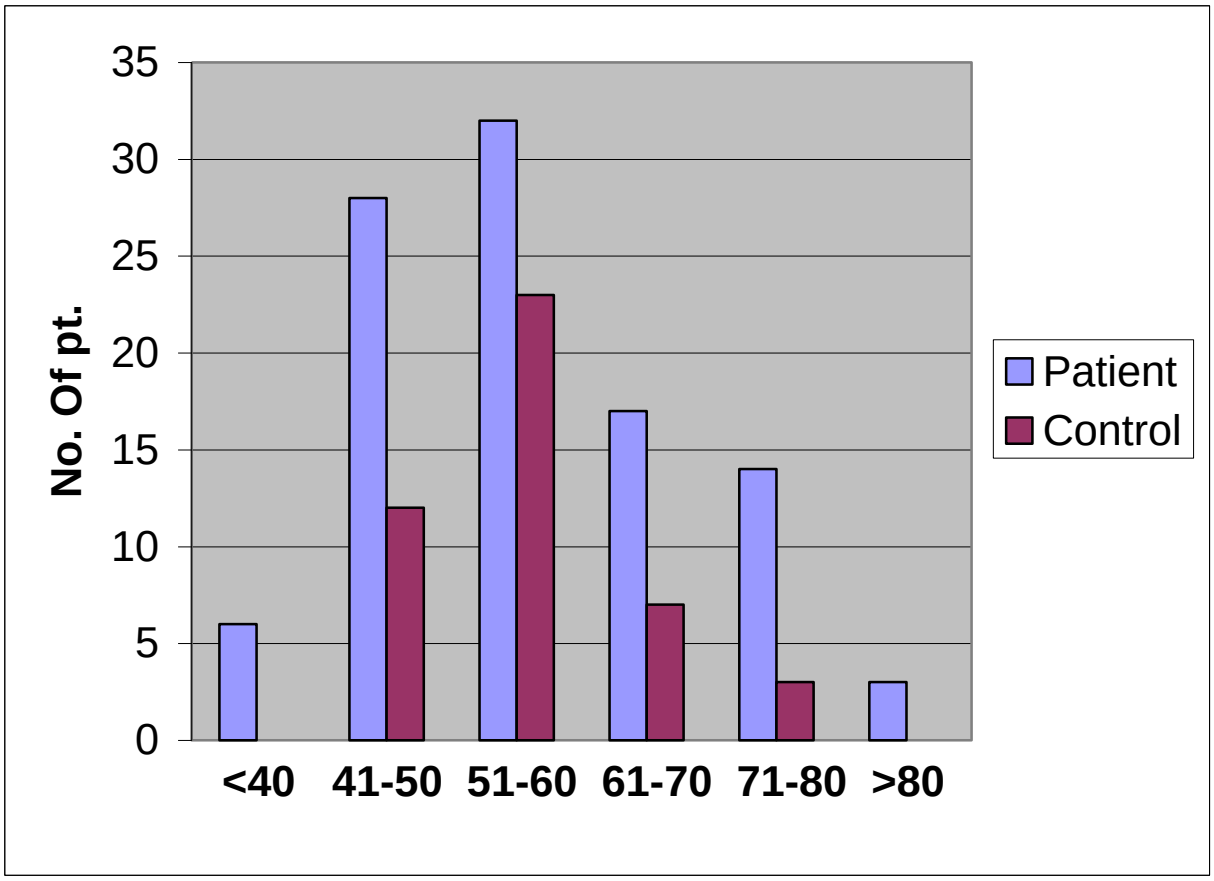
٣-١ *subjects*

The groups in this study are divided into two groups, patients group and control group, and each group subdivided into males and females. The males in both groups were more in number and older in age than females . The following table (٣- ١) contains groups with their number male and female , male to female ratio, their age and age range.

Table (٣- ١) Subjects characteristics

Groups	Male no.	Female no.	Total	Male to Female ratio	Mean age ±SD year	Age range year
Patients	٧٧	٢٣	١٠٠	١ : ٣.٣	٥٨±١٩	٣١-٨٣
Controls	٣٨	٧	٤٥	١ : ٥.٤	٥٦±١١	٤٥-٧٥
Total	١١٥	٣٠	١٤٥	١ : ٣.٨		

The age distribution in AMI shows a peak level in the age between (٥١-٦٠) years represented by ٣٢ patients and the least was in the age group above (٨١) years represented by ٣ patients. And in control group the highest number in the age between (٥١-٦٠) years represented by ٢٣ subjects and the least was in the age group (٧١-٨٠) years represented by ٣ subjects as shown in the following figure .

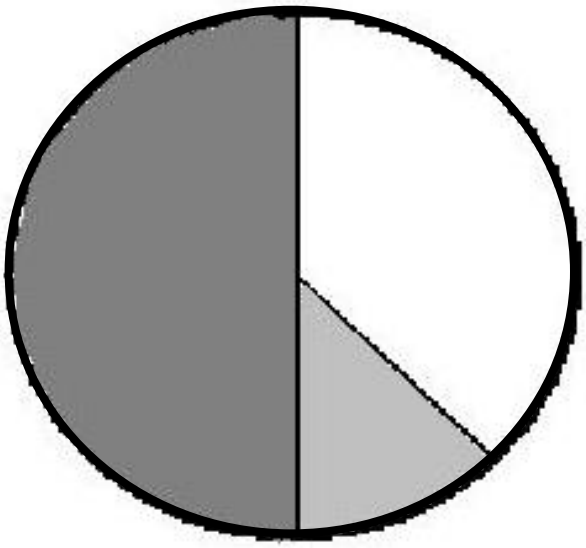


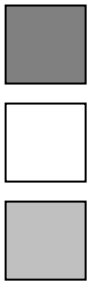
Figure(٣- ١) Age distribution in AMI and control group

The diagnosis of the patients with AMI in this study was conducted by clinical examination (typical chest pain) , ischemic changes on the ECG and cardiac biomarkers .

٥٠ cases had both clinical examination (typical chest pain) and ECG changes and the diagnosis depended on it (٥٠٪). ٣٣ cases neither have typical chest pain nor ECG changes and the diagnosis depended at early presentation on cardiac biomarkers (٣٣٪).

١٧ cases had only typical chest pain and the diagnosis needed cardiac biomarkers to be accurate(١٧٪). As shown in the following figure.





Patients have ECG changes and typical chest pain(٥٠٪) .

