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Review

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The Importance of the Troponin Biomarker in Myocardial Infarction

Masoud Negahdary[1], Seyedeh Mahdieh Namayandeh[1], Mostafa Behjati-Ardekani[1*], Samira Ghobadzadeh[2], Hamideh Dehghani[1], Mohammad Hossein Soltani[1]

[1] Yazd Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[2] Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

*Correspondence should be addressed to Mostafa Behjati-Ardekani , Yazd Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; Tell: +983535231421; Fax: +983535231421; Email: dr_behjati@yahoo.com.

ABSTRACT

The significant increase of deaths due to myocardial infarction (MI) is directly related to lifestyle and the increase of the level of its risk factors. The efforts of researchers have recently focused on finding ways to prevent and reduce the damages occurred after the occurrence of MI. Currently, the focus on measuring cardiac biomarkers has an important role in early diagnosis and prevention of irreparable damages of cardiac myocard. This study has explored the cardiac biomarkers troponin I (TnI) and troponin T (TnT) in terms of structures and their important role in MI. Also, the importance of measuring troponin, measurement methods and a comparison among different measurement methods are pointed out. Finally, the new methods and approaches for measuring and comparing new measurement methods, their advantages and properties are mentioned.

Key words: Troponin I, Troponin T, Myocardial Infarction, Cardiac biomarkers

1. INTRODUCTION

Yearly, around 1730000 individuals die cause of cardiovascular diseases and 7254000 of these individuals die due to MI (1). The MI risk factors (smoking, inappropriate diet, low physical activity, hypertension, obesity, high cholesterol and high blood sugar) have a very significant role in occurrence of this disease (2-5). The coronary ischemia over 30 minutes, leading to injury, and if it continued, will causing irreversible damage and necrosis of myocardial cells (6). There is a direct relationship between the increasing in troponin level and mortality after MI (7). whatever diagnosis of MI occurs later or be gap between onset chest pain symptoms and reperfusion, these increases mortality of patients (8). Infarction size is an important determinant for prognosis in patients (9); And efforts to reduce the size of the infarcted area is possible through reperfusion for coronary artery and myocardial cells (10). Unfortunately, in many hospitals the time required for the measurement of cardiac biomarkers by the laboratory is between 60-90 minutes, and this would be limit the usefulness of the measurement (using current techniques) cardiac biomarkers in the emergency room where the first time admission done for patients with acute coronary syndrome signs (11). Coronary reperfusion is possible in two ways (with thrombolytic therapy or percutaneous coronary intervention (PCI)). Given the importance of coronary reperfusion time in MI, the time less than or equal to 30 minutes is important for treatment of thrombolytic therapy (pharmacological reperfusion) and the time less than or equal to 90 minutes is important also for stenting till the size of the infarcted area be limited (12). Diagnosis of MI requires accurate clinical assessment, especially in examining chest pain, and accurate electrocardiogram interpretation (13). The relationship between damage to cardiac myocytes and increase the level of cardiac biomarkers has been discovered recently (14-17). The term biomarker as a term in Medical Subject Headings (MeSh) was defined in 1989 as follows: measurable biological parameters (e.g. a specific enzyme concentration, a specific hormone concentration, the distribution of the phenotype of a specific gene in a population and presence of biological materials) that are used as indices for assessment of health and factors related to physiology such as the risk of diseases, mental disorders, being exposed to

the environment and its impact, diseases diagnosis, diagnosis of metabolic processes, drug abuse diagnosis, diagnosis of pregnancy, cell line development, development of epidemiological studies, etc. (18). Cardiac biomarkers act as an important tool in diagnosis of the extent of MI after the occurrence of cardiac ischemia and damage to cardiac myocytes. The biomarkers creatine kinase (CK), CK-MB, myoglobin, TnI and TnT are released into the patient's blood after damaging to myocardial cells (19-23). Though some of these protein structures (creatine kinase, CK-MB, myoglobin) are nonspecific and are found in other muscular tissue too, cardiac TnI and TnT are completely specific and are only found in the heart (24). Different cardiac biomarkers are shown in Figure 1. The lack of TnI and TnT only indicate the lack of damage to cardiac myocytes and does not indicate the lack of a cardiac disease (25-27). If MI is suspected in a patient and the patient has a favorable cardiogram and negative troponin test result, ischemia modified albumin (IMA) test can be used (28, 29). Diagnosis of natriuretic peptides is recommended in the cases of patient's breathlessness and heart failure (30-32). For management of atherosclerosis risk factors, diagnosis and measurement of the level of C-reactive protein (CRP), lipids (cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)) and lipoprotein-associated phospholipase A2 are recommended (33-35).

