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Pathogenesis of obesity-associated cardiovascular diseases: Key role of biomolecules

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ABSTRACT

Obesity has a significant role in the emergence of severe health disorders, associated comorbidities, and morbidity. According to epidemiological and clinical evidence, obesity has been linked to a number of heart related diseases, such as heart failure, coronary heart disease, hypertension, atrial fibrillation, stroke and cardiac arrest. The obesity is characterized by changes in adipose tissue's cell size, which interferes with the tissue's normal function. Furthermore, a variety of bioactive substances are produced and secreted by adipose tissue. Both local and systemic effects of obesity's abnormal expansion of adipose tissue, such as hypoxia, inflammation, dysregular secretion of adipokine, hypertension, improper function of mitochondria, insulin resistance, abnormal lipid/glucose metabolism, pro-inflammatory/pro-thrombotic state, as well as endothelial dysfunction results in variety of heart diseases. In this review, we will discuss various biomolecules such as hormones, genes, enzymes, receptors, cytokines, etc., involved in the mechanisms linking obesity to cardiovascular diseases, and how their regulation can be helpful in the treatment of these diseases.

1. Introduction

The current lifestyle, which is defined by a lack of exercise and an energy-dense diet, has led to the global pandemic of obesity, which may soon exceed the number of undernourished people [1]. Obesity is defined in a variety of ways, but as per World Health Organization, it is demarcated as weight in relation to height (kilogram per square meter) guideline is considered as most the appropriate in describing obesity or overweight. According to this, if a person's body mass index (BMI) is greater than 30 kg/m^2, he or she is considered obese. Obesity can be classified into three categories: group I (30.0 kg/m^2 to 34.9 kg/m^2), group II (35.0 kg/m^2 to 39.9 kg/m^2), and group III (greater than/equivalent to 40 kg/m^2). Higher the BMI values greater will be the chances of risks associated with obesity [2,3]. The global prevalence of obesity is atmost expected to exceed 18% in men and over 21% in women by the year 2025 if present trends continue, placing a significant burden on people, communities, and healthcare systems [4]. Internationally, obesity ranks sixth in terms of mortality rates, and it shortens the lives of people by seven years by the time they reach age 40 [5]. Obesity-related conditions including diabetes mellitus, atherogenic dyslipidemia, and high blood pressure have surely aided in the development of cardiovascular disease, which is a major cause of death in Westernized society [6,7]. Stroke, congestive cardiac failure, heart attack, and cardiovascular death are more common in people with a centralized adipose tissue deposition, and this is apparent even after controlling of obesity and other risk factors for cardiovascular disease (CVD) [8,9]. Obesity is related with an elevated risk of CVD *via* multiple mechanisms, some of which are well-established and others that have yet to be discovered. These risk factors include dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep hypoventilation and the prothrombotic state [10].

Large cohort studies utilized as computed tomography imaging has given the extra visceral adipose tissue in the abdomen is a reliable indicator of the emergence of cardiovascular disease associated risk over the time [11]. Despite having normal levels of total and LDL cholesterol, visceral adipose tissue and abdominal adiposity is linked to dyslipidemia, which is characterized by high total and VLDL-triglycerides, low HDL cholesterol, smaller and denser particles of LDL (as measured by higher levels of apolipoprotein) [12,13]. Furthermore, in a clinical study, high visceral adipose tissue will be accompanied by hypertriglyceridemia and low HDL cholesterol, and the dyslipidemia is one of the good predictors for onset of CVD [11]. In this review, we will discuss various biomolecules and their mechanisms in the pathogenesis of obesity associated CVD and how their regulation can be helpful in the management of metabolic disorders and CVD.

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2. Biomolecules whose secretion during obesity can lead in the development of CVD

Adipose tissue plays an important role in the body's endocrine system by secreting a variety of hormone-like substances called adipokines or adipocytokines [14]. Adipokines have a role in a 'good-bad, homoeostatic balance that has significant advantages, including cardioprotection, promotion of endothelial function, angiogenesis, reduction of hypertension, atherosclerosis, regulation of fibrinolysis clotting, inflammation, insulin resistance etc. Adipose tissue and CVD may be related *via* the abnormal synthesis and release of adipokines by hypertrophic adipocytes [15,16]. Some of the important adipokines are mentioned below:

2.1. Leptin

Leptin is a hormone and cytokine, primarily secreted by adipocyte cells and production *via* autocrine and paracrine mechanisms [17]. Leptin is encoded by gene of obese (ob), which was discovered in ob/ob mice and cloned in a positional cloning study. It has 167 amino acids and a molecular weight of 16 kDa [18]. Leptin is a crucial hormone as it is involved in a modulation of intake of food and expenditure of energy and maintain a healthy weight and metabolic balance. Leptin is detected in the bloodstream as either in a bound or free hormone [3]. Leptin level is increased after eating, and decreased during fasting and as compared to normal weight people, obese people have greater amounts of plasma leptin [19]. Leptin receptors have been found in many different organs and tissues, including the heart, liver, kidneys, lungs, pancreas. In hypothalamus, leptin and its receptor is expressed and mediate biological effects [20].

