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BIOMARKERS - ITS ROLE IN MEDICINE

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ABSTRACT: Biomarker is a measurable indicator of the severity or presence of some disease state. It is introduced into an organism as a means to examine organ function or other aspects of health. Biomarkers play a major role in medicinal biology. They help in early diagnosis, disease prevention, drug target identification, drug response etc. Several biomarkers have been identified for many diseases such as cancer, cardiac diseases, nutritional epidemiology, etc. Biomarkers play a significant role in cancer prognosis, diagnosis and treatment. With discovery efforts on-going the next phase towards conversion will involve validation. This includes the steps needed to manage the new treatment model from treating clinical symptoms to targeting genomic pathways. Cardiac biomarkers are substances that are released into the blood when the heart is damaged or stressed. Measurements of these biomarkers are used to help diagnose acute coronary syndrome (ACS) and cardiac ischemia, conditions associated with insufficient blood flow to the heart. Diet is of key importance in affecting the risk of most chronic diseases in man. The introduction of biomarkers to calibrate the measurement error in dietary reports, and as additional measures of exposure, is a significant development in the effort to improve estimates of the magnitude of the contribution of diet in affecting individual disease risks in populations.

INTRODUCTION: Biomarkers also called biological markers are substances, structures or processes that can be measured in biological samples such as urine, blood or saliva. As defined by Hulka, biomarkers are cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells or fluids. They range from bio molecules like carbohydrates, proteins, lipids to genes, DNA, RNA, platelets, enzymes and hormones etc.

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Biomarkers evaluation requires an understanding of the differences among measurements of the cause of the disease, risk factors for outcome and measurements of intervention effects. Whatever biomarker is selected, it must be under the influence of the therapy/intervention and represent an important part of the casual pathway leading from the introduction of vaccine to the clinical endpoint.

Biomarkers have a significant role in diagnosis and management of disorders such as infections, cardiovascular disease, immunological and genetic disease etc. Biomarkers have also assisted in the diagnosis and treatment of nervous system disorders and to investigate their cause. Blood, brain, cerebrospinal fluid, muscle, nerve, skin and urine have been employed to gain information

about the nervous system in both the healthy and diseased state.

Biomarkers are useful in a number of ways, including measuring the progress of disease, evaluating the most effective therapeutic regime for a particular cancer type and establishing long-term susceptibility to cancer or its recurrence. Several biomarkers have been identified as tumor markers for cancer.

2. Pharmacokinetic/ Pharmacodynamics of Biomarkers: Mechanism based pharmacokinetic/ pharmacodynamic (PK/PD) models differ from empirical descriptive models in that they contain specific expressions to characterize processes on the casual path between drug administration and effect. Mechanism based PK/PD models have much improved properties for extrapolation and prediction. Within the context of mechanism-based pharmacokinetic and pharmacodynamic modelling, a biomarker is defined as a measure that characterizes, in a strictly quantitative manner, a process which is on the casual path between drug administration and effect. The new classification system of biomarkers are: [5]

1. Genotype/Phenotype determining drug response
2. Concentration of drug or drug metabolite
3. Molecular target occupancy
4. Molecular target activation
5. Physiological measures
6. Pathophysiological measurres
7. Clinical Ratings

2.1 Predictive Biomarkers: Biomarkers may be used to predict the efficacy or toxicity of a drug. Biomarkers for predicting toxicity, which is often dose related, are difficult. These effects are usually studied by increasing the dose of a compound until toxicity is observed.

In the chemo informatic approach, chemistry related toxicity can be predicted with the help of databases of known drugs that links phenotypic toxicity to a specific characteristics of a compound.

Biomarkers are used in toxicogenomics as well. Toxicogenomics is based on the idea that if the environment inside a cell's genes will likely express themselves in an a typical way. The more toxic the external stimulus, the greater the number of genes that will be altered. Conversely, if the stimulus is benign, then very few genes will change. Toxicogenomics can be used for predicting toxicity, both *in vivo* and *in vitro*, by using classification algorithms and toxicogenomics database for biomarker discovery and validation.[6]

2.2 Valid Biomarkers: A valid biomarker is defined as a biomarker that is measures in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic or clinical utility (*e.g.* predict toxicity, effectiveness or dosing) and use of epidemiology/population data are examples of approaches that can be used to determine the necessary criteria for validation. Schulte has outlined the capabilities of valid biomarkers to clinical research seen in **Table 1** and its applications in **Table 2.**

