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EVALUATION THE ACTIVITY OF LDH ENZYME AND SOME BIOCHEMICAL VARIABLES IN THE BLOOD OF PEOPLE WITH HEART ATTACK IN SALAHUDDIN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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ABDULQADER ABDULLAH ALI ALI

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EVALUATION THE ACTIVITY OF LDH ENZYME AND SOME BIOCHEMICAL VARIABLES IN THE BLOOD OF PEOPLE WITH HEART ATTACK IN SALAHUDDIN

By Abdulqader Abdullah Ali ALI

June 2022

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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ABSTRACT

EVALUATION THE ACTIVITY OF LDH ENZYME AND SOME BIOCHEMICAL VARIABLES IN THE BLOOD OF PEOPLE WITH HEART ATTACK IN SALAHUDDIN

Abdulqader Abdullah Ali ALI

Master of Science in Chemistry

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June 2022

The current study aimed to evaluation LDH activity and some parameters in heart attack patients compared to healthy controls**.** The subjects were recruited and examined in the cardiology clinic of Kirkuk General Hospital between September 2021 and February 2022, some questionnaire about the age and degree of both parents' relatives, past medical history, and antenatal history. This study included 75 patients and 50 controls as two groups. The results show a significant ($P<0.05$) increased in the activities of liver enzymes in patients compared to the healthy persons. On the other hand, the results were showed significant increase in the concentration of total cholesterol and HDL in patients compared to the healthy persons. While, results show a significant ($P<0.05$) decreased in the concentration of calcium and increased in potassium in serum of patients compared to the healthy persons. Finally, the results were showed significant increase in the concentration of troponin I and LDH in patients compared to the healthy persons.

2022, 47 pages

Keywords: Liver enzymes, Troponin, Heart attack, Potassium

ÖZET

SALAHUDDİN'DE KALP KRİZİ OLANLARIN KANINDAKİ LDH ENZİMİ VE BAZI BİYOKİMYASAL DEĞİŞKENLERİN DEĞERLENDİRİLMESİ

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Mevcut çalışma, kalp krizi hastalarında LDH aktivitesini ve bazı parametreleri sağlıklı kontrollere kıyasla değerlendirmeyi amaçladı. Denekler, Eylül 2021 ile Şubat 2022 arasında Kerkük Genel Hastanesi kardiyoloji kliniğinde işe alındı ve muayene edildi, her iki ebeveynin akrabalarının yaşı ve derecesi, geçmiş tıbbi öykü ve antenatal öykü hakkında bazı anketler yapıldı. Bu çalışmaya iki grup olarak 75 hasta ve 50 kontrol dahil edildi. Sonuçlar, sağlıklı kişilere kıyasla hastalarda karaciğer enzimlerinin aktivitelerinde önemli ($P<0,05$) bir artış olduğunu göstermektedir. Öte yandan, sonuçlar sağlıklı kişilere kıyasla hastalarda toplam kolesterol ve HDL konsantrasyonunda önemli bir artış gösterdi. Sonuçlar, sağlıklı kişilere kıyasla hastaların serumunda kalsiyum konsantrasyonunda önemli ($P<0,05$) azalma ve potasyumda artış olduğunu gösterirken. Son olarak, sonuçlar sağlıklı kişilere kıyasla hastalarda troponin I ve LDH konsantrasyonunda önemli bir artış gösterdi.

2022, 47 sayfa

Anahtar Kelimeler: Karaciğer enzimleri, Troponin, Kalp krizi, Potasyum

PREFACE AND ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Assoc. Prof. Dr. Şevki ADEM and Asst. Prof. Dr. Nadia Ahmed SALEH, For their patience, guidance and understanding. So all acclaim is due to Allah, the Exalted, for his incalculable blessings. This work is dedicated to my parents, without whom I would not have progressed to this point.

Abdulqader Abdullah Ali ALI
Çankırı-2022

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LIST OF SYMBOLS

µL	Microliter
g	Gram
mg/dL	Milligrams per decilitre
mL	Milliliter
mM	Millimeter
nm	Nanometer

LIST OF ABBREVIATIONS

A	Absorbance
ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
Ca	Calcium
CAD	Coronary artery disease
CHD	Coronary heart disease
CK	Creatine kinase
Conc.	Concentration
CTnT	Cardiac protein troponin T
ECG	Electrocardiogram
EU	European Union
HDL	High density lipid
K	Potassium
LDH	Lactate dehydrogenase
LDL	Low density lipid
MI	Myocardial infarction
NAD	Nicotinamide adenine dinucleotide
NSTEMI	Non-ST-elevation myocardial
RDW	Red cell distribution width
SCD	Sudden cardiac death
STEMI	ST-elevation myocardial infarction
TC	Total cholesterol
UAP	Unstable angina pectoris
WHO	World Health Organization

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1. INTRODUCTION

A heart attack, often known colloquially as a A decrease of blood flow to myocardium causes "myocardial infarction." While some myocardial infarctions go unreported, others are life-threatening and may lead to hemodynamic deterioration and untimely death (Thygesen *et al.* 2007). Myocardial infarctions, the most common complication of underlying cardiovascular disease (CVD), are the leading cause of death in the United States. The myocardium is deprived of oxygen when a coronary artery is blocked. So when myocardium is oxygen deprived for an extended period, cardiac cell death and necrosis can result (Reimer *et al.* 1983).

Every year, around 1730000 people die as a result of cardiovascular disorders, with 7254000 of these people dying as a result of MI. MI risk factors have important role in the occurrence of this disease (Pursnani *et al*. 2014). Over 30 minutes, cardiac ischemia causes harm, and if it continues, it causes irreparable damage and necrosis of myocardial cells (Schmidt *et al.* 2007). Following a MI, there is a definite link between growing troponin levels and higher mortality (Mahajan *et al*. 2006). Regardless of whether the diagnosis of MI happens later or there is a delay between the start of chest pain symptoms and reperfusion, this increases patient mortality (Linkermann *et al.* 2013).

MI diagnosis necessitates precise clinical evaluation, particularly when assessing chest discomfort, as well as appropriate ECG interpretation (Watkins *et al.* 2014). Recently, a link between cardiac myocyte destruction and increased levels of cardiac biomarkers has been found (Cleery *et al.* 2015, Avouac *et al.* 2015, Ravassa *et al.* 2015).

Myocardial biomarkers are useful in determining the degree of MI following the occurrence of cardiac ischemia and myocyte destruction. An increase in the blood levels of biomarkers such as creatine kinase and CK-MB are signs of myocardial cell death (Gerszten *et al.* 2008, Shlipak *et al.* 2012, Ahmad *et al.* 2012).

LDH is a crucial enzyme in the anaerobic metabolic reactions. Both plants and animals have this enzyme. Gluconeogenesis and DNA metabolism both rely on the presence of this enzyme, which is found in a wide range of tissues. Heart attacks, tissue damage, and a wide variety of cancerous tumors may all be detected with this imaging technique. The LDH level may be used to diagnose a myocardial infarction (Agarkov *et al.* 2019, Szunerits *et al.* 2020). Serum C-reactive protein and LDH levels, according to Komolafe et al., may aid in the detection of pancreatic necrosis. A high LDH level has been shown to be an independent diagnostic characteristic in sarcoma patients in European phase-I trials (Cassier *et al.* 2014, Komolafe *et al.* 2017).

1.1 Aims of Current Study

- Study the activities of liver enzymes
- Keep an eye on your total cholesterol and HDL cholesterol levels
- Study the levels of some electrolytes (calcium and potassium)
- Study the levels of troponin and LDH.

2. LITERATURE REVIEW

2.1 Myocardial Infarction

Coronary heart disease, for example, is a type of cardiovascular illness that affects both the heart and the blood vessels (CHD). The most prevalent cause of CHD is atherosclerosis, which causes stenosis or blockage of one or more branches of coronary artery. The most prevalent symptoms of CHD are stable angina pectoris, heart failure, and ACS, which includes UAP, MI, and SCD. The pathophysiology of ACS is centred on plaque rupture or erosion, which is accompanied by underlying thrombosis and a heightened vulnerability to spasm (Crea and Libby 2017). A blood test for biomarkers (the cardiac proteins troponin I, as well as the cardiac enzymes CK and CK-MB) can detect MI when there is cell death (necrosis) as a result of severe and persistent ischaemia..

Two categories of ACS patients may be distinguished based on ECG:

- More than 20 minutes of chest discomfort and ST-segment elevation. If you experience an ST-elevation myocardial infarction, you are likely to have a sudden thrombotic complete coronary obstruction as well (STEMI).
- Patients who have a sudden onset of chest pain but no sustained ST-segment elevation. Cardiac pathology's counterpart is cardiomyocyte necrosis NSTEMI or myocardial ischaemia without cell death (UAP). A partially blocked coronary artery is a common cause of UAP and NSTEMI (McManus *et al.* 2011, Crea and Libby 2017).

2.1.1 Prevalence and prognosis of CVD

CVD is the major cause of death in WHO's Europe area, accounting for half of all deaths, which comprises 53 nations and over two million people in the European Union (EU). People in low socioeconomic status die more often than those in higher

socioeconomic status (54% of all deaths against 43% of all deaths). Cardiovascular deaths are common in all parts of the industrialised world, and CVD is rapidly becoming a leading cause of mortality in developing countries (Lopez *et al.* 2006).

According to EU age-standard mortality rates for cardiovascular disease, the number of people who are living with the condition has increased, notwithstanding this trend (Graham *et al.* 2007). 9 modifiable risk factors were shown to account for 90 percent of attributable risk in men and 95 percent in women in a study of acute MI in 52 countries, according to Interheart research (Yusuf *et al.* 2004). Psychosocial factors, such as smoking and a high apoB/apoa1 ratio were also taken into account. Smoking was also a contributing factor. European recommendations on cardiovascular disease prevention emphasize the need of reducing risk factors, particularly in those at high risk, such as diabetics (Graham *et al.* 2007).