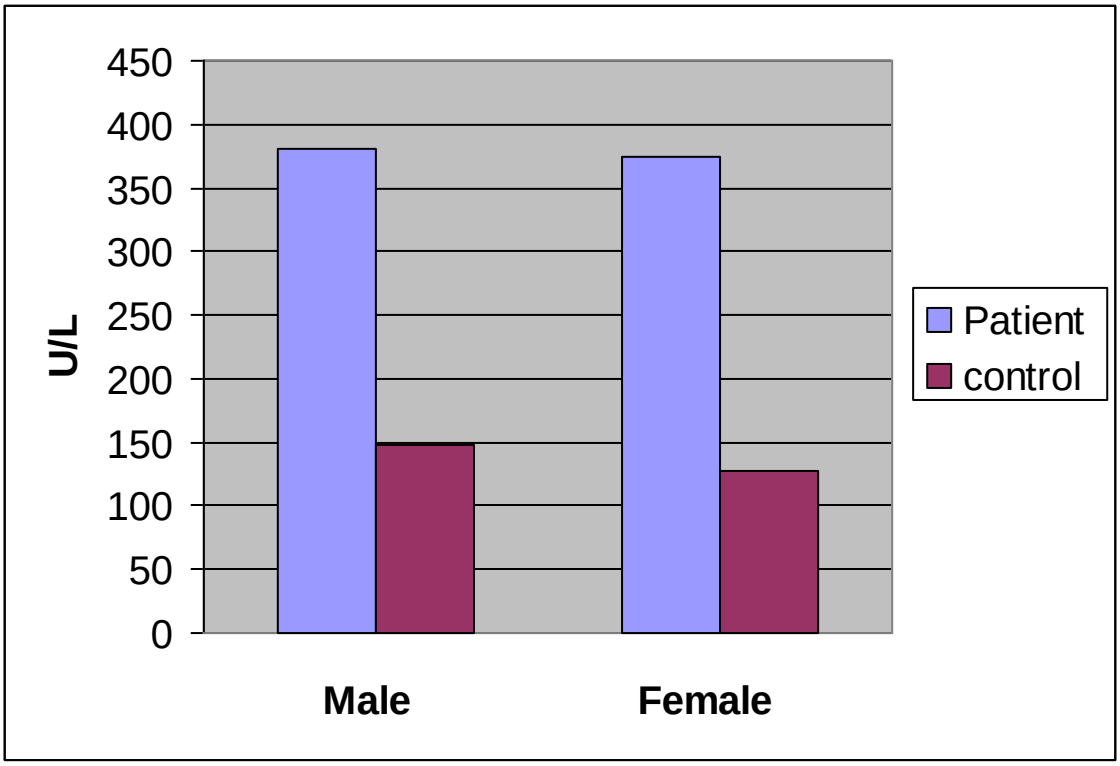
Patients neither have ECG changes nor typical chest pain(٣٣٪).

Patients have typical chest pain(١٧٪).

Figure (٣-٢) Presentation of the patients to the CCU .

٣-٢ Total CK activity

In this study the total CK activity measurement of the male patients (٣٨١ ± ١٣٨ U/L) and female patients (٣٧٣.٧ ± ١٣٩ U/L)found to be significantly very high when compared with control group(١٤٨ ± ٤٦ U/L),(١٢٧.٨ ± ١٤.٣ U/L) for male and female respectively at the level of significantly(P<٠.٠٠١). Male patient has non significant higher activity compared with female patient (P>٠.٠٥), by student T test and Chi square. The sensitivity and specificity of total CK activity measurement for male and female (٨٨.٣٪) (٨٤.٢٪) (٨٢.٦٪) (١٠٠٪) respectively.

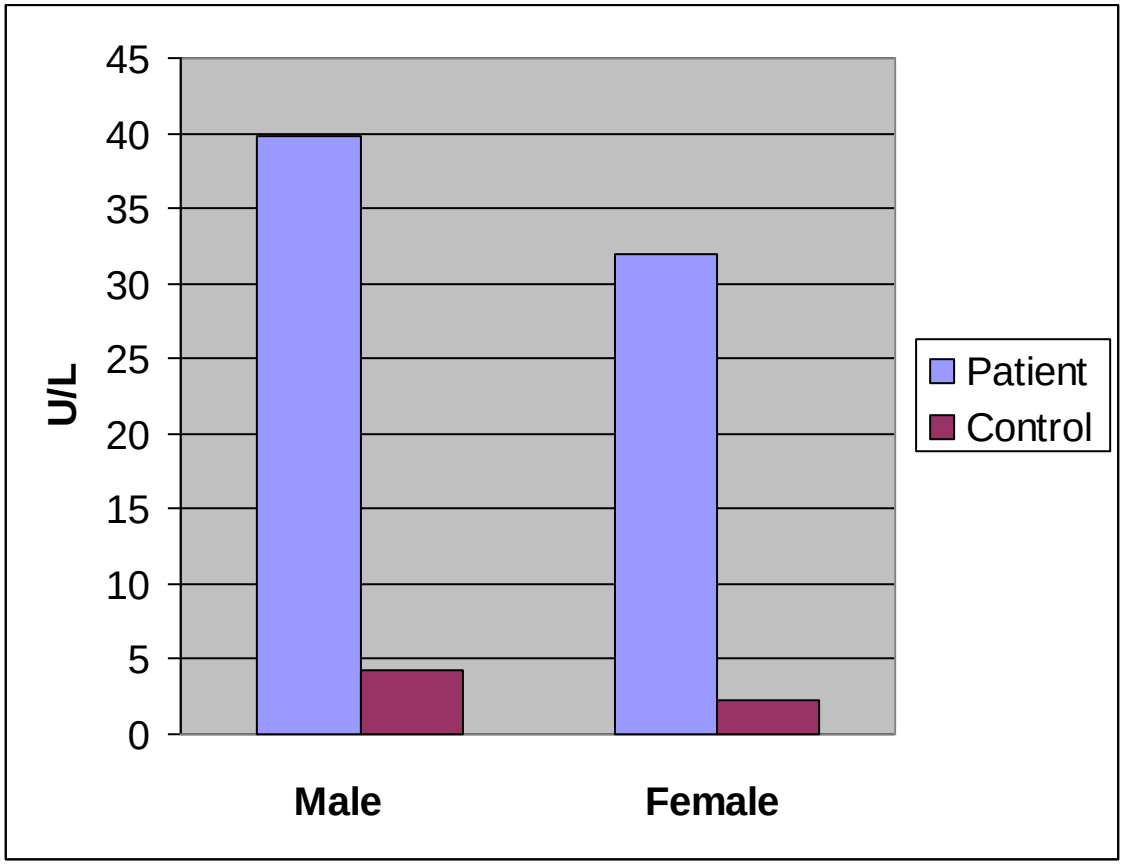


Figure(٣-٣)Total CK activity among male and female in both groups

٣-٣ CK-MB activity

In this study the CK-MB isoenzyme activity measurement for the male patients (٣٩.٨ ± ٢٨.٢ U/L) and female patients (٣٢ ±١٩.٨ U/L)found to be significantly very high when compared with control group (٤.٣ ± ٢.٨ U/L),(٢.٢ ± ١.١ U/L) for males and females respectively at the level of significantly (P<٠.٠٠١) ,Male patient has non significant higher activity compared with female patient (P>٠.٠٥) ,by student T test and Chi square as show in the following figure.

The sensitivity and specificity of CK-MB activity measurement for male and female (٩٢.٣٪) (٨٤.٢٪) (٩٠.٥.٢٪) (١٠٠٪) respectively.