TABLE 1: CONTRIBUTIONS OF VALID BIOMARKERS TO CLINICAL RESEARCH

S.no.	Contributions of biomarkers in clinical Research
1	Delineation of events between exposure and disease
2	Establishment of dose response
3	Identification of early events in the natural history
4	Identification of mechanisms by which exposure and disease are related
5	Reduction of misclassification of exposures or risk factors and disease
6	Establishment of variability and effect modification
7	Enhanced individual and group risk assessments

TABLE 2: DISEASE BIOMARKERS IN CLINICAL DEVELOPMENT

Term	Applications
Predisposition Biomarkers	To identify predisposition to a disease, *e.g*; genetic
Screening Biomarkers	To identify those suffering from a disease
Staging Biomarkers	To determine the stage of progression of the disease
Prediction Biomarkers	To predict the course of the disease
Pregnostic Biomarkers	To access disease progression and outcome
Recurrence monitoring Biomarkers	Ti identify recurrence of the disease

3. Types of Biomarkers: There are many ways of classifying biomarkers. The biomarkers may be simple molecules such as metabolites, carbohydrates, steroids and lipids, peptides such as insulin, Hb A & C, prostate specific antigen and C-reactive protein.

3.1 Genes as Biomarkers: A gene is a sequence of chromosomal DNA that is required for the production of a functional protein or a functional RNA molecule. A gene includes not only the actual coding sequences but also adjacent nucleotide sequences required for the proper expression of genes, *i.e.* for the production of a normal mRNA molecules.

Patterns in which a gene is expressed provides clues to its biological role. Malfunctioning of genes is involved in most diseases, not only inherited ones.

3.2 Proteins as Biomarkers: Different combinations of amino acids link to form proteins. A protein cannot be synthesized without its mRNA. There is, thus a relation between mRNA and protein. Peptides are small proteins that play a central role in almost all biological processes. They function as biochemical messengers (for *e.g.* insulin, calcitonin and angiotensin) or occur as metabolites of proteins.

3.3 DNA &RNA Biomarkers: Genetic information is contained in the cells in the form of DNA. DNA contains the instructions for making proteins. RNA is the other major nucleic acid besides DNA but unlike DNA, it is single stranded. The structure of an RNA molecule is determined by its DNA-derived sequence.

Characteristics of an ideal Biomarker:

- According to FDA, an ideal biomarker must be specifically associated with a particular disease or disease state and be able to differentiate between similar physiological conditions.
- It would be desirable if standard biological sources, such as serum and urine, could be used for identifying biomarkers.
- A rapid, simple, accurate and inexpensive detection of the relevant marker should be available, together with a measurable and standard baseline as a reference point.

5. Role of Biomarkers in Medicine:

5.1 Cancer biomarkers: Cancer Biomarkers refer to a substance or process that is indicative of the presence of cancer in the body. A biomarker may be a molecule secreted by a tumor or a specific response of the body to the presence of cancer. Genetic, epigenetic, proteomic, glycomic and imaging biomarkers can be used for cancer diagnosis, prognosis and epidemiology [7].

With numerous challenges existing, a no. of gene and protein based biomarkers are being used such as AFP (Liver Cancer), BCR-ABL (Chronic Myeloid leukemia), BRCA1/ BRCA2 (Breast/ Ovarian Cancer), BRAF V600E (Melanoma/ Colorectal cancer), CA-125 (Ovarian Cancer) and many others. Mutant proteins detected by Selected Reaction Monitoring (SRM) have been reported to be the most specific biomarkers for cancers because they can only come from an existing tumor.[8]

5.1.1 Diagnosis: Cancer biomarkers can also be useful in establishing a specific diagnosis, especially whether tumors are of primary or metastatic origin. To confirm, researchers screen the chromosomal alterations found on cells located in the primary tumor site against those found in the secondary site. If the alterations match, the secondary tumor can be identified as metastatic; whereas if the alterations differ, the secondary tumor can be identified as a distinct primary tumor.[9]

5.1.2 Treatment Predictions: Biomarkers are useful in determining the aggressiveness of an identified cancer as well as its likelihood of responding to a given treatment. *e.g.* metallopeptidase inhibitor 1 (TIMP1), a marker associated with more aggressive forms of multiple myeloma [10], estrogen receptor and/or progesterone receptor, markers associated with patients with breast cancer [11], HER2/ neu gene amplification, a marker indicating a breast cancer will likely respond to trastuzumab treatment [12], a marker indicating Gastro Intestinal Stromal Tumor (GIST) will likely respond to imatinib treatment [13], and mutations in the tyrosine kinase domain of EGFR1, a marker indicating a patient's non-small-cell lung

carcinoma (NSCLC) will likely respond to gefitnib or erlotinib treatment [14].

