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Udaya Ralapanawa

Department of Medicine, University of Peradeniya, Sri Lanka

Sivakanesan R

University of Peradeniya, Sri Lanka

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REVIEW ARTICLE

Biomarkers of Inflammation and Oxidative Stress in the Prediction and Management of Acute Coronary Syndrome

Udaya Ralapanawa ^a , Sivakanesan R ^b

^a Professor in Medicine and Consultant Physician, Department of Medicine, University of Peradeniya, Sri Lanka

^b Professor Emeritus, University of Peradeniya, Sri Lanka.



ABSTRACT

The assessment of patients presenting with chest pain or symptoms indicative of cardiac ischemia remains a diagnostic challenge. Many types of research have focused on the search for ideal biological markers for the rapid detection of cardiac cell injuries. Markers of inflammation and oxidative stress are the way forward. At present, the biomarker most widely used for diagnosing acute coronary syndrome is cardiac troponin though it has some limitations.

Apart from cardiac troponin, several other biomarkers, especially inflammation and oxidative stress markers in acute coronary syndrome, have been investigated. However, most of them still require validation in further studies. As markers of inflammation and oxidative stress address a particular aspect of the pathophysiology of acute coronary syndrome, these biomarkers may provide unique information to the managing clinician separate from that of markers of myocyte necrosis. Serum markers of inflammation and oxidative stress appear before cardiac necrosis markers and are valuable targets for early and timely diagnosis of an acute cardiac event. Using these markers in combination with biomarkers of plaque formation, unstable plaque development, plaque rupture, thrombosis, and myocardial necrosis (multimarker approach) could increase their diagnostic and prognostic value.

KEYWORDS: Acute Coronary Syndrome, Myocardial Infarction, Biological Markers, Oxidative Stress, Inflammation, Troponin.

Correspondence: Pr. Ralapanawa U, Adress: Department of Medicine, University of Peradeniya, Sri Lanka. Email: udayapralapanawa@yahoo.com

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INTRODUCTION

Cardiovascular disease is the worldwide leading cause of mortality and morbidity. The 2011 annual report from World Health Organization(WHO) highlighted the mortality rate prediction of the population worldwide that, in 2030, cardiovascular disease will become the leading cause of death, and mortality rate will be higher than infectious diseases such as HIV, Tuberculosis, malaria infection (1). Moreover, this report also mentioned that, among cardiovascular diseases, ischaemic heart disease(IHD) and cerebrovascular disease, reported as the top 2 causes of mortality in 2004, are expected to be still the principal cause of death in the next 20 years(1).

Acute coronary syndrome(ACS) describes a range of clinical conditions ranging from ST-elevation acute coronary syndrome (ST-elevation myocardial infarction(STEMI)) and non-ST elevation acute coronary syndrome (unstable angina(UA) and non-ST elevation

myocardial infarction(NSTEMI))(2). The syndrome results from disrupting a susceptible plaque in a coronary artery, complicated by intraluminal thrombosis, embolization, and a varying amount of hindrance to perfusion. The severity of coronary artery obstruction and the volume of affected myocardium determined clinical presentation characteristics. Patients with total occlusion may present with ST-segment elevation infarction if the lesion occludes an artery supplying a substantial volume of the myocardium. Still, the same occlusion in the presence of extensive collateralization could be marked as infarction without ST-segment elevation (Non-ST elevation ACS). Similarly, incomplete occlusion at the site of a disrupted arterial plaque could create ischemia or micro infarction depending on the size of the myocardium affected (2, 3).

MATERIALS AND METHODS

Evolution of biological markers

The assessment of patients presenting with chest pain or symptoms suggestive of cardiac ischemia remains a diagnostic challenge. STEMI is an acute and catastrophic event that results from ACS and atherosclerosis and is a leading cause of morbidity and mortality in adults in western countries and Asia. A prompt diagnosis or at least a strong suspicion of MI in the acute phase of the episode is vital in guiding the treatment decisions, such as the use of thrombolytic therapies and critical percutaneous coronary interventions (PCIs) (2,3). Diagnosis of STEMI depends on finding of the rise and/or fall of cardiac biomarker values (preferably troponin) with as a minimum of one value above the 99th percentile of the upper reference limit with at least one of the following; symptoms of angina, new or new significant ST elevation or new LBBB in ECG, development of pathological Q wave in the ECG, imaging support of a recent loss of viable myocardium, or new regional wall motion abnormality, detection of an intracoronary thrombus by angiography or autopsy(3). Although ECG is an essential means for the early diagnosis of a patient with chest pain, its diagnostic sensitivity may be as low as 50%. Equivocal ECGs are usually seen with smaller myocardial necrosis, intraventricular conduction delays, and posterior MI (4,5,6). In this context, cardiac biomarkers have grown in importance (7,8). Until 25 years before, laboratory medicine used only a few assays for the retrospective detection of cardiac tissue necrosis, such as enzymatic methods for creatine kinase (CK) and lactate dehydrogenase(LDH) catalytic activity(9). However, towards the last part of the 20th century, cardiac troponin (cTn), which is a highly sensitive and specific assay for the detection of myocardial damage, have become available, assigning to the laboratory a critical role in the diagnosis and follow up of patients with cardiac disease(7).

Limitations with cardiac troponins

Although cTn elevation persists for days, initial detection is deferred after myocardial injury, as necrosis naturally necessitates 2-4 hours to occur following ischemia. Consequently, cTnT and cTnI are measurable only after this window period after the onset of the injury. Serial measurements to be drawn at presentation and again after 6-9 h from the onset of symptoms are recommended (10). It has become evident that although a rise in cTn reflects myocardial damage, it does not indicate its mechanism. Apart from spontaneous AMI following plaque rupture and acute coronary occlusion, the ischemia produced by increased oxygen demand or decreased supply can lead to AMI, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension. Therefore, coronary, non-coronary cardiac, and non-cardiac conditions such as sepsis can lead to elevated cTns(10).