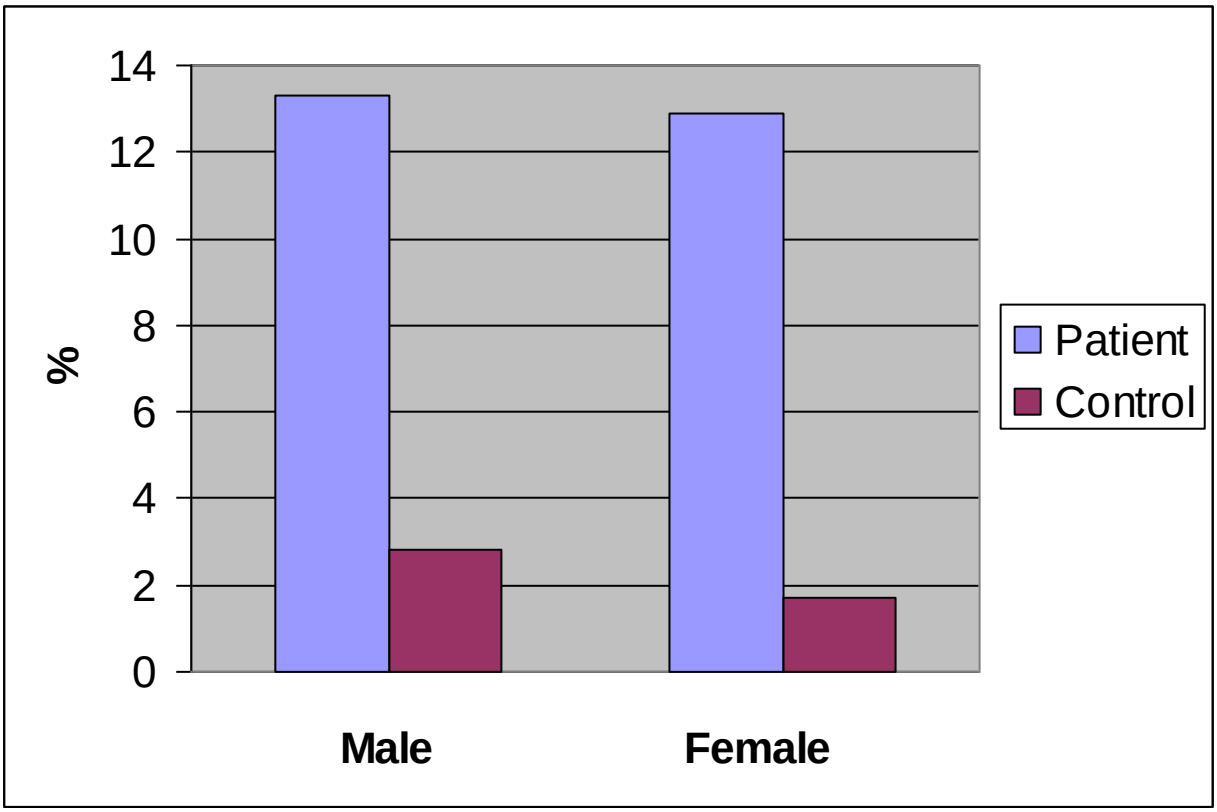
Figure(٣-٤)CK-MB activity among male and female in both groups

٣-٤ Relative index

Relative index(RI) was calculated by the following equation (CK-MB/ total CK) ١٠٠٪.

In this study RI for male patients (١٣.٣ ± ٨.٣٪)and female patients (١٢.٩ ± ٧.٣٪) ,It was found to be significantly very high percentage when compared with males and females of control group (٢.٨ ± ٢.٥),(١.٧ ± ٠.٩)respectively(p<٠.٠٠١) . Male patient has non significant higher percentage compared with female patient (P>٠.٠٥) ,by student T test and Chi square ,as shown in figure.

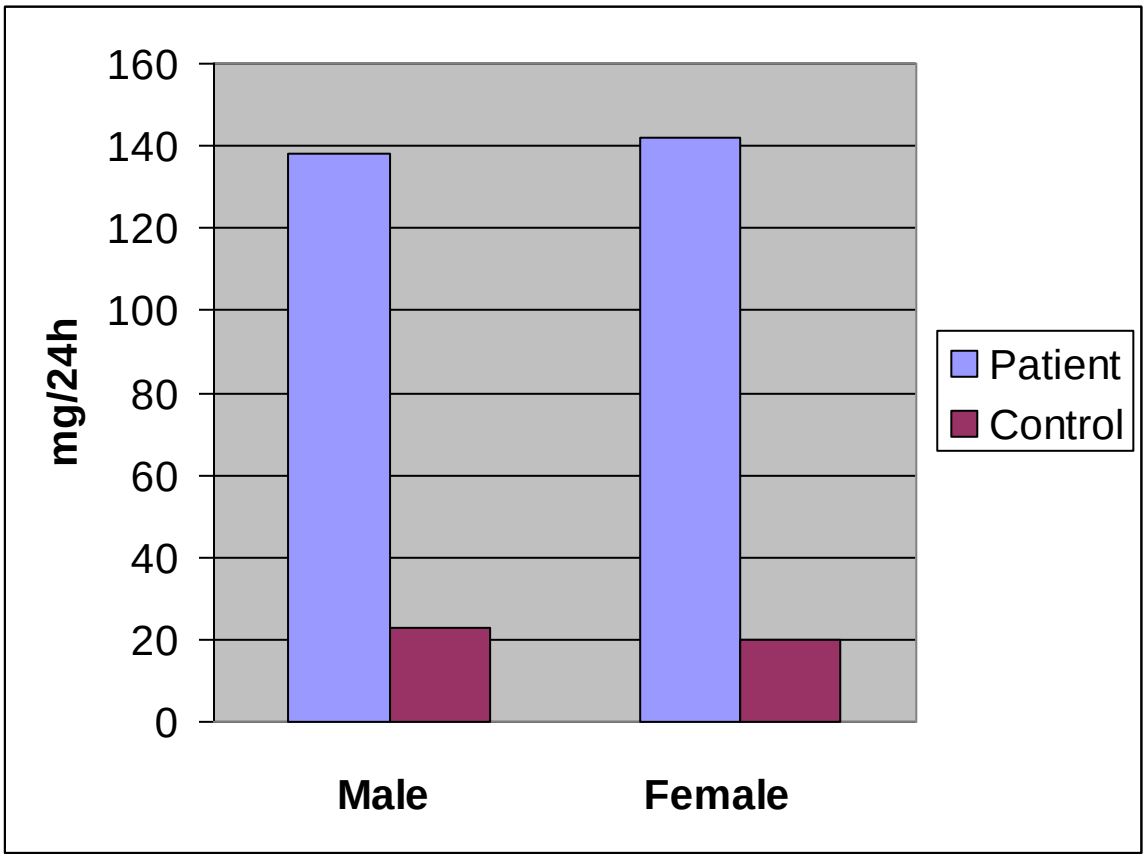
The sensitivity and specificity of RI for male and female (٩٦.٣٪) (٩٩.٢٪) (٩٥.٢٪) (١٠٠٪) respectively.



