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Original article:

Adipose Tissue, Adipokines and Cardiac Health – An overview

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Abstract

After the discovery of leptin in early 1990s, research on adipose tissue has been so enormous and concluded to state that adipose tissue is the largest diffused endocrine gland in the human body. As of now, adipose tissue is said to secrete more than 600 compounds that are hormones or hormone like substances called adipokines or adipocytokines. These secretions have widespread actions on almost all organ systems of the body contributing to both health and many health hazards. Interestingly, adipokines have a major role to play in cardiac health and it is highly relevant to Indian situation as it has been reported that Asians are more prone to cardiac problems than other races in the world. Here is an attempt to provide an overview of various adipokines and their role in heart functions in normal and abnormal conditions.

Introduction

The basic functions of thermal insulation, mechanical support, energy storage and whole-body fatty acid homeostasis of white adipose tissue (WAT) in the humans are well documented (1). But, the recent escalating prevalence of obesity and associated non-communicable diseases (NCD) such as diabetes mellitus, musculoskeletal disorders, several types of cancer, cardiovascular diseases (CVD) and other metabolic disturbances is a matter of great concern (2).

Chronic accumulation of extra body fat leading to obesity results in adjustments in the cardiovascular system such as increased cardiac output, decreased peripheral resistance, increased stroke volume or ventricular remodeling to maintain whole body homeostasis (3). A number of studies have shown a strong association between changes in adipokines secretions from WAT in obesity induced inflammatory state and the greater risk of developing metabolic syndrome (MS) and CVDs (4,5). For example, few reports have shown that a) adiponectin and retinol binding protein 4 (RBP4) levels were significantly lower in ischemic heart disease (IHD) while RBP4 levels were significantly increased in CVD as compared to their respective controls, b) significantly high circulating adipocyte fatty-acid-binding protein 4 (AFABP4) levels in CVD and significantly lower visfatin levels in both CVD and IHD with respect to controls (6,7).

White Adipose Tissue (WAT) and its Role

WAT is mainly distributed as subcutaneous and visceral fat depots in the human body (8). Subcutaneous adipose tissue (SAT) represents about 80% of total body fat, while visceral adipose tissue (VAT) accounts for up to 10-20% in men and 5–8% in women. It increases with age in both genders (9). Heart, kidneys, bone marrow, joints, eyes, lungs and vasculature also contain smaller fat depots as ectopic fat (10).

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WAT consists of mature adipocytes, pre-adipocytes, fibroblasts, endothelial cells, T-lymphocytes, macrophages and also connective, vascular and neural tissues (4). Adipocytes and macrophages in WAT release adipokines to modulate appetite, energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and homeostasis (4,8). Free fatty acids (FFAs) from the circulation will accumulate into triglycerides in the adipocytes in the postprandial period by the anabolic and anti-lipolytic actions of insulin (11). However, when adipocytes become larger, non-functional and insulin resistant, they release FFAs into the circulation due to the lipolytic effect of the adrenal catecholamines (8).

WAT and Cardiovascular Risks

Obesity is a well known condition characterized by excess fat accumulation in the body (8). Individuals with abdominal or upper body obesity will have excess visceral fat and are at a greater cardiovascular risk than those with excess gluteo-femoral or subcutaneous fat. Thus, excess VAT is associated with CVDs, while SAT is associated with a protective function (10). This difference in the role between fat depots is because of the type of adipocytes, their endocrine function, lipolytic activity and their response to insulin and other hormones (8). Moreover, VAT has a higher infiltration of macrophages which increases the release of pro-inflammatory adipokines such as interleukin-6 (IL-6) or plasminogen activator inhibitor (PAI)-1, leading to local and systemic inflammation and cardiovascular risks (10).VAT consists of large adipocytes with profuse β-adrenergic receptors as compared to the SAT that favors higher lipolytic activity and lower sensitivity to the anti-lipolytic effect of insulin which increases FFAs delivery into the bloodstream and surrounding tissues (12). VAT venous blood is drained directly into the liver through the portal vein releasing larger amounts of FFAs thereby stimulating hepatic glucose production and suppresses hepatic insulin clearance leading to dyslipidemia, hyperinsulinemia and insulin resistance at systemic level. This in turn promotes the transport of free fatty acids into myocytes where they exert lipotoxic effects (13). Cardiac myocytes are subsequently damaged by the formation of reactive oxygen species, ceramide production, and a drop in contractility due to Ca2+ depots in the sarcoplasmic reticulum, impaired insulin signaling and the development of mitochondrial dysfunction and subsequently contributing to metabolic syndrome. Thus, abdominal adiposity and insulin resistance may lead to the accumulation of triglycerides in the myocardium and cardiac steatosis and may contribute to the development of left ventricular diastolic dysfunction (14). In SAT, venous blood is drained into the systemic veins avoiding any such ill effects as seen in the case of VAT (10).