Several studies have linked leptin to increased risk of CVDs and obesity. High level of leptin can have adverse effects on cardiac functions including the promotion of inflammation and the vascular smooth muscle cell's proliferation (VSMCs) as well as oxidative stress and platelet aggregation [21]. These conditions further contribute to the aforementioned conditions, such as, endothelial dysfunction, atherogenesis, increased hypertrophic response and worse prognosis were seen in ischemic heart disease and heart failure [22]. Also, high levels of leptin in circulation are a sign of resistance of leptin, which is frequent in obesity and are independently linked to insulin resistance and CVD in humans. Genetic mutation, leptin self-regulation, restricted tissue access, and cellular or circulating molecular modulation are among potential causes of leptin resistance. Obesity is thought to be caused by a central resistance to leptin, and the damage to the liver, pancreas, platelets, blood vessels, and heart caused by this resistance is supported by the evidence. Both leptin resistance in certain tissues and the excess leptin activity caused by adiposity-associated hyperleptinemia have been linked to this metabolic and inflammatory-mediated damage [23]. Interleukin-6 and other innate immune system mediators interact functionally with the leptin pathway, which regulates metabolism and inflammation. Therefore, leptin resistance, as well as its link with inflammatory and metabolic parameters, might act as a new therapeutic and diagnostic target in obesity-associated CVD [23].

2.2. Visfatin

Visfatin is an another adipocytokine or cytosolic enzyme with nicotinamide phosphoribosyl-transferase activity. It is released by adipocytes, macrophages, and inflammatory endothelium tissue; found in excess in obese, insulin resistant, and type 2 diabetic individuals [24]. Over the last 10 years, evidence has accumulated suggesting that visfatin may be a relationship between obesity and cardiovascular disease inducing matrix metalloproteinase-9 (MMP-9) and nuclear factor B (NF-kB) in monocytes and human endothelial cells. Visfatin act as a pro-inflammatory mediator that relates to pathogenesis of inflammatory processes in obesity and type 2 diabetes, ultimately resulting in the instability of atherosclerotic plaques [25]. Recently, visfatin, discovered by Romacho et al. [26] causes mice endothelial *via* a Toll liked receptor-4 (TLR-4) related mechanisms including the nod receptor protein 3 inflammasome as well as paracrine interleukin-1 beta (IL-1β) [26]. Additionally myocardial remodeling relies heavily on visfatin, which is responsible for enhanced fibroblast proliferation and collagen production in the heart [27]. According to Wang et al. [28], Niacinamide mononucleotide associated ERK1/2 or p38 signaling also promotes the proliferation of blood vessel smooth muscle cells in response to visfatin [28]. Angiogenesis, facilitated by the proliferation and migration of VSMCs and ECs is another visfatin action implicated in atherosclerosis. These findings suggest that visfatin is linked to neovascularization in the atherosclerosis of plaques and adipose tissue that open the way to the potential of visfatin regulation in obesity [29].

2.3. Resistin

Resistin, an adipocyte-specific hormone expressed in adipocytes, which causes insulin resistance in skeletal muscle and liver [30]. Along with adipocytes, resistin are also expressed in macrophages, mononuclear leukocytes, bone marrow and spleen. Recent research on resistin explain its role in regulation of diabetes, insulin resistance, CVD, etc. Resistin expressed in endothelial dysfunction, inflammation, angiogenesis, thrombosis, and dysfunction of smooth muscle are contributors in the progression of CVD [31].

Resistin and lipopolysaccharids competitively bind to TLR-4 on human myeloid and epithelial cells [32]. Stimulation of TLR sets off a chain reaction of events inside the cell that ultimately results in changes to transcription and signaling pathways. Translocation of NF-kB may be triggered by resistin and nucleus, which then triggers the pro-inflammatory cytokine gene's transcription, aiding VSMC as well as endothelial cell growth dysfunction (Fig. 1). The PI3K/AKT pathway, which is activated by resistin, can also mediate NF-kB activation. In addition to activating c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) p38, it can increase oxidative stress that can also lead to the stimulation of MAPK and suppression of eNOS. Superoxide anions, which are produced at higher rates by resistin, suppress the expression of eNOS and lower NO bioavailability. Proliferation of VSMCs as well as dysfunction of endothelial (such as improper vasorelaxation, hyperpermeability, increased thrombosis, higher cell adhesion and angiogenesis,) all lead to the atherosclerosis development as shown in the Fig.1 [31]. Thus preventing the binding of resistin and lipopolysaccharides to TLR 4, antagonizing or blocking the activation of resistin to stop it from taking part in pathogenesis of CVD associated with obesity can be effective treatment strategy in aforementioned disease.

