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REVIEW ARTICLE - MEDICAL TECHNIQUES

Interpreting Myocardial Enzymatic Biomarkers in the Setting of Acute Myocardial Infraction AMI

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Abstract

The rates of morbidity and mortality for acute myocardial infarction (AMI) have been rising quickly in the last few years. In the systemic circulatory loop, the heart normally pumps blood to the body's extremities. Cardiovascular disease, however, results from any heart function problem. The most fatal diseases in the world are known to be those involving the cardiovascular system. Over the past decade, biochemical marker testing are an important step in the diagnosis, and management of heart failure and in lowering one's risk of developing cardiovascular disease. Early diagnosis is paramount to choosing a clear and effective treatment strategy. Cardiac biomarkers are another effective method for classifying myocardial injury. The myocardial enzymatic biomarkers, also known as myocardial necrosis biomarkers, were among the various biomarkers that were initially studied. This review aims to allow for appropriate management steps to be initiated and more efficient and effective utilization of healthcare resources.

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Keywords: Acute Myocardial Infarction (AMI); Myoglobin; Creatinine Kinas (CK); Lactate Dehydrogenase (LDH); Troponin T (TnT).

1. Introduction

A myocardial infarction (MI) occurs when blood flow to the heart's coronary artery is decreased or interrupted, leading to harm to the heart muscle [1]. According to statistics, roughly 10% of people who visit emergency rooms complaining of chest pain are later found to have had a heart attack [2]. AMI manifests when the atherosclerotic plaque ruptures and clot forms and can be caused by related coronary artery disease or ischemic heart disease. Blockage of the coronary artery, whether partial or whole, prevents the passage of blood to the heart muscle [3,4]. Clinically MI is determined when cardiac biomarkers record an elevated presence of acute myocardial infarction, and there is evidence of acute myocardial ischemia (with the help of patient signs, electrocardiographic changes, or imaging evidence). As seen in Fig. 1 [5], anterior myocardial infarction is linked to decreased blood flow to the anterior wall of the heart and an increase in levels of enzymes, hormones, biological products, and many other indicators of cardiac stress or defect. Myocyte injury collectively known as biomarkers seems to be gaining therapeutic significance [6]. There are many biomarkers to aid the diagnosis of the pathology of cardiovascular medicine as genomics and proteomics help us increase the number of biomarkers. However, perfect biochemical markers for the identification of the pathology of cardiovascular medicine have not been discovered yet. The first vital sign to increase is myocardial necrosis biomarkers which include: CK-MB fraction, Myoglobin, and cardiac troponin [7].

2. Biomarkers of Myocardial Necrosis

Clinical biomarkers are one of the most important aspects of diagnosing heart failure. In terms of definition, biochemical markers testing are clinical futures that identify blood chemicals associated with heart failure, commonly known as a heart attack [8]. Diagnosis and management of heart disease are carried out by several cardiac markers. However, the earliest biomarker in the diagnosis of heart attack is myocardial necrosis biomarkers. These symptoms as a result of an increase in the levels of muscle enzymes include CK or CPK, which is mostly released into the bloodstream from the necrosed myocardial and is present in the cytoplasm of myocytes, [8]. These tests include Myoglobin, Creatinine Kinas (CK), Troponin T or I, lactate dehydrogenase, and Glycogen phosphorylase.

Abbreviations			
AMI	Acute myocardial infarction	GPMM	glycogen phosphorylase isoenzyme MM
AHA	American Heart Association	Hr	Hour
CRP	C-reactive protein	LDH	Lactate dehydrogenase isoenzymes
G1P	glucose-1-phosphate	M-CK	Myoglobin, Creatinine Kinas
GP	Glycogen phosphorylase	RBCs	red blood cells
GPBB	glycogen phosphorylase isoenzyme BB	TnI	Troponin I
GPLL	glycogen phosphorylase isoenzyme LL	ULRR	The upper limit of the reference range