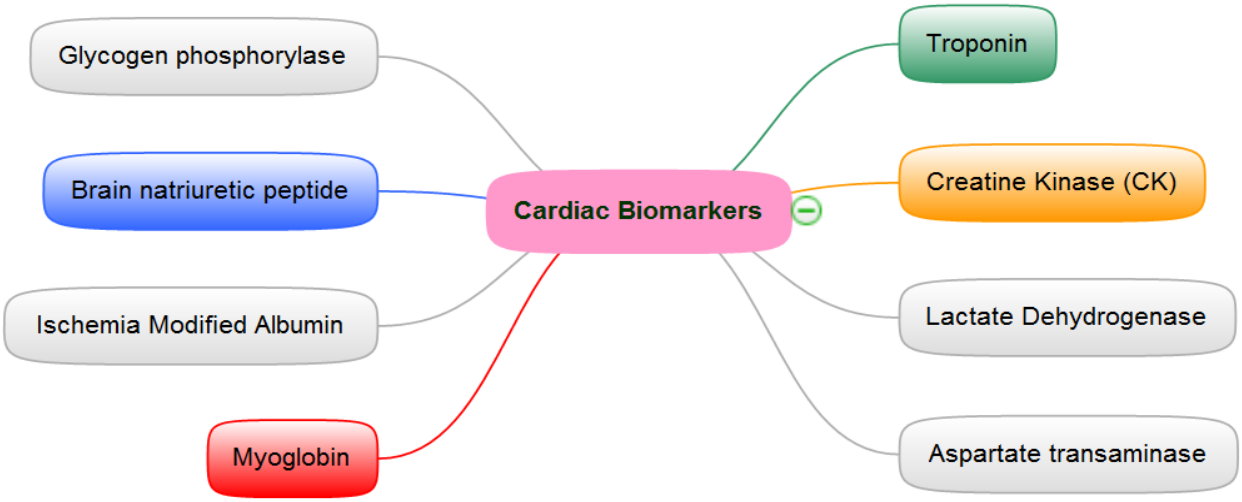

Figure 1. Cardiac biomarkers that those are effective in diagnosis of damage to myocard after MI

Increase of the patients troponin levels together with clinical characteristics act as the best tool for diagnosis of damage to myocard (36-38). The advantages of troponin compared with other cardiac biomarkers are as follows: 1. Troponin provides the most extensive diagnostic window in 4 to 5 days after acute myocardial infarction (AMI); 2. The concentration peak of the released troponin has a clear dependence on the cardiac damage level and this factor can be used quantitatively; 3. Among the cardiac biomarkers, troponin has the highest stability in the blood (6 to 10 days) while myoglobin is eliminated from the blood after 24 hours and creatine kinase is eliminated after 36 hours. 4. Troponin is the best diagnostic biomarker in minor cardiac damages, especially unstable angina. Troponin includes a set of three protein subunits (TnI, TnT and troponin C (TnC)) (Figure 2) (39, 40).

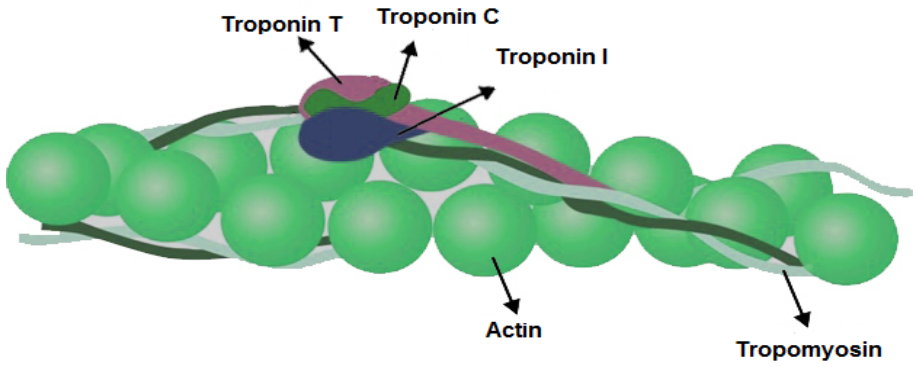

Figure 2. 3D structure of Troponin complex; Troponin is a protein that controls the connection between actin and myosin by calcium and has a significance role in contractions of different muscles including the heart muscle. The three subunits of troponin create a set that regulates the interaction between actin and myosin. These three troponin subunits are: TnC (the element connected to calcium), TnI (inhibiting element), TnT (the

unit connected to tropomyosin).

Troponin is found in both skeletal muscles and myocardium. TnT connects troponin complex to tropomyosin; TnI inhibits actomyosin ATPase using calcium concentration changes. TnC with having four points ached to calcium acts as intermediary in the dependency of troponin to calcium (39, 40). The levels of TnI and TnT are increased in the patient's blood after damaging to the myocardium due to MI. In cytosol, TnT is found in free and attached forms (41). Free TnT is the complete source of the troponin related in the blood after the first stage of damage to the myocardium (42). The attached TnT is released in the later stages of damage to the myocardium. In irreversible damages to myocardium the destruction of myofibrils occurs and this in turn results in MI; After the first necrosis in myocardium, the level of troponin is increased in 2 to 4 hours and this increase is usually maintained for 14 days (43, 44). The high level of troponin for a long time in the blood of patients with heart attack that visit treatment centers late has a diagnosis value for confirmation/rejection of MI (45). There is a direct relationship between the released levels of troponin and damage to myocardium (36). In most cases, undergoing tests for determining the levels of troponin is recommended after chest pain and suspected heart attack cases. If there is no heart attack and cardiac ischemia, the values mentioned in Table 1 are defined for TnI and TnT (46, 47).