2.4. Fibroblast growth factor (FGF-23)

The fibroblast growth factors (FGFs) are a large family of polypeptides that signals through FGF receptors and play important roles in many biological processes such as cellular proliferation, survival, migration, and differentiation [33]. In humans, there are 22 members in FGF family, each of which is found in a distinct kind of tissue and performs a unique function [34]. FGF23 an endocrine FGFs member released by the osteocytes, are correlated with atherothrombotic risk associated factors including such apo A-1 as well as high-density lipoprotein (HDL) in people without and with severe kidney disease. Patients with chronic renal disease who have elevated blood FGF23 levels have a greater likelihood of having heart disease and a more severe and extensive case of CAD, and these patients also have a worse prognosis for survival after undergoing coronary angiography. FGF23 acts directly to the heart through a signaling route of klotho-independent which is supported by the fact that it binds to FGFR and the coreceptor klotho in the parathyroid gland and kidney [34]. Despite FGF23 not being released by the VAT, research

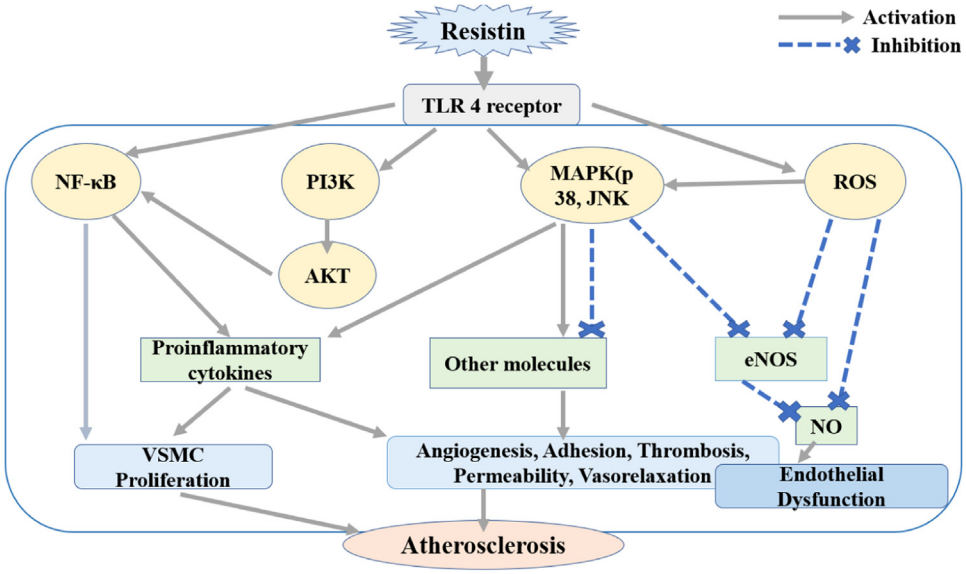

Fig. 1. Illustration of possible resistin-mediated cardiovascular dysfunction pathways.

revealed that it to be higher in the obese (especially those with abdominal obesity). This finding suggests a link between FGF23 and visceral fat accumulation [35]. Because of their metabolic effects and angiogenic properties, FGFs recently have been widely researched as possible novel agents in the prevention and treatment of cardiovascular disease.

2.5. Plasminogen stimulated inhibitor-1 (PAI- 1)

Plasminogen stimulated inhibitor-1 (PAI-1) is the 45 kDa serine proteinase inhibitor having the peptide link Arg345-Met346 at its reactive site. By inhibiting both tissue-associated plasminogen activator (t-PA) as well as urokinase-type plasminogen stimulator (u-PA), PAI-1 controls the extent to fibrinolysis [36,37]. Platelets and the endothelium are the primary sources of PAI-1, but in obese people, adipose tissue becomes a major source. Therefore, obese persons have been reported to have higher levels of PAI-1 [38]. The higher levels of PAI-1 seen in the obese may play a significant part in the development of several cardiovascular diseases by creating a hypofibrinolytic or prothrombotic state [39]. Overaccumulation of fibrin in the vasculature, known as atherothrombosis, may be caused by impaired fibrinolysis due to elevated plasma PAI-1 [40]. It has been shown *via* experiments that the associations seen in epidemiology of these CVD's are more than coincidental. Krishnamurti et al., study, normal rabbits were infused with defibrinogenating snake venom induced hypofibrinogenemia, but in rabbits treated with endotoxin by a considerably elevated plasma PAI-1 level, renal fibrin deposits are generated [41]. In another study, promotion of the endogenous thrombolysis including prevention of thrombus expansion were seen as a result of blocking PAI-1 with a monoclonal antibody in a model of rabbit's jugular thrombosis of the veins [42]. Cardiac myocytes and mast cells both have a role in the increased PAI-1 expression that leads to interstitial and perivascular fibrosis in a mice model of myocardial infarction resulted by the ligation of coronary system [43]. Hence, it has been suggested that PAI-1 might be an effective target of therapeutics for reducing the risk of cardiovascular disease.