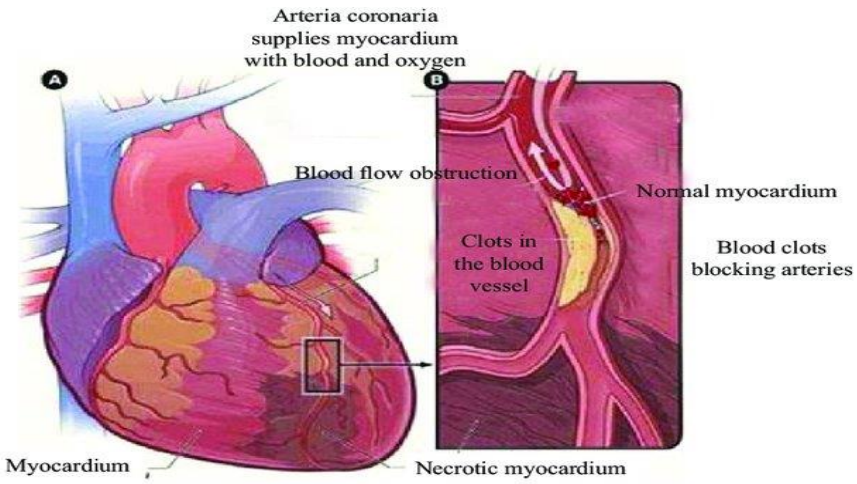

Fig. 1. The figure illustrated the myocardial infarction of the human heart [5]

2.1. Myoglobin

Myoglobin is a small protein consisting of 154 amino acids in a single polypeptide chain. The function of myoglobin is that myoglobin acts as a storehouse for intracellular oxygen concentrations and as a reservoir for oxygen. Haemoglobin is present in the muscle tissue and most mammals, it is related to iron-O_2binding protein, which is found in blood, specifically in the red blood cells (RBS). The presence of myoglobin in the bloodstream is an abnormal finding and indicates injury to the heart muscle [9]. the hem is the small part of protein contributing to the transport of oxygen in muscle tissues and releasing during less than one hour and rises more quickly than peaks of cTn or CK-MB to eight or ten hours, and returns to normal level during one day. Thus, it is specific to the myocardium, it has found use as an excellent negative indicator of myocardial injury. As shown in table 1, If there is no increase can be seen in the levels of serum myoglobin in two samples analyzed 2 to 4 hours apart, it virtually rules out AMI [7]. On the other hand, an increase in the level of myoglobin could refer to many disorder such as that causes weakness of the muscle and loss of skeletal tissue of muscle known as (muscular dystrophy), the Breakdown of muscle tissue that leads to the release of muscle fiber contents into the blood (rhabdomyolysis), general Skeletal muscle inflammation known as myositis, Skeletal muscle trauma, Skeletal muscle ischemia (O_2 deficiency) and it is rare in malignant hyperthermia [8-10].

2.2. Creatine kinase (CK)

Creatine kinase CK is considered one of the most significant biomarkers for AMI. It activates the reverse reaction of converting creatine and ATP to creatine phosphate and ADP (Fig. 2) [11]. The three isoenzyme forms of the muscle enzyme CK are CK-MM, CK-MB, and CK-BB [11]. CK-MM is expressed in Muscle tissue, CK-MB is expressed in cardiac muscle, and CK-BB is expressed in brain tissue. CK-MB is found in the heart muscle, tongue, and diaphragm, and in very little quantities in skeletal muscle [14]. In 1970 radioimmunoassay was discovered [12], and the measurement of CK activity is a more accurate predictor of myocardial infarction. Damage has been a crucial diagnostic factor for the diagnosis of AMI for the last 20 years [13].
Similar to myoglobin, the CK enzyme is the first biomarker to increase. Unlike myoglobin, the elevated level of CK-MB returns to the normal range after two days (Table 1). An increase of 0.5% in the total activity of CK indicates damage to the heart muscle. The abnormal level of CK-MB enzyme is recorded in the bloodstream 4 to 6 hours after the onset of chest pain as shown in table 1. This height reaches the top after 10 or 12 hours of myocardial infarction MI [12]. CK-MB is also of value in the assessment of reperfusion injury. An increase of 1-2 grams indicates myocardial damage. At least ten to twelve hours after the onset of clinical signs should pass for definitive benefit in the diagnosis of AMI. Its specificity is very useful, up to 97%, which increases 10-12 hours after the onset of symptoms of infection. This sensitivity provides sequential tracking of the patient's condition for up to 48 hours [14].