Table 1. The characteristics (molecular weight, specificity, time for reaching the maximum peak and cut off) of TnI and TnT

Troponin type	Molecular weight (kDa)	Specificity	Time of reaching the maximum peak	Cutoff normal value range
TnT	23.5	high	12 to 24 hours	0 to 0.1 µg/L
TnI	37	high	12 to 24 hours	< 10 µg/L

In most patients who have had heart attack the troponin values are increased in 6 hours and in all patients who have had heart attack the troponin level is definitely increased after 12 hours (48, 49). In addition to damage to myocardium, increase in troponin level can be due to the following reasons (Table 2).

Table 2. Increase of troponin values in all cases except damage to myocardium

Row	The creation factor of increase level of troponin	References
1	Tachycardia	(50)
2	Hard exercises such as Marathon	(51)
3	Pulmonary embolism	(52)
4	Cardiomyopathy	(53)
5	Myocarditis	(27)
6	Trauma caused to heart damage eg. accident	(54)
7	Chronic kidney disease	(55)
8	Congestive heart failure	(56)
9	Open Heart Surgery	(57)
10	Coronary artery spasm	(58)
11	Pulmonary hypertension	(59)
12	Angioplasty / Stenting	(60)
13	Radiofrequency ablation	(61)
14	Defibrillators/ Cardioversion	(62)

As measuring the troponin value is done through blood samples taken from patients, the following cases can challenge blood sampling (Table 3).

Table 3. Challenge blood sampling agents

Row	Challenge agent	References
1	The differences of the diameter of arteries in different individuals	(63)
2	Excessive bleeding	(64)
3	Faint	(65)
4	Hematoma (collection of blood outside blood vessels)	(66)
5	Pollution	(67)

2. THE MECHANISM FOR RELEASE OF TROPONIN IN BLOOD CIRCULATION

The proposed mechanism to release cardiac troponin include (Figure 3):

1) *Apoptosis*
2) *Normal myocyte turnover*
3) *Cellular release of products of proteolytic degradation process*
4) *Cell wall permeability increase*
5) *Creation and release through membranous blebs*