A considerable number of subjects with CVD, both acute and chronic, have glucose abnormalities (Bartnik *et al.* 2004, Hu et al. 2006). Patients with cerebrovascular or peripheral artery disease had similar proportions (Johansen *et al.* 2006). Patients who have CVD and glucose irregularities, in particular, have a poorer prognosis than those who do not (Barr *et al.* 2007, Norhammar *et al*. 2007).

Traditional risk factors like hyperlipidemia condition and the hypertension cluster in people who have poor glucose management, but hyperglycemia is also a substantial risk factor that promotes cardiovascular morbidity and mortality. There is evidence to suggest that sedentary lifestyles and metabolic illnesses like dysglycemic and dyslipidemic conditions are replacing higher risk factors like stress in myocardial infarction patients (Wilhelmsen *et al.* 2008).

2.1.2 Clinical presentations of MI

The initial step of MI's pathogenesis, myocardial ischemia, is brought on by an oxygen supply/demand mismatch. An examination of the patient's medical history and an

electrocardiogram (ECG) are the most common methods used in clinical settings to detect myocardial ischemia. Dyspnea and exhaustion are ischemic counterparts to dyspnea and other chest, upper extremity, and mandibular ischemia symptoms. As a general rule, discomfort is neither localized, positional, or influenced in any way by a shift in a person's location. Many other disorders, including gastrointestinal, neurological, respiratory, and musculoskeletal issues, may cause same symptoms. If you're experiencing palpitations, you may be suffering from a condition known as myocardial infarction (MI) (Thygesen *et al.* 2012).

cTn release and increases can be caused by very brief bouts of ischemia that are not long enough to produce necrosis. As a result of apoptosis, the myocytes implicated may perish (Weil *et al.* 2017). Myocardial damage characterized by increasing and/or declining cTn values is consistent with an acute MI diagnosis whether it is seen clinically or by ECG alterations. Myocardial infarction may be diagnosed by cTn levels if the pattern of values grows and/or declines, or if the pattern is steady, if the MI is not clinically obvious (Sarkisian *et al.* 2014).

The same issues apply when investigating occurrences that may be linked to surgeries which may lead to myocardial damage and/or MI. Another tests may need a re-evaluation of the initial prognosis. It is possible that people with ACS who have been ruled out for MI but whose cardiac biomarker values are normal really have unstable angina or another condition. These individuals should be multiplied and handled as required (Mendis *et al.* 2011, Braunwald and Morrow 2013).

2.1.3 Classification of MI

More sensitive cardiac troponin tests and lowered diagnostic criteria were used to take into consideration the various clinical manifestations of myocardial damage, which resulted in major revisions to the recommendations (Figure 2.1). The third global MI definition established global consensus on myocardial damage and infarction classification (Thygesen *et al.* 2012).

Necrosis in the myocardium in a clinical situation that is consistent with an acute MI is necessary for a diagnosis of myocardial infarction. At least one cardiac parameter reading over the 99 percent upper average limit is being raised or decreased. An increase or decrease in cardiac parameter readings must be more than or equal to one number above the 99th percentile upper average limit in order to meet these requirements:

- Myocardial ischaemia symptoms.
- T-wave changes in the ST-segment of the new left bundle branch block are feasible.
- During an ECG, pathogenic Q-waves appear.
- Imaging may reveal a new regional wall motion anomaly or evidence of a viable myocardial loss.
- Angiography or autopsy are used to detect intracoronary thrombosis.

Atherosclerotic plaque thrombosis causes type 1 myocardial infarction, whereas a myocardial oxygen supplydemand imbalance in the midst of another severe illness causes type 2 myocardial infarction (Thygesen *et al.* 2012).

Percutaneous coronary intervention (PCI), coronary artery bypass surgery (CADS), and type 3 or type 4 myocardial infarctions all lead to death (type 5). Troponin concentrations are high and show dynamic fluctuations in acute myocardial damage, while troponin concentrations remain constant over time in chronic myocardial injury in the absence of overt myocardial ischaemia. This difference is important because the pathogenic pathways that cause acute and chronic cardiac injury are likely to vary. This categorisation is open to question since it was based on expert consensus rather than evidence from prospective clinical investigations. Although it's largely acknowledged in the scientific community, it hasn't made it into clinical practice just yet (Shah *et al.* 2016, Alpert and Thygesen 2016).

Type 2 MI is common disputed diagnosis, as it is dependent on clinical theory and observed rather than a prospective mechanistic investigation. Myocardial ischaemia

develops in patients with type 2 MI as a result of a range of acute medical or surgical circumstances. Patients without coronary artery disease may be identified as having type 2 MI based on current criteria. For patients who have suffered a type 2 myocardial infarction, there is currently no guideline or consensus on the best heart evaluation, care, or treatment method. The global definition of myocardial infarction is currently being reviewed by an international task committee, which recognizes the need for more precise diagnostic criteria and recommendations (Alpert and Thygesen 2016, Alpert *et al.* 2014).

Acute myocardial infarction and type 2 myocardial infarction overlap clinically, making it difficult to distinguish between the two, according to current recommendations. This has led to uneven categorization of the two in clinical practice. Similarly, without an agreed-upon definition, standardised assessments across different healthcare settings and randomised studies to establish the efficacy of investigative techniques or preventative medicines for these people are problematic (Alpert *et al.* 2014, Sandoval *et al.* 2014).

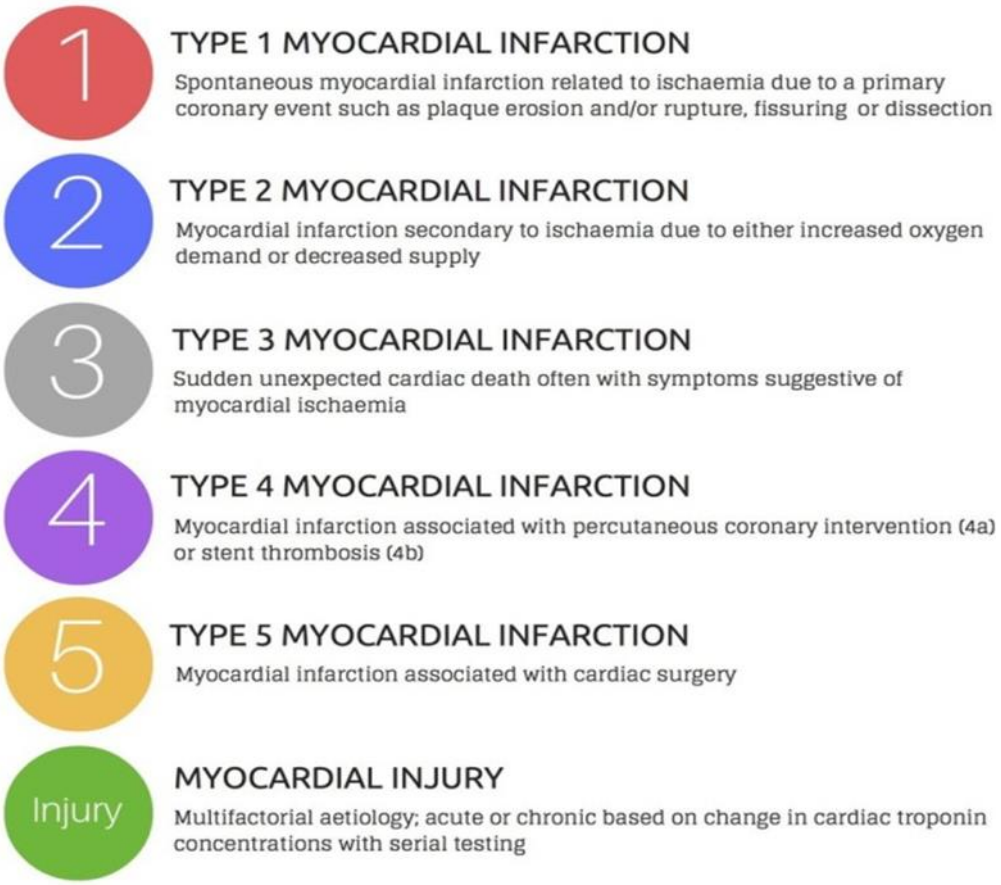

Figure 2.1 Classification of myocardial infarction (Thygesen *et al.* 2012)

2.1.4 Myocardial infarction type 1

There are two types of ischemic strokes: type 1 (atherothrombotic) and type 2 (thrombotic). With time, the amount of atherosclerosis and thrombosis in the culprit lesion might alter, resulting in distal coronary embolism and myocyte death. Intraluminal thrombosis can exacerbate plaque rupture, but so can bleeding into plaque as a result of the damaged surface (Figure 2.2) (Bentzon *et al.* 2014, Falk *et al.* 2013).

Integrating ECG data with the purpose of determining whether a type 1 MI is a STEMI or an NSTEMI is crucial in determining the proper treatment based on current recommendations (Ibanez *et al.* 2018).