Figure(٣-٥)Relative index among male and female in both groups

٣-٥ Urinary albumin

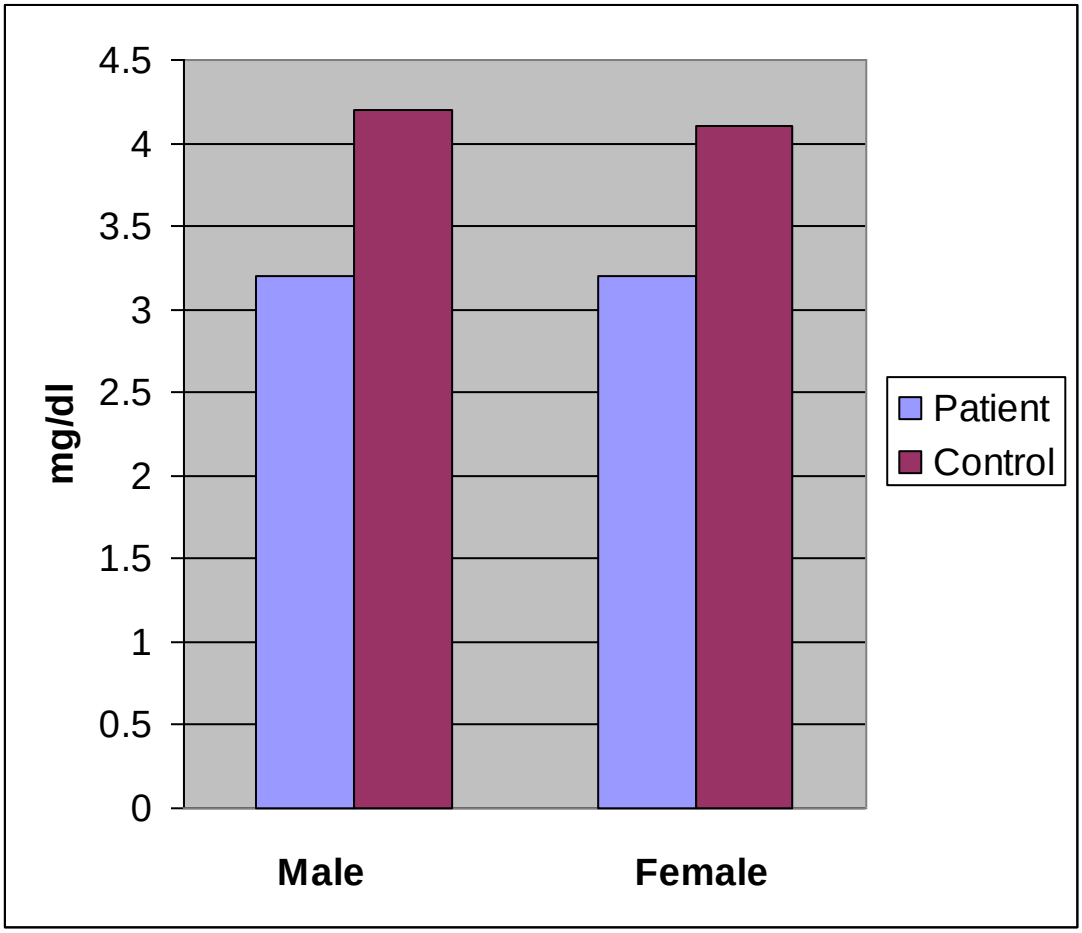
In this study the urinary albumin measurement of the male patients(١٣٨ ± ٨٩.٣ mg/day) and female patients(١٤٢.٩ ± ٧٥.٣ mg/day)found to be significantly high when compared with control group (٢٣ ± ٦ mg/day),(٢٠ ± ٥.١ mg/day) for males and females respectively at the level of significantly(P<٠.٠٥). Female patient has non significant higher concentration compared with male patient (P>٠.٠٥) ,by student T test and Chi square as shown in the following figure .The sensitivity and specificity of measurement for male and female (٨١.٤٪) (٨٤.٢٪) (٨٩.٤٪) (١٠٠٪) respectively.



Figure(٣-٦)Urinary albumin concentration among male and female in both groups

٣-٦ *Serum albumin*

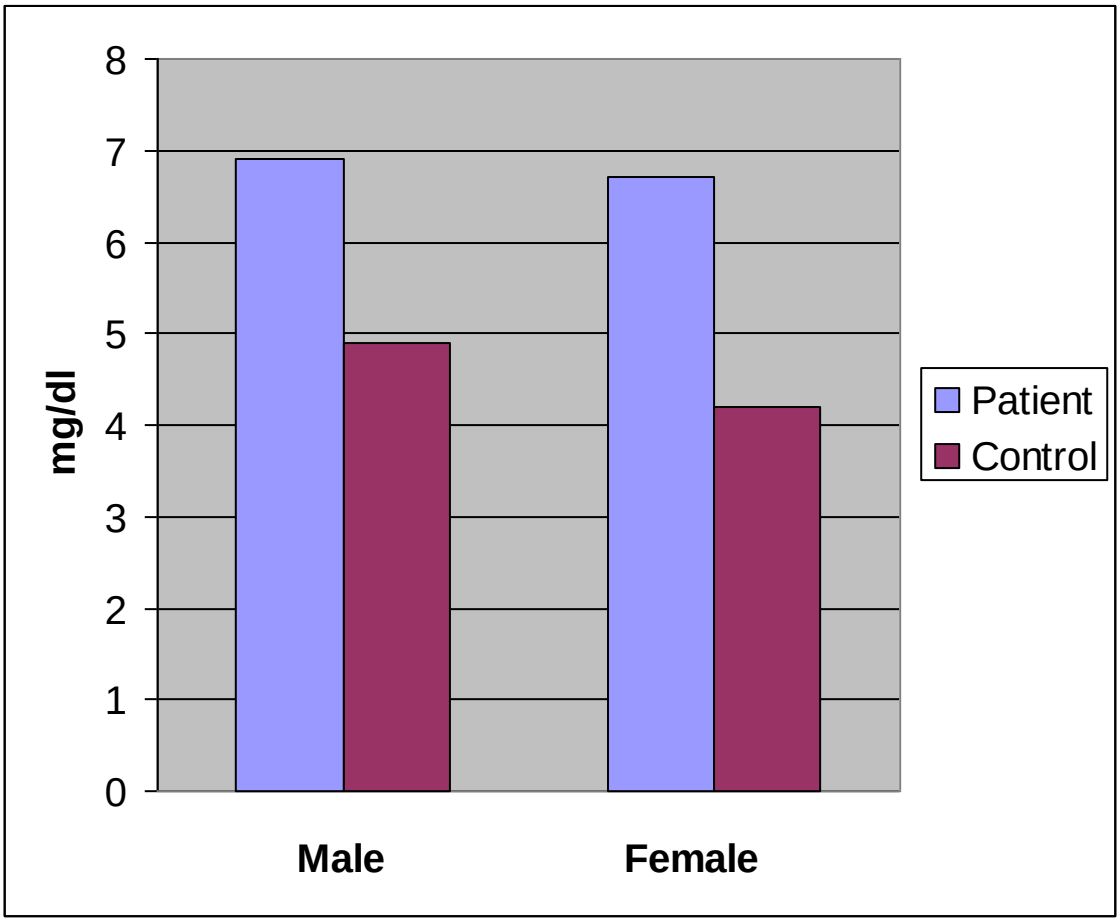
In this study the serum albumin concentration measurement of the male patients (٣.٢ ± ٠.٩ g/dl) and female patients (٣.٢ ±١ g/dl)found to be significantly low when compared with control group (٤.٢ ± ٠.٥ g/dl),(٤.١ ± ٠.٩ g/dl) for male and female respectively at the level of significantly (P<٠.٠٥), No significant difference serum albumin concentration in male and female patient (P>٠.٠٥),by student T test and Chi square as shown in the following figure.



