Chapter 5

Novel Biomarkers to Understand Cardiovascular Complications in Diabetes

Ramu Adela and Sanjay K. Banerjee

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62595

Abstract

Diabetic subjects have shown two- to fourfold increased risk of cardiovascular diseases (CVDs) than without diabetes. Diabetes can be prevented if detected early at prediabetes stage. Progression of diabetes not only causes hyperglycaemia; it also increased the risk of macrovascular and microvascular complications. Different mechanisms, i.e. inflammation, abnormal adipocyte signalling, insulin resistance, endothelial dysfunction, and oxidative stress, are involved in the progression of diabetes and associated cardiovascular complication. These mechanisms alter different signalling molecules in blood and other body fluids. These altered molecules offer potential biomarkers for the identification and early detection of the disease progression. If we are able to detect the early biomarkers based on the alteration of different mediators responsible for cardiac complications in diabetes, we can prevent the cardiac diseases in diabetes by selective therapy. Different kinds of biomarkers, i.e. miRNA, protein, metabolites, cytokines, and adipokines, can be used together to detect the different stages of the disease. In the present book chapter, we are explaining briefly about characteristics of biomarkers and their applications and different approaches that were used to identify biomarkers. Different existing and novel biomarkers and their scope to detect patients with prediabetes, diabetes and cardiovascular complication in diabetes have been discussed.

Keywords: type 2 diabetes, biomarkers, cardiovascular diseases, metabolic syndrome, coronary artery diseases

1. Introduction

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" [1]. Research interest

on biomarkers has increased in recent years. In MedLine search in 1990, there were only 21 hits on cardiovascular risk markers, while by 2010, it is increased to 2032 hits, thus indicating huge increase in number of publications in biomarkers in the last decade [2]. There were 37% more biomarker studies in 2014 as compared to 2013 [3]. However, only few biomarkers are routinely used in clinical practice. For example, fasting blood sugar, glycated haemoglobin, cardiac troponin T (cTnT), cardiac troponin I (cTnI), and B-type natriuretic peptide (BNP) are used regularly for diabetes, myocardial infarction, and heart failure. Biomarkers should have specific characteristics, i.e. specific to the particular diseases and easily detectable. Biomarker can be predictive to identify disease progression after treatment. The detection method should be fast, simple, and low cost. It should be stable at any time of the day and samples should be available easily by invasive method (blood and urine). Identified biomarker should be proven of its importance preclinically and clinically. Biomarker can be used for different purposes such as the early detection of disease, evaluation of acute and chronic clinical condition, risk stratification of patients to suspect or confirm the diagnosis, selection of appropriate therapeutic treatment, and observation of patient response for the treatment (**Figure 1**) [4]. Identification of early biomarkers for noncommunicable chronic diseases such as diabetes is very important for finding appropriate therapeutic strategy.

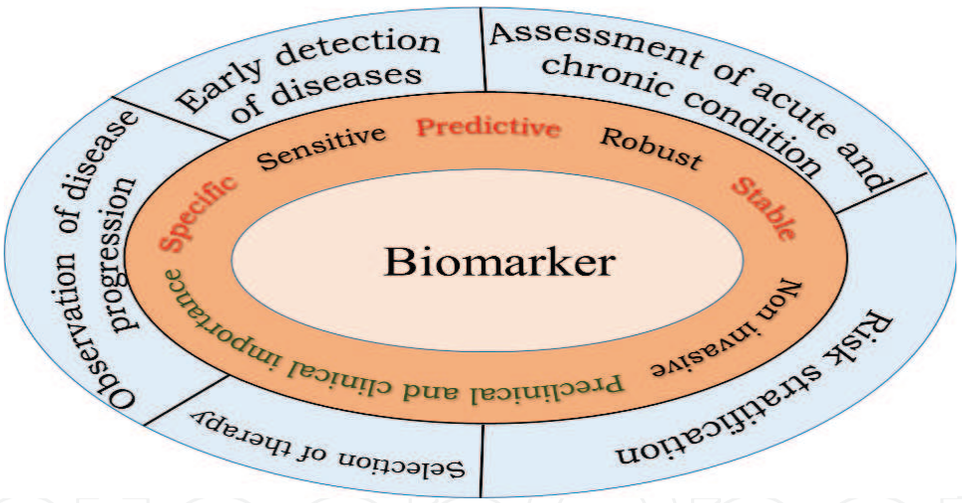

Figure 1. Biomarker characteristics (inner circle) and applications (outer circle).

Prevalence of diabetes is reaching epidemic proportions in developed and developing nations due to increase in life expectancy, sedentary lifestyle, and obesity. As per the International Diabetic Federation (IDF) Diabetes Atlas (Sixth Edition 2013), the number of people with diabetes is 382 million and it is going to rise to 592 million by 2035. Global burden of diabetes is huge and 548 billion dollars was spent in 2013. In India, approximately 65.1 million people are with diabetes. Cardiovascular diseases (CVDs) are the major complications of diabetes. The prevalence, incidence, and mortality of cardiovascular diseases are two- to fourfold higher in persons having diabetes than those without diabetes [5]. Prediction of cardiovascular disease (CVD) risk among people with diabetes is important not only to give better clinical therapy but also to distinguish higher risk patients for extra care. Biomarkers may help in early

http://dx.doi.org/10.5772/62595

detection of diseases, distinguishing patients based on disease severity, and find the cardiovascular risk among diabetic patients.

1.1. Diabetes and its cardiovascular complications

Diabetes is characterised by high glucose level in blood due to either less insulin secretion from pancreas or developing insulin resistance in skeletal muscle. Type 2 diabetes (T2DM) is the commonest form and it is characterised by insulin resistance mostly in skeletal muscle and deficiency of insulin release at end stage. In general, T2DM causes elevation of blood glucose level and other components of metabolic syndrome. Parameters of metabolic syndrome are elevated blood pressure, increased triglycerides, reduced high density lipoprotein levels, and abdominal obesity [5]. In obese condition, increased adipocytes secrete adipocytokines. Released adipocytokines integrate the endocrine, autocrine, and paracrine signals to mediate the insulin sensitivity, oxidative stress, energy metabolism, blood coagulation, and inflammatory responses. Elevated levels of free fatty acids (FFAs) induce insulin resistance and increase fibrinogen and plasminogen activator inhibitor-1 (PAI-1). In the long run, high FFA and glucose together impair beta-cell function through lipotoxicity and glucotoxicity and develop macro- and microvascular complications [6,7].

Diabetes and cardiovascular diseases are involved in different abnormalities in genes, proteins, metabolites, and lipids by different mechanisms such as oxidative stress, inflammation, and endothelial dysfunction. Identification of highly sensitive and specific potential biomarkers would be beneficial for the detection of cardiovascular diseases risk among diabetic patients with different advanced omics approaches such as genomics (genes), metabolomics (metabolites), proteomics (proteins), transcriptomics (mRNA), and lipidomics (lipids) (**Figure 2**). These

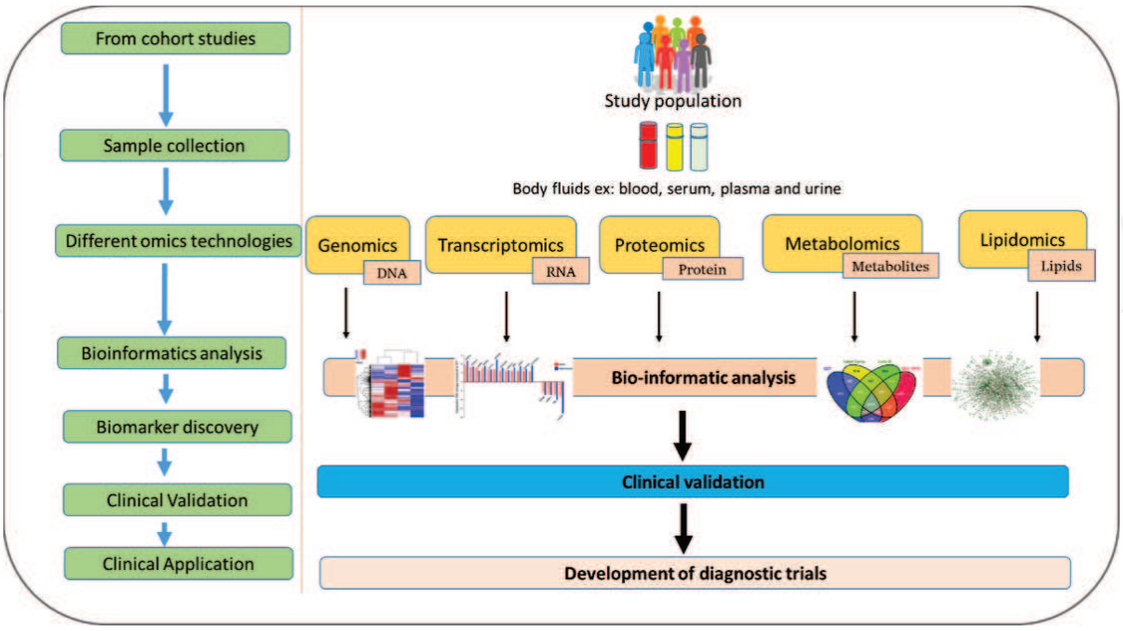

Figure 2. Development of biomarkers with the help of different omics approaches.

new techniques are useful for simultaneous investigation of multiple molecules and to identify different kinds of biomarkers (**Table 1**).