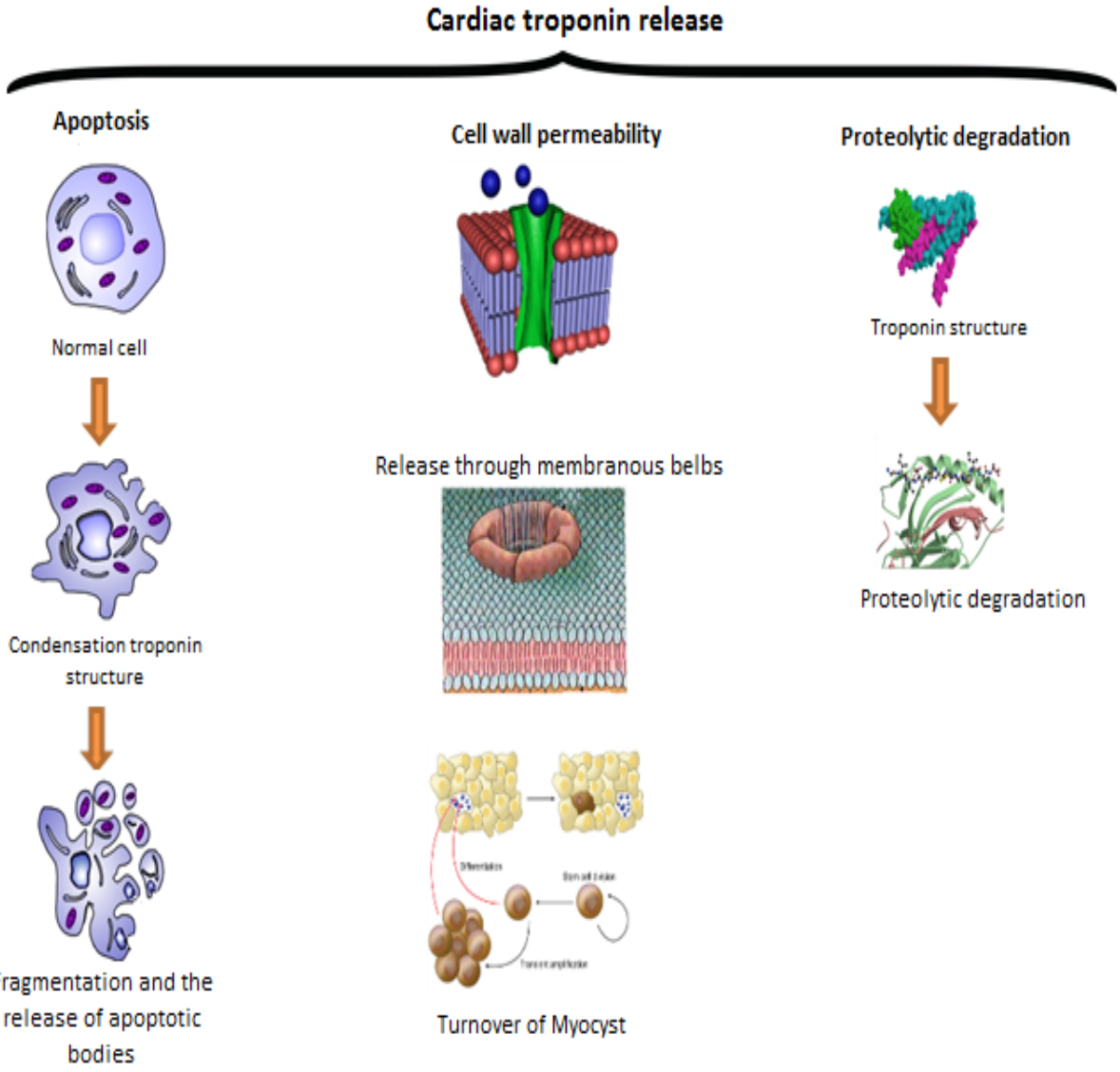

Figure 3. The proposed mechanism to release cardiac troponin

3. TNT (PROPERTIES, CHARACTERISTICS AND BIOCHEMISTRY)

There is most cardiac TnT in the contractile apparatus (about 10 mg/g tissue) that is released through proteolytic degradation (68). About 6 to 8 percent of the cardiac TnT exists as free cytosolic element and no accurate value can be determined for it as tissues with different sources (such as the tissue of the individual donating the organ, tissue of dead bodies or atrial tissue) have been used in the conducted studies (69). Releasing Cardiac TnT happens during an ischemia through a cytosolic chain. Currently, accepted evidence confirm that releasing the cardiac TnT occurs due to irreversible cell death (70). Of course there are some reports regarding the release of cardiac troponin in reversible ischemic damages (71). The half-life of cardiac TnT in blood stream is about 120 minutes and considering the continuous release from myofibril chain (as contractile system in degrading cells during necrosis), it creates a long detection range (72). The cleaning process and the destruction of the remaining of cardiac TnT are not known yet. Ethylenediaminetetraacetic acid (EDTA) is used as the breaker of troponin structure into subunits for

measuring cardiac TnT and it seems that the effect of this matter is minimum in measuring cardiac TnT (73); while the difference between serum and plasma has been reported in some methods for measuring cardiac TnI (74, 75). The initial reports showed that there is a changing difference between the values of cardiac TnT and TnI for serum and plasma treated with Heparin (74). Of course, this aforementioned difference has been corrected by new measurements of cardiac TnT (76, 77). In samples of patients it seems that cardiac TnT is highly stable; not only in room temperature and temperature of 4 ^{o}C but even if it freezes and thaws repeatedly (the samples did not show significant change after 5 times of freezing-thawing cycle) (78). Three different types of isoforms of TnT have been discovered so far in cardiac muscle, fast-twitch skeletal muscles and slow-twitch skeletal muscles that are encoded by specific genes (79). There is a high-level of homology between skeletal TnT and cardiac TnT in terms of sequence and the number of amino acids (80, 81). In fast twitch skeletal muscle TnT there are 125 different amino acids, compared with TnT in cardiac muscle (56.6%); also, in TnT related to slow twitch skeletal muscle, there are 120 different amino acids, compared with TnT in cardiac muscle (58.3%); The potential impact of the reconstruction of growing cardiac and skeletal muscles on gene expression has been explored in different reactions in different isoforms of TnT (79, 82). The use of a specific antibody pair for cardiac TnT indicated that there was no evidence of the isoform of cardiac TnT with TnT in the skeletal muscle of patients with kidney disease. The existence of a fetal exon similar to the completely homogenous with an exon in fast twitch skeletal muscle TnT and cardiac TnT may verify the previous reports related to the occurrence of cross-reactivity in immunohistochemical studies which anti-cardiac TnT antibodies have been used (83).