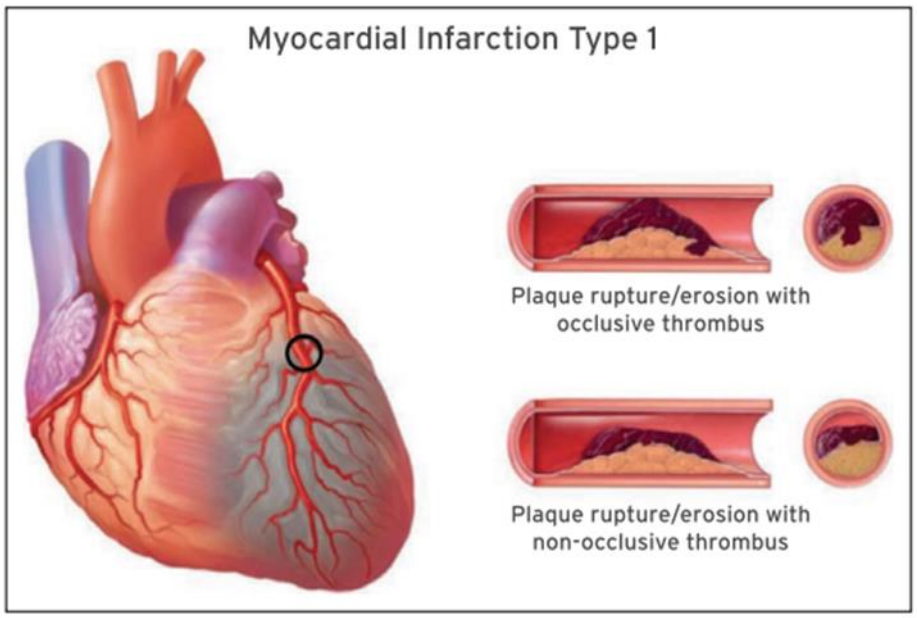

Figure 2.2 A first-time myocardial infarction (Bentzon *et al.* 2014)

2.1.5 MI Type 2

Type 2 MI refers to the pathophysiological process that causes ischemic myocardial damage when oxygen supply and demand are out of sync (Thygesen *et al.* 2012). Acute atherothrombotic plaque disruption does not, by definition, occur in type 2 MI. Type 2 MI may occur in people with stable CAD who are subjected to an acute stressor, such as gastroenteritis with a fast drop in hemoglobin levels, tetany, or an extended period of tachyarrhythmia with symptoms of myocardial ischemia. The stressor's increased myocardial oxygen demand necessitates a lack of blood flow to the ischemic myocardium, which results in these effects. The degree of underlying CAD and structural heart defects, as well as the severity of the stressor and the frequency of noncardiac comorbidities, may all affect an individual's ischemia threshold. Variable rates of type 2 MI have been recorded in studies, depending on the diagnostic criteria used. Research like (Saaby *et al.* 2013, Cediel *et al.* 2017) utilize more stringent oxygen mismatch criteria, whereas other studies use more flexible ones (Saaby *et al.* 2013). According to the majority of studies, women have a higher chance of getting type 2 MI than men. Patients with type 2 MI died at a greater rate than those with type 1 MI in both the short and long term in most studies, but not all. As a result of the rise in the

number of people with several medical diseases, this has become an issue (Baron *et al.* 2015, Shah *et al.* 2015, Gupta *et al.* 2017, Cediel *et al.* 2017).

Atherosclerosis of the coronary arteries is more likely to occur in patients with a type 2 MI who have coronary angiography. A person's prognosis is worse if they have CAD than if they don't (Lambrecht *et al.* 2018, Chapman *et al.* 2018). It is essential to undertake additional evaluations of the significance of CAD in type 2 MI using consistent criteria and methodology. 3 to 24 percent of patients with Type 2 MI had elevated ST-segment elevation. 53 Type 2 MI may be caused by thrombosis, calcium, or vegetation from the atria or aortic dissection. spontaneous coronary artery dissection with or without intramural necrosis is a non-atherosclerotic disease in young women. Allowing blood to collect in the fake lumen and squeezing the true lumen, coronary artery walls spontaneously rupture (Figure 2.3) (Saw *et al.* 2016).

2.1.6 MI Type 3

In order to determine the cause of a heart attack, blood biomarkers must be identified (Thygesen and colleagues, 2012). Before blood can be drawn for cardiac biomarker analysis, individuals might present with classic symptoms of myocardial infarction, such as suspected new abnormalities on the electrocardiogram or ventricular fibrillation. Patients with type 3 MI are still classified as having a type 3 MI even if there is no indication of MI in cardiac biomarkers (Thygesen *et al.* 2007).

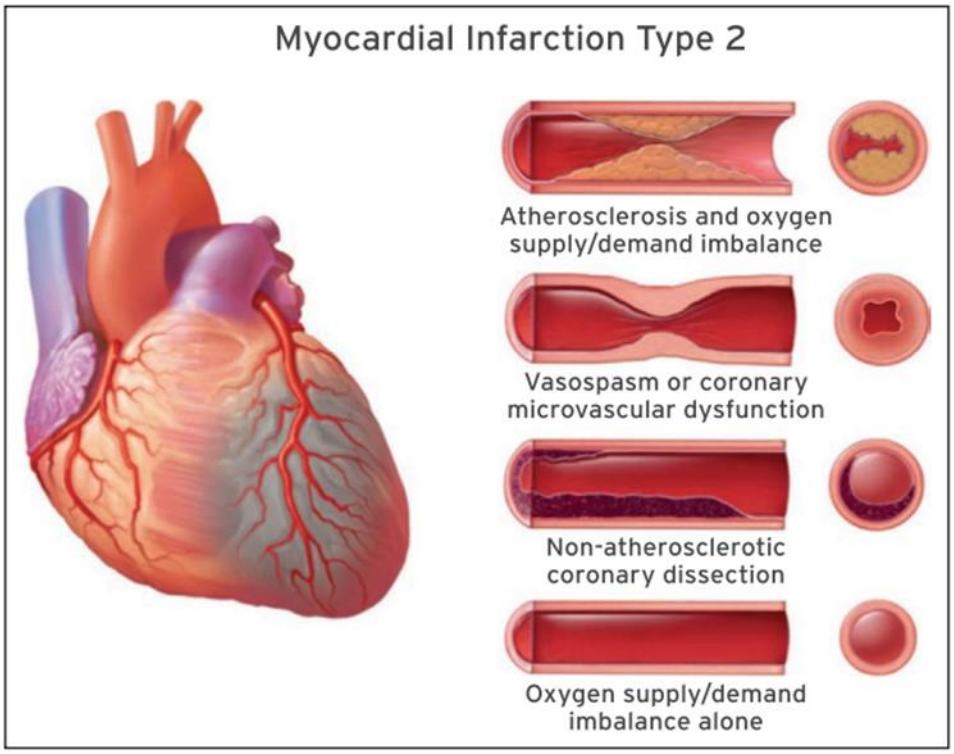

Figure 2.3 Myocardial infarction type 2 (Saw *et al.* 2016)

Fatal MI occurrences are categorised separately from other sudden death events, which may be either cardiac or noncardiac in nature. Reclassifying a MI from type 3 to type 1 after an autopsy that demonstrates fresh or recently formed thrombuses in the infarct-related arterial artery is recommended. One research found that the yearly incidence of type 3 MI was less than 10 per 100,000 person-years and that the frequency of all MI types was between 3 and 4 percent, despite the fact that there are few original studies on the incidence (Jangaard *et al.* 2017).

2.1.7 Mechanisms of MI

More than 90 percent of cardiac troponin isoforms are found inside the sarcomere, with the remaining troponin isoforms found in the cytoplasm. Proteolytic troponin breakdown products, the production of membranous blebs, increased membrane permeability, and necrosis of myocytes are all hypothesized to play a role in the release of cardiac troponin into the circulation (White 2011). Numerous processes have been

proposed to explain why cardiac troponin is produced in the presence of myocardial ischaemia and necrosis. Intracellular proteases associated to troponin breakdown may be triggered when cardiomyocytes are physically stretched in response to pressure (Wang *et al.* 2002).

Tachycardia may activate stress-sensitive integrins in the cardiomyocyte, resulting in the generation of intact cardiac troponin I from cardiomyocytes that survive (Hessel and coworkers 2007). Nuclear perfusion imaging and stress testing have been shown to induce troponin production in patients with reversible ischaemia in vitro. An ultrasensitive cardiac troponin I test was used to count each and every molecule of troponin I in the circulation to determine the degree of myocardial ischaemia (Sabatine and colleagues, 2009).

A type 2 MI differs from a myocardial damage by having symptoms and signs of myocardial ischaemia, however there is substantial overlap and no prospective mechanistic investigations have been done to date to determine the breadth of underlying pathophysiology in these individuals. As part of the pathogenesis of acute left ventricular failure, sepsis, viral myocarditis, or a mismatch in myocardial oxygen transport may induce acute myocardial damage (hypertension, tachycardia, or hypoxemia). It is also possible that a previously quiet susceptible plaque might now cause cardiac injury as a result of the platelet aggregation and thrombosis that occurs when the presenting sickness is associated to a proinflammatory and prothrombotic condition (Chin and colleagues, 2014).

A myocardial oxygen supply-demand mismatch may lead to myocardial damage in the setting of stable coronary artery disease that has a poor prognosis. As a consequence, it is incorrect to write off instances of acute myocardial infarction as an untreatable bystander effect. Structural and non-cardiac diseases such as CRF may both induce chronic myocardial damage. In aortic stenosis patients, therapeutic benefit from long-term myocardial injury may be possible; high levels of cardiac troponin I in blood are linked to cardiac mass, replacement fibrosis, and prognosis in valvular heart disease (Chin *et al.* 2014).

Those who have suspected ACI may have increased cardiac troponin levels, which have been linked to these diseases. Patients with non-ST-segment elevation MI should only get invasive treatment if the relative change in cardiac troponin concentration of at least 20% or the cardiac troponin concentrations are more than fivefold larger than the 99th centile at the time of presentation can be shown (Thygesen *et al.* 2012, Roffi *et al.* 2016).

2.2 Lactate Dehydrogenase (LDH)

Lactate dehydrogenase (LDH, EC 1.1.1.27) uses NAD+ as a cofactor to help in the interconversion of pyruvate and lactate. Bacteria, plants, and microbes all contain LDH, a kind of 2-hydroxyacid oxidoreductas (Fiume *et al.* 2014). Lactate dehydrogenase is a 144 kDa homo- and heterotetrameric enzyme with two major subunits A and B (36 kDa) that catalyses the reversible conversion of pyruvate and lactate to produce five isoenzymes.