Need for novel cardiac markers

Because of these limitations, researchers have been trying to establish the ideal cardiac biomarkers for the rapid and early establishment of ACS. Many noninvasive biochemical measures have been used, for example, lipid and lipoprotein metabolism, inflammation, and oxidative stress (13). However, it is necessary to develop a more readily available specific and prognostic biomarker that allows diagnosing or ruling out ACS. Because ACS is the

leading cause of disability and sudden death worldwide, rapid tests for the timely detection of ACS would have a widespread application (1). There is growing interest in finding novel biomarkers that are more sensitive or require shorter periods for testing than the common markers like cardiac-specific troponins, which may require up to 6-12 hours to exclude ACS. Furthermore, it may reduce the time of assessment to rule out ACS in patients who present less than 6hrs to the emergency department, thus reducing the length of stay times and potentially hospital costs (14).

In ACS, myocardial ischemia and necrosis trigger the inflammation and subsequent repair process. Oxidative stress and chronic inflammatory response play a mysterious role in initiating and evolving myocardial infarction (15). Plaque rupture and succeeding thrombosis at the site of the plaque rupture are the most common underlying pathophysiological mechanisms of ACS (15). Atherosclerosis is considered ‘an inflammatory disease,’ and inflammatory mechanisms in the atherosclerotic plaque could be activated, maintained, and enhanced by numerous factors like oxidized low-density lipoproteins (oxLDL), an increased concentration of superoxide species, activated macrophages, and an increase in cytokines production. Recently it has been established that susceptible atherosclerotic plaques have an augmented number of macrophages and activated lymphocytes. These plaques demonstrate increased inflammation in which macrophages secrete matrix metalloproteinases that degrade the fibrous cap, leading to rupture, in situ thrombosis, and associated clinical events (16).

Coronary atherosclerosis, the main pathological process of cardiovascular disease, represents a state of excessive oxidative stress characterized by lipid and protein oxidation in the vascular wall. These changes of rupturing of atheroma and vessel wall protein and lipid oxidation most probably proceed to an acute coronary event (15,17). During these events, inflammatory markers are released into circulation. These serum markers of inflammation open an avenue of insight into the pathophysiology of atherosclerosis and its complications. The cardiac necrosis markers like CK-MB and troponins appear later following an acute cardiac event. So serum markers of inflammation and oxidized products of membrane proteins and lipids appear before cardiac necrosis markers are valuable targets for early and timely diagnosis of an acute cardiac event. Further, as markers of inflammation and oxidative stress address a particular aspect of the pathophysiology of ACS, these biomarkers may deliver specific information to the managing clinician separate from that of biomarkers of myocyte necrosis.

The need for an ideal biomarker or group of biomarkers for early diagnosis of ACS is a need today, and biomarkers of inflammation and oxidative stress are a way forward. Such ideal biomarker should be specific to myocardial muscle cells (no false positive), should release rapidly on the onset of cardiac event, should be able to detect even minor damage, should not have false-negative results. The level should relate to the extent of damage and should stay longer in blood to diagnose even delayed admissions. The procedure should depend on evidenced principles, can be performed anywhere at a low cost, and does not need highly qualified personnel. Results should be available within a short time, i.e. preferably within 30 minutes (maximum 1 hour) of hospital admission (17).

A literature search using PubMed, Medline, ISI, IBSS, Cochrane library, Science direct, Scopus, and Google Scholar databases (2000-2020) was performed by prof Udaya Ralapanawa to identify and evaluate all relevant English-language studies of cardiac biomarkers in the prediction of ACS. The previously published principles were followed when the search strategy was conducted. The following keywords, “myocardial infarction,” “acute coronary syndrome,” “cardiac biomarkers,” “oxidative stress,” “inflammation,” and “troponin,” were used. Articles were also identified by a manual search of bibliographies from the retrieved articles, excluding letters, editorials, conference abstracts, reviews, and comments. Further, the studies which do not have access to the full report were excluded. Then the selected articles were reexamined for relevance and repetition. Detailed notes and impressions were written down after reading the selected articles and deciding which pieces of data possess values. Data were clustered into relevant categories and subcategories, allowing them to be studied together and searched. Then, data were evaluated in detail, and interpretations were made.

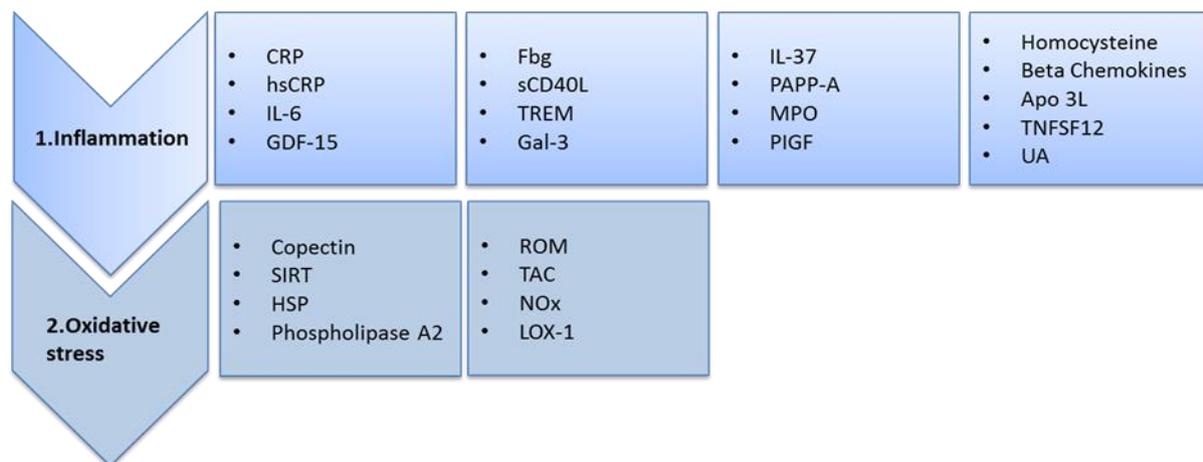


Fig 1: Biomarkers of inflammation and oxidative stress in acute coronary syndromes