Figure(٣-٧) Serum albumin concentration among male and female in both groups

٣-٧ Serum uric acid

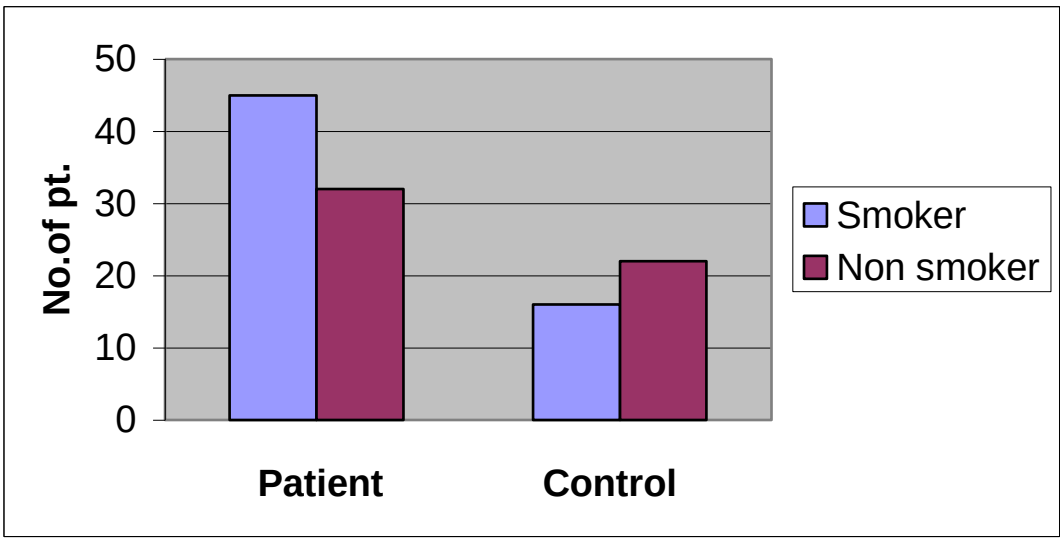
In this study the serum uric acid concentration measurement of the male patients (٦.٩ ± ١.٧ mg/dl) and female patients (٦.٧ ± ١.٧ mg/dl)found to be significantly high when compared with control group (٤.٩ ± ٢.٢ mg/dl),(٤.٢ ± ١.٦ mg/dl) for males and females respectively at the level of significantly (P<٠.٠٥) ,Male patient has non significant higher concentration compared with female patient (P>٠.٠٥) ,by student T test and Chi square as shown in the following figure:-



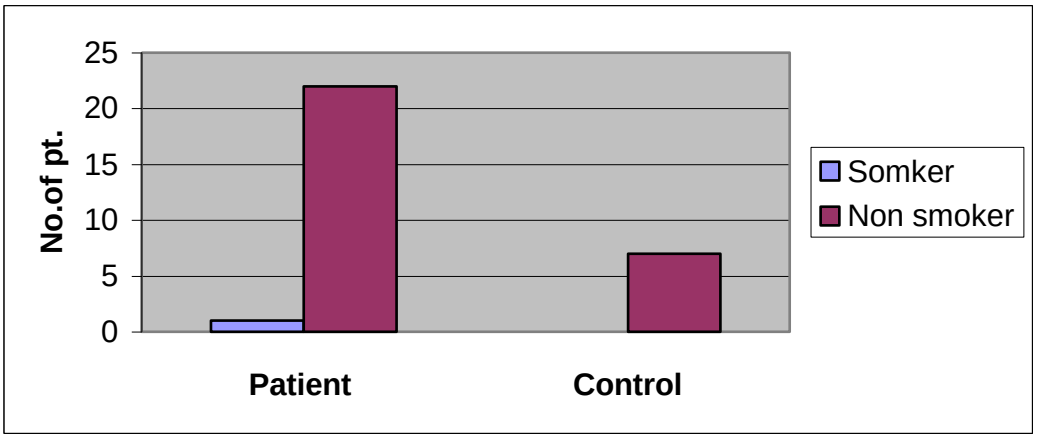
Figure(٣-٨) Serum uric acid concentration between male and female in both groups

٣-٨ *Risk factors* :- Four risk factors are included in this study as indicated below :-

٣-٨-١ Smoking*:* The male patients found to be significantly smoking more (٦٣٪) compared with males of control group (٣٠٪) at level (p<٠.٠٥), among females in both groups showing no significant difference, at level of (p> ٠.٠٥) as shown in the following figures:-

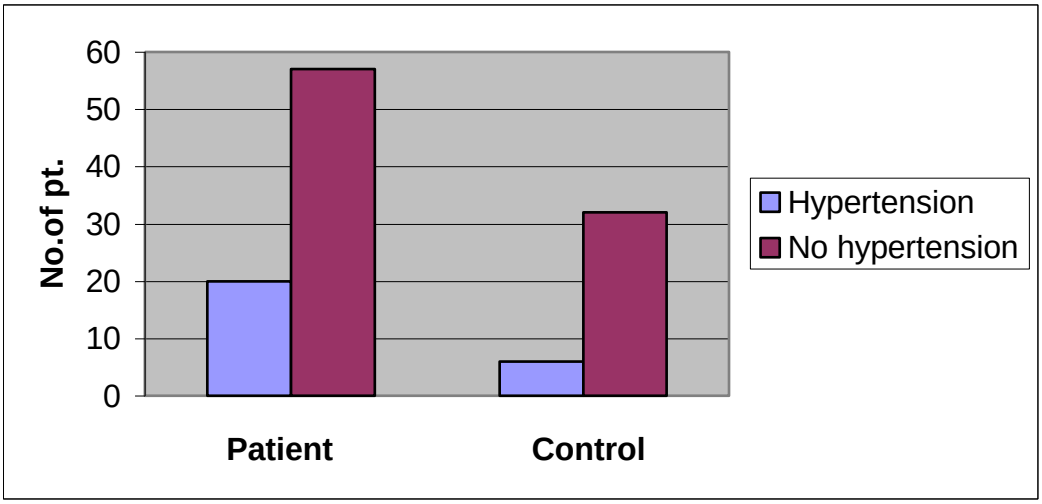


Figure(٣-٩)Effect of smoking on males in both groups

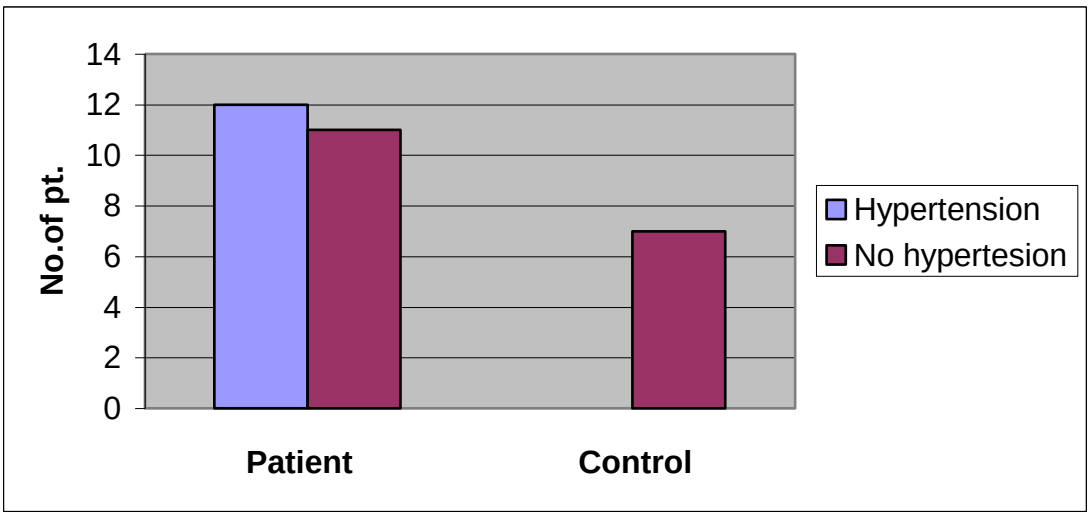


Figure(٣-١٠) Effect of smoking on females in both groups

٣-٨-٢ Hypertension: The patients found to have significantly more hypertensive percentage compared with control and the female patients found to have significantly more hypertensive percentage (٥٥٪) compared with male patients (٤٣٪), at level of (p<٠.٠٥) ,as shown in the following figures:-