Electrophoretic mobility of different LDH isoenzymes is determined by the presence or absence of the B subunit. LDH isoenzymes are divided into two categories: rapid and slow. LDH and LDHB have differing metabolic properties, with LDH needing more substrate to reach its maximum activity, and LDH requiring less. Both LDHA and LDHB have pyruvate Km values of around 158 and 58 M, respectively. It is also shown that the activity of the LDHB isoenzyme is reduced when the pyruvate substrate concentration necessary for optimal LDHA activity is exceeded, with a Ki for pyruvate substrate of 3900 M for the enzyme and 770 M for the substrate, respectively. Thus, the Km value for LDHA indicates that the pyruvate substrate has a low affinity for the enzyme, which makes it more suitable for tissue deprived of oxygen; on the other hand, the Km value for LDHB indicates that the enzyme has a high affinity for the pyruvate substrate, which makes it more suitable for aerobic metabolism. In 1975, Kaplan proposed the so-called "aerobic anaerobic hypothesis." Later study revealed that LDHB is largely expressed in human erythrocytes, which lack mitochondria. The Kaplan theory fails to explain the variation in LDH isoenzyme distribution patterns amongst organs of the same sort in different animal species (Granchi *et al.* 2010).

2.2.1 Lactate dehydrogenase structure

LDHA is found in form called tetrameric form, according to crystallography. Each LDHA subunit consists of around 330 amino acids, and each LDHA monomer possesses complete biological activities (Kohlmann *et al.* 2013). It was shown that the LDHA protein has two distinct domains, one of which has a Ross-mann fold and may bind to the NADH cofactor at the 20-162 and 248-266 residue areas. The smaller domain is a substrate binding pocket that may be occur at interface with mixed α/β domain next to it (Fiume *et al.* 2014).

The NADH cofactor interacts with LDHA at a His195 location to prepare the binding site for pyruvate, which starts the enzyme substrate reaction. Substance then interacts with Arg109 and His195 to gain access to the cavity of the binding site. His195 acts as a proton exchanger, assisting pyruvate orientation in preparation for its interaction with NADH. Arg109 closes the active site loop by forming an H-bond with a polarised carbonyl group of the pyruvate substrate. As a result, the active site loop favours hydride transformation over solvent access (Read *et al.* 2001, Granchi *et al.* 2010).

The crystallographic analysis further indicated that the human LDHA active site is located deep within the enzyme, with very restricted access to this cavity. Under normal circumstances, the pyruvate substrate and the NADH cofactor are both housed in cavity of active site. Furthermore, active site loop of LDHA is quite polar and contains a lot of cation residues, especially arginine, which explains why carboxylate groups have been detected in the inhibitors reported so far (Granchi *et al.* 2011, Fiume *et al.* 2014).

2.2.2 Pathophysiology Associated with LDH

Because concentrations LDH isozyme reflect the states of tissue-specific disease, LDH testing is significant in clinical practice. Due to its isozyme form and widespread incidence, LDH may be employed as a marker for a variety of tissue injuries. LDH is released into the bloodstream when cells are injured. Depending on the kind of tissue

injury, the enzyme may stay elevated in the blood for up to seven days. Significant cell death and cytoplasm loss produce a rise in LDH as a result of organ damage.

Tissue damage may be caused by a wide range of conditions, including anemia, hepatitis, and renal failure. As an indicator of sickness severity, prognosis, and non-blood bodily fluids, LDH is essential. Patients with AMI or liver injury who have their LDH levels reduced during treatment have a better prognosis and/or an excellent therapeutic response. Following an acute coronary syndrome, the LDH-1 isozyme remains high for up to four days. When the liver is damaged, the level of LDH-5 rises. Injuries to the liver, such as hepatitis or cirrhosis, lead to a substantial rise in LDH-5 above LDH-4.

After an effusion, LDH levels rise in vital bodily fluids such as pericardial and peritoneal fluids. Effusion is often used to characterize it as a result. Bacterial meningitis raises LDH levels in CSF, but viral meningitis does not. LDH levels in the exudate indicate an inflammatory state if they surpass the upper limit of normal blood LDH (>0.6) (Rogatzki *et al.* 2015).

3. MATERIALS AND METHODS

List of equipment used in this investigation as shown in Table 3.1.

Table 3.1 A list instruments used in the present study

Instruments and glasses	Company	Country
ELISA	Labon	China
Spectrophotometer	Biobase	India
Centrifuge	Memmert	Germany
Light microscope	Olympus	Japan
Oven	Memmert	Germany
Water bath	Memmert	Germany
Shaking water bath	Memmert	Germany
Sysmex device	Sysmax	Japan
Pipette	BioSan	Germany
Different glasses	-----	China
Refrigerator	BEKO	Turkey

3.1 Study Design

The current study is a case (patient with heart attak) -control (healthy persons) study.

3.2 Subjects

The subjects were recruited and examined in the cardiology clinic of Salah al-Din General Hospital between September 2021 and February 2022, some questionnaire about the age and degree of both parents' relatives, past medical history, and antenatal history. This study included 75 patients and 50 controls. The participants were divided into two groups.

- Group 1 consisted of individuals in good health.
- Patients with MI made up the second group.

Blood samples were collected within one day of the beginning of symptoms and three days after the occurrence of MI in each patient.

3.3 Liver Enzymes

3.3.1 Determination of ALT activity

Alanine aminotransferase is performed by spectrophotometry as shown in Table 3.2.

Table 3.2 Steps of ALT procedure

Sample	50 µL
Reagent R	1000 µL
For two minutes, mix and incubate. 34 nm absorbance changes every minute for 3 minutes at 37 oC. Absorbance changes per minute (ΔA/min) should be calculated	

The activity of ALT is calculated according to the Equation 3.1:

$$\frac{\Delta A}{min} \times Factor \tag{3.1}$$

3.3.2 Determination of AST activity

Aspartate aminotransferase is performed by spectrophotometry as shown in Table 3.3.

Table 3.3 Steps of AST procedure

Sample	50 µL
Reagent R	1000 µL
Two minutes of incubation are required. For three minutes, the change in absorbance at 34 nm is measured every minute at 37 ^{o}C. Determine the average rate of change in absorbance (ΔA/min) during the course of one minute.	

The activity of AST is calculated according to the Equation 3.2:

$$\frac{\Delta A}{min} \times Factor \tag{3.2}$$

3.4 Lipid Profile

3.4.1 Total cholesterol

Equation 3.3 was used to get the total cholesterol concentration.

$$\text{Conc. of cholesterol} = \frac{\text{Abs (Test)}}{\text{Abs (Standard)}} \times \textit{Concentration of Standard}\ (200\,\frac{mg}{dL}) \quad (3.3)$$

3.4.2 High density lipid (HDL)

HDL concentration was calculated according to the Equation 3.4.

$$\text{Conc. of HDL} = \frac{\text{Abs (Test)}}{\text{Abs (Blank)}} \times \textit{Concentration of Standard}\ (200\,\frac{mg}{dL}) \quad (3.4)$$

3.5 Electrolytes

3.5.1 Calcium

The steps of calcium procedure in curret work performed according to procedure of manfecture company, Kit provides by BIOLABO, France, as shown in Table 3.4.

Table 3.4 Calcium procedure steps

Tubes	Blank	Sample	CAL. standard
Reagent for use in the laboratory	1.0 mL	1.0 mL	1.0 mL
Sample	-	10 µL	-
CAL. Standard	-	-	10 µL
Using a reagent blank as a reference, measure absorbance (A) at 570 nm for each sample and the standard .			

Calculations: Calcium concentration was calculated from the absorbance depending on the Equation 3.5 below:

A Sample x C Standard = mg/dL total calcium A Standard (3.5)

3.5.2 Potassium

The steps of potassium procedure in curret work performed according to procedure of manfecture company, Kit provides by BIOLABO, France, as shown in Table 3.5.

Table 3.5 Potassium procedure steps

Tubes	Blank	Sample	Calibrator
R1 Reagent	1 mL	1 mL	1 mL
Calibrator	-	-	25 µL
Sample	-	25 µL	-
5 minutes incubation at 37 degrees Celsius, after which the mixture should be tested.			
R2 Reagent	250 µL	250 µL	250 µL
1 minute at 37 °C, and then read the (A1) at 405 nm for step A1. 3 minute at 37 °C, and then read the (A1) at 405 nm for step A1.			

Calculations: Potassium concentration was calculated from the absorbance depending on the Equation 3.6 below:

$$\text{Results} = \frac{\text{A2}-\text{A1 (sample)}}{\text{A2}-\text{A1 (standard)}} \times C\ Standard\ = \frac{mg}{dL} total\ potassium\ A\ standard \quad (3.6)$$

3.6 Lactate Dehydrogenase (LDH)

Each reaction in the Master Reaction Mix requires 50 L of Master Reaction Mix, according to Table 3.6. (well).

Table 3.6 LDH procedure

Reagent	Master reaction mix
LDH assay buffer	48 µL
LDH substrate mix	2 µL

- Each well should have 50 mL of the Master Reaction Mix added to it.
- Repeat the test in 2–3 minutes after you take the first measurement. Read the absorbance at 450 nm for the first time (A450).
- Take measurements every 5 minutes while the plate is incubated at 37 °C (A450).
- When the most active sample is more than the highest standard (12.5 nmole/well), continue collecting measurements.
- For calculating enzyme activity, this is the final measurement.

3.7 Troponin I

Troponin is a striated muscle inhibitory or contractile regulatory protein complex. Each of these proteins may be found at regular intervals along the muscle's thin thread, which is called the troponin filament. Troponin is a hormone that is produced by the body.