CRP: C-reactive protein, Fbg: fibrinogen, Gal-3: galectin-3, GDF-15: growth-differentiation factor-15, hsCRP: high sensitive C-reactive protein, HSP: Heat shock Protein, IL-6: interleukin-6, IL-37: interleukin-37, LOX-1: lectin-like oxidized low-density lipoprotein receptor-1, MPO: Myeloperoxidase, NOx: Nitrite/Nitrate ratio, PAPP-A: pregnancy-associated plasma protein-A, PIGF: placenta growth factor, ROM: reactive oxygen metabolites, sCD40L: soluble CD40 ligand, SIRT: sirtuin, TAC: total antioxidant capacity, TNFSF12: TNF Super Family 12, TREM: triggering receptor expressed on myeloid cells, UA: Uric acid

Here we discuss some biomarkers related to initial inflammation and oxidative stress in the pathophysiological processes associated with ACS in detail.

RESULTS

Biomarkers of inflammation

- High sensitivity c-reactive protein.

Inflammation plays a vital role in atherosclerosis, and analysis of inflammatory markers like high sensitive C-reactive protein (hs-CRP) will offer a novel means for

Potential Biomarkers of acute coronary syndromes

In accordance with the WHO, a biomarker is defined as any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease' (18,19).

At present, no available biomarker offers ideal diagnostic properties for ACS, such as early detection, high sensitivity and specificity, easy availability, and cost-effectiveness (20). So it is a timely need to develop an ideal biomarker or combination of such markers reflecting different pathophysiological entities of ACS, such as atherosclerosis, inflammation. Oxidative stress, angiogenesis, plaque instability, platelet activation, thrombosis, myocardial ischemia or necrosis, hemodynamics enhance the early and accurate diagnosis of ACS (21,22). The release of selected markers and enzymes during the initial stages of this process, inflammation, and oxidative stress can be detected in the peripheral circulation and are shown in Fig 1. The arrows indicate the sequence of initial events during an acute coronary syndrome. Biomarkers that may be raised at each phase of the disease are demonstrated.

exposing individuals to a high chance of plaque rupture (23). Standard (conventional) clinical assay for CRP processes a lower detection limit of 3 to 8mg/dL, thus cannot be used effectively for vascular risk prediction. Several “high sensitivity” or “ultra-sensitive” tests for CRP are now commercially existing or in development to establish CRP levels with exceptional reliability and reproducibility across the normal range (23). High sensitivity procedures like immunonephelometry, high sensitivity enzyme-linked immune sorbent assay (ELISA), and resonant acoustic profiling (RAP) can detect CRP with a sensitivity range of 0.01-10mg/dl (24).

CRP is an acute-phase reactant exhibiting many properties which may intervene in atherogenesis. CRP was first introduced in 1930 by Tillet and Francis. CRP is a 206-amino acid portion of the short pentraxin family, and there are two different conformational forms: the native pentameric isoform (pCRP) and monomeric isoform (mCRP). CRP is predominantly synthesized in the liver. IL-6 seems to be the main regulator. IL-6 effect is augmented by IL-1 β and TNF. Following synthesis and secretion into circulation, serum CRP level tends to increase significantly 6-8 hrs after initial stimulation, peaking at 24-

48 hours with a half-life of 19 hours (25). Though the liver is the leading site of synthesis, CRP synthesis can take place in other areas such as adipose tissue, lungs, renal cortical tubular epithelium, lymphocytes, and atheromatous plaque (25).

CRP actively plays a role in atherogenesis by directly influencing processes such as activation of the complement system, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation, and thrombosis. Both pCRP and mCRP participate in different processes: pCRP can produce inflammatory responses binding to the phosphatidylcholine on the exterior of oxidized-LDL and the surface of apoptotic cells. In contrast, mCRP can modulate platelet-induced aggregation (25). Tissue necrosis is a potent acute-phase stimulus, and, following MI, there is a significant CRP response. The magnitude of this reveals the extent of myocardial necrosis. Also, deposition of CRP together with activated complements is observed within all acute myocardial infarcts (26).

The measurement of hsCRP has been integrated into the Reynolds risk scoring system to forecast cardiovascular risk (24). The Intervention Trial Evaluating Rosuvastatin (JUPITER) reveals that cardiovascular benefits are more apparent when systemic inflammation is reduced (as evidenced by hsCRP reduction) in addition to the intensive reduction of LDL-C (24,27,28).

According to the study done by Nurkic et al. hsCRP is a highly sensitive but weakly specific marker of plaque rupture (29). A study done by Arima et al. among Japanese people (the Hisayama Study) showed that hsCRP in Japanese (median 0.43mg/dl) was much lower compared to those in Western populations (median nearly 1.5-2.0mg/dl). According to this study, hsCRP levels were linked with the future coronary events of Japanese. In the Japanese population, the hsCRP cut-off point for high-risk future CHD is >1.0 mg/dl, much lower than the western population (30). Meta-analysis of all published studies till 2000 exhibited a relative risk of 2.0 for a future coronary event in an individual with a single baseline CRP value in the upper third compared with those in the lower third of the distribution in the general population (26,31). According to Rezk et al, patients with ACS who had a higher measurement of serum hsCRP had higher levels of SYNTAX score and subsequently more complex and severe atherosclerotic lesions (31). Ribeiro et al. studied 300 patients to discover the link between hsCRP and recurrent major adverse cardiovascular events (MACE) in an individual with STEMI who undergo primary percutaneous intervention. According to their observation, though hsCRP was not predictive of composite MACE within the first 30 days after acute STEMI who underwent primary angioplasty and stenting, it was an independent predictor of 30-day mortality (32).