5.1.3 Pharmacodynamics and Pharmacokinetics: Cancer biomarkers can also be used to determine the most effective treatment regime for a particular person's cancer. Because of differences in each person's genetic makeup, each individual has a different rate of metabolism. Decreased metabolism of certain drugs can create dangerous conditions in which high levels of the drug accumulate in the body. Therefore drug dosing decisions in cancer treatments can benefit from screening of such biomarkers.

Table 3 lists the type of cancer biomarkers.

TABLE 3: TYPE OF CANCER BIOMARKERS

Tumour type	Biomarker
Breast	ER/PR, HER-2/ neu
Colorectal	KRAS, UGT1A1
Gastric	HER-2/ neu
GIST	c-KIT, CD 20 Antigen, CD 30
Leukemia	PDGFR, TPMT,UGT1A1
Lung	ALK, EGFR KRAS
Melanoma	BRAF
Pancreas	Elevated levels of leucine, isoleucine & valine

5.2 Biomarkers in nutritional epidemiology: A dietary biomarker can be defined as a biochemical indicator of dietary intake/nutritional status (recent or long term), or it may be an index of nutrient metabolism, or a marker of the biological consequences of dietary intake [15]. The main advantage of—or the main assumption behind—dietary biomarkers is that they are objective measures and are independent of all the biases and errors associated with study subjects and dietary assessment methods [16].

An 'ideal' dietary biomarker would accurately reflect its dietary intake level and it would be specific, sensitive and applicable to many populations. Existing dietary biomarkers are not 'ideal', but they are functional and have found wide spread applicability in modern nutritional epidemiology. In general, dietary biomarkers can be divided into several classes (recovery, predictive, concentration, replacement). One of the main applications of dietary biomarkers is to use them as reference measurements to assess the validity and accuracy of dietary assessment methods.

The most important dietary biomarkers for this application are the 'recovery' biomarkers (*i.e.* doubly labelled water which is utilized to measure the metabolic rate and total energy expenditure; urinary total nitrogen/ potassium which are utilized to estimate total daily protein consumption and potassium intake, respectively) [17]. Recovery biomarkers are based on the concept of the metabolic balance between intake and excretion over a fixed period of time and so provide an estimate of absolute intake levels. In other words, excretion levels are highly correlated with intake [18]. However, before being applied to the task of questionnaire validation, such biomarkers need to be tested in calibration studies under controlled conditions (*e.g.* in a metabolic suite) in order to establish that their predictability in humans consuming varying diets is comparable to the dietary intake method under consideration. Unfortunately, the cost and complexity of these techniques makes them largely inapplicable for widespread epidemiologic use and they are best applied either in post hoc analyses of ongoing investigations, or built-in to the design of new studies, for example the use of doubly labelled water in the OPEN study [19] and markers of potassium and nitrogen in 24 h urine collections.

The recently defined class of 'predictive' biomarkers can also be utilized to assess the degree of measurement errors in dietary assessment methods. Like recovery biomarkers, predictive biomarkers are sensitive, time dependent and show a dose-response relationship with intake levels but the distinction is that their overall recovery is lower [20]. The only current examples are 24 h urinary sucrose and fructose which are closely correlated with intake of sugars, despite the very small fraction of intake which is actually present in urine collections.

The class of 'concentration' biomarkers (*e.g.* serum vitamins, blood lipids, urinary electrolytes) are also available for comparison with estimates of dietary intake. For example, results from a dietary intake method which agreed most closely with such biomarkers would be expected to yield more reliable estimates of intake than one which did not.

Concentration biomarkers cannot be translated into absolute levels of intake but the biomarker concentrations do correlate with intakes of corresponding foods or nutrients, although the strength of the correlation is often lower (0.8).

'Replacement' biomarkers are closely related to concentration biomarkers and refer specifically to compounds for which information in food composition databases is unsatisfactory or unavailable, for example aflatoxins, some phytoestrogens [21], salt or metabonomic factors. Depending on the specific dietary biomarker (*e.g.* some fatty acids), the distinction between the concentration and replacement classes may be vague. A common application of concentration or replacement dietary biomarkers is for the estimation of diet-disease risk associations. This use is increasingly finding application in population studies such as prospective cohort studies, where biological samples are collected before disease onset, or intervention/controlled clinical studies looking at the effect of dietary treatments or nutrient supplementation on disease risk or progress. The underlying concept is that the use of such biomarkers may lead to a better ranking of subjects for exposure to a particular food group or nutrient than would dietary assessment methods. In fact, the biomarker level measured in the blood or other biological samples takes into account any effects of absorption, influences of microbiota (*e.g.* bioconversion, release of bioactive dietary compounds, enterohepatic circulation), interactions between nutrients, tissue turnover, metabolism and excretion. Additional considerations are issues pertaining to nutrient bio accessibility and bioavailability.