Different omics approaches	Study of different molecules	Technology used
Genomics	DNA	DNA microarray Single nucleotide polymorphism Hot spot mutation Epigenomics
Transcriptomics	mRNA tRNA rRNA Noncoding RNA	RNA microarray New-generation sequencing (NGS) Exome sequencing
Proteomics	Proteins and their abundance, variation, modific ations, and interactions	2D-PAGE Protein microarray Mass spectrometry MALDI-TOF-MS ESI-MS
Metabo lomics	Metabolites	NMR Mass spectrometry–LC–MS
Lipi domics	Lipids	Mass spectrometry–LC–MS/MS

Table 1. Omics approaches target for different molecules.

2. Different omics approaches used for the identification of biomarkers

(*i*) *Genomics* is a systematic study of structure, function, and expression of organism's genome. This involves DNA sequencing, assembly, as well as analysis of an annotation of structure and function of the gene. The single nucleotide polymorphism array (SNP array) is a type of DNA microarray that can be used to detect polymorphisms within the whole genome. Next-generation sequencing (NGS) has gained considerable attention for investigations at the nucleotide levels including both DNA and RNA sequences. (*ii*) *Transcriptomics* is a study of total set of RNA including mRNA, tRNA, rRNA, and microRNA. Single gene was analysed by single-gene detection method individually, and thousands of gene expression are analysed simultaneously by high-throughput analysis such as DNA microarrays. (*iii*) *Proteomics* is a study of all expressed proteins and it gives information about protein abundance, variation, modification, and interaction through signalling pathway and network analysis. Initially two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) technique was used to determine whole protein expression. In this method we can separate a large number of protein mixture based on molecular weight and isoelectric point. This technique has initially been used to find global changes of protein expression. However, recently mass spectrophotometer has been used to identify protein alterations. Mass spectrometry has been utilised to separate ions from

proteins, peptides, or metabolites according to their mass-to-charge ratio (*m*/*z*) and to provide data as mass spectrum that can be further analysed to determine characteristics of molecular mass and structure. However, proteomics studies are more complicated due to presence of high-abundant proteins such as albumin and immunoglobulins (serum) that may mask the important biomarker candidates. To overcome this problem, different depletion columns are available for removing high-abundant proteins and immunoglobulins. With mass spectrometry the two types of approaches were targeted (preselected panel of proteins) and untargeted (without any assumptions total proteins are captured). Protein microarray has also been developed to detect thousands of proteins based on specific antibody detection. (*iv*) *Metabolomics* is a systemic approach to evaluate the metabolic profile, which can be useful in biomarker discovery. Metabolites are usually considered as good biomarkers due their stability. Metabolome analysis can be performed using a variety of techniques such as nuclear magnetic resonance (NMR) as well as mass spectrometry. Metabolites were also studied in two ways as same as proteomics, i.e. targeted and untargeted [8]. (*v*) *Lipidomics* is systemic approach to study large-scale changes in lipids and understand the regulation of lipid metabolism. This will be analysed with the help of LC–MS/MS. These omics approaches offer simultaneous estimation of different molecules through high-throughput screening. After identification of set of proteins/genes/metabolites/lipids by omics approach, there is a need for validation of each marker by other methods. **Table 2** shows a list of biomarkers identified by different omics approaches.

Diseases	Study name	Approach	Sample type	No. of patients	Biomarkers identified	Reference
Prediabetes	KORA	Metabo lomics	Serum	4297	Three metabolites (glycine, lysoph osphatid', and acetylcarnitine) that altered significant levels in impaired glucose tolerance (IGT) as compared with normal glucose tolerance	[98]
Type 2 diabetes	–	Prote omics (2D-LC–MS/MS)	Saliva	40 (10 control, 10 I FG, 10 IGT, 10 T2DM patients)	487 biomarkers identified	[99]
T2DM	Frami ngham Off spring	Metabo lomics	Plasma	Rando mly se lected	Out of 70 metabolites 2-AAA (2-amino adipic acid) had the	[100]

Diseases	Study name	Approach	Sample type	No. of patients	Biomarkers identified	Reference
	Study			1561 individuals	strongest association with risk of future diabetes mellitus	
Cardiovascular diseases	Bruneck study	Lipidomics	Plasma	685 subjects with 10-year observation period	Cholesterol esters (CEs), lysophosphatidylcholines, phosphatidylcholines, phosphatidylethanolamines (PEs), sphingomyelins, and triacylglycerols (TAGs) were associated with cardiovascular disease	[101]
Obesity and insulin resistance	The Western Australian Pregnancy Cohort (Raine) Study	Lipidomics	Plasma	1126 patients with 20-year follow-up	Sphingomyelins, particularly those with two double bonds, and lysophosphatidylcholines were identified between subjects with normal weight and obesity independent of LDL-C and HDL-C concentrations	[102]
Cardiovascular diseases	National Finnish FINRISK study, SABRE study, and BWHH Study	Metabolomics	Serum	FINRISK (n = 7256; 800 events), SABRE (n = 2622; 573 events), and British Women's (n = 3563; 368 events)	Higher phenylalanine and monounsaturated fatty acid levels were associated with increased cardiovascular risk, while higher omega-6 fatty acids and docosahexaenoic acid levels were associated with lower risk	[103]
Cardiovascular diseases	–	Metabolomics	Plasma	2023 consecutive patients undergoing cardiac catheterisation	Five metabolite factors were independently associated with mortality: factor 1 (medium-chain acylcarnitines, short-chain dicarboxylacylcarnitines,	[104]

Diseases	Study name	Approach	Sample type	No. of patients	Biomarkers identified	Reference
					long-chain dicarboxylacyl carnitines), factor 6 (branched-cha in amino acids)	
Type 2 diabetes	–	Lipidomics	Plasma	104 wo men with previ ous ges tational diabetes; 21 (20%) developed diabetes during the median follow-up period of 8.5 years	Cholesteryl ester species CE 20:4 , alkenylphosphatidylethan olamine species PE (P-36:2), and the phosphatidyls erine species PS 38:4 were independently and positively associated with the development of type 2 diabetes	[105]

Table 2. Biomarkers identified by different omics approaches in diabetes and cardiovascular diseases.

Although there are a high number of research articles describing existing and promising biomarkers for diabetes and cardiovascular disease, here we are providing an overview of a few standard and exciting biomarkers that regularly used in clinic.

3. Existing and standard biomarkers in diabetes and cardiovascular diseases

Glycated haemoglobin (HbA1c) and glucose levels are mostly used for the diagnosis of diabetes. These two tests give idea about sugar levels in the body in the presence and absence of medication. However, these tests can be used to predict the disease in the later stages not in the early stages. So, there is an urgent need to identify novel biomarkers to detect the early stage of diabetes, i.e. prediabetic stage.

Troponin T (cTnT), troponin I (cTnI), and creatinine kinase-MB (CK-MB) are the common markers for the diagnosis of myocardial injury and stratification of the risk in acute coronary syndrome. cTnI is as effective as cTnT in diagnosing myocardial necrosis in the setting of trauma and coronary bypass grafting [9]. Increased hs-cTnT concentrations are associated with extent and complexity of CAD as well as diabetic patients with stable CAD [10]. Recently, Brendan et al. reported that cardiac troponin T concentration was an independent predictor

of death from cardiovascular causes, myocardial infarction, or stroke in patients who had both type 2 diabetes and stable ischemic heart disease [11]. European Society of Cardiology (ESC) and the American College of Cardiology (ACC) guidelines have recommended cardiac troponins are markers for the acute myocardial infarction. These sensitive markers (cTnT and cTnI) begin to rise in the first 4–8 h following injury and peak at 12–24 h. However, cTnT may remain raised for more than two weeks while cTnI for more than 5–7 days. These two detect myocardial injury below the detection limit of CK-MB. Some of the clinicians measured CK-MB to rule out myocardial infarction and to monitor for additional cardiac muscle injury over time [9].

Natriuretic peptides [brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP)] and their N-terminal pro-hormones [N-terminal pro-atrial natriuretic peptide (NT-pro-ANP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP)] were increased in patients with heart failure, i.e. left ventricular dysfunction. In general, these markers are produced initially within the heart and released into the circulation in response to increased wall tension. BNP and ANP are secreted not only from the atria but also from the ventricles, especially in patients with heart failure. BNP and NT-pro-BNP may be superior to ANP and NT-pro-ANP in the detection of left ventricular dysfunction [12].