- **Growth-differentiation factor-15.** The growth-differentiation factor (GDF-15) is previously known as macrophage-inhibit cytokine-1 and is produced by activated macrophages (33,34). GDF-15 is linked with cellular oxidative stress, ischemia, and strain. Data suggest that GDF-15 inhibits leukocyte recruitment in the heart and is a main predictor of all-cause, cardiovascular and non-cardiovascular mortality in community-dwelling older individuals (33,35). A significant number of trials, including the PLATO and PIVUS studies, have used GDF-

15 for cardiovascular risk stratification. It was recognized that GDF-15 is a potential indicator of risk stratification and decision-making in treatment. (33,36-41).

- **Fibrinogen.** Fibrinogen was discovered in the early half of the nineteenth century and was the first identified clotting factor (33,42). It is produced in the liver as an acute-phase protein, and its serum levels can exceed 7ng/ml during acute inflammation. It involves endothelial injury, platelet aggregation, plasma viscosity and has a significant role in thrombus formation (33). ESC guideline on prevention of CVD recommends measuring fibrinogen in the risk assessment of patients with an unusual or moderate cardiovascular risk (33).

Fibrinogen and its metabolic products may lead to endothelial dysfunctions through various mechanisms. Some atherosclerotic lesions are rich with fibrin, either in-wall thrombus or diffusely all over the plaque (43); fibrin triggers cell proliferation, migration, and adhesion (43). Fibrinogen decomposition products located in the intima can stimulate the mitogenesis and synthesis of collagen. The close linkage between fibrin and LDL resulted in the lipid core of advanced atherosclerotic plaque (44,45). Pro-inflammatory cytokines produced by vasculature during atherogenesis can trigger liver production of acute-phase proteins like fibrinogen, which involves atheroma formation in the initial phase (46). In the Gothenburg study, plasma fibrinogen level was identified as an independent risk factor for MI (47). The Framingham study showed the progressively increased risk of developing MI coupled with fibrinogen level (48,49). The EPIC-Norfolk study demonstrated significantly higher fibrinogen levels in fatal and nonfatal CHD (50). The effect of fibrinogen levels on cardiovascular risk is the same as diabetes, hypertension, and smoking, which is even more significant in young people (48,49). Researchers identified several gene polymorphisms of the fibrinogen chain, which influence the fibrinogen levels and cardiovascular events (43).

- **Uric acid.** In humans, the end product of purine is uric acid (UrA). UrA level, even blood level below the threshold for hyperuricemia, can contribute to atherosclerosis and CVD development by enhancing inflammation, increasing oxidative stress, and promoting endothelial dysfunction (33,51-55). Studies imply that a high serum UrA is causally linked to unfavorable cardiovascular outcomes, especially cardiovascular deaths (33). According to 32 years of follow-up data from the Framingham study, men with gout have a 60% chance to develop CHD than those without gout (56). Further, the Coronary Artery Risk Development in Young Adults (CARDIA) study concluded that serum UrA is a risk factor for subclinical atherosclerosis (56). UrA can possibly trigger the immune system by releasing monosodium urate crystals (56,57) once macrophages engulf these crystals, immune system activation pointers to the development and activation of the nod-like receptor pyrin domain 3 (NLRP3) inflammasome protein complex, which eventually leads to the release of pro-inflammatory cytokine IL-1 β (58,59). IL-1 β , together with other factors, stimulates the influx of leukocytes (neutrophils) into the affected area. This inflammation process leads to aggregation of extracellular lipids leading to cell injury/death and increasing the advancement of atheroma (58). In vitro study has demonstrated the capacity of UrA to promote LDL oxidation, a critical step in

atherosclerosis progression(60). In China, a study done by Song et al. found a longitudinal association between serum UrA levels and multi-territorial atherosclerosis, especially in men(52). According to Wannmethee et al., there was a significant upswing in the development of heart attacks in middle-aged men with raised serum urate(54). The PIUMA study showed a significant association between acid levels and future cardiovascular events in people with hypertension(61). Another study done by Chang et al. in non-hypertensive and non-diabetic individuals showed that serum UrA level was an independent risk factor for a high Framingham risk score(62).

- **Triggering receptor expressed on myeloid cells-1.**

Triggering receptor expressed on myeloid cells-1(TREM-1) is a 30KD glycoprotein surface receptor that belongs to the immunoglobulin family was first recognized by Bouchon A et al. in 2000(67,68,69-71). The transmembrane and soluble(or secreted) forms have two relevant forms. The soluble form of TREM-1(sTREM-1) is secreted into body fluid, including plasma, pleural effusion, sputum, and urine, and TREM-1 activation is assessed by the measurement of its sTREM-1 in plasma(69,72). Neutrophils and mature monocytes predominantly express it. Also, TREM-1 has been recognized in macrophages, natural killer cells, and endothelial cells(73,74-77). TREM-1 is pro-atherogenic and prompts the formation of atheroma and the evolution of atherosclerotic lesions by enhancing the infiltration of monocytes and macrophages into atheroma. TREM-1 has a powerful impact on foam cell generation; hence contributes to atheroma growth locally(78). The up-regulation of TREM-1 in atheroma leads to the destabilization of plaque through its up-regulation in macrophages and vascular smooth muscle cells by persuading the secretion of MMP-1 and MMP-9, which hydrolyzes the gelatine and collagen and pointers to the plaque vulnerability, plaque rupture, and coronary event(67). After the myocardial event, due to the secretion of cytokines and chemokines after the myocardial event, there is an influx of myeloid cells such as monocytes and neutrophils to the ischaemic tissue area(67). TREM-1 receptors expressed by neutrophils, macrophages, and mature monocytes act as an enhancer of the innate immune response(72,79). Studies found that acute MI patients with on admission increased concentration of TREM-1 have a significant risk of death after two years of follow-up (72). Animal studies have shown that inhibiting TREM-1 in mice after acute MI can improve heart functions during follow-up (72).