2.6. Inflammatory cytokines

There is a robust correlation between obesity and inflammatory indicators, both of which have a role in the etiology and progression of cardiovascular diseases [44]. Chronic inflammation from obesity promotes atherosclerosis. Some of the pathophysiologic processes of obesity that leads to inflammation and atherosclerosis include the activation of adipokines/cytokines and elevations of circulating aldosterone. The increased level of aldosterone in the bloodstream have several detrimental effects on the body, including high blood volume, platelet aggregation, vascular endothelial dysfunction, thrombosis, fibrosis, etc., [45]. The level of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), high-sensitivity C reactive protein and interleukin-6 (IL-6) are consistently elevated in obese people [46]. Various signal transduction systems work together to help these inflammatory mediators accomplish their effects [47]. To a large extent, the progression from the simpler obesity to the associated metabolic and cardiac complications can be attributed to immune cells, as they are a major source of the inflammatory cytokines as well as other products of pro-inflammatory products. Further, they affect not only the involving tissues but through the systemic circulation it will affects the whole organism [48].

2.6.1. Interleukin 6 (IL-6)

The cytokine IL-6 has several metabolic regulatory functions [49]. It is released by a variety of tissues, but adipose tissue stands out as a prominent source, with the ability to generate substantial circulating quantities of this protein [50]. The elevated levels of IL-6 during obesity act on the adipose tissue, which causes the secretion of leptin. As it has been previously discussed that leptin is an adipokine directly or indirectly, involved in the processes such as endothelial dysfunction and atherosclerosis. Therefore, IL-6 associated leptin secretion can be a major risk factor in developing CVDs. Along with this IL-6 has multiple other characteristics that promote the development of cardiovascular diseases. These include the stimulation of endothelial cells, the induction of pro-thrombotic actions in platelets, the stimulation of SMC proliferation, and the accumulation of lipids in macrophages [51]. Hence inhibition of cytokine IL-6 can act as a novel approach in the amelioration of several heart complications associated with obesity.

2.6.2. Tumor necrosis factor alpha (TNF- α)

TNF- α is another key player in the systemic inflammatory response brought on by obesity, and its participation in this response has been examined extensively [52]. The first evidence between inflammation and obesity was discovered in 1993; observed that TNF- α activated in adipose tissue in models of diabetes and obesity [53]. TNF- α has been found to play numerous pathogenic functions in the cardiovascular system. TNF-α expression is increased in both adipose tissue and serum in obese people, and weight reduction in the obese is related with a decrease in TNF-α levels [54]. The increased levels of TNF-α have seen in both humans and animals with acute and chronic ischemia damage, as

well as in heart failure [55]. Recently, TNF- α antagonist treatment has been shown to be therapeutically useful in inflammatory illnesses (such as, arthritis, rheumatoid, etc.), and studies are underway to examine the use of these drugs in cardiovascular diseases [56].

2.7. Angiotensinogen (AGN)

AGN is α2-globulin precursor of angiotensin. Adipose tissue has high levels of AGN expression, and during the adipogenic differentiation process AGN gene expression enhances [57]. AGN is converted to angiotensin (Ang) I by renin, which is subsequently converted to Ang II by angiotensin converting enzyme (ACE). The Ang II is a potent vasoconstrictor and have an important role in the regulation of the blood pressure [58]. Hence, it serves as an important link between obesity and hypertension. There are substantial evidences that being overweight or obese is a risk factor for developing hypertension by as much as 65–75% [59]. Ang II promotes VCAM-1, ICAM-1, and MCP-1 endothelial expression, leading to vascular inflammation [60]. The peptide Ang II plays a critical role in the retention of salt. On the other hand, 5′AMP-stimulated protein kinase (AMPK) has been shown to have a role in transport of ion control. According to a research, Ang II and AMPK has a key-role in the progression of hypertension in salt sensitive models. The reported data showed that Ang II reduces AMPK activity in kidney, which results in retention of sodium and higher salt-sensitivity. The activation of AMPK and blocker of Ang II can be a potential treatment target for the obesity-associated salt-related hypertension [61].

2.8. Proprotein convertase kexin/subtilisin type 9 (PCSK-9)

Proprotein convertase kexin/subtilisin type 9 is a glycoprotein, produced in the liver and measured in blood plasma. There are nine serine proteases in the proprotein convertase superfamily, PCSK-9 is one of them [62]. PCSK-9 has a molar mass of 72 kDa and is made up of 692 amino acids [63]. Among the many proteins involved in LDL metabolism, PCSK-9 plays a crucial role in regulating the lipid homeostasis, atherosclerosis process, glucose and blood pressure [64]. *In-vitro* and *in-vivo* studies demonstrated that released PCSK-9 attaches to the LDL receptors and carries it to lysosomes for destruction, preventing the receptors from being recycled within the cell and protect them. The high risk of coronary artery disease is associated with PCSK-9 gain-of-function mutations, which may manifest as familial hypercholesterolemia. While PCSK-9 deficiency causes in low LDL-cholesterol and protection towards the coronary artery disorders [65,66].