C-reactive protein (CRP) is a liver-derived pattern recognition molecule and systemic inflammatory marker that is increased in inflammatory states. It releases rapidly after immediate tissue injury and work as host defence [13]. Interleukin-6 (IL-6) is the most potent inducer of CRP production, and hsCRP (high-sensitivity C-reactive protein) is released from activated leukocytes in response to infection or trauma and from vascular smooth muscle cells in response to atherosclerosis [14]. Inflammation plays a major role in type 2 diabetes and cardiovascular diseases. Inflammation is the one of the risk factors for the development of T2DM and CVD. Researchers have identified that increased hsCRP levels were associated with obesity, metabolic syndrome, type 1 diabetes, type 2 diabetes, atherosclerosis, and coronary artery diseases (CADs) [15]. Increased blood hsCRP levels indicate the coexistence of subclinical systemic inflammation and insulin resistance and correlated with elevated insulin, C-peptide, and HOMA-IR (Homeostatic Model Assessment-insulin resistance) [16]. Treatment with aspirin, statins, cyclooxygenase-2 inhibitors, and fibrates are able to reduce hsCRP levels [13]. Treatment with peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist pioglitazone also decreased hsCRP along with other cardiovascular risk markers [17].

Pro-inflammatory cytokines, i.e. tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-1-beta, and IL-8 and monocyte chemoattractant protein (MCP-1); cell adhesion molecules, i.e. intra-cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1); and markers of cardiovascular risk, i.e. C-reactive protein (CRP), homocysteine, and plasminogen activator inhibitor-1 (PAI-1) and reactive oxygen species (ROS) are the common markers for inflammation and oxidative stress. Metabolic hormones such as resistin, leptin, adiponectin, ghrelin, and visfatin were also altered in diabetes and metabolic disorder and considered as important biomarkers for understanding the diabetic complication.

All these above markers are used to predict diabetes and cardiovascular diseases independently but not in a combination to understand the disease complexity. Even these biomarkers

http://dx.doi.org/10.5772/62595

are not able to predict the disease in the early stages. Thus, there is an urgent need to identify novel biomarkers to predict the early detection of the disease and disease progression.

4. Exploring novel biomarkers for diagnostic and prognostic biomarkers for diabetes and its cardiovascular complications

4.1. Galectin-3

Galectin-3 (Gal-3) a 30-kDa β-galactoside-binding lectin mainly present in the cytoplasm, and also in the nucleus, is expressed by different types of cells and regulates various T-cell functions and innate immune responses. Expression of galectin-3 increased in activated macrophages and involved in inflammation, tumour growth, and fibrosis [18,19]. Gal-3 protects β-cells from the cytotoxic effect of IL-1β [20] and advanced glycation end product (AGE)-induced tissue injury. Removal of Gal-3 accelerates AGE-induced kidney injury in diabetes [21], enhances atherogenesis [22], accelerates high-fat diet-induced obesity, and increases inflammation in adipose tissue and pancreatic islets. Gal-3 shows protective effect in obesity-induced inflammation and diabetes [18]. Ohkura et al. reported that low levels of Gal-3 were associated with insulin resistance in T2DM patients [23]. On the contrary, elevated levels of Gal-3 are associated with increased risk of heart failure and mortality [24]. Recently, Ozturk et al. identified that Gal-3 concentrations were significantly higher in the coronary artery disease (CAD) group than in the non-CAD group. Gal-3 levels were correlated positively with BMI (Body mass index), high-sensitivity C-reactive protein, the total number of diseased vessels, the number of plaques, and the calcified plaque type. In addition, galectin-3 levels were found to be independent predictor of coronary atherosclerosis in type 2 diabetic patients. Gal-3 is a novel and promising biomarker that may help to identify type 2 diabetic patients who may require early CAD intervention because of the potential risk of coronary atherosclerosis [25]. Jin et al. reported that elevated galectin levels were associated with increase in vascular complications, i.e. the heart failure, nephropathy, and peripheral artery diseases. Several research articles have shown association of Gal-3 with diabetes and cardiovascular diseases. However, many questions still need to be answered before considering Gal-3 as a biomarker in diabetes and cardiovascular diseases: Can Gal-3 specifically be used as a biomarker for diabetes-associated cardiovascular diseases (Gal-3 is usually expressed in the inflammatory and fibrinolytic conditions in the liver, kidney, and lungs; this shows lack of tissue specificity)? Can Gal-3 alone predict the disease prevention strategy? Can it be used with any other established marker to predict diabetes-associated cardiovascular complications?

4.2. Irisin

Irisin is a newly discovered hormone which is mainly secreted by the heart, skeletal muscle, liver, and kidneys. Bostrom et al. reported that cardiac muscle produces more irisin than skeletal muscle. Irisin is mainly produced within heart and skeletal muscle [26]. Irisin is essential to convert white adipose tissue to brown adipose tissue. He et al. found that irisin levels were decreased and urotensin II (UII) levels were increased in type 2 diabetic subjects.

Circulating urotensin II levels were increased in diabetes and could inhibit the glucose transport in skeletal muscle in diabetic mouse and aggravated the insulin resistant [27]. The study found the association between both irisin and urotensin II and concluded that urotensin II and high glucose may inhibit the release of irisin from skeletal muscle in diabetic patients [28]. Increased circulating irisin predicts the insulin resistance onset in association with weight regain and authors concluded that irisin could be secreted as an adaptive response to counteract the deleterious effect of excess adiposity on glucose homeostasis [29]. Two-week treatment with simvastatin increased circulating irisin concentrations in healthy individuals and also in primary human skeletal muscle cells. Simvastatin induces both cellular stress markers as well as protective response markers. Simvastatin-induced irisin secretion can block mitochondrial oxidative stress and thus play an important role in the regulation of oxidative stress in human skeletal muscle [30]. Irisin is also secreted in response to the activation of PGC-1α. Previous studies have explained well regarding the regulation of PGC-1α in mitochondrial biogenesis, oxidative metabolism, mitochondrial function, and modulation of insulin resistance. Decreased PGC-1α levels in type 2 diabetic subjects as reported earlier [31–33] might be responsible for reduced irisin levels. There is a controversy regarding irisin levels in obesity, insulin resistance, and metabolic syndrome in type 2 diabetic patients. While some reported higher irisin levels in diabetic patients, others reported the opposite [34–36]. These discrepancies were due to the data analysed from different stages of diseases and the presence of other complications [26]. Researchers have reported that serum irisin levels were decreased in type 2 diabetes and myocardial infarction patients [37,38]. Aronis et al. reported that increased irisin levels predict the development of major cardiovascular events, especially unstable angina, in patients with CAD after percutaneous intervention (PCI) [39]. Hanatani et al. also reported that irisin is a novel biomarker providing prognostic information in patients with heart failure with reduced ejection fraction. However, further clinical studies are needed to find whether irisin is associated with cardiometabolic disease and evaluate whether circulatory irisin levels could serve as an independent prognostic marker in diabetic patients with cardiovascular complications and also elucidate beneficial effects by finding molecular mechanism and intervention studies in different animal models.

4.3. Apelin

Apelin is identified as a 36-amino acid peptide and is an endogenous ligand of G-protein-coupled receptors (GPCRs) of apelin receptor. Recently, apelin was recognised as adipokine and secreted from white adipose tissue. Apelin receptor is present in ventricular cardiomyocytes, vascular smooth muscle cells (VSMCs), and intra-myocardial endothelial cells (ECs) [40]. Apelin stimulates endothelium-dependent nitric oxide-mediated vasorelaxation and reduces arterial blood pressure. Apelin synthesis in adipocytes is stimulated by insulin, and apelin plasma levels are markedly increased in obesity associated with insulin resistance [41]. Apelin shows antioxidant effects and attenuates reactive oxygen species (ROS)-induced adipogenesis, lipogenesis, lipolysis, and release of free fatty acids [42]. Apelin knockout mice show diminished insulin sensitivity [43]. Tumour necrosis factor-α (TNF-α) induces the expression of apelin via phosphatidylinositol 3-kinase (PI3K), c-Jun N-terminal kinase (JNK) and MEK1/2 signalling pathways in adipocytes [44]. Chronic treatment with apelin ameliorates both

glucose and lipid metabolism and also increases muscle mitochondrial performance through increased mitochondrial biogenesis and a tighter matching between fatty acid oxidation and the tricarboxylic acid cycle. Therefore, chronic apelin treatment can be a targeted therapy for type 2 diabetes and its complications [45]. Furthermore, in studies using lipopolysaccharide (LPS) and cytokines to elicit an immune response in rodents, the expression of apelin mRNA has been reported to be upregulated, involving the JAK/STAT pathway [40]. Ma et al. reported that plasma apelin is a novel biomarker for predicting type 2 diabetes in men [46]. It was reported that suppressed apelin levels were associated with increased cardiovascular risk in women with previous history of gestational diabetes [47]. Recently, Abd-Elbaky et al. reported that omentin levels were significantly lower and serum apelin and IL-1β concentrations were significantly higher in obese diabetic groups compared to nonobese controls. This study concluded that abnormal production of omentin and apelin can contribute to the pathogenesis of obesity-related complications including T2DM and cardiovascular disease [48]. However, further research is needed to confirm whether apelin can be used as biomarker in diabetes and cardiovascular diseases.