- **Placental Growth Factor.** Placental Growth Factor (PlGF) is a fellow of the vascular endothelial growth factor family. Though it was first discovered in the placenta, it also presents in several other tissues, including the heart (80-83). PlGF is a functional cytokine, and it stimulates angiogenesis and atherogenic migration of monocytes/macrophages into the arterial wall. According to animal studies, PlGF is an early and primary inflammatory instigator of atherosclerotic plaque instability (82-83). PlGF was revealed to be upregulated in early and advanced atherosclerotic lesions. PlGF stimulates vascular smooth muscle cell growth, recruits macrophages into atherosclerotic lesions, enhances the production of TNF- α and monocyte chemoattractant protein one by macrophages, and stimulates pathological

angiogenesis (84). Inhibiting the PlGF effect in an animal model can suppress both the growth and vulnerability of atherosclerotic plaque through inhibition of inflammatory cell infiltration (84). By administering recombinant human PlGF to mouse model of acute MI showed significant improvement of the survival rate following MI and preserved cardiac function relative to control mice (85).

- **Homocysteine.** Homocysteine (Hcy) is a sulfur-containing thiol amino acid formed during methionine metabolism. About 50 years ago(in 1969), Kilmer McCully proposed Hcy as atherogenic(86-88). Hyperhomocysteinemia promotes atherosclerosis and is significantly due to vitamin B deficiency, especially folic acid, B6, and B12; genetic disorders, certain drugs; and renal impairment(87,89-91). Elevated Hcy promotes atherosclerosis through enhanced oxidative stress, impaired endothelial function, and induction of thrombosis(86,88,92). Hyperhomocysteinemia drives the initial phase of atherogenesis, possibly through 3 mechanisms. Firstly, hyperhomocysteinemia may activate inflammatory responses leading to the recruitment of monocytes to the arterial wall. Secondly, hyperhomocysteinemia promotes the oxidative modification of LDL and promotes the uptake of LDL-cholesterol by macrophages. Thirdly, hyperhomocysteinemia may deregulate cholesterol and triglyceride metabolism in vascular cells(86,92,93). According to some studies, hyperhomocysteinemia increases cardiovascular disease risk twofold (89). Cross-sectional analyses showed that elevated Hcy is linked with CAD in both genders. Now, hyperhomocysteinemia is considered an independent risk factor for atherosclerotic vascular diseases, which is adjustable by nutrition and exercise (86,89,94).

- **Chemokines.** Chemokines are small molecules(8-12kDa) that belong to the enormous family of cytokines(95-97). This family can be categorized into four canonical subclasses: CC, CXC, CX3C, and XC(95,98-100). Chemokines and their receptors are extensively expressed by activated endothelial cells, smooth muscle cells, and immigrated leukocytes, which play an avital role in atherosclerosis. Chemokines play a crucial role in all stages of the development of atherosclerosis(95,101-104). In addition to directing leukocytes to the site of inflammation, chemokines involve in controlling cell homeostasis and activation(98). The inhibitors of chemokines and their receptors have been studied and proven to be effective experimentally in managing atherosclerosis (98,105).

- **Tumour Necrosis Factor-Like Weak Inducer of Apoptosis.** According to data, inflammatory cytokines of tumor necrosis factor super family, Tumor Necrosis Factor-Like Weak Inducer of Apoptosis (TWEAK) partakes in the formation and progression of atherosclerosis (106-108). Once TWEAK binds to its receptor fibroblast growth factor inducible molecule 14(Fn14), it influences adverse biological functions of atherosclerosis including, endothelial cell dysfunction, phenotypic change of smooth muscle cells, and inflammatory response of monocytes / macrophages (106,109,110). In addition to binding to Fn14 receptors, TWEAK binds to a cluster of differentiation 163 (CD163) receptors exert various biological functions (106). Studies have shown that TWEAK/Fn14 axis may exhibit an

essential role in the development of cardiac dysfunction(111).It was shown that atorvastatin can decrease the pro-inflammatory response induced by TWEAK in human smooth muscle cells(106).

Biomarkers of Oxidative stress

Oxidative stress is critical in the pathogenesis of atherosclerosis and ACS. Under the umbrella term “oxidative stress,” many biomarkers belonging to different pathways have been proposed (112,113). Though traditional risk factors construe a large percentage of cardiovascular risk, they are not effective in some cases. They cannot explain why some individuals with high risk did not develop a cardiovascular event while some low-risk patients did. These patients may be better classified by using alternative biomarkers as risk markers in conjunction with traditional risk factors (112).

Oxidative stress is marked by unevenness between oxidants and antioxidants in favor of oxidants, leading to redox signaling and physiological function disruption. Also, oxidative stress may point to irreversible chemical modifications (114). According to Frijhoff et al biomarkers of oxidative stress can be categorized as indicators of ROS-induced changes, ROS generation, markers of antioxidant defense, and functional markers of ROS-induced damage (114-16).

Accordingly, assessment of oxidative stress can be done by directly measuring free radicals or by the indirect size of oxidation products of lipid, protein, lipoprotein, and DNA and by measuring antioxidant capacity (117,118).

Lubrano et al described the emerging biomarkers of acute coronary artery disease (112). According to them, reactive oxygen metabolites (ROM), antioxidant capacity (TAC), Nitrite/Nitrate ratio (NOx), and lectin-like oxidized low-density lipoprotein receptor-1(LOX-1) can consider as new indicators of oxidative stress.

For a new biomarker to be established for routine clinical use, it should process additional benefits over installing clinical markers. Oxidative stress biomarkers might aid in recognizing groups of patients that benefit from particular treatments, permitting patients categorization based on pathogenesis rather than just severity of disease (114,119,120).