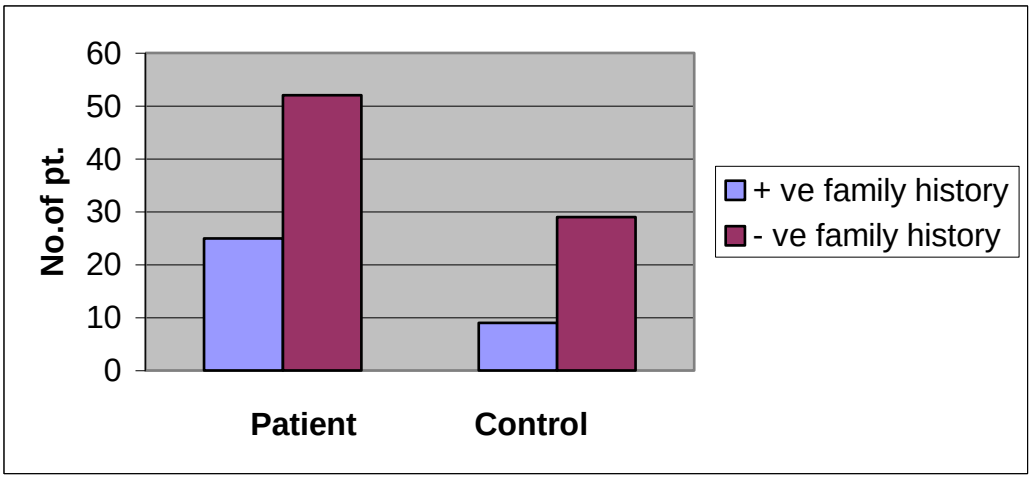


Figure(٣-١١) Effect of hypertension on males in both groups

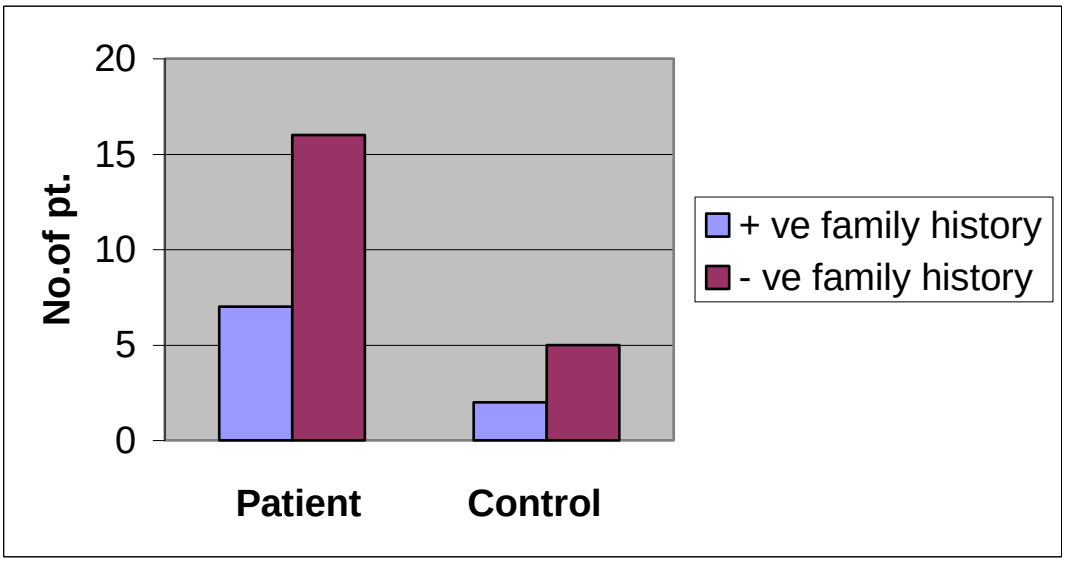


Figure(٣-١٢) Effect of hypertension on females in both groups

٣-٨-٣ Family history of ischemic heart diseases: The percentage of patients with family history of ischemic heart diseases were significantly less compared with patients without family history of ischemic heart diseases at level of ($p<٠.٠٥$) as shown in the following figures .

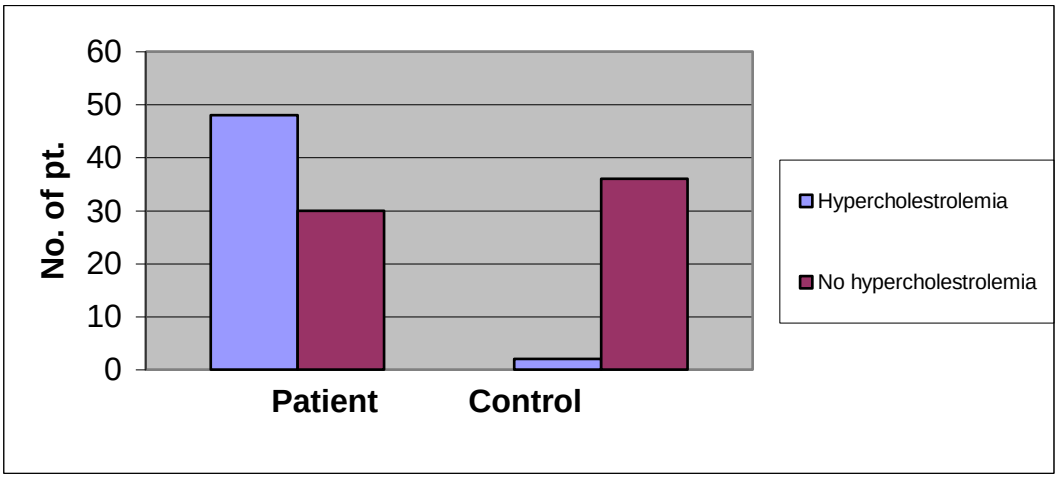


Figure(٣-١٣) Effect of family history of IHD on males in both groups

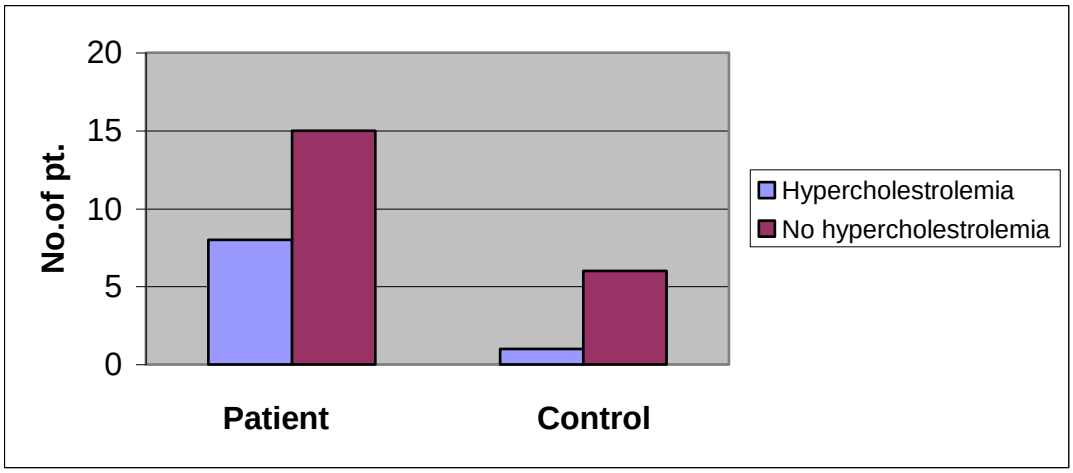


Figure(٣-١٤) Effect of family history of IHD on females in both groups

٣-٨-٤ Hypercholesterolemia: The male patients with hypercholesterolemia have significantly higher percentage compared with male control , at level of (p<٠.٠٥), among females no significant difference in cholesterol level in both groups at level of (p>٠.٠٥) as shown in the following figures:-