- Fill suitable wells with 100 mL of standards, samples, and controls.
- Fill each well with 100 mL of Enzyme Conjugate Reagent.
- Mix well for 30 seconds. It is critical to thoroughly combine the ingredients.
- Incubate for 90 minutes at room temperature (18–25 °C).
- Empty the incubation mixture into a garbage container by flicking the contents of the plate into it.
- Drain all liquid from the wells. 300 mL of 1x Wash buffer washed three times through the wells. Blot with a paper towel or absorbent paper.
- Using a sharp strike, tap the wells on absorbent paper or a paper towel to remove any remaining water droplets.
- Fill each well with 100 mL TMB Reagent. 5 seconds of gentle mixing
- Incubate for 20 minutes at room temperature.
- Add 100 mL of Stop Solution to each well to stop the reaction.
- Mix for 30 seconds on low speed. It's critical to ensure that all of the blue hue fades entirely to yellow.
- Use a microplate reader to read absorbance at 450 nm within 15 minutes.

Calculation: The concentration of troponin after absorbance measurement by EILSA was obtained by Figure 3.1 below:

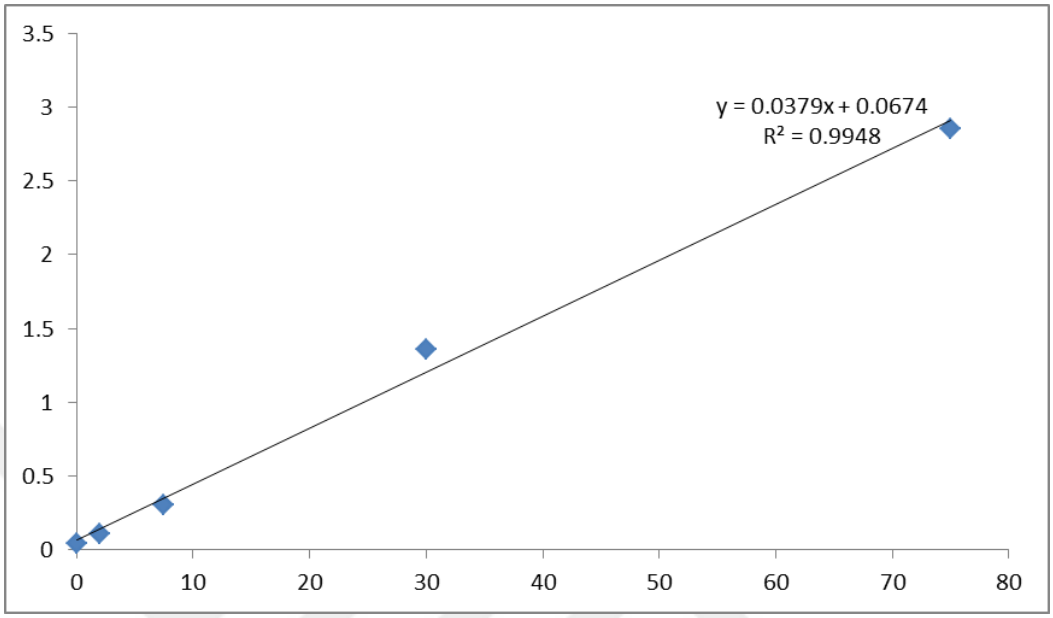

Figure 3.1 Standard curve of troponin

3.8 Statistical Analysis

Statisticians utilized SPSS 15.01 Statistical Package for Social Sciences and Excel 2003 to conduct the study. Chi-square and independent sample t-tests were employed for tables containing frequencies and averages and standard deviations, respectively. We set the threshold of importance to 0.05. These data were analyzed using descriptive statistics such as mean and standard error.

4. RESULTS AND DISCUSSION

4.1 Liver Enzymes

Table 4.1 show the levels of AST in serum of heart diseases patients, where CK levels demonstrated significant (P <0.05) increase in patients (63.38 ± 8.96 U/L) compared to control group (19.46 ± 4.47 U/L) as shown in Figure 4.1. ALT levels in serum of heart diseases patients demonstrated significant (P<0.05) increase in (51.37 ± 6.62 U/L) compared to control group (21.68 ± 5.31 U/L) as shown in Figure 4.2.

Table 4.1 Liver enzymes levels in studied groups

Groups Parameter	Control (50)	Patients (75)	P-Value
AST U/L	19.46 ± 4.47	63.38 ± 8.96*	0.000
ALT U/L	21.68 ± 5.31	51.37 ± 6.62*	0.001

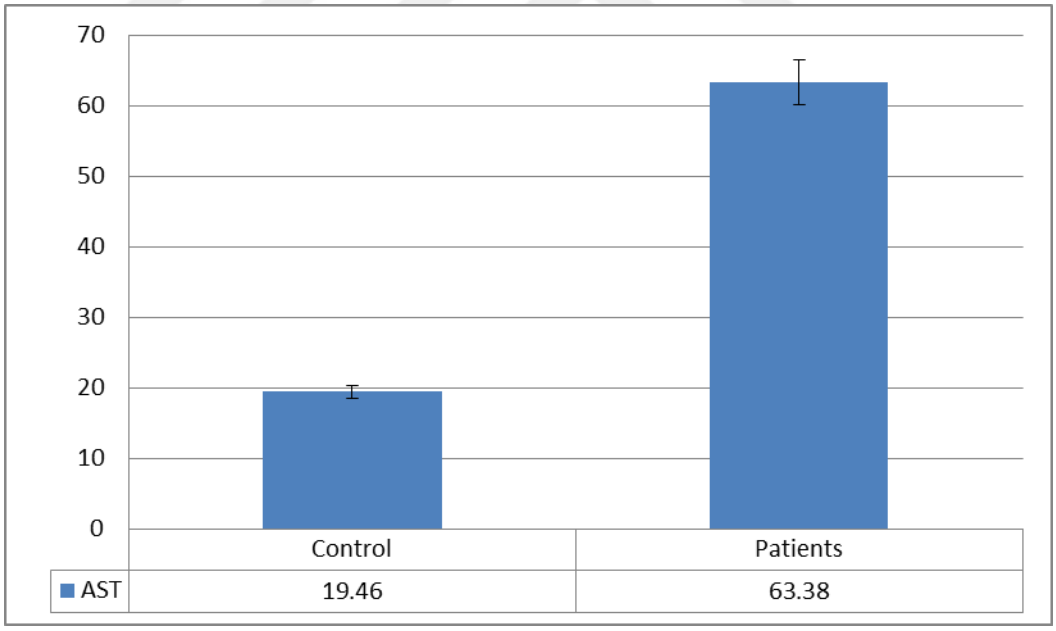

Figure 4.1 AST activities in both groups

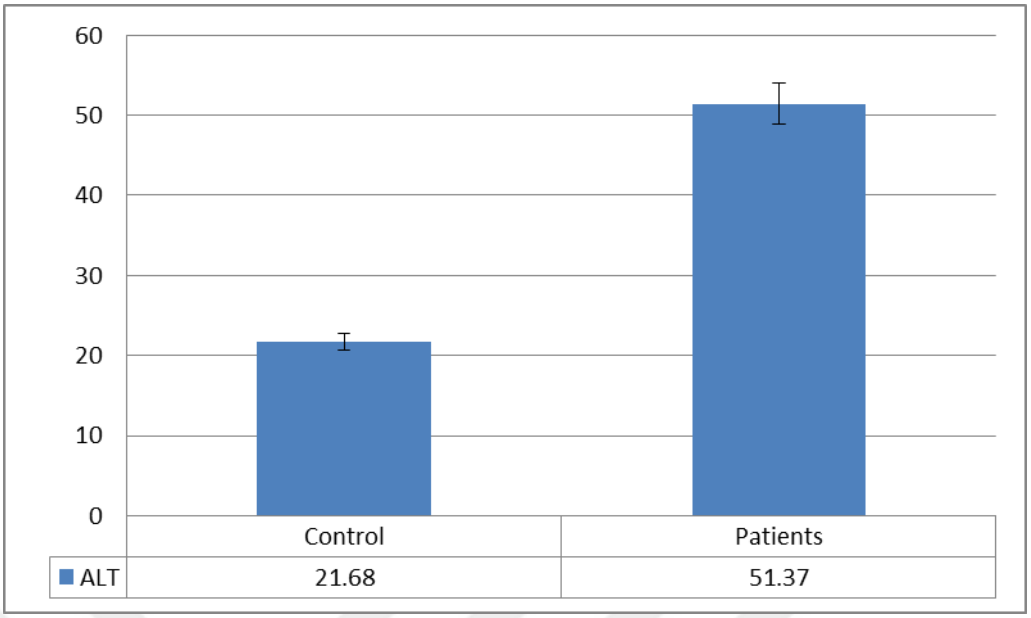

Figure 4.2 ALT activities in both groups

The evidence that suggest a relationship between liver enzymes and the risk of heart diseases is accumulating. ALT and AST are markers of NAFLD which is emerging as a hepatic component of MS, and markers of liver diseases (ALT and AST) predict MS (Hanley *et al.* 2005, Schindhelm *et al.* 2006). Abnormal levels of ALT and AST have been found in MS (Hsieh *et al.* 2009). In addition, ALT was associated with insulin resistance (IR) independent of conventional metabolic parameters.26 IR is considered as is the major pathogenetic mechanism in the development of MS which is also termed as "insulin resistance syndrome" (Grundy 2004, Hanley *et al.* 2007).

MS, a cluster of disorders including abdominal obesity, atherogenic dyslipidaemia (low HDL-C and elevated TG), hypertension, impaired glucose tolerance as well as proinflammatory and thrombotic state, is in turn associated with an increased risk of development of T2D atherosclerotic CVD, and CV events (Banaszewska *et al.* 2006, Hoerger and Ahmann 2008).

The present study clearly demonstrated strong association between liver enzymes, ALT and AST with CHD. This finding is similar to the observation of other studies (Monami *et al.* 2008, Chen *et al.* 2008). In NAFLD, an association between elevated ALT levels

and MS has been found, and the MS-component cluster may act as a predictor of elevated ALT levels (Chen *et al.* 2008).