4.4. Growth differentiation factor-15

Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine produced as a ≈40 kDa propeptide form and N-terminal cleaved to release as a ≈30 kDa disulphide-linked dimeric active protein form. It is highly expressed in cardiomyocytes, adipocytes, macrophages, endothelial cells, and vascular smooth muscle cells in normal and pathological condition. GDF-15 increases during tissue injury and inflammatory states and is associated with cardiometabolic risk. Increased GDF-15 levels are associated with cardiovascular diseases such as hypertrophy, heart failure, atherosclerosis, endothelial dysfunction, obesity, insulin resistance, diabetes, and chronic kidney diseases in diabetes. Researchers have reported that GDF-15 shows cardioprotective effect through activation of ALK (Activin receptor-like kinase) type 1 receptor (ALK 1–7) and GDF-15 phosphorylates Smad2/3 and Smad1/5/8 which translocate to the nucleus in the form of heteromeric complex with Smad4 and activates PI3K/AKT/eNOS/NO pathway. It also inhibits epidermal growth factor receptor (EGFR) transactivation and NF-kB/JNK/caspase-3 pathway. Many patents have been filed reporting GDF-15 as a marker for the diabetes and cardiovascular diseases. Patent no. EP2439535A1 claimed that GDF-15 can be distinguished between diabetes and diabetes with coronary artery diseases subjects. Recently, we have also shown that GDF-15 levels can be useful to distinguish diabetic patients from cardiovascular complications [5]. However, a large multinational study has to be conducted to validate GDF-15 as a biomarker to detect specific cardiovascular complication in diabetes.

4.5. Growth differentiation factor-11

Growth differentiation factor-11 (GDF-11) is a cytokine that belongs to TGF-β super family and also known as bone morphogenetic protein-11 (BMP-11). GDF-11 works like myostatin to modulate metabolic function [49]. Previous scientific literature claimed that GDF-11 is an anti-ageing factor. Fadini et al. showed that circulating GDF-11 levels were decreased with age [50].

Peripheral supplementation of GDF-11 protein in mice attenuated the age-related dysfunction of skeletal muscle [51]. In recent years, researchers are focusing their interest on circulatory GDF-11 levels in heart diseases. GDF-11 levels reversed the age-related hypertrophied heart into a young heart [52]. GDF-11 is also an essential factor for the regeneration of pancreatic islets in diabetic patients [53]. The plasma GDF-11 levels with age and disease condition remain controversial. Egerman et al. in his study showed that an increased GDF-11 protein level was observed with age in rat skeletal muscle. However, serum GDF-11 levels in rat and human were not significantly increased [54]. In contrast, Poggioli et al. explained age-dependent decline in GDF-11 levels in multiple mammalian species such as mice, rats, horses, and sheep. They also showed that exogenous GDF-11 administration rapidly activates SMAD signalling to reduce cardiomyocyte size [55]. This property of reducing cardiomyocytes can be useful against cardiac hypertrophy. Two more recent studies supported the above statement. Heidecker et al. showed that low levels of GDF-11 and high levels of its inhibitor follistatin-like 3 are associated with adverse cardiovascular outcomes in humans [56]. Similarly Olson et al. reported that high levels of GDF-11 are associated with lower prevalence of left ventricular hypertrophy [57]. Recently, Adela et al. reported that plasma GDF-11 levels were decreased in diabetes and diabetes with cardiovascular complications as compared with control subjects [58]. To use GDF-11 as a biomarker for diabetes and diabetes associated with cardiovascular diseases, more research needs to be carried out with a different population. GDF-11 could be used as a biomarker or as an intervention therapy to reduce the disease progression.

4.6. Cyclophilin A

Cyclophilin A (CyPA) was discovered three decades ago as the intracellular receptor of the immunosuppressive drug cyclosporine. CyPA is secreted from vascular cell components of endothelial cells and vascular smooth muscle cells in response to the reactive oxygen species (ROS) and also expressed in T cells, neutrophils, monocytes, macrophages, and foam cells and shows cellular effects such as proliferation, migration, activation of NF-kB, induction of matrix metalloproteinases, adhesion of molecules, and induction of ROS [59]. Extracellular CyPA initiates expression of adhesion molecules in endothelial cells (EC), induces apoptosis, and works as a chemoattractant for inflammatory cells. Intracellular and extracellular CyPA promotes intimal thickening, abdominal aortic aneurysms, atherosclerosis, and cardiac hypertrophy in mice [60]. Recently Tsai et al. reported that hyperglycaemia causes release of CyPA in mesangial (MES-13) and tubular (HK-2) cells. Urinary CyPA correlated with the progression of renal function. Significant increase in urinary CyPA was noted in stage 2 diabetic nephropathy and persisted in later stages of the disease. This study concluded that CyPA is a new biomarker for diabetic nephropathy and can be used as an early maker [61]. Type 2 diabetes subjects have increased circulating levels of CyPA than the healthy subjects. CyPA is secreted by monocytes in response to high glucose treatment and responsible for the progression of atherosclerosis in type 2 diabetes [62]. Further authors found that plasma CyPA levels were increased in diabetes subjects with coronary artery disease. This study concluded that CyPA play important role to progress vascular disease in type 2 diabetes subjects. The scientific literature thus provides strong evidence that CyPA work as inflammatory mediator

in the progression of atherogenesis [63]. Therefore, all data indicate that CyPA is a promising and potential biomarker for the detection of vascular diseases in type 2 diabetes [64].

4.7. Prolactin

Prolactin is a polypeptide released as a pituitary hormone. Prolactin is named so for its ability to promote lactation in post pregnancy in female mammals. Other than lactogenic property, prolactin plays important role in the regulation of reproduction, growth and development, metabolism, immune regulation, brain function, and behaviour [65]. Prevalence of obesity was increased in hyperprolactinaemic patients [66]. Circulating levels of prolactin increase in diabetic patients. Increased prolactin levels were associated with lower prevalence of diabetes and impaired glucose regulation [65,67]. However, Balbach et al. reported that low circulatory prolactin concentration is associated with increased T2DM risk. However, this study did not show any evidence to prove prolactin as a cardiometabolic risk factor [68]. Prolactin levels were increased in essential hypertension, acute coronary syndromes, ischemic strokes, transient ischemic attacks, pre-eclampsia, and heart failure. Carrero et al. also reported that increased prolactin levels were associated with endothelial dysfunction, increased risk of cardiovascular events, and increased mortality in chronic kidney disease (CKD) patients [69]. In vitro studies show that prolactin stimulates integrin-mediated adhesion of circulating mononuclear cells to endothelium and induces vascular smooth muscle cell proliferation. Reuwer et al. study did not predict the prolactin as predictor for the coronary artery diseases in spite of presence of prolactin receptors in human coronary artery plaques [70]. On the other hand, increased plasma prolactin can protect rat cardiomyocytes against hypoxia through the p-JAK2 and p-STAT5 pathways and the PI3Kα/AKT and MAPK survival pathways [71]. Landberg et al. reported that prolactin concentrations were not associated with cardiovascular mortality and thus not a marker of heart failure [72]. However, a cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy and authors claimed that inhibition of prolactin may be a new therapeutic strategy for the paripartum cardiomyopathy [73].