All of these points are very important because they highlight that food components and nutrients are influenced by a large number of host factors, both metabolic and genetic, that may affect the correlation of a biomarker with the relevant dietary exposure. In addition, other factors such as the type of biological sample obtained, how the sample was collected, treated, and stored, the laboratory methodology used to measure the biomarker (precision, accuracy and detection limits of the analytical technique; variations from method to method or laboratory to laboratory) can also affect the measurement and utility of dietary biomarkers **(Fig. 1**).

FIG. 1: FACTORS THAT MAY AFFECT THE MEASUREMENT AND UTILITY OF A DIETARY BIOMARKER TO PROPERLY REFLECT DIETARY EXPOSURES IN INDIVIDUALS OR TARGET POPULATIONS

Genetic Variability:

- genes that may affect dietary intake patterns, taste, attraction to specific foods or food types
- biological variation in nutrient absorption, metabolism, tissue turnover, excretion
- epigenetic variation, gene-gene interactions

Lifestyle or Physiologic Factors:

- smoking, alcohol consumption, exercise, gender, age, body weight, socioeconomic status
- influence of colonic microbiota (bioconversion, release of bioactive dietary compounds)
- enterohepatic circulation of nutrients (*e.g.* phytoestrogens, lignans) metabolic and inflammation related disorders, stress, occult / underlying disease

Dietary Factors:

- range or frequency of intake for a particular nutrient
- nutrient-nutrient interactions, nutrient bioavailability, influence of food matrix

Biological Sample:

- type of sample collected for analysis of biomarkers (*e.g.* whole blood, plasma, serum, urine)
- conditions of sample collection, transport, treatment, storage conditions, length of storage
- diurnal variation, day of the week or season of sample collection

Analytical Methodology:

- precision, accuracy, detection limits of the analytical technique
- variations from method to method or laboratory to laboratory.

The combination of all of the above factors makes it very difficult to compare absolute concentrations of certain dietary biomarkers across various studies which are based on different populations and utilize different biological samples and analytical techniques. Currently, very little is known about how genetic variation may influence dietary intake, food choices, nutrient metabolism, or affect the bio-availability, absorption, transport, biotransformation, and excretion of nutrients or bio-active dietary components. Extensive information already exists on genetic variation in taste and how that may affect food preferences and dietary habits [22].

It is probably safe to assume that genetic variability, gene-diet/nutrient interactions and gene-gene (epistatic) interactions may result in differential response to dietary factors along with changes in nutrient metabolism and dietary biomarker levels. Some examples that have yet to be confirmed in different populations are folate and the MTHFR gene, Vitamin D and the VDR gene and iron and the HFE gene. This may significantly affect the measurement and utility of a dietary biomarker to properly reflect dietary exposures and suggests that the validity of some dietary biomarkers may well be population (or even individual) specific with respect to genetic background or other characteristics [23].

Nevertheless, very few studies to date have considered possible gene-diet/ nutrient or gene-gene interactions as potentially determining factors in the validity and application of dietary biomarkers. The interaction of genes and diet is engendered in the concepts of nutrigenomics (study of how diet influences gene transcription, protein expression and metabolism) and nutrigenetics (study of how genetic disposition affects response to diet and its components), which are extensively reviewed elsewhere [24].

A key message is that the consideration of genetics is important for nutritional scientists and the consideration of dietary assessment methodology and dietary biomarker measurement is of relevance to geneticists. The issues raised above are all pertinent to the validity, application and interpretation of dietary biomarkers.

5.3 Cardiac Biomarkers: Cardiac biomarkers are protein components of cell structures that are released in to circulation when myocardial injury occurs. They play a pivotal role in the diagnosis, risk stratification and treatment of patients with chest pain and suspected acute coronary syndrome (ACS) as well as those with acute exacerbations of heart failure. Cardiac markers are central to the new definition of acute myocardial infarction (AMI) [25, 26].

Therefore, the cardiac markers can be classified as markers of necrosis, markers of inflammation. The features of an ideal cardiac marker would be:

- High sensitivity and specificity
- Rise and fall after ischemia
- Able to perform reliably and uniformly
- Be simple to perform
- Have turnaround time<60 min
- Not influenced by functioning of other organs, functioning of kidney.