In addition to a higher chance of getting MS, those with NAFLD and raised ALT levels are also more likely to develop diabetes and cardiovascular disease (CVS) (Forlani *et al.* 2008, Adams *et al.* 2009). This might be owing to the presence of metabolic risk factors. 34 In addition, T2D may be predicted by AST and ALT on their own. Baseline elevations of these enzymes may reflect NAFLD or related diseases (Hanley *et al.* 2005).

Unfortunately, ultrasonographic diagnosis of NAFLD of CHD patients and controls participated in this study was not feasible because of technical difficulties. ALT activity in NAFLD patients has been linked to obesity, insulin resistance (IR), and high sensitivity C-reactive protein (hs-CRP). Adiposity in the midsection, raised TG and FBG, low HDL-C, and low HDL-C were all associated with an enhanced ALT response in people with multiple sclerosis (Oh *et al.* 2006).

4.2 Total Cholesterol (TC) and HDL

Table 4.2 show the levels of TC in serum of heart diseases patients, where TC levels demonstrated significant ($P < 0.05$) increase in patients (229.65 ± 16.04 mg/dl) compared to control group (157.72 ± 8.62 mg/dl) as shown in Figure 4.3. HDL levels in serum of heart diseases patients demonstrated significant ($P < 0.05$) decrease in (27.56 ± 1.04 mg/dl) compared to control group (34.55 ± 1.02 mg/dl) as shown in Figure 4.4.

Table 4.2 Total cholesterol and HDL levels in studied groups

Groups Parameter	Control (50)	Patients (75)	P-Value
TC mg/dl	157.72 ± 8.62	229.65 ± 16.04*	0.0٤٥
HDL mg/dl	34.55 ± 1.02	27.56 ± 1.04*	0.041

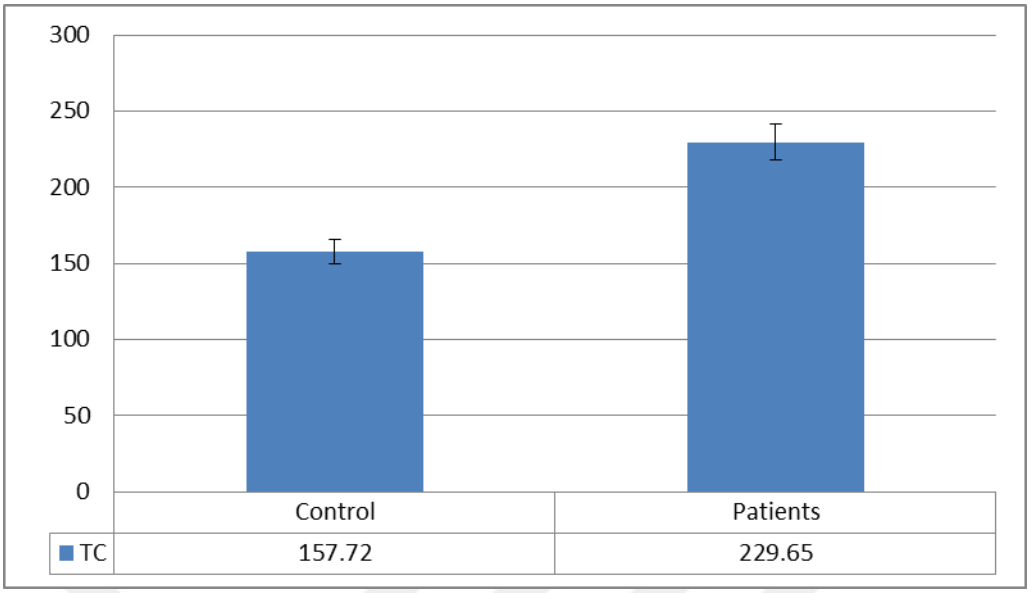

Figure 4.3 TC levels in both groups

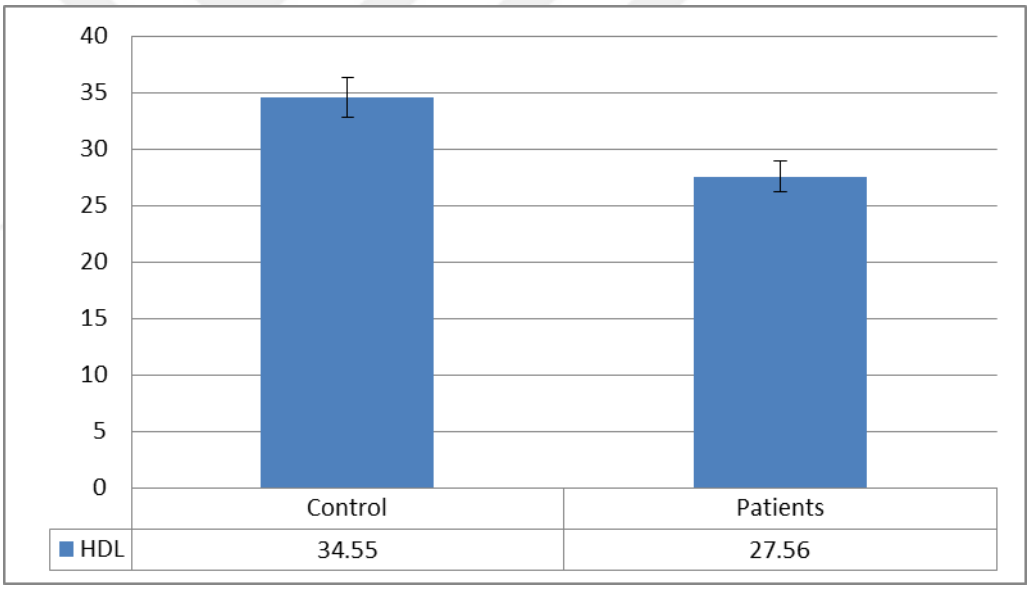

Figure 4.4 HDL levels in both groups

Study participants exhibited greater TC levels than control participants, according to findings (P 0.05). Heart disease patients had greater amounts of HDL in their blood compared to a healthy control group (P 0.05). The findings agree with the researchers that the higher cholesterol level than normal when developing diabetes and heart attack. There are many evidences that confirm the existence of a relationship between the levels of Hcy and high blood lipids (total cholesterol) in the serum of patients with

cardiac stroke higher than the level in the control group. Similar results have been recorded by (Stea *et al.* 2008).

Both hypercholesterolemia (Erhardt *et al.* 2002) and hypertriglyceridemia (Austin 1991) cause chest discomfort and ischemia of the heart muscle owing to coronary artery blockage; they are risk factors for heart disease (Stampfer *et al.* 1991, Austin 1991). Atherosclerosis is caused by elevated blood cholesterol levels because cholesterol precipitates on the arterial walls, increasing shear stress on the arteries, decreasing lumen size, and increasing resistance to the vascular system (Stampfer *et al.* 1991, Austin 1991). One of the important factors in the progression of ischemic heart disease is oxidative stress, which also plays a role in the pathogenesis of coronary artery disease. Statins, which are often used to decrease blood cholesterol, may be connected to an increase in CPK levels in some people, as statins can cause muscle cell death. (Stampfer *et al.* 1991, Austin 1991, Erhardt *et al.* 2002).

4.3 Calcium and Potassium

Table 4.3 show the levels of calcium in serum of heart diseases patients, where calcium levels demonstrated significant ($P < 0.05$) decrease in patients (1.005 ± 0.09 mmol/L) compared to control group (2.157 ± 0.165 mmol/L) as shown in Figure 4.5. Potassium levels in serum of heart diseases patients demonstrated significant ($P < 0.05$) increase in (6.57 ± 0.122 mg/dl) compared to control group (5.44 ± 0.145 mg/dl) as shown in Figure 4.6.

Table 4.3 Calcium and potassium levels in studied groups

Groups Parameter	Control (50)	Patients (75)	P-Value
Calcium mmol/L	2.157 ± 0.165	1.005 ± 0.09*	0.0٠٣٦
Potassium mg/dl	5.44 ± 0.145	6.57 ± 0.122*	0.0268