Several studies indicated that obese have higher PCSK-9 level than the normal weight individuals. Since, PCSK-9 promotes apoB-100, triglyceride and VLDL synthesis. It is possible that hepatic VLDL overproduction represents a causative link between high PCSK-9 level and the dyslipidemia in obesity development [67]. Further, *in-vivo* and *in-vitro* studies suggest that PCSK-9 may promote vascular inflammation and hasten the progression of atherosclerosis [68]. PCSK-9 is also found to be involved in the regulation of epithelial sodium channel surface expression which may influence hypertension, a significant cardiovascular risk factor. It can be concluded that targeting PCSK-9 or its inhibition can be helpful in reducing CVD's risk factors.

3. Biomolecules whose secretion in obese is helpful in the amelioration of CVD associated to obesity

3.1. Adiponectin

Adiponectin is a hormone-like protein that has been shown to have anti-cancer and vaso-protective effects [69]. The normal range for adiponectin in the blood is 3–30 g/ml. There are three receptors (AdipoR) in two families that adiponectin may bind to are AdipoR1, AdipoR2, and T-cadherin. It is the very first class of receptors that have seven transmembrane domains. Skeletal muscle is particularly rich in AdipoR1 expression, whereas the liver is where AdipoR2 is at its most abundance [70,71]. Key metabolic threats for cardiovascular disease, such as inflammation and oxidative stress, are reduced when AdipoR1 and AdipoR2 are activated [72]. These receptors increase mitochondrial biogenesis, improve oxidation of fatty acid in the liver and skeletal muscle, increase glucose uptake in cells, decrease hepatic gluconeogenesis, raise lactate production in skeletal muscle [73]. Some evidence suggests that AdipoR1 and AdipoR2 act in opposite ways on the glucose and lipid metabolism pathways [74]. Previous studies suggests that AdiopR1-null mice developed more fat and glucose intolerance after following a diet. While AdipoR2-null mice, which are naturally thin, have the opposite effect [75]. The ablation of AdipoR2 increased type 2 diabetes but decreased the dyslipidemia and insulin resistance brought on by a high-fat diet [76].

Adiponectin is the third receptor, which has a T-cadherin shape and a large molecular weight, is expressed in a variety of tissues, including smooth muscle cells (SMCs), vascular endothelial cells and pericytes [77]. In cases of recurrent atherosclerosis, its manifestation dramatically rises. For instance, vascular endothelial cells are shielded from apoptosis by activated T-cadherin. Both *in-vivo* and *in-vitro* studies have shown that T-cadherin expression is essential for the revascularization action of adiponectin [78]. Adiponectin affects human myocardium in an indirect way by acting as an antioxidant [79]. It regulates intracellular redox signaling in blood vessels by activating adenosine monophosphate-activated protein kinase as well as peroxisome proliferator dependant receptor [80]. Adipocytokine and adiponectin increase insulin sensitivity in both the skeletal and liver muscle. Atherosclerosis formation in vascular walls is also inhibited by adiponectin's anti-inflammatory properties [81,82]. In addition, it stimulates NO production by increasing the activity of endothelial nitric oxide synthase (eNOS). Endothelial-derived NO protects the vascular system by increasing vasodilation and decreasing platelet aggregation, monocyte adhesion, and inflammation [83]. Adiponectin preferentially inhibits endothelial cell apoptosis and upregulates IL-10 synthesis in macrophages, both of which lead to greater expression of tissue inhibitor of metalloproteinase mRNA and protein production. As a result, adiponectin may prevent plaque rupture by blocking the activity of matrix metalloproteinases [84].

The expression of adiponectin is found to be suppressed in the defective adipocytes associated with obesity, despite the fact that adipocytes in lean people manufacture the maximum amounts of this protein [85]. Pro-inflammatory cytokines, hypoxia, and oxidative stress are all features of the adipose tissue microenvironment that are linked with obesity and hence suppress adipocyte adiponectin production, supporting this hypothesis [50]. Obesity associated CVDs, such as high blood pressure, ventricular hypertrophy, and high risk of heart attack are all interlinked to low serum levels of adiponectin [86]. As lower circulating adiponectin levels and increased oxidative stress are correlated, therefore they are likely to have the significant role in pathophysiology of the obesity associated metabolic and cardiovascular disease [87]. Weight loss or caloric restriction leads to increasing adiponectin levels, and this increase is associated with increased insulin sensitivity.

3.2. Prokineticin

Prokineticins are immunoregulatory proteins or adipokines that are involved in angiogenic (raising vessel development), or aneroxic (reducing food intake) activities [88]. Two known isoforms of prokineticins are Prokineticin-1 (PK1) and Prokineticin-2 (PK2). They are secreted by monocytes, macrophages, reproductive organs, and exerts their effects by binding to prokinectin receptors which are G protein-coupled receptors PKR1 and PKR2 [89]. PK2 has been found to be involved in the regulation appetite and stops the accumulation of fat *via* binding to the PKR1 receptor [88]. Prokineticins have been identified in abundance in obese human WAT, leading to their classification as an adipokine in recent years [90].