- **Oxidized low-density lipoprotein.** Atherosclerosis is a chronic inflammatory vascular condition leading to atheromatous plaque formation. Retention of low-density lipoprotein (LDL) in subendothelium and its oxidative modification initiate the event of atherosclerosis. Oxidized low-density lipoprotein (OxLDL) has several involvements in atherosclerosis. Many oxLDL-induced effects are mediated through low-density lipoprotein receptor-1(LOX-1)(121-123).OxLDL binds to LOX-1 and prompts the activation of endothelium and dysfunction, supports the recruitment of circulating leukocytes, triggers foam cell formation, and promotes migration and proliferation of smooth muscle cells, promoting atherosclerotic plaque development. Also, oxLDL-LOX-1 integration results in plaque destabilization by inducing smooth muscle cell apoptosis and, therefore, the release of matrix-degrading enzymes (121,124,125). OxLDL is a biomarker of oxidative stress and is generally measured in plasma or isolated LDL using immunological methods (126). To date, three monoclonal antibodies have been developed to measure circulating oxLDL by ELISA:

oxLDL-4E6, oxLDL-E06, and oxLDL-DLH3 antibody(127,128).

- **Copeptin.** In 1972, Holwerda was the first to describe Copeptin, an acute endogenous neuropeptide. Copeptin is the C-terminal part of pro-arginine vasopressin hormone (AVP) and release alongwithAVPduring precursor processing. Unlike AVP, copeptin is very stable in plasma at room temperature and easy and robust to measure(129-131,132). According to studies were done by McAlpine et al., there was an elevation of plasma level of AVP and other neuroendocrine hormones within six hours of the onset of symptoms in acute MI(133). Though it is a potential marker to diagnose acute MI with its very early increase in plasma level, this was not followed up owing to a significant limitation in measuring AVP levels (129). A study done among 980 MI patients by Khan and Ng is recorded as the first study demonstrating rising copeptin among MI patients (133). The use of copeptin and cTn combination has been offered to be used for early evaluation of individuals suspected of having MI. The rapid release and readily available results of copeptin within 60 min possibly will aid to cover the “troponin-blind” period and will be a handy marker at Emergency Department (134-143).

- **Sirtuin.** The sirtuins (SIRT) are a family of nicotinamide adenine dinucleotide (NAD⁺)-dependent histone deacetylases. There are seven closely related SIRT family members (Sirt1-7), and these are divided into four classes (144-147). The best-known function of SIRT is deacetylation (148). According to the preclinical studies, SIRT regulate several pathophysiological processes of atherosclerosis, including oxidative stress, inflammation, macrophage infiltration, and deposition of oxidized low-density lipoprotein cholesterol in the blood vessels' wall dysfunction of the endothelium (148). Research has publicized that SIRT 1,3 and 6 have beneficial effects against atherosclerosis, dyslipidemia, oxidative stress, endothelial dysfunction, and inflammation(148-150). Further, SIRT 1 and 3 might stimulate cardio protective pathways in acute MI patients, lessen the infarct size, and improve the prognosis(148).

- **Heat Shock Protein 70.** Heat Shock Protein 70(HSPs) are a family of stress-activated proteins involved in protein folding and repair. These polypeptide proteins are abundant soluble intracellular proteins and seem to perform various biological activities such as apoptosis, carcinogenesis, and defense against cytotoxic damage(154,155). Their molecular weight range from 10-170kDa and is classified based on their molecular weight in families, e.g., HSP27, HSP70, etc. (151-153). HSPs are produced in nearly all species and could be excreted from cells in the absence of cellular necrosis(154).

The HSPs synthesis, particularly the HSP 70 family, is highly upregulated under physiological, environmental, and pathophysiological stress (154). The 70kDa HSP (HSP70), which is only seen in primates, plays a fundamental role in protecting cells against stresses of various types and origins. When induced, HSP70 stops the immediate cell apoptosis and permits cell adaptation, which is vital for the existence of cells (151,156).HSP70, an acute phase reactant, is formed in the liver and spleen. Increased serum levels of HSP70 reflect systemic inflammation and oxidative stress (154).HSP 70 has defensive action against atherosclerosis and myocardial

ischemia. HSP 70 is cardio protective and counteracts important mechanisms of ischaemic injury, including unfolding, misfolding, or pathological modification of critical proteins (155,157)). According to Dybdahlet al, in a patient who developed acute MI, serum HSP70 concentration increased and declined more rapidly than the myocardial necrosis indicators like cTns and CK-MB (155). Studies have shown that a rise in expression of HSP70 results in a decrease in areas of infarction and offers an improvement in the recovery of post-ischaemic-perfusion injury of the myocardium (153).

- **Lipoprotein-associated phospholipase A2(Lp-PLA2).** Another name for Lp-PLA2 is platelet-activating factor acetylhydrolase and is a fellow of the phospholipase A2 superfamily. Monocytes and macrophages mainly produce Lp-PLA2, and it modifies the surface of LDL, increasing susceptibility to oxidation(33). Following LDL oxidation, Lp-PLA2 causes the excretion of lysophosphatidylcholine and oxidized fatty acids, which trigger the inflammatory cascade.

- **Reactive oxygen metabolites.** With oxidative stress, reactive oxygen species (ROS) or free radicals, that is $O_2^{\bullet-}$, H_2O_2 , and $\bullet OH$ are produced extra- or intracellularly, resulting in toxic effects on cells. One of the principal organs affected by ROS is the heart. The origin of ROS in cardiac myocytes is mitochondrial electron transport chain, NADPH oxidase, nitric oxide synthase (NOS), xanthine oxidase, cyclooxygenase/ lipoxygenase, and the auto-oxidation of various substances like catecholamine (158,159). The role of oxidative stress in the formation of atherosclerosis is also well established (160-163). Due to the biochemical instability of ROS, it isn't easy to measure ROS and free radicals directly in an ordinary laboratory. Recently, a technique of quantifying reactive oxygen metabolites (ROMs) in blood has been developed (164,165). The test is the reactive oxygen metabolites test (dROMs test). The critical element of ROMs is hydroperoxide (164,166).