Therefore , cardiac biomarkers is an umbrella term which is used to define present day used necrosis markers as well as all the upstream markers of necrosis studied /under study including pro inflammatory cytokines, cellular adhesion molecules, acute phase reactants, plaque destabilization biomarkers, plaque rupture biomarker and pre necrosis ischemia biomarkers. This can be simply visualized with the help of **Fig. 2**.

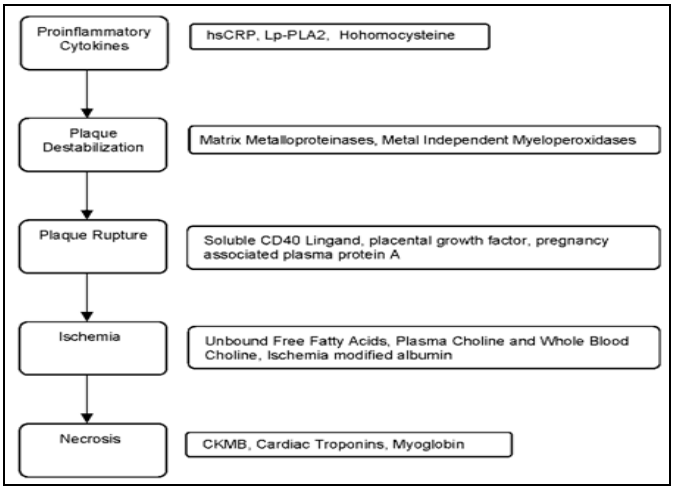

FIG. 2: CLASSIFICATION OF CARDIAC BIOMARKERS

5.3.1 Early markers of cardiac necrosis: Cardiac markers are used in the diagnosis and risk stratification of patients with chest pain and suspected acute coronary syndrome (ACS). The cardiac troponins, in particular, have become the cardiac markers of choice for patients with ACS. Indeed, cardiac troponin is central to the definition of acute myocardial infarction (MI) in the consensus guidelines from the American college of cardiology (ACC) and the European Society of Cardiology.

A typical rise and/or gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis, with at least one of the following is required:

- Ishemic symptoms
- Development of pathologic Q waves on the ECG
- ECG changes indicative of ischemia(ST segment elevation or depression)
- Imaging evidence of new loss of
- Viable myocardium or a new regional wall motion abnormality.

Cardiac markers and those used in the past have been outlined in the **Table 4**.

TABLE 4: LIST OF CARDIAC BIOMARKERS

Current Cardiac Markers	Cardiac Markers of the Past
CK-MB	Total CK Activity
Myoglobin	Aspartate Aminotransferase Activity
CKMB Isoforms	Lactate Dehydrogenase Activity
Troponin I and T	LD1/LD2 Ratio

Creatinine Kinase: [26] The enzyme creatinine kinase (formally referred to as creatinine phosphokinase) exists as three isoenzyme forms: CK-MM, CK-MB and CK-BB. These isoenzymes are found in the cytsol and facilitate the egress of high energy phosphates into and out of mitochondria. Creatinine kinase exits as dimer and composed of 2 monomers: M (43,000Da) and B (44,500 Da) and the isoenzymes of creatinine kinase are CK BB, CK MB or CK MM. The level of CK BB increases in neurological disease; prostectomy and digestive cancers however ,the level of CK MB increases with Acute Myocardial Infarction(AMI) and the level of CK MM increases in myopathy, hypothyroidism, polymyosistis, rhabdomyolysis, muscle trauma, intensive exercise, intensive exercise, AMI. Creatine kinase isoenzyme activity is distributed in a number of tissues but the percentage of CK-MB fraction found in the heart is higher than in most other tissues.

Its presence is diagnosed in case of Myocardial injury after cardiopulmonary resuscitation, cardioversion, Defibrillation, cardiac and non-cardiac surgical procedures, Blunt chest trauma with possible cardiac contusion and it starts rising in the blood 4-6 hours after the onset of chest pain which peaks at 10-24 hours and then returns to normal after 48-72 hours. Since CK levels return to baseline 48 to 72 hours after infarction, it can be used to detect reinfarction.

5.3.3 Cardiac Troponins: Cardiac Troponins (cTn) is a complex which control the calcium-mediated interaction of actin and myosin. It exists in three isoforms: Troponin C(18 KD) functions as calcium binding subunit, Troponin I(26.5 KD) functions as Actomyosin-ATP-inhibiting subunit and the last one is Troponin T(39 KD) which anchors troponin complex to the tropomyosin strand [27].

The genes that code for the skeletal and cardiac isoforms of Troponin C are identical, thus no structural difference exists between them. However, the skeletal and cardiac subforms for Troponin I(TnI) and Troponin T(TnT) are distinct and these can be detected during the assays of heart muscle injury with great specificity and sensitivity.