It has been suggested in several studies that adipocyte hyperplasia, inflammatory changes in adipose tissue, and disruptions in extracellular matrix remodeling, are the main factors leading to the development of obesity. By limiting food intake and restricting the proliferation and differentiation of preadipocytes, PK2 can limit the unwanted growth of adipose tissue. In mice, a lack of PKR1 in adipose tissue has an opposing effect on the central control of body weight. In a study, when the PKR1 was deleted from the adipocytes ($PKR1^{ad-\backslash-}$) of the mice, abnormally large amounts of fat around their abdomens were observed [90]. Accelerated preadipocyte proliferation and differentiation led to the production of new adipocytes in both PKR1 null and $PKR1^{ad-\backslash-}$ animals. Adipose tissue phenotype of mice that fed with high-fat diet, has found to be changed from proliferative to hypertrophic and increase in calories that involve in the transition from hyperplasia to hypertrophy [91]. Due to the fact that adipocytes are not generated from other adipocytes but rather from precursor cells (preadipocytes), PKR1 inhibits the differentiation of preadipocytes into adipocytes [88,90].

The biological actions of prokineticins are mediated mostly by Gq protein signaling. The Gq/G11 signaling pathway plays a crucial role in stimulating heart growth and hypertrophy [92]. The signaling of PKR1 is also essential for the survival of cardiomyocyte under hypoxic stress as well as promotes the angiogenesis either by stimulating MAPK and Akt signaling or directly triggering endothelial cells' proliferation and migration [93]. Transient intracardiac PKR1 transfection in an animal model of myocardial infarction prevents function loss and tissue [94]. Prokineticin-2 and PKR1 expression is elevated in a mouse model of acute myocardial infarction and reduced in the hearts of individuals with end-stage heart failure. Akt, acting as a cardioprotector, was also shown to be elevated by 60% *in-vivo* in treated PKR1 hearts as well as by the same amount in PK2-treated cardiomyocytes. As a result of these findings, prokineticin-2/PKR1 signaling is thought to be crucial for proper myocardial growth and coronary repair [91]. Some new evidences suggests that postnatal neovasculogenesis may be triggered by PKR1 by stimulating epicardial progenitor cell differentiation in the adult, while PRK2 activation in the heart has deleterious effects on cardiomyocytes, causing dilated cardiomyopathy and the production of a paracrine substance that causes capillary fenestration and leakage of vascular system. Based on the results of the studies, researchers have proposed a model in which PKR2 and PKR1 exert signaling antagonistic effects on cardiac physiology and pathophysiology, and agonists and antagonists that specifically target PKR1 and PKR2 can be helpful in the treatment of cardiovascular diseases [94].

3.3. Apelin

The word "apelin" derives from "APJ Endogenous Ligand," which describes the receptor orphan G protein-coupled APJ [95]. Apelin is one of the members of adipokines secreted by adipocytes. Apelin and its receptors are distributed throughout the body, and involved in numerous physiological and clinical processes, such as blood pressure control, fluid balance, the stress response in the endocrine system, cardiac contraction, angiogenesis, cellular energy metabolism and clinical conditions, including congestive heart failure, obesity, diabetes, and cancer [96]. It acts by enhancing coronary blood flow by means of vasodilation and has robust inotropic effects [97]. The apelin-APJ axis controls cardiac hypertrophy, myocardial remodeling, and cardiac smooth muscle contraction in response to pathological stress [98]. Age-related cardiac failure in apelin-deficient animals may be avoided by intravenous infusion of apelin, indicating a crucial role for the apelinergic system in sustaining heart function throughout life [99]. Patients with chronic heart failure have lower amounts of apelin in their blood and hearts, indicating a possible role for a depressed apelinergic system in the pathogenesis of heart failure. Contrarily, plasma apelin concentrations are higher in obese -patients, and therapy with apelin in obese situations promotes glucose consumption in adipose tissue and skeletal muscle, leading to enhanced insulin sensitivity [100]. The high-fat nutrition obesity model was used to further illustrate the positive impacts of the apelinergic pathway on heart function and structure [101]. Apelinase treatment reversed the weight increase, metabolic impairment, and endothelial resistance stress seen in patients with established obesity cardiomyopathy. Apelin enhanced cardiac diastolic role as well as increased the size of cardiac myocytes by re-establishing sarco/endoplasmic reticulum, Ca^{2+}-ATPase levels, lowering phospholamban phosphorylation, and enhancing mitochondrial respiration efficiency [29].These findings support a protective and helpful function for apelin in obesity-related cardiac problems such as hypertrophic cardiomyopathy and myocardial infarction.