4. TNI (PROPERTIES, CHARACTERISTICS AND BIOCHEMISTRY)

The TnI cardiac biomarker is made in cardiac muscular tissue and is a single-stranded isoform consisted of 209 amino acid sequences and its molecular weight is about 23-24 kDa (84). There are three isoforms of TnI (cardiac TnI, fast twitch skeletal muscle TnI and slow twitch skeletal muscle TnI) (85, 86). The overlap between sequences of amino acid in cardiac TnI and slow-twitch skeletal muscle TnI is 40 % and the overlap between sequences of amino acid in cardiac TnI and fast-twitch skeletal muscle TnI is higher (87, 88). Therefore, it is necessary to test the antibody that is selected for measuring cardiac TnI and to ensure that the antibody that no interaction with the skeletal isoforms of this protein. Cardiac TnI molecule has two serines that can be phosphorylated by protein kinase A in *in vivo* conditions (89, 90). Therefore, dephosphorylated, monophosphorilated and biphosphororilated forms of this protein can exist in a cell. The phosphorylation of cardiac TnI results in the change of the conformation of this protein and changes its interactions with other related troponins and antibodies. A significant amount of the cardiac TnI released in the patient's blood circulation is phosphorylated (91, 92). However, other isoforms containing changes after translation, such as: oxidated state, reduced state and digested by proteases have also been identified in the blood circulation. Cardiac TnI is found mostly in the contractile system (about 4-6 mg/g tissue) and is released mostly by the proteolytic destruction but there are 2 to 8 % of it in the form of free cytosolic compound (93, 94). The first immunoassay method for cardiac TnI was explained by Cummins et al. (95, 96). The first commercial measurement device for cardiac TnI called Stratus I analyzer was produced in 1987 (97, 98). The immunoassay method for cardiac TnI have significantly changed in the last two decades (99, 100). The new cardiac TnI immunoassay methods have hundreds of times more detection power, compared with older methods. Specific monoclonal antibodies related to several selected epitopes of the cardiac TnI are able to detect all known changes in the circulation (101, 102). Various forms of used antigen as the standard or precision instruments lead to improve multiple correlation coefficients between the various commercial measurements, but have not yet been standardized. Manufacturers of cardiac TnI assay systems are trying to find a way to create an integrated and standard system for the measurement of cardiac TnI (103, 104). The most commonly reason for the difference measurement of cardiac TnI, is the difference in the epitopes specificity of the used antibodies in various assay methods (105). It is noteworthy that the measurement of cardiac TnI is influenced by interfering factors such as proteolytic degradation and phosphorylation as well as complex formation with other molecules (such as heparin, TnC, heterophile antibodies, etc.) (106). The used polyclonal and monoclonal antibodies in the cardiac TnI assay methods categorize to varying types due to the impact of the aforementioned factors. Therefore, the use of measurement systems that are providers specific antibodies to epitopes in the central region of the troponin molecule is very important; because in this state the assay system does not influence by mentioned interfering factors (107). Monoclonal antibodies producer companies are trying to offer a best assay method for cardiac TnI; these companies had concluded that now there is no possibility of a single antibody pairs (e.g. detection antibody and capture antibody) and if the fulfillment of this, the effect of interfering factors will disappear and the sensitivity and specificity of cardiac TnI assay will rise (108). It seems that the combination of monoclonal antibodies can lead to increase accuracy in this type of cardiac TnI assay system and so the detection and capture monoclonal antibodies can be used in conjugated state with a specific label (93, 109). If interested to use of this method, monoclonal antibodies should be selected so that if one of these monoclonal antibodies (detection antibody or capture

antibody) is sensitive to the presence of an antigen in a sample, other monoclonal antibodies be insensitive to that specific antigen (110). Therefore, the positive or negative interference effect is minimized. In addition, the antibodies used in the assay, should be specific to cardiac isoform's troponin and also should not have interaction with two isoforms of troponin in skeletal muscle (84). Specificity of antibodies is different according to various parts of a molecule, for example, the purified cardiac TnI is very susceptible to proteolytic degradation; however, the central region of this biomarker reacts perfectly with TnC in troponin complex and this factor protects cardiac TnI from proteolytic degradation (111); And as a result the epitopes that located in the central region of cardiac TnI molecule are significantly more stable than the epitopes that are located in the endpoints. Simultaneously TnC for binding to cardiac TnI compete with antibodies and only a small number of specific antibodies to central region of cardiac TnI can detect a combination form of TnC-cardiac TnI (112). It was recently shown that cardiac TnI can be cleaved by proteases androgens during the incubation process in necrosed myocard after AMI and thus a mixture of cardiac TnI molecule and its proteolytic fragments can be detected after the first chest pain within hours in the bloodstream (108, 113). However, the ratio of molecular fragments against normal troponin molecules, the size of fragments, relationship of fragments with infarction and also there are many other questions that need to find definitive conclusions. Given that about 95% of cardiac TnI in the blood is found in combination with TnC, the used antibodies for the detection of cardiac TnI should have ability to detect cardiac TnI in combination with TnC in the blood and in the ideal state the used assay system should be capable to detect all forms of cardiac troponin in the bloodstream (114, 115).