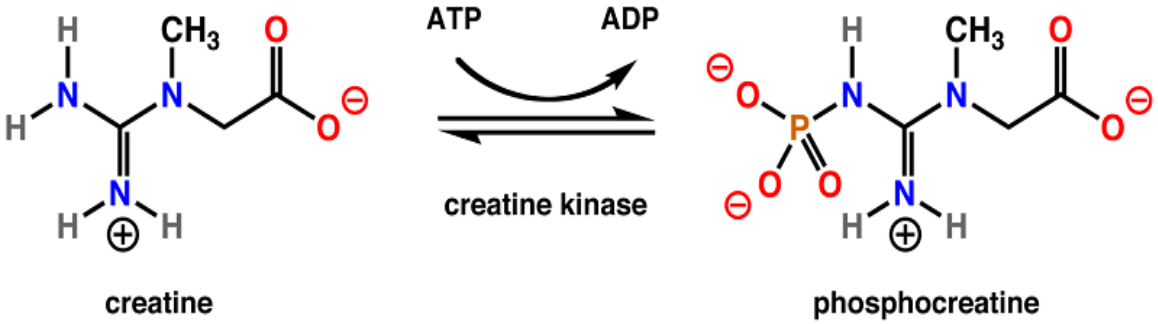

Fig. 2. The figure illustrated the molecular structure of creatin kinase- CK [11]

2.3. Troponin

TnI and TnT, cardiac troponin complex subunits, are now often employed in the diagnosis of AMI. Ebashi et al. identified the troponin complex (Tn) as the structurally heterotrimeric complex that serves as the thin filament's regulatory unit (1967). It controls the contraction of striated muscle via Ca2+. Troponin type C (TnC) is the component that binds to calcium, Troponin type I (TnI) is considered a subunit that acts as an inhibitor, and Troponin type T (TnT) is the subunit that connects or binds to tropomyosin then both make up the 78 kDa protein complex. Actin monomers and the tropomyosin dimer (Tm), along with the troponin complex (Tn), are thought to be the main constituents of thin filaments (Fig. 3). Each Tn complex interacted with the Tm molecule and both bind to seven actin monomers [15].
These proteins bind with tropomyosin to form a complex that functions as the backbone of striated muscle. Both TnI and TnT are considered the ideal biomarkers for diagnosis of AMI because they address various characteristics such as sensitivity, specificity, stability, ease of measurement, and rapidity of result [16, 17]. Myocyte damage leads to an increase in the level of Troponin. It releases into the peripheral blood at different times, first from the cytosolic pool and then from the contractile apparatus (Fig. 4) [18]. Therefore, TnI and TnT reached measurable amounts within 4 to 6 hours after AMI and reach peak levels in 12- 24 hours (Table 1). cTnI levels are high for 2–3 weeks and back to basal levels during three to ten days, while Troponin T remains raised for 24 to 48 hours and then drops to the normal level [19]. The persistent increase of cTn from the contractile system in the late stage is the cause of the prolonged rise of serum troponin (Fig. 4). To rule out heart disease in patients with chest symptoms, point-of-care testers are frequently employed in hospitals [19, 20].

2.4. Lactate dehydrogenase (LDH)

Lactate dehydrogenase isoenzymes (LDH) were widely used in the past for the diagnosis of myocardial infarction. However, more recently, due to the availability of troponin immunoassays, the lactate dehydrogenase isoenzyme test has been mostly used in evaluating certain liver diseases [22]. LDH is an enzyme found in the cytoplasm of all the cells of the body. LDH can exist in five forms, each isoenzyme different from another in the structure and concentrations in different tissues including red blood cells, cardiac myocytes heart muscle, white blood cells, lung tissue, pancreas, kidney, hepatic and skeletal muscle. Therefore, LDH1 present in the heart is not specific for the diagnosis of heart diseases [21, 17]. It can be released from RBC and also be found in other tissues or organs such as the kidney, skeletal muscle, brain, pancreas, and stomach. Usually, levels of LDH isoenzyme raise within 24–72 hrs following myocardial infarction and the concentration of LDH reach a peak during 3–4 days then returns to the normal level during eight to fourteen days and then. That is why the level of LDH used distinguishes between acute (occurring less than 30 days,) from subacute (occurring between 30 days and 1 year) Myocardial infarction (MI) in patients with late-stage, after a few days of chest pain history.