- **Total Antioxidant Capacity.** Total antioxidant activity/capacity (TAC) indicates oxidative stress in the body(167).The serum TAC is determined to evaluate the antioxidant defense against ROS, indicating the body's antioxidant status(168,169). Oxidative stress is owed to disruption in the balance between ROS formation and antioxidant defense, and it has a fundamental role in the development of coronary atherosclerosis and its complications (168). When there is increased oxidative stress, TAC shows low values (167). Though different antioxidant levels can be measured in plasma separately, it fails to offer an overall measure of cumulative antioxidant status in the body (167). Thus TAC is expressed as the "cumulative action of all the antioxidants existing in plasma and body fluids, thus providing an integrated parameter instead of the simple sum of measurable antioxidants" (170). It is common practice to measure plasma TAC, and numerous systems have been developed to measure it, including spectrometry, electroanalytical methods, and chromatography (167,171).

The formation of a large quantity of ROS may affect four basic mechanisms of atherogenesis: oxidation of LDL, endothelial dysfunction, vascular smooth muscle cell growth, and monocyte migration (168).ROS can remove anti-atherogenic nitric oxide (NO) and produce pro-atherogenic peroxynitrite anion(ONOO). So an imbalance

in the pro-and anti-atherogenic effects of NO can point to the development of atherosclerotic CAD. Antioxidants that are effective against ROS might have a crucial role in limiting atherosclerosis and its clinical manifestations such as CHD. The measure of serum TAC is a significant marker (168). According to the previous TAC studies, no unequivocal solution has been grasped whether the incidence of CHD is associated with a reduction in antioxidant potential (171,173). The relationship of CHD to antioxidant defenses may be modified by various other insults like cigarette smoking, medications, and many anthropometric, physiological, and demographic confounders (172). According to a study done by Sayedda et al., unstable angina patients showed decreased ($p<0.0001$) serum and salivary total antioxidant activity than in control. Also, this decreased total antioxidant activity was positively associated with the severity of the disease process (174). A study done by Miller et al. on a patient with myocardial infarction couldn't show any difference in serum total antioxidant activity on admission, day one and day 2(175). Another study done by Nojiri et al. to find the correlation of serum antioxidant capacity with CAD in middle-aged men demonstrated an association of antioxidant parameters with atherosclerosis progression (176). Sedlakova et al. showed that TAC in acute MI patients on admission was lower than in control patients (177). A paper" Oxidant and antioxidant status in coronary artery disease" published by Bastani et al. concluded that significant differences were observed between the plasma TAC in the ACS, chronic CAD, and healthy control. Also, plasma TAC was significantly reduced in ACS patients than patients with regular CAD (178). A study was done by Lubrano et al., Hirata et al., and Pisoschi et al. demonstrated a decrement pattern of total antioxidant capacity overtime during acute MI, reflecting a progressive increment of the systemic oxidative stress status in compulsory MI course (112,179,180).

- **Nitrite/Nitrate.** Nitrite/Nitrate (NOx) is the end product of NO's metabolism and is a dependable marker of NO production (112). During the stable phase of CAD, there is a decline in nitrite and nitrate (NOx) due to endothelial dysfunction. During the acute stage of MI, there is a rise in inducible nitric oxide synthase (iNOS) activity and consequently in NO oxidative products leading to high oxidative stress in acute MI (112,181). Studies have shown that the peak increase of NOx happened 2-3 days after the commencement of symptoms, suggesting that the rise of NOx is associated with the iNOS activation induced by cytokines (112,181-183).

- **Lectin-like oxidized low-density lipoprotein receptor-1.** Augmented oxidative stress leads to raised production of ROS, which points to the oxidation of native LDL to oxidized LDL (ox-LDL), which has a fundamental involvement in atherosclerosis(184). Ox-LDL produces numerous effects on endothelial cells, macrophages, platelets, fibroblasts, and smooth muscle cells via the 50-kD, a transmembrane glycoprotein; Lectin-like oxidized low-density lipoprotein receptor-1(LOX-1). LOX-1, which belongs to the class E scavenger receptor family, has a crucial role in atherosclerosis (184-187). In 1997, Sawamura and the team cloned LOX-1 on bovine aortic endothelial cells (187,188). LOX-1, other than the binding and internalization of ox-LDL, contributes to the

dysfunction of endothelium and apoptosis and aids in the development of foam cells. LOX-1 expression is up-regulated by ROS, angiotensin II, sheer stress, cytokines, TNF α , IL-1, IFN- γ , diabetes mellitus, hypertension, dyslipidemia, etc. (184,188,189). As LOX-1 is involved in numerous paths in the pathogenesis of atherosclerosis and related diseases, it is valued as a potential treatment target. Also, the soluble form of the LOX-1(sLOX-1) receptor is currently being studied as a potential marker for CVD (184,185).

- Lipid oxidation marker - Thiobarbituric acid reactive substance. Due to oxidative stress, ROS and free radicals can damage nearby biomolecules. This lipid damage due to lipid peroxidation could form an end product called malondialdehyde (MDA). This plasma MDA could be quantified by thiobarbituric acid reactive substance (TBARS) assay (168). TBARS are highly predictive of cardiovascular events, independent of traditional risk factors (190,191).

During atheroma formation and rupture, lipid peroxidation will take place under the effect of free radicals. During the pathogenesis of atherosclerosis, when LDL particles become stuck in an artery, they could go through oxidation which is progressive and internalized by macrophages with the aid of the scavenger receptors on the surface of macrophages (168). With this internalization, the production of lipid peroxides occurs and assists the accumulation of cholesterol esters, leading to the generation of foam cells (168). Accordingly, lipid peroxidation commences in the polyunsaturated fatty acids in LDL surface phospholipids, then propagates to core lipids resulting in an oxidative change of polyunsaturated fatty acids, cholesterol moiety, and phospholipids. During cardiac ischemia-perfusion injury, ROS's lipid peroxidation of membrane polyunsaturated fatty acids is considered the major mechanism that precedes the infarction (173). MDA is such an end product of lipid peroxidation (168). During atheroma rupture, the release of MDA into circulation is expected. As atheroma rupture and lipid peroxidation of membrane lipids precede the clinical event of ACS, detection of MDA as TBARS will help diagnose ACS early.