3.4. Fibroblast growth factor 21 (FGF 21)

Fibroblast growth factor 21 (FGF 21) is a metabolic hormone that prevents the emergence of obesity and diabetes in animal models by regulating energy homeostasis. Humans with metabolic disorders such as obesity and cardiovascular disease i.e., coronary heart disease, atherosclerosis have increased levels of this substance [102]. It has been shown that the liver, adipose tissue, and pancreas are the primary organs responsible for secreting fibroblast growth factor 21 (FGF 21) [103]. The peroxisome proliferator-stimulated receptor-α increases FGF 21 expression in the livers of animals and humans, while PPAR γ does the same in adipose tissue. Both PPAR γ and PPAR α play crucial roles in regulating cholesterol and glucose levels, as well as in the development of cardiovascular disease [104]. FGF 21 has been demonstrated to enhance lipid profiles and suppress essential events in the etiology of atherosclerosis in *in-vivo* and *in-vitro* experiments [105]. According research by Zhang et al., to explore the effects of FGF 21 as a therapy and its principal mechanism using a vitamin D_3 and high-fat diet rat model of atherosclerosis. Forkhead box O (FOXO) protein expression levels were analysed in atherosclerosis model mice treated with varying dosages of FGF 21, and the role of FGF 21 on neointimal cell production and endothelial-dependent relaxation was also studied. The results showed that FGF 21 dramatically reduced blood lipid, Rho kinase, and NF-κB levels, all of which contributed to the treatment of atherosclerosis and may be the processes behind anti-atherosclerotic effects in the rat model [103]. Furthermore, FGF 21 stimulates in adipocytes the generation of adiponectin which has antihypertensive properties, and works on the hypothalamus to release corticosterone. Accordingly, FGF 21's effects on the liver, the brain, and adipose tissue may contribute to a reduction in blood pressure [106].

3.5. Peroxisome proliferator-activated receptors (PPARs)

PPAR's are the ligand-activated factors of nuclear transcription that control the various genes expression involved in cholesterol, glucose and lipid metabolism, the dysregulation of which may contribute to obesity and cardiovascular disease [107]. These are of three types: PPAR δ, PPAR α (also called as PPAR β or PPAR δ/β) and PPAR γ [108]. Tissues such as the liver, kidney, heart, and muscles, where fatty acid catabolism plays a significant role, are rich in PPAR α expression. PPAR δ/β is most abundant PPAR isoform in skeletal muscle, while PPAR-γ are found in adipose tissue, where it plays a role in regulating adipocyte development and lipid storage and making the body more insulin sensitive [109]. The subtypes of PPARs offer great therapeutic potential in many diseases [110]. PPAR's upon activation form heterodimers with that of retinoid X receptor in the nucleus, which binds to peroxisome proliferator response elements (PPREs) in region of target genes promoters and initiates transcription [111].

Fibrates are the pharmacological compounds that are involved in the activation of PPAR α [111]. They upregulate lipase activity and downregulate Apolipoprotein C- III (apo C-III) expression, both of which enhance intravascular lipolysis [112]. In addition to promoting fatty acid absorption and retention, improving fatty acid catabolism, and lowering fatty acid synthesis in hepatocytes, PPAR activation may also contribute

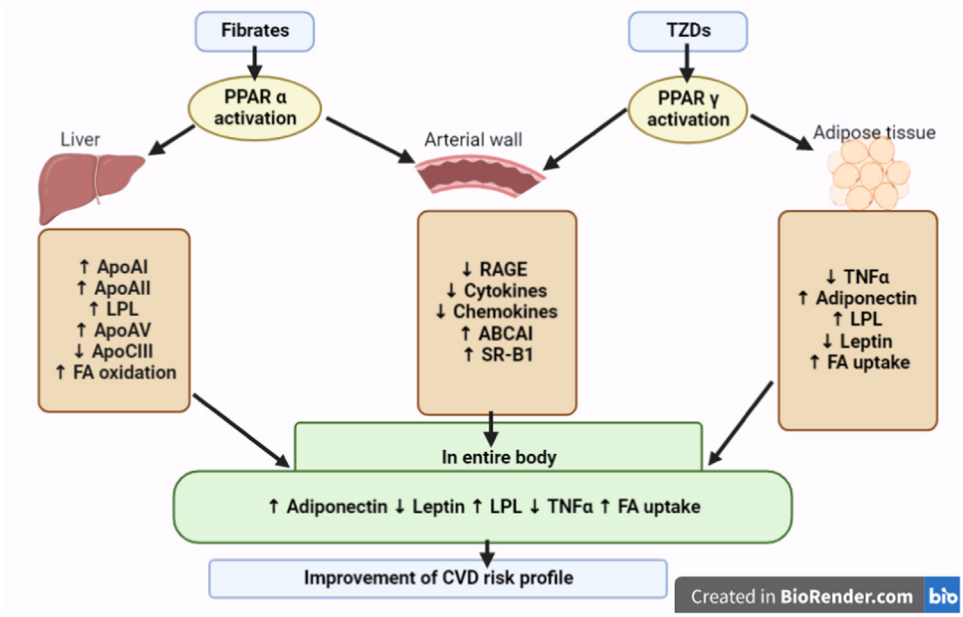

Fig. 2. Effect of biochemical changes on metabolism and vascular system of the body on activation of PPAR α and PPAR γ by their pharmacological agonists.

to suppression of triglyceride synthesis and VLDL lipoprotein formation. These PPAR α activators may also lower triglyceride levels in the blood, increase LDL clearance by shifting the distribution of LDL in the plasma from tiny dense particles to big buoyant ones with a greater affinity for the LDL receptor and boost HDL synthesis by stimulating the formation of apo A-II and apo A-I in the human liver. Beside these it also increases apo A-V expression [112,113].