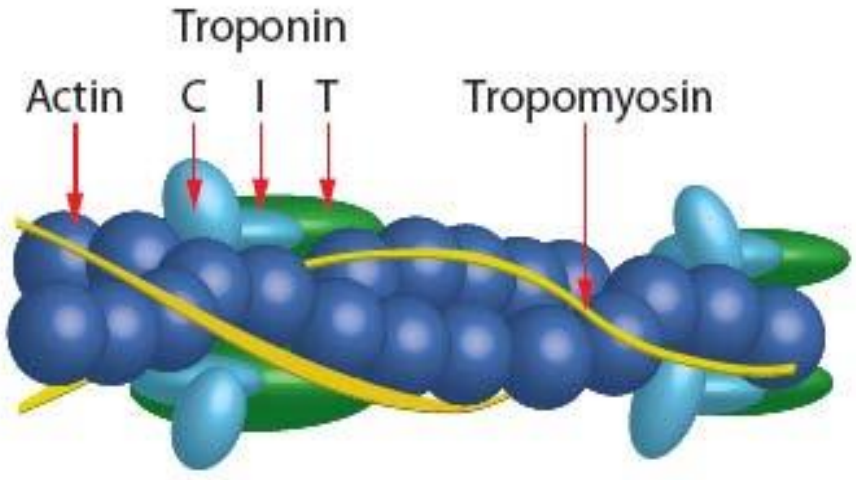

Fig. 3. Cardiac troponins consist of three types of proteins: Troponin type I (TnI), Troponin type C (TnC), and type Troponin C (TnT) [15]

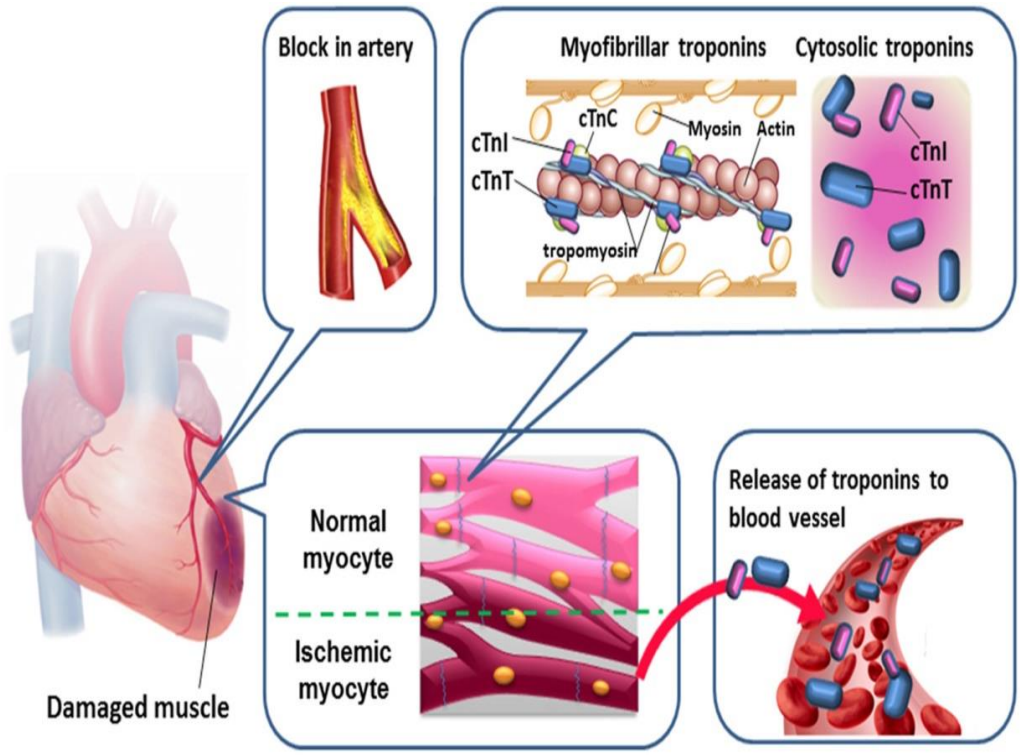

Fig. 4. The figure illustrates the Myocyte damage and increased level of Troponin in blood vessels [18]