5. EVALUATION METHODS IN TROPONIN ASSAY

With advances in technology, a new generation is emerging for troponin Assay (72, 116). Syne the troponin assay has been used in patients as a diagnostic and prognostic method (117); in addition, existing detection methods for troponin lead to risk stratification, guide triage decisions and help in the choice of treatment (118). High-sensitivity troponin assay represents an important advance in diagnosis and sensitivity of this method to myocyte necrosis but obtained results of this method still have need to conscious commentary (119, 120). New assay and detection methods for troponin can have several distinct roles in clinical trial:

- Facilitate the early detection and prevention of MI
- Risk stratification in acute cardiac conditions and disease prognostic information in several areas
- Therapeutic monitoring and evaluate drug toxicity
- To confirm or refute the diagnosis of MI
- To decide on the treatment of patients with unstable angina
- To detect myocard infarction without increasing the ST peak elevation, the usage of unstable angina in addition to the history and ECG changes, is very important for diagnosis heart attack

However, detection of troponin is not a specific cause for the death of heart cells and physicians have a great responsibility on the interpretation of various tests in the clinical fields; (patients with unstable angina who have Troponin increase are in the risk of death or MI and there is a direct relationship between the increase in troponin level and mortality rates after heart attack) (121). From quantitative methods for troponin assay, immunological assay with monoclonal antibody and sandwich ELISA can be noted (antibodies are in two forms: conjugated to enzymes and labeled with biotin (122-124); in the presence of troponin in serum, On the one hand create a sandwich complex that antigen binds to the conjugated antibody with an enzyme and on the other hand binds to antibody labeled with biotin) (125, 126). In clinical centers, quantitative methods (ELISA kits) can assay troponin levels in the range of 4-75 ng/ml (127, 128). Specificity and sensitivity of mentioned method is depends on the specificity of exists antibodies in this method. Monoclonal antibodies are used in fourth generation assay of cardiac TnT that detect epitope with 5 amino acids away from the central region of the molecules (120, 129, 130); Two examples of this antibodies include M7 that detect an epitope with amino acids from No: 125 to 131 and M11.7 that detect an epitope with amino acids from No: 136 to 147 (106, 131). This selection of antibody is related to specific sequences of cardiac TnT and there is not any similarity with embryonic TnT (132). In high sensitive assay of human cardiac TnT, the antigen-binding fragments of mouse monoclonal antibodies directed to epitopes in the central region of human cardiac TnT are used (132). The M7 capture antibody is biotinylated and directed against an epitope in the amino acid sequences 125-131 and is similar to the sample that used in fourth generation troponin detection methods (133). The detection antibody is directed to an epitope in the amino acid sequences 136-147 (134). A new method for measuring cardiac troponin against produced recombinant TnT is calibrated in *Escherichia coli* cell culture. Measurement's calibration is not similar to fourth generation measurement methods (135); but in general can create a fixed and comprehensive relationship between different measurement methods, for example, the detection threshold of 30 ng/L in the fourth-generation assay is equal with detection threshold of 50 ng/ml in high sensitive assay. Although the accuracy, specificity and sensitivity of these antibody-dependent methods are high, but considering the high cost of commercial kits for these tests, it is necessary to replace these methods with new methods that have high sensitivity, specificity and also lower cost (136). Already for troponin assay in patients with a heart attack, the blood samples tested at intervals of 6 and 12 hours and troponin test will

done; if the troponin assay be with high sensitivity, not required to measure serial blood tests and this leads to earlier diagnosis and faster decide to treat the patient (137). Reperfusions of blocked coronary after MI lead to rapidly increase of cardiac biomarkers in the blood and reach to its maximum reperfusion because more quickly leached of interstitial space form infarcted area (138, 139). The regular methods for assay cardiac TnI and TnT are including immunological and molecular measurements (antigens or antibodies) that mentioned in Table 4.

Table 4. TnI and TnT usual assay methods

Type of Immunological Assay	Measurement Accuracy	Limitations
enzyme-linked immunosorbent assays (ELISA)	Picograms-Nanograms/ml	High Cost - pseudo Positive and Negative
Radioimmunoassay	Picograms-Nanograms/ml	Risks of using radioactive material
RT qPCR	Expression in the desired gene number of copies	Measuring the expression in the level of mRNA - low sensitivity and accuracy- lack offer the results as a number
Fluorogenic immunological assay. eg. Protein microarrays	High sensitivity	Non-specific interactions of proteins
Electrochemiluminescence	High sensitivity	The high cost and fixed system

6. THE USE OF BIOSENSORS AS A NOVEL METHOD FOR DETECTION OF BIOMARKERS

The comparison development of diagnostic electrochemical biosensors in four countries: Iran, India, Turkey and Pakistan shown in Diagram 1. This raw data, extracted from Scopus scientific database (140). Among these four countries, India has the highest rate of expansion in the use of biosensors and Iran has the highest growth rate among these countries. Until 2002 Turkey was considered a serious rival for Iran in this field, but until the end of 2014, the growth rate of Iran 5 times is more than turkey. Some biosensors can be used as an important tool in the early diagnosis of cardiovascular disease, out of the hospital, with low cost and fast detection ability (141-143). Biosensors are devices that provide response for a particular material in an environment and generate measurable signals. A biosensor consists of at least two components (bioreceptor and transducer) (144, 145).