4.8. Vitamin D

Vitamin D is a secosteroid that exists in two forms, i.e. ergocalciferol (D2) and cholecalciferol (D3). Ergocalciferol (D2) is synthesised from the vegetable sources. Unlike D2, cholecalciferol (D3) is synthesised by the epidermis on exposure to the UV radiation (sunlight) and also from oily fish supplementation. Vitamin D (D2 and D3) is converted into active metabolite 1, 25(OH)2 D by the two hydroxylation steps. These active metabolites bind with the vitamin D receptor and exert its biological action [74]. Vitamin D receptors are present in many cells such as pancreatic β cells, cardiomyocytes, endothelial cells, and vascular smooth muscle cells. Vitamin D plays a pivotal role in the bone and mineral metabolism. Vitamin D deficiency is a common health problem worldwide and is the cause for osteoporosis and osteomalacia, rickets, and other bone-related disorders. In the recent decades, researchers have also identified that lower vitamin D levels were associated with metabolic diseases such as type 1

diabetes, obesity, insulin resistance, hypertension, cardiovascular diseases, and cancer [75,76]. Many epidemiological studies have reported that people from different countries are more prevalence to vitamin D deficiency [77–82]. Eight-week vitamin D replacement therapy in type 2 diabetic patients potentially has beneficial effects on cardiovascular disease risk factors such as HbA1c, total cholesterol, LDL-C, and diastolic blood pressure [83]. Tarcin et al. reported that 25(OH)D-deficient subjects has lower flow-mediated dilatation (FMD) which is useful to measure endothelial dysfunction and was improved after acute treatment with calcitriol [84]. Vitamin D is a negative regulator of renin–angiotensin system and blood pressure [85]. Recently Jisu et al. reported that deletion of macrophage vitamin D receptor promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice. This study suggested that vitamin D plays an important role in inflammation and thus responsible for the development of type 2 diabetes and atherosclerosis [86]. Vitamin D can be used as a biomarker to predict the disease severity of diabetes and cardiovascular complications. However, for better understanding the role of vitamin D in pathophysiology of diabetes and cardiovascular diseases, more intervention studies with long-term follow-up are required.

4.9. Pregnancy-associated plasma protein-A (PAPP-A)

PAPP-A is a zinc-binding matrix metalloproteinase that regulates extracellular matrix remodelling. PAPP-A degrades IGFBP-4 and increases the levels of local IGF-1 in response to injury and involved in the pathogenesis of atherosclerosis. Two inflammatory cytokines, i.e. TNF-α and IL-1, are involved in insulin resistance development and most potent stimulators of PAPP-A [95]. Many researchers reported that elevated levels of PAPP-A were associated 36 with coronary artery diseases, e.g. acute coronary syndrome [[88]-[93]]. On this contrary, Pellitero et al. reported in their study that serum PAPP-A concentrations were significantly lower in diabetic subjects and correlated negatively with HbA1C. PAPP-A concentration was lower in patients with HbA1C > 8.2% (0.35 mUI/l [0.07–0.43]) compared with that in patients with HbA1C < 5.9% (0.72 mUI/l [0.2–0.92], $P < 0.03$). However, PAPP-A levels were not changed in hypercholesteraemic subjects when compared with normal cholesterolaemia subjects. It is also reported that genetic deletion of PAPP-A is associated with resistance to atherosclerotic lesion development in apolipoprotein E-deficient mice fed with a high-fat diet by decreasing bioavailability of IGF-1. This study indicates that PAPP-A is essential to promote lesion formation through regulation of IGF-1 action [94]. Serum PAPP-A and IGF-1 do not appear to be useful serum biomarkers for carotid atherosclerosis in type 2 diabetic patients with stable glycemic control, despite scientific evidence of their local role in atherosclerosis. [87]. However, Hjortebjerg et al. have reported that PAPP-A is a prognostic marker for acute coronary syndrome [96]. Recently Conover et al. reported that targeted inhibition of PAPP-A reduces atherosclerotic plaque burden in mice. This study is giving evidence that inhibition of PAPP-A can be used as therapeutic strategy in atherosclerosis [97]. However, further studies need to be conducted to find its role in diabetes and associated cardiovascular complication.

http://dx.doi.org/10.5772/62595

5. Conclusion

Cardiovascular complication is the major cause of the death of diabetes worldwide. At present, all standard available markers are useful to detect diabetes and cardiovascular disease separately but not suitable for identifying the cardiovascular complication at early and late stages of the diseases progression. There is an urgent need to identify novel biomarkers by using different omics approaches using large number of patients having desired phenotype. Identified markers can also able to assist in clinical decision making such as interventions and medications. Recently all new markers such as vitamin D, GDF-15, galectin-3, and cyclophilin-A identified have a strong association with type 2 diabetes and cardiovascular disease. However, these yet have not been implemented in the clinical practice. Before accepting any new markers as clinical biomarkers, the following questions need to be answered: whether new identified biomarkers can be used to take clinical decision for any particular diseases, whether it can be useful in therapeutic management and provide any diagnostic and prognostic information, and whether identified biomarkers can be used as a single marker or in a combination with other biomarkers. Identifying new biomarker may also help to understand the affected signalling pathways related to the disease and discover novel therapy against diabetes and cardiovascular complications.

Future biomarker discovery is showing excitement and raising many challenges. One of the major challenges in biomarker discovery is to develop biomarkers for personalised medicine. Biomarkers can play a critical role in classifying patients into subpopulations. In the present days, predicting the therapeutic strategy through personalised medicine is more familiar. However, more research needs to be done to develop specific biomarker to make personalised medicine successful. Personalised medicine is developing tremendously in cancer treatment. However, researchers should focus more on diabetes and cardiovascular disease to initiate personalised medicine in metabolic diseases. Other challenges in biomarker discovery include active collaboration between basic scientists and clinicians. Formation of different societies and organisations need to be established like HUPO (Human Proteome Organization) organisation for the proteomics and to prepare biomarkers databases for free access. Scientific communities need to debate with the issue whether individual diagnostic and prognostic biomarker or combined panel of biomarkers are more useful to predict the cardiovascular outcome among diabetic patients.

Author details

Ramu Adela and Sanjay K. Banerjee*

*Address all correspondence to: skbanerjee@thsti.res.in; banerjees74@hotmail.com

Drug Discovery Research Centre (DDRC), Translational Health Science and Technology Institute (THSTI), Faridabad, Haryana, India

References

[1] Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med. 1989; 8:431–440.

[2] Lindahl B. The story of growth differentiation factor 15: another piece of the puzzle. Clin Chem. 2013; 59(11):1550–2. DOI: 10.1373/clinchem.2013.212811.

[3] Audette J. Chart of the week: clinical trials involving biomarkers seeing huge growth. Available from: http://www.amplion.com/biomarker-trends/chart-of-the-week-how-many-trials-will-be-using-biomarkers-in-2020. [2016-02-05].

[4] Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation. 2006; 113(19):2335–62. DOI: 10.1161/CIRCULATIONAHA.104.482570.

[5] Adela R, Banerjee SK. GDF-15 as a target and biomarker for diabetes and cardiovascular diseases: a translational prospective. J Diabetes Res. 2015; 2015:490842. DOI: 10.1155/2015/490842. Epub 2015 Jul 27.

[6] Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014; 2014:943162. DOI: 10.1155/2014/943162.

[7] Sivitz WI. Lipotoxicity and glucotoxicity in type 2 diabetes. Effects on development and progression. Postgrad Med. 2001; 109(4):55–9, 63–4.

[8] Seeree P, Pearngam P, Kumkate S, Janvilisri T.An omics perspective on molecular biomarkers for diagnosis, prognosis, and therapeutics of cholangiocarcinoma. Int J Genomics. 2015; 2015:179528. DOI: 10.1155/2015/179528.

[9] Maynard S, Menown I, Adgey A. Troponin T or troponin I as cardiac markers in ischaemic heart disease. Heart. 2000; 83:371–373. DOI:10.1136/heart.83.4.371

[10] Ucar H, Gur M, Seker T, Kaypakli O, Elbasan Z et al. High-sensitivity cardiac troponin T is associated with SYNTAX score and diabetes mellitus in patients with stable coronary artery disease. J Clin Exp Cardiol. 2013; 4:263. DOI:10.4172/2155-9880.1000263

[11] Everett BM, Brooks MM, Vlachos HE, Chaitman BR, Frye RL, Bhatt DL; BARI 2D Study Group. Troponin and cardiac events in stable ischemic heart disease and diabetes. N Engl J Med. 2015; 373(7):610–20. DOI: 10.1056/NEJMoa1415921.

[12] Bay M, Kirk V, Parner J, Hassager C, Nielsen H, Krogsgaard K, Trawinski J, Boesgaard S, Aldershvile J. NT-proBNP: a new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function. Heart. 2003; 89(2):150–4.

[13] Pfutzner A, Forst T. High-sensitivity C-reactive protein as cardiovascular risk marker in patients with diabetes mellitus. Diabetes Technol Ther. 2006; 8(1):28–36.

[14] Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, Blumenthal RS, Budoff MJ. High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? J Am Coll Cardiol. 2013; 62(5):397–408. DOI: 10.1016/j.jacc.2013.05.016.

[15] Santos AC, Lopes C, Guimaraes JT, Barros H. Central obesity as a major determinant of increased high-sensitivity C-reactive protein in metabolic syndrome. Int J Obes (Lond). 2005; 29(12):1452–6.

[16] Mahajan A, Tabassum R, Chavali S, Dwivedi OP, Bharadwaj M, Tandon N, Bharadwaj D. High-sensitivity C-reactive protein levels and type 2 diabetes in urban North Indians. J Clin Endocrinol Metab. 2009; 94(6):2123–7. DOI: 10.1210/jc.2008-2754.