Table 1. Cardiac biomarker and time course after Serial assay of AMI [21]

	Biomarkers of Myocardial Necrosis			
	Myoglobin mg/dl	CK-MB ug/ml	Troponin I ng/L	Troponin T ng/L
Detectable of ULRR (hr)	1-3	3-8	3-6	3-6
Peak of ULRR(hr)	6-9	1-12	12-24	12-48
Duration of ULRR(days)	≤ 1	1-2	5-9	7-14
Normal Value(days)	≤ 1	3	7	14
Specificity (%)	---	68	95	95
Sensitivity (%)	---	95	89	89

Abbreviations: AMI, acute myocardial infarction; ULRR, the upper limit of the reference range; hr, hour

2.5. Glycogen phosphorylase (GP)

Glycogen phosphorylase is one of the phosphorylase enzymes in the glycogenolysis process. It dominates the rate-limiting step by releasing the glucose subunit [glucose-1-phosphate (G1P)] from the terminal alpha-1,4-glycosidic bond as shown below [23].

(α-1,4 glycogen chain) n + Pi ⇌ (α-1,4 glycogen chain) n-1 + α-D-glucose-1-phosphate.

There are three different GP isoenzymes: GPMM (glycogen phosphorylase isoenzyme MM) is primarily found in human skeletal muscle; GPLL (glycogen phosphorylase isoenzyme LL) is primarily found in the liver and all other organs except the heart, skeletal muscle, and brain; and GPBB (glycogen phosphorylase isoenzyme BB) is primarily produced by brain and heart [23]. When brain damage and the resulting disruption of the blood-brain barrier have been ruled out, an increase in GPBB in the serum should be highly selective for myocardial injury [24]. GPBB is the most sensitive and specific biomarker to detect myocardial infarction when compared to other parameters such as myoglobin and CKMB cardiac markers and GPBB. GPBB was statistically higher in patients with AMI within 4 h of chest pain when compared to that of healthy controls [25].

3. Discussion

There are many tests used in the diagnosis and management of AMI, but the search for an ideal test is a goal of a lot of research that is still ongoing. Ideal biomarkers need to cover. Firstly, it should be highly sensitive so that it can detect the least damage to the heart. Secondly, it must be very specific to the cardiac muscle. Thirdly, it should diagnose the degree of disease in terms of the severity of the infarction, whether the infarction is reversible or non-reversible, and measures the degree of recovery from the disease. Additionally, optimal biomarkers also must be easy to measure, quick, cheap, and quantitative [26-28]. Based on the above, we will discuss the characteristics of the biomarker for diagnosis of AMI which include myoglobin, creatine kinase CK-MB, and cardiac troponin I and T (Table 1).

The most sensitive substance is troponin [27-31]. It gets into the blood after a heart attack. Until all other indicators return to normal levels, it also remains in the bloodstream for several days. The levels of troponin T and I, which come in both forms, are far more specific to cardiac function than creatine kinase-MB [31, 32]. It is the best biomarker for detecting a heart attack, according to the most recent American Heart Association (AHA) recommendations. The AHA advises using the other biomarkers sparingly. These include myoglobin, CK, and CK-MB [32, 33]. Both CK and CK-MB can be measured many times over one day if the patient had a heart attack. However, CK is not very specific because its levels can go up in many other conditions besides a heart attack. GPBB is found in normal tissues of the brain and myocardium. At the same time, it effectively contributes to the early diagnosis and early detection of acute myocardial infarction compared to other parameters [25].