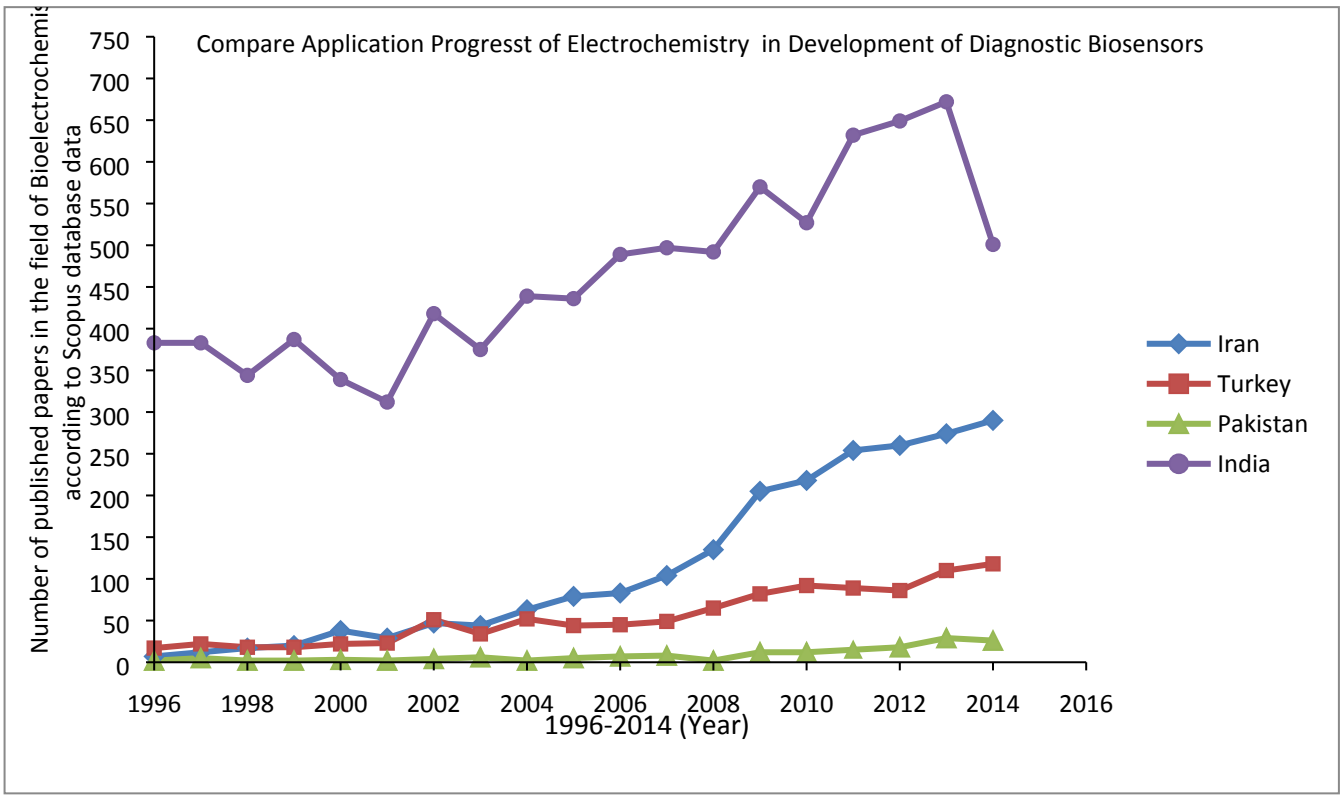

Diagram 1. Comparison of application development of diagnostic electrochemical biosensors in development in four countries: Iran, India, Turkey and Pakistan

The bioreceptor can be a chemical or biological agent such as small organic molecules, peptides, proteins, nucleic acids, carbohydrates, tissue or whole cell (146). An aptamer is used as the bioreceptor in aptasensors (147, 148). In perfect condition, this component should be high affinity (lower detection limit), high specificity (least of interfere), wide dynamic range and fast response time (149). Signal transducer converts the molecular recognition event into a measurable signal, such as fluorescence, produce color or electrical signals. The combination of

aptamers with nanomaterials, has created biosensors with high sensitivity and specificity (150, 151). Aptamers are single-stranded oligonucleotide ligands (either DNA or RNA) that their length is between 30-70 nucleotides. The organic bases in single-stranded nucleic acid sequences was paired together according to Watson-Crick theory and this in-chain arrangement create specific and unique three-dimensional (3D) structure for aptamer that is similar to the Grape clusters structure of RNA molecule (147, 148). Probably adjacent aptamer with particular foreign compounds (target) is facilitator for formation of this structure and lead to effective binding of aptamer and target. This connection is performed through van der Waals interactions, hydrogen bonding, electrostatic interactions or a combination of interactions between electric charges of target surface and aptamer molecule (152). In the design of aptasensors it is important that whatever the three-dimensional structure of aptamer be higher compliance with the target, the binding of aptamer-target will be with more affinity, in a way that aptamer tends to its specific target will be up to ten thousand times more than aptamer and a similar molecule (153). The comparison of aptamers and antibodies, also advantages of aptamers were listed in Table 5.