[17] Hanefeld M, Marx N, Pfützner A, Baurecht W, Lubben G, Karagiannis E, Stier U, Forst T. Anti-inflammatory effects of pioglitazone and/or simvastatin in high cardiovascular risk patients with elevated high sensitivity C-reactive protein: the PIOSTAT Study. J Am Coll Cardiol. 2007; 49(3):290–7.

[18] Pejnovic NN, Pantic JM, Jovanovic IP, Radosavljevic GD, Milovanovic MZ, Nikolic IG, Zdravkovic NS, Djukic AL, Arsenijevic NN, Lukic ML. Galectin-3 deficiency accelerates high-fat diet-induced obesity and amplifies inflammation in adipose tissue and pancreatic islets. Diabetes. 2013; 62(6):1932–44. DOI: 10.2337/db12-0222.

[19] de Boer RA, Yu L, van Veldhuisen DJ.Galectin-3 in cardiac remodeling and heart failure. Curr Heart Fail Rep. 2010; 7(1):1–8. DOI: 10.1007/s11897-010-0004-x.

[20] Karlsen AE, Størling ZM, Sparre T, et al. Immune-mediated beta-cell destruction in vitro and in vivo—a pivotal role for galectin-3. Biochem Biophys Res Commun. 2006; 344:406–415.

[21] Pugliese G, Pricci F, Iacobini C, et al. Accelerated diabetic glomerulopathy in galectin-3/AGE receptor 3 knockout mice. FASEB J. 2001; 15:2471–2479.

[22] Iacobini C, Menini S, Ricci C, et al. Accelerated lipid-induced atherogenesis in galectin-3-deficient mice: role of lipoxidation via receptor-mediated mechanisms. Arterioscler Thromb Vasc Biol. 2009; 29:831–836.

[23] Ohkura T, Fujioka Y, Nakanishi R, Shiochi H, Sumi K, Yamamoto N, Matsuzawa K, Izawa S, Ohkura H, Ueta E, Kato M, Miyoshi E, Taniguchi S ,Yamamoto K. Low serum galectin-3 concentrations are associated with insulin resistance in patients with type 2 diabetes mellitus. Diabetol Metab Syndr. 2014; 6(1):106. DOI: 10.1186/1758-5996-6-106.

[24] Ho JE, Liu C, Lyass A, Courchesne P, Pencina MJ, Vasan RS, Larson MG, Levy D. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. J Am Coll Cardiol. 2012; 60(14):1249–56. DOI: 10.1016/j.jacc.2012.04.053.

[25] Ozturk D, Celik O, Satilmis S, Aslan S, Erturk M, Cakmak HA, Kalkan AK, Ozyilmaz S, Diker V, Gul M. Association between serum galectin-3 levels and coronary atherosclerosis and plaque burden/structure in patients with type 2 diabetes mellitus. Coron Artery Dis. 2015; 26(5):396–401. DOI: 10.1097/MCA.0000000000000252.

[26] Chen JQ, Huang YY, Gusdon AM, Qu S.Irisin: a new molecular marker and target in metabolic disorder. Lipids Health Dis. 2015; 14:2. DOI: 10.1186/1476-511X-14-2.

[27] Wang HX, Wu XR, Yang H, Yin CL, Shi LJ. Urotensin II inhibits skeletal muscle glucose transport signalling pathways via the NADPH oxidase pathway. PLoS One. 2013; 8(10):e76796. DOI: 10.1371/journal.pone.0076796.

[28] He WY, Bai Q, A LT, Tang CS, Zhang AH. Irisin levels are associated with urotensin II levels in diabetic patients. J Diabetes Investig. 2015; 6(5):571–6. DOI: 10.1111/jdi.12331.

[29] Crujeiras AB, Zulet MA, Lopez-Legarrea P, de la Iglesia R, Pardo M, Carreira MC, Martínez JA, Casanueva FF. Association between circulating irisin levels and the promotion of insulin resistance during the weight maintenance period after a dietary weight-lowering program in obese patients. Metabolism. 2014; 63(4):520–31. DOI: 10.1016/j.metabol.2013.12.007.

[30] Gouni-Berthold I, Berthold HK, Huh JY, Berman R, Spenrath N, Krone W, Mantzoros CS. Effects of lipid-lowering drugs on irisin in human subjects in vivo and in human skeletal muscle cells ex vivo. PLoS One. 2013; 8(9):e72858. DOI: 10.1371/journal.pone.0072858.

[31] Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol. 2008; 9(5):367–77. DOI: 10.1038/nrm2391.

[32] Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature. 2008; 454(7203):463–9. DOI: 10.1038/nature07206.

[33] Yan J, Feng Z, Liu J, Shen W, Wang Y, Wertz K, et al. Enhanced autophagy plays a cardinal role in mitochondrial dysfunction in type 2 diabetic Goto-Kakizaki (GK) rats: ameliorating effects of (−)-epigallocatechin-3-gallate. J Nutr Biochem. 2012; 23(7):716–24. DOI: 10.1016/j.jnutbio.2011.03.014.

[34] Moreno-Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinahones F, Ricart W, Fernández-Real JM. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J Clin Endocrinol Metab. 2013; 98(4):E769–78. DOI: 10.1210/jc.2012-2749.

[35] Choi YK, Kim MK, Bae KH, Seo HA, Jeong JY, Lee WK, Kim JG, Lee IK, Park KG. Serum irisin levels in new-onset type 2 diabetes. Diabetes Res Clin Pract. 2013; 100(1):96–101. DOI: 10.1016/j.diabres.2013.01.007.

[36] Sanchis-Gomar F, Alis R, Pareja-Galeano H, Sola E, Victor VM, Rocha M, Hernández-Mijares A, Romagnoli M. Circulating irisin levels are not correlated with BMI, age, and other biological parameters in obese and diabetic patients. Endocrine. 2014; 46(3):674–7. DOI: 10.1007/s12020-014-0170-9.

[37] Liu JJ, Wong MD, Toy WC, Tan CS, Liu S, Ng XW, Tavintharan S, Sum CF, Lim SC. Lower circulating irisin is associated with type 2 diabetes mellitus. J Diabetes Complications. 2013; 27(4):365–9. DOI: 10.1016/j.jdiacomp.2013.03.002.

[38] Aydin S, Aydin S, Kobat MA, Kalayci M, Eren MN, Yilmaz M, Kuloglu T, Gul E, Secen O, Alatas OD, Baydas A. Decreased saliva/serum irisin concentrations in the acute myocardial infarction promising for being a new candidate biomarker for diagnosis of this pathology. Peptides. 2014; 56:141–5. DOI: 10.1016/j.peptides.2014.04.002.

[39] Aronis KN, Moreno M, Polyzos SA, Moreno-Navarrete JM, Ricart W, Delgado E, de la Hera J, Sahin-Efe A, Chamberland JP, Berman R, Spiro A 3rd, Vokonas P, Fernández-Real JM, Mantzoros CS. Circulating irisin levels and coronary heart disease: association with future acute coronary syndrome and major adverse cardiovascular events. Int J Obes (Lond). 2015; 39(1):156–61. DOI: 10.1038/ijo.2014.101.

[40] O'Carroll AM, Lolait SJ, Harris LE, Pope GR. The apelin receptor APJ: journey from an orphan to a multifaceted regulator of homeostasis. J Endocrinol. 2013; 219(1):R13–35. DOI: 10.1530/JOE-13-0227.

[41] Papadopoulos DP, Makris T, Perrea D, Zerva K, Tsioufis C, Faselis C, Papademetriou V. Apelin and relaxin plasma levels in young healthy offspring of patients with essential hypertension. J Clin Hypertens (Greenwich). 2010; 16(3):198–201.DOI: 10.1111/jch.12260.

[42] Than A, Zhang X, Leow MK, Poh CL, Chong SK, Chen P. Apelin attenuates oxidative stress in human adipocytes. J Biol Chem. 2014; 289(6):3763–74. DOI: 10.1074/jbc.M113.526210.

[43] Yue P, Jin H, Aillaud M, Deng AC, Azuma J, Asagami T, Kundu RK, Reaven GM, Quertermous T, Tsao PS. Apelin is necessary for the maintenance of insulin sensitivity. Am J Physiol Endocrinol Metab. 2010; 298(1):E59–67. DOI: 10.1152/ajpendo.00385.2009.

[44] Daviaud D, Boucher J, Gesta S, Dray C, Guigne C, Quilliot D, Ayav A, Ziegler O, Carpene C, Saulnier-Blache JS, Valet P, Castan-Laurell I. TNF alpha up-regulates apelin expression in human and mouse adipose tissue. FASEB J. 2006; 20(9):1528–30.