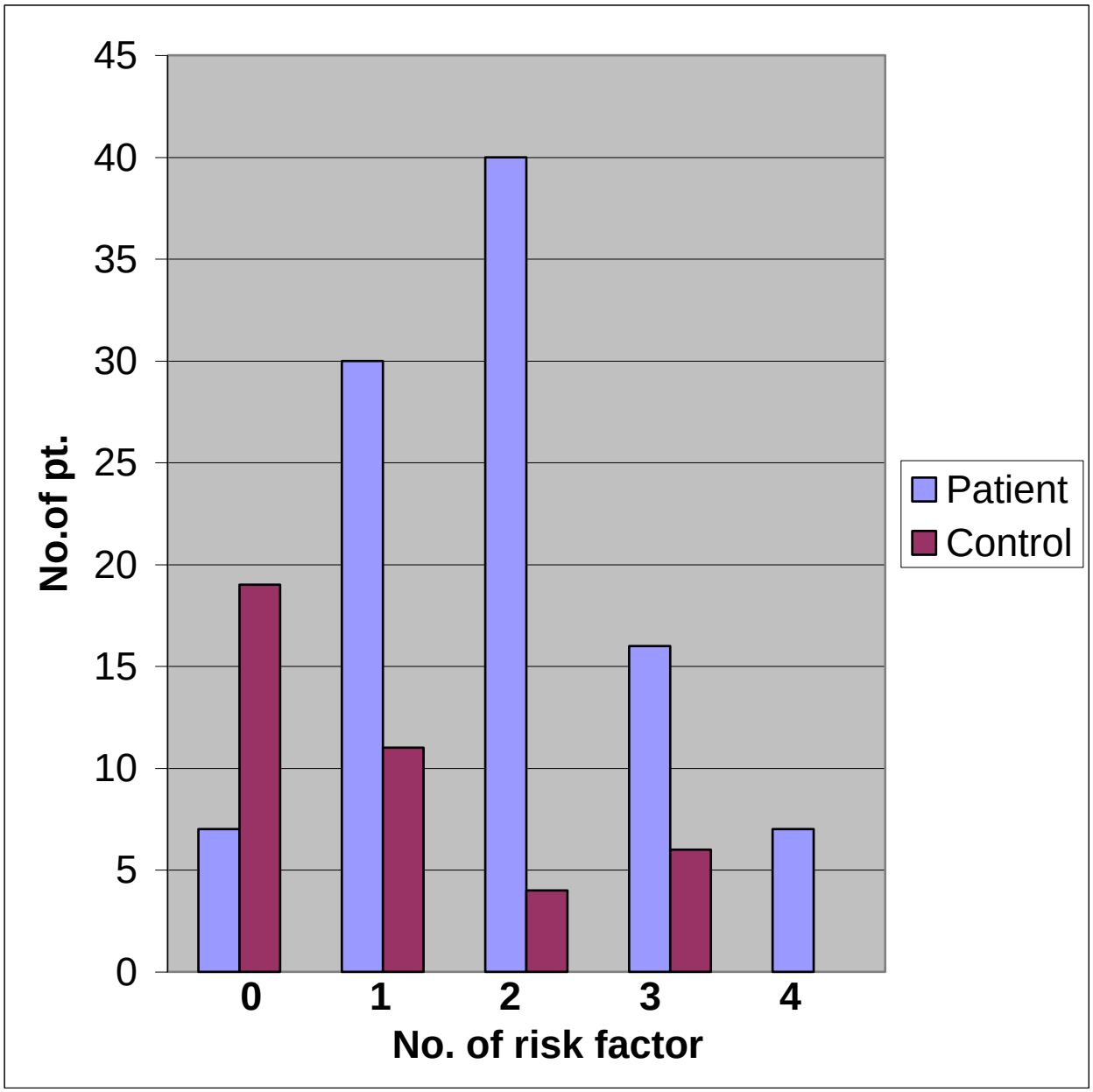


Figure(٣-١٥) Effect of hypercholesterolemia on males in both groups



Figure(٣-١٦) Effect of hypercholesterolemia on females in both groups

The following figure shows the number of risk factors that occur in each subject of both groups, the patients with two risk factors have significant higher percentage than patients without , one, three, four or more risk factors, Among control group, subjects without risk factor have significant higher percentage than subject with one, two or more risk factors at level of significantly ($p<٠.٠٥$).



Figure(٣-١٧)Number of Risk factors in both groups

4-1 Subject characteristic

A significant proportion of the patients presented to the ED with acute chest pain. triage of these patients is one of the most

difficult challenges for emergency physician [٥]. In our study we found that the AMI was peaked in the age ٥١ to the ٦٠ years in contrast with other studies in western countries in which peak incidence is older than ٥٧ years [٩٨] , our explanation is due to the following points :-

١- Most of the Iraqi people suffer from stressful conditions.

٢- The type of food used by the Iraqi people is rich with fat.

٣- Most of the Iraqi people continue to work until advanced age .

٤- Most of the western people alcoholic intake (the conception ١ to ٣ unite increase level of HDL) [٩٩].

Clinical presentation and ECG are critically important components for diagnosis and management of acute coronary syndrome (ACS). But myocardial ischemic manifestations are vague and multiple, and in ٢٠٪-٥٠٪ of cases, the ECG is non diagnostic at the hospital admission .Thus ,biochemical cardiac markers have become important diagnostic tools for ACS. However ,these markers merely detect the myocardium after AMI , but totally fail to detect stable and unstable angina ,thus ,identification of biochemical marker is specific and sensitive for myocardial ischemia that can be rapidly measured in the serum and would be clinically valuable [٥].

Also more than ٥٠٪ of the patients hospitalized of chest pain are discharged with diagnosis other than ACS, Thus the biochemical markers ,which make rapid rule out of the suspected cases of ACS will be useful in cost limitation and early discharge of less risky cases especially in over crowded or services limited center ,So in our study we tried to diagnose AMI by biochemical cardiac markers and know the more risky

patients to have AMI and its complication by the biochemical markers[٢].

4-2 Total CK, CK – MB, relative index.

In this study , total CK activity found to be increasing during AMI but this increment is neither sensitive nor specific for AMI, this increment is due to the injury of cardiac muscle with rupture of cell membrane and the release of it's cytoplasmic proteins which include (GOT, CK,LDH), The poor circulation in the ischemic area which results in gradual clearance of these proteins (mainly by lymphatic system), and gradual increase in circulating these proteins lead to the elevation beyond the reference range within (٤-١٢hours) after AMI ,and this contributed to the CK-MB isoenzyme[١٠٠] .

The level of total CK activity is highly dependable on the muscle mass of the patient and level of exercise, so females have lower CK activity than males due to the different muscle mass [١٠١] .So total CK falls as patients get older as muscle mass diminishes [٩٦, ٨٧] . In this study and several other studies ,the total CK activity dose not have high sensitivity and specificity that help us diagnose of AMI by its activity level and this contributed mainly to the two reasons[١٠٢]:-

١- Elevation of total CK not specific for AMI but it may increase in other conditions such as intramuscular injection (total CK), cardiac electrical defibrillation which is used when the patient develops ventricular fibrillation, coronary angiography and coronary bypass surgery. [١٠٣] .

٢- Some drugs used in the CCU affect total CK activity like anticoagulant, aspirin, frusemid, dexamethasone, and ampicillin [١٠٠] .