Cardiac troponins begin rising in the blood 4-6 hours post infarction, it peaks in 12-24 hours but may take weeks to return to normal. Cardiac troponins are as sensitive as CK-MB during the first 48 hours after acute myocardial infarction. The sensitivity is 33% from 0-2 hours, 50% from 2-4 hours, 75% from 4-8 hours and approaching 100% from 8 hours after onset of chest pain. The following is a list of some of the causes for the elevation of troponin in the absence of a thrombotic occlusion of the coronary artery:

- Tachy-or bradyarrhythmias, or heart block
- Critically ill patients, especially with diabetes, respiratory failure or sepsis
- Hypertrophic cardiomyopathy
- Coronary vasospasm, congestive heart failure, Renal failure, Pulmonary embolism
- Acute neurological disease, including stroke or subarachnoid hemorrhage
- Transplant vasculopathy, Extreme exertion, Drugs toxicity, inflammatory disease

Myoglobin: Myoglobin is a heme protein found in skeletal and cardiac muscle that has attracted considerable interest as an early marker in Myocardial Infarction. Its low molecular weight accounts for its early relaease profile: myoglobin typically rises 2-4 hours after onset of infraction, peaks at 6-12 hours, and returns to normal within 24-36 hours. Assays shows that myoglobin lacks cardio specificity, however there are some conditions where the level of myoglobin increases like acute myocardial infarction, vigorous exercise, open heart surgery, rhabdomyolysis, progressive muscular dystrophy, shock and renal failure.

5.3.5 Markers of Inflammation: In this section, cardiac inflammatory markers are dealt with which is at the verge of entering into clinical practice as tool for diagnosing and predicting future cardiovascular events at earlier stage and risk of stratification. Highly Sensitive Creative Protein (hsCRP), Myeloperoxidase (MPO), Matrix Metalloproteinase (MMP), Pregnancy Associated Protein A (PAPP-A), Placenta Growth Factor (PIGF) are reviewed.

5.3.6 C-reactive Protein: C-reactive protein is an acute phase reactant synthesized in liver and found in serum or plasma at elevated levels during an inflammatory process. It is a sensitive marker of acute and chronic inflammation and infection and in such cases, is increased several hundred-fold. Clinical studies have shown CRP to be associated with short-term and long term morality risk not only for patients with acute or chronic heart disease but also for those at risk for atherosclerosis [28]. Increases in CRP levels detected by assays with expanded sensitivity to a very low levels of CRP, so called high sensitivity-sensitivity CRP(hs-CRP), showed a strong correlation as an independent risk factor for future cardiac events [29].hs-CRP predicts new coronary events in patients with ACS and unstable angina(UG), AMI and restenosis after revascularization procedures, independent of Troponin T [30]. The estimations that more than 30% of patients with severe UA do not present with elevated hs-CRP levels along with its non-specific nature pose a limitation to its use [31].

5.3.7 Myeloperoxidase (MPO): Released from activated neutrophils, myeloperoxidase(MPO) is a leukocyte enzyme possessing powerful pro-oxidative and pro-inflammatory properties that play important role in pathogenesis of destabilization of coronary artery disease(CAD). MPO catalyzes the conversion of chloride and hydrogen peroxide to hypochlorite and also been implicated in the oxidation of lipids contained in LDL cholesterol and consumption of endothelial-derived nitrous oxide thereby reducing nitrous oxide bioavailability and impairing its vaso dilating and anti-inflammatory properties CAD than angiographically verified normal individuals [32]. New rapid tests for MPO levels have been developed and studies suggest that a value of more than 350 µg/l is associated with a considerably increased risk of heart disesase [33]. MPO plays a role in the degradation of the fibrous cap, making it both a marker of inflammation (neutrophil activation) and plaque instability (that precedes ACS), which makes it a useful marker for short term stratification.

5.3.8 Matrix Metalloproteinasaes (MMP): MMP are endogenous zinc dependent endo peptidases or basically a family of proteolytic enzymes that cleave the extracellular matrix and have been shown to be regulated by the class of

proteins called tissue inhibitors of metalloproteinases. They are categorized based on substrate specificity and structure, with MMP-2 and MMP-9(gelatinases) being of most current interest in inflammation and cardiac disease. Several studies have shown that extracellular matrix degradation by MMPs, specifically MMP-9, are involved in the pathogenesis of a wide spectrum of cardiovascular disorders, including artherosclerosis, restenosis, cardiomyopathy, congestive heart failure, MI and arotic aneurysm [34 35]. Similar to MPOs, the proteinases MPP-2 and MMP-9 are released from macrophages within the artherosclerotic plaques and have attracted attention as markers of plaque rupture. In patients with ACS MMP-2 and MMP-9, levels at hospital admission are found to be two or three-fold higher as compared to the patients with stable angina pectoris [36- 37].