[45] Attane C, Foussal C, Le Gonidec S, Benani A, Daviaud D, Wanecq E, Guzmán-Ruiz R, Dray C, Bezaire V, Rancoule C, Kuba K, Ruiz-Gayo M, Levade T, Penninger J, Burcelin R, Pénicaud L, Valet P, Castan-Laurell I. Apelin treatment increases complete fatty acid oxidation, mitochondrial oxidative capacity, and biogenesis in muscle of insulin-resistant mice. Diabetes. 2012; 61(2):310–20. DOI: 10.2337/db11-0100.

[46] Ma WY, Yu TY, Wei JN, Hung CS, Lin MS, Liao YJ, Pei D, Su CC, Lu KC, Liu PH, Lin CH, Chuang LM, Kao HL, Lin JW, Chuang YJ, Li HY. Plasma apelin: a novel biomarker for predicting diabetes. Clin Chim Acta. 2014; 435:18–23. DOI: 10.1016/j.cca.2014.03.030.

[47] Akinci B, Celtik A, Tunali S, Genc S, Yuksel F, Secil M, Ozcan MA, Bayraktar F. Circulating apelin levels are associated with cardiometabolic risk factors in women

with previous gestational diabetes. Arch Gynecol Obstet. 2014; 289(4):787–93. DOI: 10.1007/s00404-013-3070-y.

[48] Abd-Elbaky AE, Abo-ElMatty DM, Mesbah NM, Ibrahim SM. Associations of serum omentin and apelin concentrations with obesity, diabetes mellitus type 2 and cardiovascular diseases in Egyptian population. Endocrinol Metab Synd. 2015; 4:171. DOI: 10.4172/2161-1017.1000171.

[49] McPherron AC. Metabolic functions of myostatin and GDF-11. Immunol Endocr Metab Agents Med Chem. 2010; 10(4):217–231.

[50] Fadini GP, Menegazzo L, Bonora BM, Mazzucato M, Persano S, Kreutzenberg SV, Avogaro A. Effects of age, diabetes, and vascular disease on growth differentiation factor 11: first-in-human study. Diabetes Care. 2015:e1–e2.

[51] Sinha M, Jang YC, Oh J, Khong D, Wu EY, Manohar R et al. Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. Science. 2014; 344 (6184):649–652.

[52] Loffredo FS, Steinhauser ML, Jay SM, Gannon J, Pancoast JR et al. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell. 2013; 153(4):828–39.

[53] Harmon EB, Apelqvist AA, Smart NG, Gu X, Osborne DH, Kim SK. GDF-11 modulates NGN3+ islet progenitor cell number and promotes beta-cell differentiation in pancreas development. Development. 2004; 131(24):6163–74.

[54] Egerman MA ,Cadena SM , Gilbert JA, Meyer A, Nelson HN, Swalley SE et al. GDF11 increases with age and inhibits skeletal muscle regeneration. Cell Metab. 2015; 22(1): 164–74.

[55] Poggioli T, Vujic A, Yang P, Macias-Trevino C, Uygur A, Loffredo FS, Pancoast JR, Cho M, Goldstein J, Tandias RM, Gonzalez E, Walker RG, Thompson TB , Wagers AJ, Fong YW, Lee RT. Circulating Growth Differentiation Factor 11/8 Levels Decline With Age. Circ Res. 2016; 118(1):29–37. DOI: 10.1161/CIRCRESAHA.

[56] Heidecker B, Olson K, Beatty A, Dubin R, Kato S, Lawn R, Murthy A, Regan M, Sterling D, Whooley M, Ganz P. Low levels of growth differentiation factor 11 and high levels of its inhibitor follistatin-like 3 are associated with adverse cardiovascular outcomes in humans. JACC. 2015; 65(10S): A999.

[57] Olson K, Beatty A, Heidecker B, Regan M, Whooley M, Ganz P. High levels of growth differentiation factor 11 are associated with lower prevalence of left ventricular hypertrophy: data from the heart and soul study. JACC. 2014; 63(12):A780

[58] Adela R, Reddy PN, Banerjee SK. Alteration of plasma gdf-11 levels in type 2 diabetes patients with cardiovascular complications: A pilot study. J Pract Cardiovasc Sci 2015; 1:262–6. Doi:10.4103/2395-5414.177246

[59] Seizer P, Gawaz M, May AE. Cyclophilin A and EMMPRIN (CD147) in cardiovascular diseases. Cardiovasc Res. 2014; 102(1):17–23. DOI: 10.1093/cvr/cvu035.

[60] Satoh K. Cyclophilin A in cardiovascular homeostasis and diseases. Tohoku J Exp Med. 2015; 235(1):1–15. DOI: 10.1620/tjem.235.1.

[61] Tsai SF, Su CW, Wu MJ, Chen CH, Fu CP, Liu CS, Hsieh M. Urinary cyclophilin A as a new marker for diabetic nephropathy: a cross-sectional analysis of diabetes mellitus. Medicine (Baltimore). 2015; 94(42):e1802. DOI: 10.1097/MD.0000000000001802.

[62] Ramachandran S, Venugopal A, Sathisha K, Reshmi G, Charles S, Divya G, Chandran NS, Mullassari A, Pillai MR, Kartha CC. Proteomic profiling of high glucose primed monocytes identifies cyclophilin A as a potential secretory marker of inflammation in type 2 diabetes. Proteomics. 2012; 12(18):2808–21. DOI: 10.1002/pmic.201100586.

[63] Ramachandran S, Venugopal A, Kutty VR, A V, G D, Chitrasree V, Mullassari A, Pratapchandran NS, Santosh KR, Pillai MR, Kartha CC. Plasma level of cyclophilin A is increased in patients with type 2 diabetes mellitus and suggests presence of vascular disease. Cardiovasc Diabetol. 2014; 13:38. DOI: 10.1186/1475-2840-13-38.

[64] Ramachandran S, Kartha CC. Cyclophilin-A: a potential screening marker for vascular disease in type-2 diabetes. Can J Physiol Pharmacol. 2012; 90(8):1005–15. DOI: 10.1139/y2012-038.

[65] Wang T, Lu J, Xu Y, Li M, Sun J, Zhang J, Xu B, Xu M, Chen Y, Bi Y, Wang W, Ning G. Circulating prolactin associates with diabetes and impaired glucose regulation: a population-based study. Diabetes Care. 2013; 36(7):1974–80. DOI: 10.2337/dc12-1893.

[66] Pereira-Lima JF, Leães CG, Freitas Neto FM, Barbosa MV, da Silva ALM, Oliveira MDC. Hyperprolactinemia and body weight: prevalence of obesity and overweight in patients with hyperprolactinemia. Res J Endocrinol Metab. 2013; 1:2. DOI: 10.7243/2053-3640-1-2

[67] Arnold E, Rivera JC, Thebault S, Moreno-Páramo D, Quiroz-Mercado H, Quintanar-Stéphano A, Binart N, Martínez de la Escalera G, Clapp C. High levels of serum prolactin protect against diabetic retinopathy by increasing ocular vasoinhibins. Diabetes. 2010; 59(12):3192–7. DOI: 10.2337/db10-0873.

[68] Balbach L, Wallaschofski H, Völzke H, Nauck M, Dorr M, Haring R. Serum prolactin concentrations as risk factor of metabolic syndrome or type 2 diabetes? BMC Endocr Disord. 2013; 13:12. DOI: 10.1186/1472-6823-13-12

[69] Carrero JJ, Kyriazis J, Sonmez A, Tzanakis I, Qureshi AR, Stenvinkel P, Saglam M, Stylianou K, Yaman H, Taslipinar A, Vural A, Gok M, Yenicesu M, Daphnis E, Yilmaz MI. Prolactin levels, endothelial dysfunction, and the risk of cardiovascular events and mortality in patients with CKD. Clin J Am Soc Nephrol. 2012; 7(2):207–15. DOI: 10.2215/CJN.06840711.

[70] Reuwer AQ, Twickler MT, Hutten BA, Molema FW, Wareham NJ, Dallinga-Thie GM, Bogorad RL, Goffin V, Smink-Bol M, Kastelein JJ, Boekholdt SM, Khaw KT. Prolactin

levels and the risk of future coronary artery disease in apparently healthy men and women. Circ Cardiovasc Genet. 2009; 2:389–395. DOI: 10.1161/CIRCGENETICS.109.853572.

[71] Hsieh DJ, Huang CY, Pai P, Wang SG, Tsai YL, Li CN, Kuo WW, Huang CY. Prolactin protects cardiomyocytes against intermittent hypoxia-induced cell damage by the modulation of signaling pathways related to cardiac hypertrophy and proliferation. Int J Cardiol. 2015; 181:255–66. DOI: 10.1016/j.ijcard.2014.11.154.

[72] Landberg E, Dahlström U, Alehagen U. Serum prolactin and macroprolactin in heart failure: no relation to established laboratory or clinical parameters. Ann Clin Biochem. 2011; 48(Pt 1):51–6. DOI: 10.1258/acb.2010.010164.