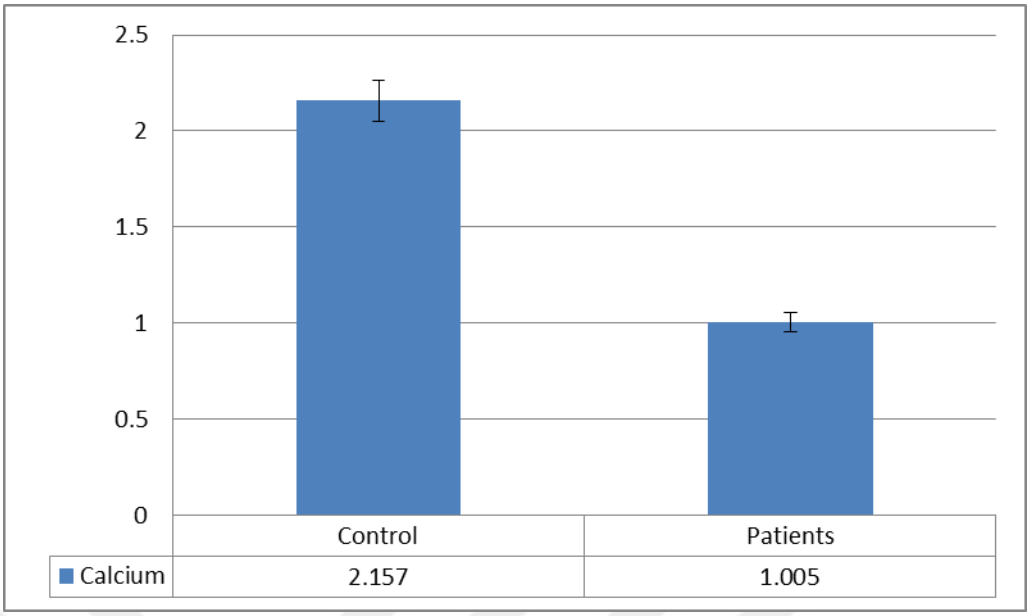

Figure 4.5 Calcium levels in both groups

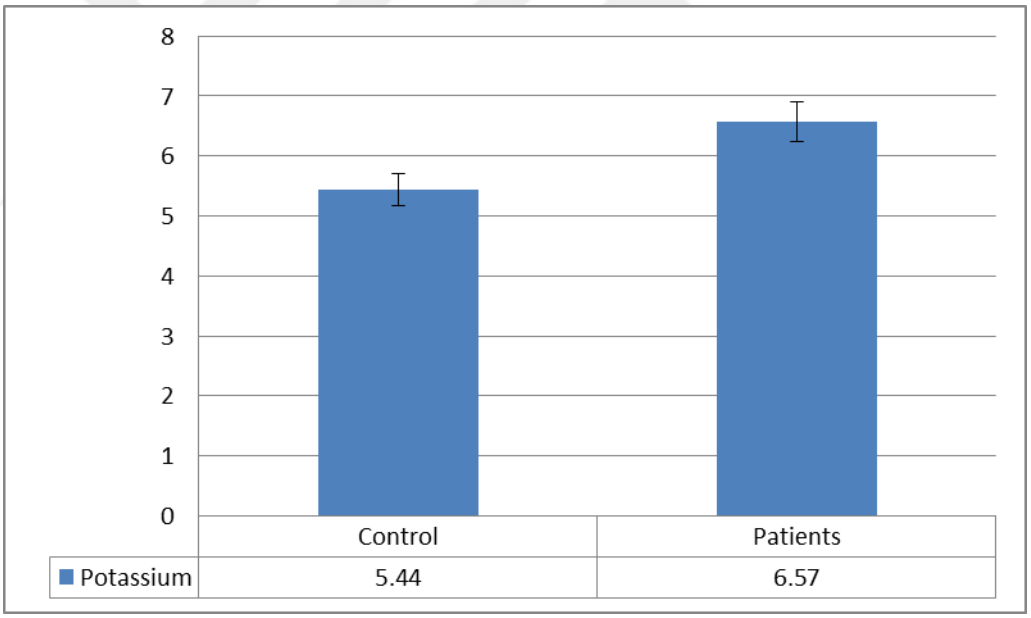

Figure 4.6 Calcium levels in both groups

The results show the levels of calcium in serum of heart diseases patients, decrease compared with control group. Potassium levels in serum of heart diseases patients demonstrated significant (P <0.05) increase compared with control.

Calcium supplements can support in the treatment of congestive heart failure by enhancing the contractility of the heart muscle. Slow calcium channel activity in cardiac cells is regulated by a variety of factors, including cyclic nucleotide levels, ATP levels, and PH levels (Austin 1991). Calcium concentration was substantially lower than usual in all situations of patients with congestive heart failure, condition angina pectoris, and MI, which may impede the capacity to transfer ATP to energy-consuming systems.

Significant reductions in calcium concentration, otherwise, might be triggered by a variety of factors. A high phosphate:calcium ratio, which causes excessive calcium loss in urine, or insufficient vitamin D consumption, or, otherwise, increased stress or calcium excretion, might be one explanation (Hunter *et al.* 2003, Panela *et al.* 2005).

The burden of hyperkalemia in patients with cardiorenal syndrome is substantially larger than previously considered, according to our findings (Luo *et al.* 2016). In the PARADIGMHF research, 15% of patients developed hyperkalemia within a median of 27 months, while the risk of hyperkalemia in patients with HF was generally lower in a UK observational study11 and in multiple prior randomized controlled studies (Murray *et al.* 2014, Desai 2009).

Our study found a much increased risk of hyperkalemia, which presumably reflects various universal healthcare system that includes all hospital contacts with HF, incluvise sick, and frail subjects. current outcomes suggest that the hyperkalemia effect is significantly higher than previously thought, and that individuals with the cardiorenal syndrome are more vulnerable to hyperkalemia. Chronic renal disease, DM and spironolactone use were all identified as risk factors for hyperkalemia in our current study, which was backed up by other research (Vardeny *et al.* 2014, Khan *et al.* 2015, Tromp *et al.* 2017).

4.4 Troponin and LDH

Table 4.4 show the levels of troponin in serum of heart diseases patients, where troponin levels demonstrated significant (P <0.05) decrease in patients (43.59 ± 4.515 ng/ml) compared to control group (0.327 ± 0.087 ng/ml) as shown in Figure 4.7. LDH levels in serum of heart diseases patients demonstrated significant (P <0.05) decrease in (350.52 ± 17.21 mg/dl) compared to control group (202.49 ± 14.85 mg/dl) as shown in Figure 4.8.

Table 4.4 Troponin and LDH levels in studied groups

Groups Parameter	Control (50)	Patients (75)	P-Value
Troponin ng/ml	0.327 ± 0.087	43.59 ± 4.515*	0.0·07
LDH mg/dl	202.49 ± 14.85	350.52 ± 17.21*	0.0029

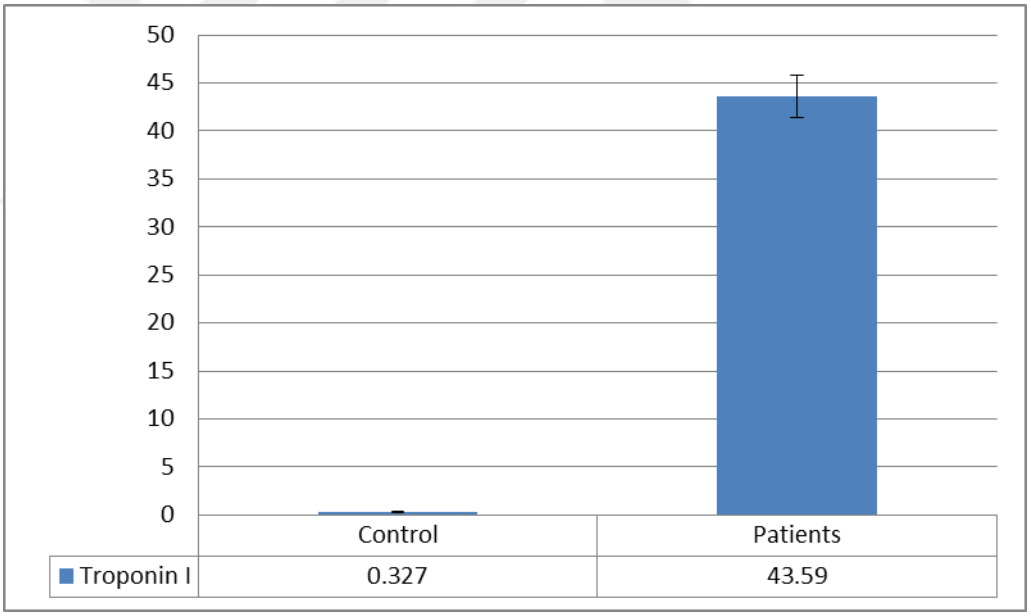

Figure 4.7 Troponin I levels in both groups

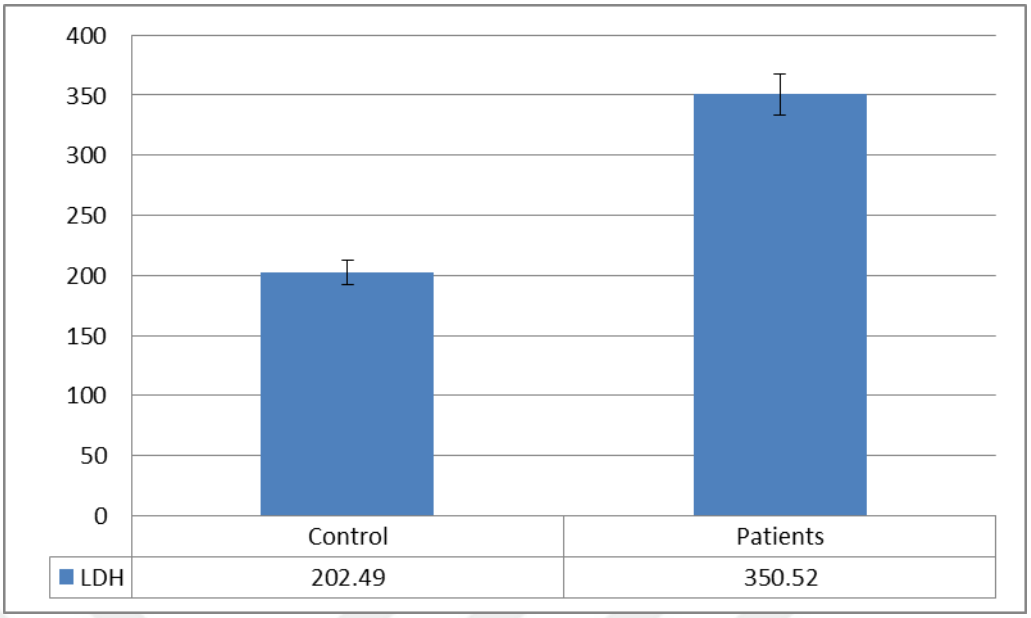

Figure 4.8 LDH levels in both groups

Biomarkers are molecules which occur naturally and can be used as an indicator of a particular disease state or some other physiological state of an organism. Troponins were medium-sized proteins which have an important role in regulating the cardiac muscle contractile elements (myosin and actin) (Cardinale *et al*. 2004). Acute myocarditis, for example, may be diagnosed by analyzing the blood levels of cTnI and cTnT, components of the troponin complex of muscle cells, which are important in determining whether myocardial damage has occurred in a variety of situations, including heart failure (O'brien *et al.* 2006, Kubo *et al.* 2010, Daubert *et al.* 2010).