4. Conclusion

This review has focused on some biomarkers which became important to the diagnosis of acute myocardial infarction. These biomarkers include myoglobin, creatine-kinase-MB, troponin, lactate dehydrogenase isoenzymes, and glycogen phosphorylase. In recent years, Troponin replaced CK-MB and LDH markers for diagnosing an acute myocardial infarction. For the GPBB, science still needs more evidence to consider it a standard cardiac biomarker used for the early diagnosis of MI. Over time, it has become evident that early diagnosis of AMI is crucial to have the most possible benefit from treatment and follow-up with the patients. In conclusion, cardiac biomarker analysis is a key component of the front-line diagnostic process for AMI, enabling doctors to make an accurate diagnosis and initiate effective treatment plans quickly, significantly lowering mortality. Cardiovascular troponin I and cardiac troponin C are class I recommendations for AMI prognosis and detection, according to the majority of recent research.

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References

[1] Reindl M, Reinstadler SJ, Feistritzer HJ, et al. Acute myocardial infarction as a manifestation of systemic vasculitis. Wien Klin Wochenschr. 2016; 128(21-22):841–843.
[2] Haasenritter J, Stanze D, Widera G, et al. Does the patient with chest pain have coronary heart disease? Diagnostic value of single symptoms and signs--a meta-analysis. Croat Med J. 2012;53(5):432–441.
[3] Liakos M, Parikh PB. Gender disparities in presentation, management, and outcomes of acute myocardial infarction. Curr Cardiol Rep. 2018; 20(8):64.
[4] Aydin S, Aydin S. Irisin concentrations as a myocardial biomarker. In: Patel VB, Preedy VR, editors. Biomarkers in Cardiovascular Disease. Dordrecht: Springer; 2016. pp. 489–504.
[5] G. Yao et al. Comparative study of ticagrelor and clopidogrel in therapeutic effect of acute myocardial infarction patients undergoing percutaneous coronary intervention. Saudi Journal of Biological Sciences. 2017; 24: 1818–1820.
[6] J. Boeddinghaus, T. Reichlin, T. Nestelberger, et al., "Early diagnosis of acute myocardial infarction in patients with mild elevations of cardiac troponin," Clinical Research in Cardiology. 2017; 106(6): 457–467, 2017.
[7] Chaulin, Aleksey M., Duplyakov, Dmitry V. Biomarkers of acute myocardial infarction: diagnostic and prognostic value. Journal of Clinical Practice. 2020; 11(3): 75-84.
[8] Yuqi Chen, Yifei Tao, Lan Zhang, Weiting Xu, Xiang Zhou. Diagnostic and prognostic value of biomarkers in acute myocardial infarction. Postgrad Med J 2019;95:210–216.
[9] Rachel Jacob and Mahmood Khan: Cardiac Biomarkers: What Is and What Can Be, Indian J Cardiovasc Dis Women-WINCARS 2018;3:240–244.
[10] McLeish MJ, Kenyon GL. Relating structure to mechanism in creatine kinase. Crit Rev Biochem Mol Biol. 2005;40(1):1–20.
[11] Bong SM, Moon JH, Nam KH, Lee KS, Chi YM, Hwang KY. Structural studies of human brain-type creatine kinase complexed with the ADP-Mg2+-NO3- -creatine transition-state analogue complex". FEBS Letters.2008, 582 (28): 3959–65. doi:10.1016/j.febslet.2008.10.039. PMID 18977227.
[12] Wallimann T, WKnudsen J, Steenstrup B, Byrjalsen I, Hildebrandt P, Sørensen S. At what level of serum total creatine kinase activity can measurement of serum creatine kinase MB isoenzyme activity be omitted in suspected myocardial infarction? Scand J Clin Lab Invest. 1989;49(7):661–665.
[13] Kim S, Um TH, Cho CR, Jeon JS. False-positive elevation of creatine kinase MB mass concentrations caused by macromolecules in a patient who underwent nephrectomy for renal cell carcinoma. Ann Lab Med. 2014;34(5):405–407.
[14] N. Kume, H. Mit-suoka, K. Hayashida and M. Tanaka, “Pentraxin 3 as a Biomarker for Acute Coronary Syndrome: Comparison with Biomarkers for Cardiac Damage,” Journal of Cardiology, Vol. 58, No. 1, 2011, pp. 38-45. doi:10.1016/j.jjcc.2011.03.006.
[15] Nicola J.Kluger MB and ChBMalcolm E.LeggetMD. Emerging Biomarkers in Acute Coronary Syndromes. A Pathophysiologic Perspective. 2022; 31(6): 779-786.
[16] Suleyman Aydin, Kader Ugur, Suna Aydin, et al. Biomarkers in acute myocardial infarction: current perspectives. Vascular Health and Risk Management. 2019; 15:1-10.
[17] Korff S, Katus HA, Giannitsis E. Differential diagnosis of elevated troponins. Heart. 2006;92(7):987–993.
[18] Peacock WF, Baumann BM, Bruton D., et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. JAMA Cardiol 2018;3(2):104–111.
[19] Aydin S, Aydin S. Irisin concentrations as a myocardial biomarker. In: Patel VB, Preedy VR, editors. Biomarkers in Cardiovascular Disease. Dordrecht: Springer. 2016;489–504.
[20] Holmes RS., Goldberg E. Computational analyses of mammalian lactate dehydrogenases: human, mouse, opossum and platypus LDHs. Computational Biology and Chemistry.2009, 33 (5): 379–85. doi:10.1016/j.compbiolchem.2009.07.006. PMC