[73] Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, Forster O, Quint A, Landmesser U, Doerries C, Luchtefeld M, Poli V, Schneider MD, Balligand JL, Desjardins F, Ansari A, Struman I, Nguyen NQ, Zschemisch NH, Klein G, Heusch G, Schulz R, Hilfiker A, Drexler H. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell. 2007; 128(3):589–600.

[74] Bartoszewicz Z, Kondracka A, Jaźwiec R, Popow M, Dadlez M, Bednarczuk T. Can we accurately measure the concentration of clinically relevant vitamin D metabolites in the circulation? The problems and their consequences. Endokrynol Pol. 2013; 64(3):238–45.

[75] Talaei A, Mohamadi M, Adgi Z. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. Diabetol Metab Syndr. 2013; 5(1):8.

[76] Mozos I, Marginean O. Links between vitamin D deficiency and cardiovascular diseases. Biomed Res Int. 2015; 2015:109275.

[77] Vishwanath P, Kulkarni P, Prashant A. Vitamin D deficiency in India: are we overconcerned? Int J Health Allied Sci. 2014; 3:77–8.

[78] Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi. Am J Clin Nutr. 2000; 72(2):472–5.

[79] Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D. Vitamin D status in Andhra Pradesh: a population based study. Indian J Med Res. 2008; 127(3):211–8.

[80] Goswami R, Kochupillai N, Gupta N, Goswami D, Singh N, Dudha A. Presence of 25(OH) D deficiency in a rural North Indian village despite abundant sunshine. J Assoc Physicians India. 2008; 56:755–7.

[81] Garg MK, Tandon N, Marwaha RK, Menon AS, Mahalle N. The relationship between serum 25-hydroxy vitamin D, parathormone and bone mineral density in Indian population. Clin Endocrinol (Oxf). 2014; 80(1):41–6.

[82] Roy A, Lakshmy R, Tarik M, Tandon N, Reddy KS, Prabhakaran D. Independent association of severe vitamin D deficiency as a risk of acute myocardial infarction in Indians. Indian Heart J. 2015; 67(1):27–32.

[83] Bonakdaran S, Nejad AF, Abdol-Reza V, Hatefi A, Shakeri M. Impact of oral 1,25-dihydroxy vitamin D (calcitriol) replacement therapy on coronary artery risk factors in type 2 diabetic patients. Endocr Metab Immune Disord Drug Targets. 2013; 13(4):295–300.

[84] Tarcin O, Yavuz DG, Ozben B, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. J Clin Endocrinol Metab. 2009; 94:4023–30. DOI: 10.1210/jc.2008-1212.

[85] Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin–angiotensin system and blood pressure. J Steroid Biochem Mol Biol. 2004; 89–90(1–5):387–92.

[86] Oh J, Riek AE, Darwech I, Funai K, Shao J, Chin K, Sierra OL, Carmeliet G, Ostlund RE Jr, Bernal-Mizrachi C. Deletion of macrophage vitamin d receptor promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice. Cell reports. 2015; 10(11):1872–1886.

[87] Pellitero S, Reverter JL, Granada ML, Pizarro E, Pastor MC, Tàssies D, Reverter JC, Salinas I, Sanmartí A. Association of the IGF1/pregnancy-associated plasma protein-A system and adipocytokine levels with the presence and the morphology of carotid plaques in type 2 diabetes mellitus patients with stable glycaemic control. Eur J Endocrinol. 2009; 160(6):925–32.

[88] Bayes-Genis A, Conover CA, Schwartz RS: The insulin-like growth factor axis: a review of atherosclerosis and restenosis. Circ Res. 2000; 86:125–130.

[89] Bayes-Genis A, Conover CA, Overgaard MT, Bailey KR, Christiansen M, Holmes DR, Virmani R, Oxvig C, Schwartz RS: Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. N Engl J Med. 2001; 345:1022–1029.

[90] Cosin-Sales J, Kaski JC, Christiansen M, Kaminski P, Oxvig C, Overgaard MT, Cole D, Holt DW: Relationship among pregnancy associated plasma protein-A levels, clinical characteristics, and coronary artery disease extent in patients with chronic stable angina pectoris. Eur Heart J. 2005; 26:2093–2098.

[91] Conti E, Andreotti F, Zuppi C: Pregnancy-associated plasma protein-A as predictor of outcome in patients with suspected acute coronary syndromes. Circulation. 2004; 109:e211–e212.

[92] Crea F, Andreotti F: Pregnancy associated plasma protein-A and coronary atherosclerosis: marker, friend, or foe? Eur Heart J. 2005; 26:2075–2076.

[93] Piñon P, Kaski JC: Inflammation, atherosclerosis and cardiovascular disease risk: PAPP-A, Lp-PLA2 and cystatin C: new insights or redundant information? Rev Esp Cardiol. 2006; 59:247–258.

[94] Harrington SC, Simari RD, Conover CA. Genetic deletion of pregnancy-associated plasma protein-A is associated with resistance to atherosclerotic lesion development in apolipoprotein E-deficient mice challenged with a high-fat diet. Circ Res. 2007; 100(12):1696–702.

[95] Pellitero S, Reverter JL, Pizarro E, Pastor MC, Granada ML, Tàssies D, Reverter JC, Salinas I, Sanmartí A. Pregnancy-associated plasma protein-A levels are related to glycemic control but not to lipid profile or hemostatic parameters in type 2 diabetes. Diabetes Care. 2007; 30(12):3083–5.

[96] Hjortebjerg R, Lindberg S, Hoffmann S , Jensen JS, Oxvig C, Bjerre M, Frystyk J . PAPP-A and IGFBP-4 fragment levels in patients with ST-elevation myocardial infarction treated with heparin and PCI. Clin Biochem. 2015; 48(4–5):322–8. DOI: 10.1016/j.clinbiochem.2014.11.022

[97] Conover CA, Bale LK, Oxvig C.Targeted Inhibition of Pregnancy Associated Plasma Protein A Activity Reduces Atherosclerotic Plaque Burden in Mice. J Cardiovasc Transl Res. 2016; 9(1):77–9. Doi: 10.1007/s12265-015-9666-9.

[98] Wang-Sattler R, Yu Z, Herder C, Messias AC, Floegel A, He Y, Heim K, Campillos M, Holzapfel C, Thorand B, Grallert H, Xu T et al. Novel biomarkers for pre-diabetes identified by metabolomics. Mol Syst Biol. 2012; 8:615. DOI: 10.1038/msb.2012.43.

[99] Rao PV, Reddy AP, Lu X, Dasari S, Krishnaprasad A, Biggs E, Roberts CT, Nagalla SR. Proteomic identification of salivary biomarkers of type-2 diabetes. J Proteome Res. 2009; 8(1):239–45. DOI: 10.1021/pr8003776.

[100] Arora P. Metabolomics yield a novel biomarker for predicting diabetes mellitus risk in humans. Circ Cardiovasc Genet. 2014; 7(1):95–6. DOI: 10.1161/circgenetics.114.000528

[101] Stegemann C, Pechlaner R, Willeit P, Langley SR, Mangino M, Mayr U, Menni C, Moayyeri A, Santer P, Rungger G, Spector TD, Willeit J, Kiechl S, Mayr M.. Lipidomics profiling and risk of cardiovascular disease in the prospective population-based Bruneck study. Circulation. 2014; 129(18):1821–31. DOI: 10.1161/CIRCULATIONAHA.113.002500

[102] Rauschert S, Uhl O, Koletzko B, Kirchberg F, Mori TA, Huang RC, Beilin LJ, Hellmuth C, Oddy WH. Lipidomics reveals associations of phospholipids with obesity and insulin resistance in young adults. J Clin Endocrinol Metab. 2015:jc20153525. [Epub ahead of print].

[103] Wurtz P, Havulinna AS, Soininen P, Tynkkynen T, Prieto-Merino D, Tillin T, Ghorbani A, Artati A, Wang Q, Tiainen M et al. Metabolite profiling and cardiovascular event

risk: a prospective study of 3 population-based cohorts. Circulation. 2015; 131(9):774–85. DOI: 10.1161/CIRCULATIONAHA.114.013116.

[104] Shah SH, Sun JL, Stevens RD, Bain JR, Muehlbauer MJ, Pieper KS, Haynes C, Hauser ER, Kraus WE, Granger CB, Newgard CB, Califf RM, Newby LK. Baseline metabolomic profiles predict cardiovascular events in patients at risk for coronary artery disease. Am Heart J. 2012; 163(5):844–850.

[105] Lappas M, Mundra PA, Wong G, Huynh K, Jinks D, Georgiou HM, Permezel M, Meikle PJ. The prediction of type 2 diabetes in women with previous gestational diabetes mellitus using lipidomics. Diabetologia. 2015; 58(7):1436–42. DOI: 10.1007/s00125-015-3587-7.

IntechOpen