5.3.9 Placental Growth Factor (PGF): Placental Growth Factor is a member of VEGF (vascular endothelial growth factor) subfamily-a key molecule in angiogenesis and vasculogensis, in particular during the embryogenesis. Recent studies established the role of different inflammatory markers such as hs CRP, sr amyloid A, IL-6 not only gets elevated during acute coronary syndrome (ACS) but predicts its adverse outcomes. PGF was recently shown that it is upregulated in all forms of atherosclerotic lesions. Plasma PIGF levels may be an independent inflammatory biomarker of poor outcome in patients with suspected ACS [38-39].

5.3.10 Pregnancy-Associated Plasma Protein Alpha (PAPP-A): Human pregnancy-associated plasma protein-A (PAPP-A) is a 200kDa metalloproteinase belonging to the metzincin superfamily of zinc peptidases originally identified in the serum of pregnant women before delivery [40-42] The role of PAPP-A in tissue other than placenta including fibroblasts, vascular smooth muscle cells, and male and female reproductive tissues has been explored [43-44]. Circulating PAPP-A levels increase during pregnancy and they are used in the fetal diagnosis of Down Syndrome. It is one of six different proteases that degrades insulin like growth factor binding proteins. This proteolytic degradation of the insulin like growth factor binding proteins mechanism for the release of bioactive insulin growth factor-1(IGF-1) [45]. It is believed that PAPP-A is released during plaque destabilization and appears to be a valuable indicator of UA and AMI in patients lacking other indicators of necrosis [46]. In a study of patients with angiographically confirmed ACS, an elevated level of serum PAPP-A was a strong independent predictor of non fatal AMI or death and also able to identify patients at risk [47].

5.3.11 Soluble CD40 Ligand: The CD40 and CD40 ligand (CD40L) system is expressed on a variety of cell types including activated platelets, vascular endothelial cells, vascular smooth muscle cells, monocytes and macrophages. After expression on the cell surface, CD40L is partly cleaved by proteases and subsequently released into the circulation as soluble CD40L that can be detect in serum and plasma. The main source of circulating sCD40L is platelets [48]. Several clinical studies have consistently reported that sCD40L is elevated in patients with ACS and that it provides prognostic information with therapeutic implications independent of established cardiac markers, for example cardiac troponins [49].

5.3.12 Interleukin-6: Interleukin-6(IL-6) is a cytokine, a non antibody protein and intercellular mediator. Cytokine IL-6 is produced by a variety of cells in the body; plasma concentrations reflect body; plasma concentrations reflect both the intensity of plaque vulnerability to rupture and following coronary intervention, restenosis [50]. Elevation of circulating IL-6 is a strong and independent marker of increased mortality in acute coronary events [51-52].

5.3.13 Markers of Ischemia: An ideal marker is one in which there is a specific easily measurable increase that clearly aligns with a predictable outcome be it evidence of ischemia, inflammation, myocardial necrosis, plaque rupture, plaque destabilization or heart failure.

5.3.14 Ischemia Modified Albumin: Albumin loses its ability to bind transitional metal like copper, cobalt, and nickel in its N terminus region as it undergoes conformational change because of ischemia. This alteration may likely to be caused by hypoxia, acidosis, free radical injury or energy dependent membrane disruption [53-55]. Studies also shown that ischemia-modified albumin (IMA) is a

sensitive biomarker for the identification of ACS in patients presenting the ED with typical pain in the chest at rest [56]. The albumin cobalt binding test has been approved by the FDA for use as a rule out marker for acute myocardial ischemia. The optimum cut-off for IMA, for ruling out ACS is 85 KU/I and the higher values of 100KU/I or more can be used for risk stratification. It is estimated that approximately 1-2% of the total albumin concentration in the normal population is IMA compared to 6-8% in patients experiencing ischemia and it is also found to be elevated in most patients with cirrhosis, bacterial and viral infections, advance cancers, stroke (brain ischemia) and end –stage renal disease [57].