[21] Heinova D, Rosival I, Avidar Y, Bogin E. Lactate dehydrogenaseisoenzyme distribution and patterns in chicken organs. Res Vet Sci.1999;67(3):309–312.
[22] Livanova NB., Chebotareva NA., Eronina TB., Kurganov BI. Pyridoxal 5'-phosphate as a catalytic and conformational cofactor of muscle glycogen phosphorylase B. Biochemistry. Biokhimiia. 2002; 67 (10): 1089–98. doi:10.1023/A:1020978825802.
[23] Lippi G, Montagnana M, Salvagno GL, Guidi GC. Potential value for new diagnostic markers in the early recognition of acute coronary syndromes. CJEM. 2006;8:27–31.
[24] Neelima S., Vedika R., Roshan K., and Puneet R. Glycogen Phosphorylase BB: A more Sensitive and Specific Marker than Other Cardiac Markers for Early Diagnosis of Acute Myocardial Infarction. Indian J Clin Biochem. 2018 Jul; 33(3): 356–360. Published online 2017 Aug 3. doi: 10.1007/s12291-017-0685-y.
[25] Khan IA, Wattanasuwan N. Role of biochemical markers in diagnosis of myocardial infarction. Int J Cardiol. 2005;104(2):238–240.
[26] Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R. National academy of clinical biochemistry standards of laboratory practice: recommendations for the use of cardiac markers in coronary Clin Chem; 1999 Jul;45(7):1104-21.
[27] Sheref A., Ahmed K, Debvarsha M, Mounika V, Ahmed E, Tamam M.Copeptin plus troponin in the rapid rule out of acute myocardial infarction and prognostic value on post-myocardial infarction outcomes: a systematic review and diagnostic accuracy study. Heart Vessels, 2022; 6. doi: 10.1007/s00380-022-02123-x.
[28] Richard O., Saadu H. and Chinanu L.Acute Myocardial Infarction (AMI) Diagnosis; Impact of Technology in Developing Highly Sensitive Biomarkers and Assays. Cardiology and Angiology. 2022; 11(4): 124-134.
[29] Westermann D, Neumann JT, Sörensen NA, Blankenberg S. High-sensitivity assays for troponin in patients with cardiac disease. Nat Rev Cardiol 2017;14(8):472–483.
[30] Peacock WF, Baumann BM, Bruton D, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. JAMA Cardiol. 2018; 3(2):104–111.
[31] Shah AS, McAllister DA, Mills R, et al. Sensitive troponin assay and the classification of myocardial infarction. Am J Med. 2015;128(5): 493–501.
[32] Neumann JT, Sörensen NA, Ojeda F, et al. Early diagnosis of acute myocardial infarction using high-sensitivity troponin I. PLoS One. 2017;12(3):e0174288.
[33] Yader Sandoval, Bradley R. Lewis, Ramila A. Mehta, Olatunde O., Jonathan D. Knott. Rapid Exclusion of Acute Myocardial Injury and Infarction With a Single High-Sensitivity Cardiac Troponin T in the Emergency Department: A Multicenter United States Evaluation. Circulation. 2022;1.