A study done by Surekha et al. revealed that the mean values of MDA of individuals with MI were significantly higher than control (168). According to the observation made by Cavalca et al., lipid peroxidation is playing a pivotal role in CAD (168). Walter et al. concluded that serum levels of TBARS were strongly predictive of cardiovascular events in people with stable CAD. Also, they noted that these discoveries were independent of inflammatory markers and traditional risk factors (192). A study done among Egyptian patients with ACS by Ragab et al. demonstrated that significantly higher levels of serum TBARS in individuals presenting with MI and unstable angina than in controls ($P < 0.001$) (16). Studies done by Dubois-Rande and Uppal showed an upsurge in MDA plasma levels in patients with ACS (unstable angina and MI) than in patients with stable angina. This finding stresses the involvement of oxidative stress in the progression of regular CAD to unstable angina and MI (193,194).

- Protein oxidation marker - Protein Thiol/Free Thiol. Thiols are organic compounds that contain a sulfhydryl group(-SH) (195-197). Among the antioxidants prevailing

in the body, thiol constitutes the significant share of the total body antioxidants, plays a crucial role in defense against ROS, and ameliorates ROS's lipid peroxidative effects. So total thiol is a critical antioxidant in body fluid, and mammalian tissue is rich in protein thiol (20-40mM) (195,196). A significant part of thiol in plasma is derived from albumin and protein thiol and, to a lesser extent, by low molecular weight thiols such as cysteinyl glycine, cystine, homocysteine, glutathione, and γ -glutamylcysteine (195,198). Thiols have an important place in detoxification, signal transduction, apoptosis, and other molecular functions. Excessive oxidative stress leads to indiscriminate and irretrievable oxidation of protein thiols, diminution of glutathione, and cell death (199). Thiol could experience oxidation through oxidants and form disulfide bonds. Oxidation of Cys residues could result in reversible production of mixed disulfides between low-molecular-mass thiol and protein thiol groups with increased oxidative stress. Thiol disulfide bonds can be converted back to thiol groups. Therefore the homeostasis of thiol-disulfide is maintained (200). The thiol state in the body can be assessed by determining the thiol level in serum. Decreased amount of thiol is observed in diverse medical conditions, including cardiovascular disorders (192).

A study done by Tanriverdi et al. showed that the total amount of serum thiol could be suitable as a confirmatory test to diagnose individuals with NSTEMI-ACS. Further, it could differentiate patients with NSTEMI-ACS into NSTEMI and unstable angina (201). Studies show significantly reduced levels of total thiols during MI indicating high use of these thiol groups to neutralize the increased amount of ROS in these conditions (195). According to Suresh et al., decreased levels of total thiols point to augmented lipid peroxidation in acute MI patients (202). Altipark et al. found that absolute thiol levels were significantly decreased with critical CAD (203). Kundi et al. concluded that thiol/disulfide homeostasis might be a worthy biochemical risk indicator in acute MI patients on admission to hospital because this novel test is easily obtainable and comparatively cheap (200).

- Estimation of arylesterase activity.

In humans, the paraoxonase (PON) gene family has three members (PON1, PON2, and PON 3) that are positioned on chromosome 7q21.3-22.1(204,205). Enzymes: paraoxonase 1(PON1), paraoxonase 2(PON2), and paraoxonase 3(PON3) are the outcomes of those three genes (205). PON1 is principally linked with HDL, and a minor amount of PON1 enzyme is attached to very-low-density lipoprotein (VLDL) and postprandial chylomicrons. PON1 has 3 known enzymatic molecules, including organophosphate, arylesterase (ARE), and lactonase activity. PON2 is an intracellular protein, and PON3 is attached to HDL, like PON1(205-209). The arylesterase activity of PON1 is engaged in lipid peroxides detoxification, which is linked with numerous medical disorders (210).

CONCLUSION

Inflammation and oxidative stress play a crucial role in atherosclerosis and coronary heart disease. Inflammatory processes of the coronary arterial wall are involved in plaque formation, evolution, and, lastly, plaque instability sequentially leading to the clinical manifestations of acute

coronary syndromes. Over the decades, many biological markers have been measured and helped physicians arrive at ACS diagnosis. A rapid diagnosis or at least a strong suspicion of MI in the acute phase of the event is vital in directing the treatment decisions, such as using thrombolytic therapies and critical percutaneous coronary interventions. At present, diagnosis of NSTEMI depends on recognition of increase and/or decrease of cardiac biomarker concentrations (preferably troponin). Though many inflammations and oxidative stress biomarkers have been investigated, further studies need to validate them. There is growing interest in finding novel biomarkers that might be more sensitive or require shorter periods for testing than common biomarkers like cardiac-specific troponins, which may require up to 6-12 hours to exclude ACS.

Of all the above-stated biomarkers of inflammation and oxidative stress, some markers can be utilized as point-of-

care testing, which could be used in an emergency department but need further evaluation. On the other hand, various biological markers discussed above represent the initial steps of the pathogenesis of ACS. They may appear before the markers of myocardial necrosis, which are used currently in clinical practice and could utilize for early diagnosis of ACS. Using these markers in combination with biomarkers of plaque formation, unstable plaque development, plaque rupture, thrombosis, and myocardial necrosis (multimarker approach) could increase their diagnostic and prognostic value. Furthermore, it may reduce the time of assessment to exclude ACS individuals present less than six hours to the emergency department, thus reducing the duration of stay and potentially hospital costs. A multimarker approach could be the future of research.

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AUTHORS' CONTRIBUTIONS

UR conceived the research idea and conducted the literature searches, collected and collated articles, and drafted this paper. UR and RS commented in detail on drafts and contributed to the final version of the manuscript.

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