5.3.15 Glycogen Phosphorylase Isoenzyme BB: Glycogen phosphorylase (GP) plays an essential role in the regulation of carbohydrate metabolism by mobilization of glycogen [58]. It catalyses the first step in glycogenolysis in which glycogen is converted to glucose-1-phosphate, utilizing inorganic phosphate.GP is a dimer composed of two identical subunits and three different isoenzymes have been described in human tissues: GPLL(brain), GPMM(muscle) and GPBB(brain). Although isoenzymes BB and MM are found in the heart, GPBB is predominant [59]. In cardiomyocytes, GP is associated with glycogen and the sarcoplasmin reticulum and forms macromolecular complex known as the sarcoplasmin reticulum glycogenolysis complex [60]. With the onset of tissue hypoxia, GP is thereby converted from a particulate, structurally bound form into a soluble, cytoplasmin form. A higher GPBB concentration gradient is immediately formed in the peri sarcoplasmatic reticulum compartment and GPBB is released from cardiomyocytes upon an increase in the cell membrane permeability which makes GPBB an early marker for detection of ischemic myocardial damage [61], hence GPBB is a promising marker for the early diagnosis of ACSs and could probably act as a marker of ischemia [62].

5.3.16 Unbound Free Fatty Acids: Free fatty acids (FFA) play several essential roles in physiologic homeostasis, also plasma long chain fatty acids are either esterified to glycerol or non esterified (or FFAs) most of which are bound to albumin. Under aerobic conditions, non esterified long-chain FFAs represent the primary metabolic sources for the myocardium, accounting for almost two-thirds of the ATP generated [63]. During hypoxia and ischemia, non esterified fatty acids/FFAs have damaging effects on heart tissue and have been associated with an increased incidence of ventricular dysrhythmias and death in patients [64].

5.3.17 Fatty Acid Binding proteins (FABPs): FABPs are relatively small (15kDa) intercellular transport proteins that carry fatty acids and other lipophilic molecules like eicosanoids and retinoids across the membranes also actively produced in the tissues having active fatty acid metabolism including the heart, liver and intestine [65].These are bind long chain fatty acids and currently occur in nine different isoforms in a predictable tissue distribution and fairly long half life of several days. The heat type FABP(H-FABP) is released following myocardial death within 6 hours and is not specific to heart like myoglobin *i.e*. it is produced not only in cardiomyocytes but also, to a lesser extent, in skeletal muscle, distal tubular cells, brain, lactating mammary glands and placenta [66]. H-FABP is not found in the circulation (plasma concentration <5 µg/ml) under non pathological conditions and is rapidly released after AMI [67].

Therefore H-FABP has been touted as an alternative to myoglobin but its limitation include lack of complete cardiac specificity, a relatively small diagnostic window of 24-30 h after acute event, and the probability of falsely increased values in patients with renal insufficiency cardiac specificity [68]. Several immunosensors have been developed using enzyme amperometric, immuno-optical or immunoassay technologies. At present there is only one immuno chromatographic POCT assay for H-FABP (rennesens Cardio Detect) available commercially [69].

5.3.18 Phospholipase Enzyme and Choline: The idea of a marker of plaque destabilization for the very early diagnosis of patients with MI is very attractive because the marker is effectively a surrogate for direct detection of ischemia, also plaque rupture or erosion is the underlying pathophysiological event, which lead to ischemia then to infraction. There is a great sense of possibility that choline and phospholipase A_2 and choline are good markers of plaque instability and drawn much attention in assessing their role in

ischemia associated coronary artery disease. Basically phospholipases are enzyme sub grouped into four major categories (A-D) that catalyse phospholipids into fatty acids and another lipophilic substance [70]. Lipoprotein associated phospholipase A_2 was associated with an almost 2-3 fold increase in stroke [71]. Phospholipase D catalyzes membrane-bound phospholipids producing phosphatidic acid and choline. It also involved with the promotion of fibrinogen binding to platelets [72]. Several experimental studies support the concept that phospholipase D activation is a key event in early ischemic membrane damage and in coronary plaque destabilization. Choline has been identified as a promising marker for ACS by metabolic screening of human blood [73]. Increased levels of plasma choline and whole blood choline levels have been seen n tissue ischemia in patients with negative troponin values. Choline is not a marker for myocardial necrosis but indicated high-risk unstable angina in patients without acute myocardial infarction (sensitivity 86.4%, specificity 86.2% [74]. Therefore obtaining levels of both plasma choline and whole blood choline may prove to be a useful aid in patients suspected of ACS.

CONCLUSION: In most scenarios this array of biomarkers can only adjuvant the over-all clinical picture that spans findings of history-examination and the laboratory values in navigating towards the diagnosis and severity of diseases such as cancer.[75, 76, 77] Nevertheless the quest for the ideal biomarker goes on and clinicians need to be abreast of such relentless developments.

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