Thiazolidinediones (TZDs) is a class of an insulin sensitizers which activates PPAR γ. As PPAR γ ligands, TZDs alter lipid profiles (by elevating HDL cholesterol levels) and circulating free fatty acids, plasma lipolysis of triglycerides, absorption of fatty acids, and triglycerides storage in the adipocytes. PPAR γ activation occurs because of the induction of the gene's expression governing adipocyte metabolism of fatty acids, and transport proteins of fatty acids. Thus, PPAR γ activation results in reduced free fatty acids release and insulin-resistance-related adipocytokines (including tumour necrosis factor (TNF- α), leptin, and resistin), increased synthesis of adiponectin (Fig. 2), which has anti-atherosclerotic property [111].

At the arterial wall level, PPAR-α and PPAR-γ activators suppress expression of the markers of pro-inflammatory, limit cytokine and chemokine production, and stimulate efflux of macrophage cholesterol *via* Scavenger receptor class B type I and ATP-binding cassette transporter ABCA1 stimulation. PPARs also inhibit the production of a vasoconstrictor peptide endothelin-1 [114] and promote the vasodilatory mediator nitric oxide release [115]. Furthermore, TZDs modify endothelial function in diabetes patients by suppressing the development of advanced receptors for the glycation end-products (AGE) present in the endothelial cells. In addition, PPAR β/δ is responsible for regulating glucose metabolism of glucose, amounts of various antioxidants that are endogenous and present in the heart, cardiomyocyte apoptosis, mitochondrial biogenesis, the mechanism that insulin uses to send signals, and responses of lipid-associated myocardial inflammatory responses. As a consequence of this, PPARβ/δ ligands have the potential to enhance cardiac function and slow down the progression of the pathological conditions such as cardiac hypertrophy, heart failure, ischemia-reperfusion injury, damage to cardiac oxidative system, dysfunction of cardiac lipotoxic heart and lipid associated inflammation of heart [116]. This reduces the cells' sensitivity to AGE-induced pro-inflammatory responses [117]. Therefore, risk profile that is predisposed to cardiovascular disease is improved by PPAR's agonists (Fig. 2).

Although lipids are necessary for the heart to operate by providing the energy it needs, but too much lipids or an improper distribution of lipids, further can lead to condition known as dyslipidemia. Dyslipidemia can result in cardiac dysfunction due to aberrant cardiac shape and function. In patients with dyslipidemia, plasma levels of HDL cholesterol are low, while levels of triglyceride-rich VLDL and small-and-dense LDL cholesterol are increased. Obesity is one of the most common causes of atherogenic dyslipidemia, which is a significant risk factor for cardiovascular diseases [118]. PPAR β/δ have a synergistic impact on several organs, including the liver, adipose tissue, and skeletal muscle, which allows them to maintain normal levels of lipids in the body. Gene expression profiling shows that hepatic PPARβ/δ regulation of the genes expression based in lipoprotein metabolism (VLDLR, ApoA5, ApoA4, ApoC1), which is consistent with the triglyceride-lowering activity of PPARβ/δ *in-vivo* [119]. PPAR β/δ controls many aspects of metabolism of fatty acid and therapeutic intervention at this site has been shown to ameliorate heart disorders associated with alterations in this pathway [120].

4. Conclusion and future perspective

Individuals with identical BMIs may have wildly different metabolic and CVD risk profiles due to the complexities of obesity. Obesity influence hemodynamics and alter cardiac anatomy that proliferate the risk of CVDs. Therefore, a need arises to investigate the mechanisms that are at the root of obesity-related cardiac dysfunctions and to find ways to improve the treatment of patients who suffer from both obesity and cardiovascular disease through the conduct of additional research. Although the specific processes between obesity and CVDs are not fully known, adipose tissue's propensity to grow and create pro-inflammatory cytokines that impair cardiac systolic and diastolic functions and atherosclerotic plaque formation plays a crucial impact. In recent years, biomarkers and surrogate endpoints have grown along with genetic and physiological understanding of obesity and related CVDs. These biomarkers belong to a diverse category that is mostly associated with obesity-related processes such as inflammation, oxidative stress, adipocyte physiology, and dietary control. These biomolecules involved in these processes have a major role in the detection, treatment, and follow-up of these features; yet, the intricacy of the networks involved hinders their validation as a biomarker of risk, diagnostic, and/or predictive.

Declaration of Competing Interest

Authors have no conflict of interest. All agreed for the submission.

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