Otherwise, the current findings indicated a significant ($P<0.05$) rise in LDH levels in the blood of heart disease patients as compared to the control group. Following arteriosclerosis, higher levels of LDH concentration were linked to an increased risk of cardiovascular disease (CVD). This is in line with our study's results, which showed that higher levels of LDH were connected with an increased risk of CVD. There are a number of risk factors for cardiovascular disease (CVD) that have varied impacts on the circulatory system, leading to varying degrees of cell alterations in tissues (such as muscle) and organs (such as the heart, the liver, and kidney) (Cipolla *et al.* 2018, Leska-Mieciek *et al.* 2020). LDH is released into the bloodstream by many cell types, resulting

in a rise in serum LDH levels. When LDH levels rise to a specific point, it means there are major tissue lesions, MI, liver function disorder, or damage to other vital organs.

4.5 Hematological Parameters

Table 4.5 show the count of RBC in heart diseases patients, where count of RBC demonstrated significant (P <0.05) increase in patients (5.739 ± 0.053) compared with control group (5.402 ± 0.095) as shown in Figure 4.9. Hb levels in serum of heart diseases patients demonstrated significant (P <0.05) increase in (15.46 ± 0.065 mg/dl) compared with control group (14.32 ± 0.193 mg/dl) as shown in Figure 4.10. PCV levels in serum of heart diseases patients demonstrated significant (P <0.05) decrease in (51.63 ± 0.851 %) compared with control group (43.08 ± 0.89 %) as shown in Figure 4.11.

Table 4.5 Hematological parameters in studied groups

Groups Parameter	Control (50)	Patients (75)	P-Value
RBC count	5.402 ± 0.095	5.739 ± 0.053*	0.037
Hb mg/dl	14.32 ± 0.193	15.46 ± 0.065*	0.018
PCV %	43.08 ± 0.89	51.63 ± 0.851*	0.0004

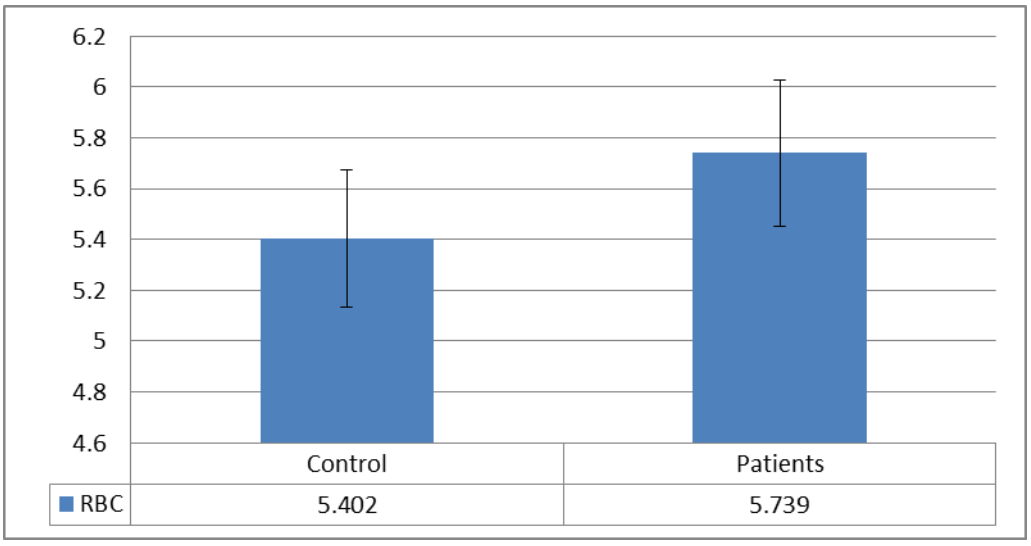

Figure 4.9 RBC count in both groups

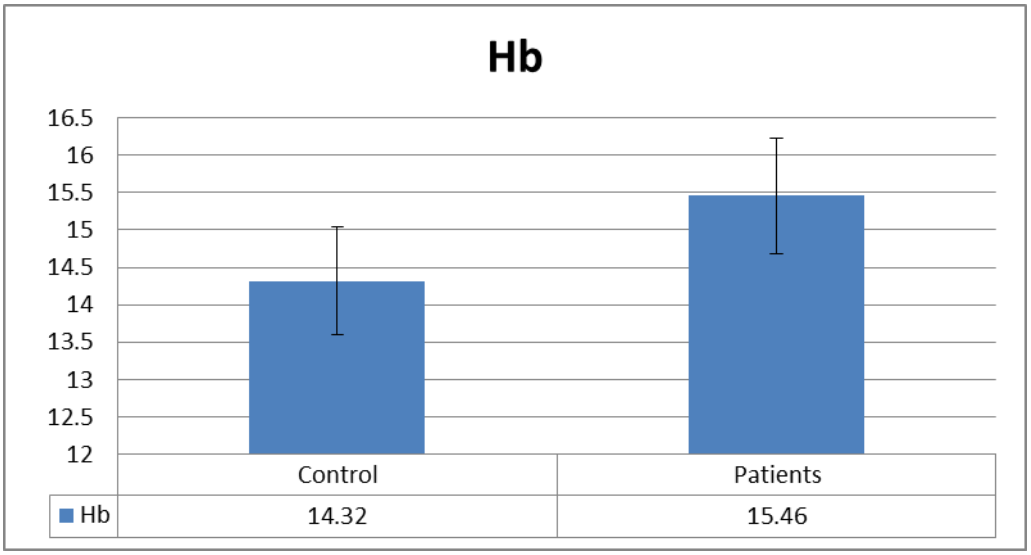

Figure 4.10 Hb concntration in both groups

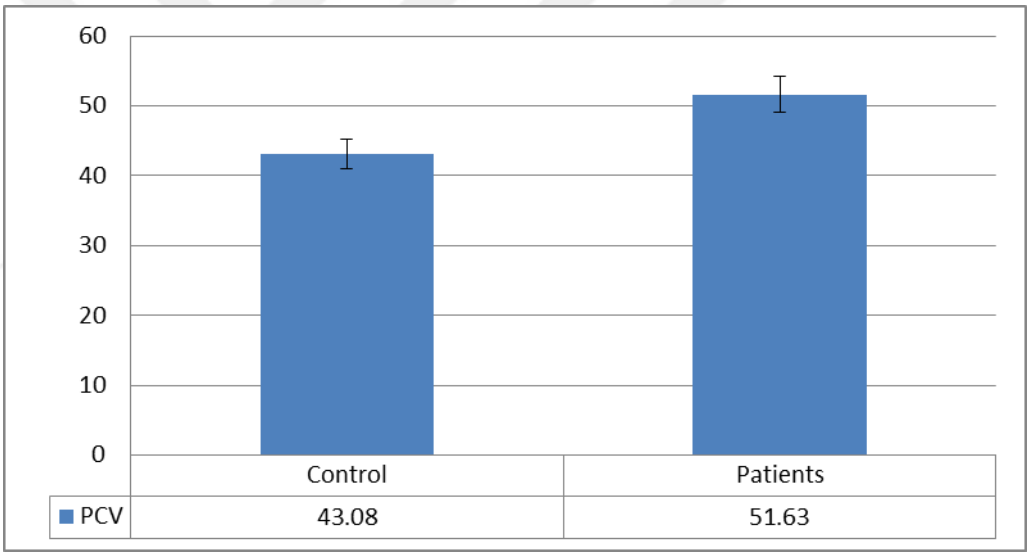

Figure 4.11 PCV in both groups

A elevated blood viscosity has long been thought to be a risk factor for coronary artery disease (Ernst *et al.* 1986, Simone *et al.* 1990). In a recent research, 109 people with ischemic heart disease and 59 healthy people were shown to have greater blood viscosity and fibrinogen concentrations (Kesmarky *et al.* 1998). Conversely, a research by (Chonchol 2008) identified a link between low hemoglobin levels and an increased risk of coronary heart disease. Despite this, our study found that a high hemoglobin

level was related with an increased risk of heart disease. The long-term prognosis of individuals with acute coronary syndrome seems to be affected by changes in their blood cell counts (Papa *et al.* 2008).

The variations in hematological parameters are of interest to me. Heart disease and all-cause mortality may be predicted by the red cell distribution width (RDW), which has been seen in a number of different cardiovascular disorders (CDC 2010). The RDW was also revealed to be a significant independent predictor of all-cause death in the ACS subset of patients in a multivariate model by (Cavusoglu *et al.* 2010). A higher CAD risk class was related with a gradual increase in the RDW value in a work by (Zalawadiya *et al.* 2010), demonstrating that the RDW is a powerful predictor of CAD risk (Tonelli *et al.* 2008) suggest that individuals with CAD and heart failure who had elevated RDW values had a considerably higher death rate than individuals who had RDW levels that were within the normal range.

5. CONCLUSIONS AND RECOMMENDATION

5.1 Conclusions

- In comparison to healthy volunteers, heart attack patients had significantly (P0.05) higher levels of liver enzyme activation, according to the results of this research.

- Patients having heart attacks had significantly (P0.05) higher levels of total cholesterol and HDL cholesterol than healthy individuals, according to the results of the present research.

- There was a significant (P 0.05) difference in calcium and potassium concentrations in heart attack patients as compared to healthy people in this research.

- According to the findings of this study, heart attack patients had considerably greater levels of troponin and LDH than healthy controls (P0.05).

5.2 Recommendation

- Investingating the concentration of types of cytokines in serum of heart attack patients.

- Investingating the concentration of other types of hormones in serum of heart attack patients.

- Investingating the concentration of some interleukins in serum of in serum of heart attack patients.

- Investingating the concentration of Cluster of Differentiation (CD Markers) in serum of COVID-19 patients.

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