Table 5. Comparison aptamers and monoclonal antibodies in terms of different aspects

Row	Aptamers	Antibodies	References
1	Aptamer selection method based on a chemical process that is performed *in vitro*.	The antibodies Selection require using of biological systems.	(147)
2	For each protein and non-protein target is available.	For some cases, such as toxins and non-immunogenic compounds are not available.	(153)
3	The production time of Aptamers is few weeks.	The time for antibodies production are several months	(147)
4	Aptamers shelf life is long and in the frozen state are for several years; And aptamers in some applications is reusable.	Antibodies shelf life is limited (6 months) and they are single use.	(153)
5	The Selecting of aptamers can be done for a variety of ligands and under different conditions.	The antibodies are produced under physiological conditions and generally for materials with immunogenicity.	(154)
6	Aptamers are usable *In vitro* for a variety of applications.	Generally under similar conditions to physiological status are applicable.	(153)
7	Only the Time-consuming step of aptamer selection is Systematic evolution of ligands by exponential enrichment (SELEX) that by the use of advanced techniques or automated systems can reduce this time.	Selection and production of antibodies is time-consuming and costly process.	(155)
8	In the aptamer generation various batches, the uniformity activity is expected.	Batch to batch variations in the production of antibodies is well evident.	(147)
9	Pharmacokinetic parameters of aptamers easily can be manipulated and changed by applying chemical modification.	Pharmacokinetic changes in antibodies are difficult.	(156)
10	In the production of aptamers, the aptamer binding and effective site on target protein is the designable and selective.	In antibodies, the effective site selection is done by immune system.	(156)
11	A wide range of chemical changes can lead to functional diversity of aptamers.	Chemical changes in antibodies have some limitations	(153)
12	Aptamers, even after suffering extreme temperature changes can return to proper basic conformation.	Antibodies are sensitive to temperature changes and be involved in irreversible denaturation.	(147)
13	Unlike antibodies, aptamers have an unlimited shelf life.	Have limited shelf life and are sensitive to keeping conditions.	(155)
14	Use and maintenance of aptamers is possible at room temperature and not need to freeze or put in the refrigerator.	Use and maintenance of antibodies at room temperature is not possible and need to freeze or put in the refrigerator, and otherwise of optimal thermal conditions will be denatured.	(155)
15	There is not any evidence about immunogenicity of aptamers.	If used as a drug, the risk of immunogenicity is very high.	(156)
16	The aptamers antidote can be designed to inhibit or reverse the activity of it.	Design antidote about antibodies is not easily possible.	(157)
17	There is a variety of laboratory methods for controlling aptamers cross-reactions with different targets and remove or apply a cross-reaction is easily possible.	Control cross-reactions have some limitations.	(156)

The use of biosensors and aptasensors for detection of biomolecules such as proteins and biomarkers has been followed by various researchers (142, 143, 147, 148, 158). A biosensor using modified electrodes with multi-walled carbon nanotubes (MWCNTs) is designed to detect CRP (hs-CRP) and this able to detect CRP in 500 pg/ml levels (159). In another study a biosensor was designed for detection of lipoprotein associated with phospholipase A2 (Lp-PLA2) that in this research the modified carbon paste electrode with Iridium nanoparticles was used (160). In another study an immunosensor was designed for the detection of TnI and CRP using CdTe and ZnSe quantum dots that this immunosensor could detect these biomarkers in 20 samples of human serum (160). In another study Kunduru et al, tried to design a nano-based biosensor to detect CRP by using of micro and nano polystyrene polymers; the results of this research showed that if the nanoscale is used, the sensitivity and power detection of analyte greatly increases (161). In a study the electro-deposit gold nanoparticles on Indium tin oxide (ITO) was used to detect TnI and specific antibody interactions by measuring the open circuit potential (OCP) (162). In this study, a new strategy in order to obtain an electrical signal based on the catalytic reaction of the immune's enzyme was introduced and was able to detect TnI in the range of 1-100 ng/ml (162). He et al designed an electrochemical method for thrombin detection with direct determination of nuclease adenine redox activity in a modified electrode

with aptamer (163). In this study, the thrombin was fixed with anti-thrombin antibodies and was detected with gold nanoparticle-aptamer barcodes. In this research, extensively active surface that was provided by gold nanoparticles led to the detection of thrombin in the scale 0.1 ng/ml. In one study, an aptasensor was designed to detect ATP and thrombin that could detect ATP (in the range: 10μM-10nM) and thrombin (in 0.1 nM level) (164). Ye Hu et al used gold nanoparticles to design an aptasensor to detect AGR2 protein's biomarker of cancer cells and this try was successfully (165).

7. CONCLUSION

Cardiac troponin as the gold standard in the diagnosis of MI is used in hospitals and emergency rooms. Accurate and fast diagnosis of this cardiac biomarker plays an important role in preventing the risks of adverse effects of heart attack. With the advancement of knowledge and technology, finding new ways to medical diagnosis have been a lot of growth. New diagnostic options should have higher accuracy, good repeatability, and low cost. Any diagnostic method has some advantages and disadvantages; but in order to optimization, the future of systems design for medical diagnostics will be accompanied with definitive combining of these sciences with new sciences such as nanotechnology, biotechnology, etc.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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