Elevated total CK activity can be assumed to be due to CK-MM isoenzyme which obtained from skeletal muscle damage, except in AMI and sever unstable angina in which elevated total CK activity assumed to be due to CK-MB and partially CK-MM isoenzyme [١٠٠].

AMI diagnosis can not be based on the total CK only because of high negative and positive predictive value as the increment of total CK is not more than ٢ to ٣ folds in small infarction and in the patients with low muscle mass [١٠٤][١٠٥][١٠٦].

In such situation CK-MB isoenzyme and relative index were used to get the true diagnosis of AMI, small elevation of CK-MB isoenzyme accompanied by relative index value more than ٥٪ give confirmative diagnosis of AMI [١٠٧].

The main objective for the use of the CK-MB in this study is to establish the diagnosis of AMI in the suspected cases CK-MB isoenzyme found to be more sensitive and specific indicator for AMI , Milzman , show that at ٠-٤ hours after AMI , CK-MB isoenzyme activity sensitivity and specificity (٥٨.٩٪) (٩٠.٥٪) and after ٢٤ hours (٩٢٪) (٩٥.٣٪) respectively, and this is consistent with our results[١٠٨].

Janchar found that CK-MB isoenzyme activity is better tested after presentation of AMI, and in the patient with elevated CK-MB and normal level of total CK activity had higher cardiac complication at initial presentation and ٦ months follow up[١٠٩].

To detecting myocardial necrosis, measuring total CK activity, CK-MB isoenzyme activity and taking relative index, we found that the relative index is the corner stone in the detective diagnosis of AMI, this is agreed by Robert [١١٠][١١١].

4-3 Urinary albumin excretion.

The urinary albumin excretion in this study has non significant difference between males and females, in which female patients with AMI show higher urinary albumin than male patients, and this finding agree with Cosling P. in which he found albumin excretion was slightly higher in women than the men and don't give an explanation for this result[١١٢]and our finding in contrast with which they found that prevalence of microalbuminuria was one fold higher in males than females, and this is explained by the vasculature more sensitive in males to give risk factor than in female, and increase urinary albumin excretion is considered as a marker of damage of vascular endothelium . microalbuminuria as very early stage of diabetic nephropathy[١١٣].

Several studies show that microalbuminurea is significantly higher in the patient with AMI compared with healthy patient[١١٣][١١٤] , others show that microalbuminurea not specific only for renal disease and diabetic nephropathy but it may also be associated with AMI ,poor controlled hypertension and some lipid abnormalities [١١٥] [١٠٩] microalbuminuria seen to be independent and stronger as a risk factor than the effect of the conventional atherosclerotic risk factors such as smoking , dyslipidemia , obesity , high blood pressure , male gender and advanced age [١١٦], and other studies strongly indicate that microalbuminuria is highly correlated with development of atherosclerosis[١١٧] .

If urinary albumin excretion begins to increase late in the atherosclerotic process ,microalbuminurea may be a marker of

prevalent sub clinical atherosclerosis as suggested [١١٨] [١١٩] .

And if urinary albumin excretion is already increased early in the atherosclerosis process, microalbuminurea may reflect an endothelial dysfunction and perhaps an augment atherogenic susceptibility to other risk factors [١٢٠] .

In Copenhagen city ,a heart study found that any degree of increased level of albumin in urine (i.e. not due to the renal disease or diabetic nephropathy) is associated with higher rate of cardiovascular events and increased morbidity and mortality [٧٠] [١٢١],even in general population and also found that healthy individuals with microalbuminurea have high blood pressure , lower plasma concentration of apolipoprotein A-١, and low HDL cholesterol concentration . Further more they had a generalized transvascular leakage for albumin , these observation suggest that individual with slightly increased urinary albumin excretion may be at increased risk for subsequent development of ischemic heart disease [١٢٢] [١٢٣] [١٢٤] [١٢٥] .

4-4 Serum albumin concentration.

We found that lower serum albumin concentration is associated with an increased risk for AMI among both sexes . This finding has been suggested that the relation between serum albumin and ischemic heart disease may vary across sex age and level of serum cholesterol[١٢٦], Corti and Colleagues found an association between serum albumin and ischemic heart disease among older women but not older men [١٢٧].

Our finding shows that no significant difference in serum albumin Concentration between women and men [١٢٨].

In the NHANEST study Gillum and Makuc reported an increased risk of IHD and cerebral stroke increased with low serum albumin concentration [١٢٩] [١٣٠]. LUC Djousse found that patient with AMI and low serum albumin concentration not have causal role for IHD but could be an indicator of an underlying other disorders[١٢٦].

The effect of serum albumin concentration on cardiovascular system is poorly understood but some suggest that it's effect on the blood viscosity and free fatty acid transport .

Hypoalbuminemia in the AMI may be due to the combination of microalbuminuria[١١٣], increased albumin leakage into extra vascular spaces and increased of degradation plasma protein by free oxygen radicals ,since protein sulfuhydryls serve as sacrificial antioxidant , prevent plasma lipid peroxidation as well as being targets for oxidative damage [١١٤] , Hypoalbuminemia leads to a reduction in the antioxidant scavenging capacity of plasma proteins and this in turn induces myocardial muscle damage by free oxygen radicals [٨٢].

4-5 Serum uric acid.

Serum uric acid found to be higher in the females but it is within upper normal limit in the males with AMI , several studies have demonstrated the mechanism by which uric acid could be directly injurious to the endothelium and cardiovascular function [١١٥][١٣١] and these micro injuries caused accumulation of platelets in the sites of these micro injuries which may lead to form very small clots, others studies show that raised serum uric acid concentration in both male and female are powerful

predicator for CVS risk but the mechanism remained unclear [١٣٢]. Kojima suggests that hyperuricemia after AMI is associated with the development of heart failure. Serum uric acid level is a suitable marker for predicating AMI-related future adverse events, and the combination of Killip's class and serum uric acid level after AMI is a good predicator of mortality in patients who have AMI[١٣٣]. In a study of ٣١٦ angiography patients with coronary artery disease followed for ٥ years, uric acid more than ٥.٢ mg/dl independently imparted a ٣.٥ -fold increased risk for cardiovascular death and major clinical events over a ٥-year period. Uric acid may be a contributing factor to the progression of atherosclerosis and its complications[١٣٤].

4-6 Risk factors.

In this study we found that AMI occur at older age and in the males more than younger age and females , these findings related to the rate of development of atherosclerosis , which appear in the patient who have susceptibility of atherosclerosis in early life but become clinical significant when patient become older age [١٣٥].

The reason why atherosclerosis is more in males, is that females have a protective mechanism against atherosclerosis due to the effect of estrogen hormone and after menopause women loss this effect so atherosclerosis developed and took long time to become clinically significant in compares with corresponding males in same age [١٣٦].

The smoking had adverse effects on the coronary arteries which causes the following:-

١. Decrease HDL.
٢. Increase LDL.

٣. Vasoconstriction.
٤. Increase fibrinogen, and clot formation. So the smoking had
direct effect in the development of AMI [١٣٧].

Hypertension shows important association with AMI in our study in agreement with Gaze that show direct association of systolic and diastolic hypertension with AMI [١٣٦].

Family history of ischemic heart disease is significantly low with AMI and this is in contrast with Gamm , who found that atherosclerosis runs in members of the same family especially in first degree relatives , Some conditions are directly inherited such as familial hypercholesterolemia and familial combined Hyperlipidemia [١٣٦].

Hypercholesterolemia has significant association with AMI as it has strong association with atherosclerosis that lead to AMI [١٣٧].

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