Though, excess deposits of visceral fat is now considered as a key modifiable CVD risk factor, it can worsen the CVD risk through inflammation, altered adipokine profile, impaired fibrinolysis and increased risk of thrombosis and endothelial dysfunction (3). However, the contribution of different fat depots to the development of CVDs varies according to their distribution and function and the underlying mechanisms in this regard need to be explored further.

Epicardial Adipose Tissue (EAT) and Cardiovascular Risk

Currently, epicardial fat is recognized as a marker of visceral fat using echocardiographic evaluation and cardiovascular risk (15). EAT is the intra-pericardial fat depot that constitutes about 20% of the total weight of ventricles of the human heart. It generally protects the heart against high fatty acid levels and acts as a local energy source of fatty acids during times of extra energy demand by the myocardium (16). EAT is located between

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the myocardium and pericardium without a structure separating it from the myocardium and as a result, FFAs could diffuse across concentration gradients between the epicardial fat and the myocardium in both directions (16). EAT increases in obesity which has been related to cardiac hypertrophy, impaired diastolic function and coronary artery occlusions (16). It secretes pro- and anti- inflammatory adipokines, vasoactive factors and growth factors that influence the myocardium and coronary arteries homeostasis and trigger atherosclerosis, cardiovascular disorders associated with obesity and diabetes mellitus (17).

Epicardial fat also includes perivascular adipose tissue (PVAT) that covers the surface of the heart and surrounding adventitia of coronary arteries. It is deposited more in the right heart than the left. A study on PVAT has reported that it differs from subcutaneous and perirenal adipose tissue in that there are large number of less differentiated adipocytes which produce largely pro-inflammatory cytokines, (e.g. IL-6, IL-8 and MCP-1) and conversely, production of adiponectin in PVAT is reduced (18). Pericardial fat as assessed by CT has demonstrated that its volume is directly proportional to the severity of coronary heart disease in patients with preserved ejection fraction (19). Increased number of macrophages, T-lymphocytes and mast cells in epicardial fat but not in SAT has been reported in patients with coronary artery disease by several researchers [20]. A few studies have shown the regression of epicardial fat in relation to weight reduction, exercise or following administration of either atorvastatin or ezetimibe (21).

Adipokines and Cardiovascular Functions

A dipose tissue dysfunction and associated adipokine secretion can contribute to a spectrum of obesity-related conditions including CVD. Adipokines influence cardiovascular function either by direct action on the vessel wall through paracrine effects or by affecting endothelial function through changed plasma and tissue levels (22). Some adipokines have anti-inflammatory and cardio-protective effects (eg. omentin, apelin, adiponectin) and some are pro-inflammatory with negative impact on cardiovascular function (eg. leptin, visfatin, resistin, adipocyte fatty-acid-binding protein). The secretory products of PVAT are also involved in proliferation and migration of smooth muscle cells of blood vessels (23). The importance of a few major adipokines in cardiac health is considered here.

Leptin

Leptin is mainly produced by SAT. Liver, skeletal muscle, kidneys, heart and EAT also secretes leptin. Leptin receptors are expressed in both central and peripheral tissues and are in plenty in cardiomyocytes. Leptin functions as an energy regulator, has a role in rheumatoid arthritis, Alzheimer's disease, some types of cancer and also in the regulation of reproductive functions (24). Leptin regulates inflammation through monocytes and macrophages activation to release the pro-inflammatory molecules IL-6, tumor necrosis factor (TNF)-α and IL-12 (25).

Leptin has a role in regulating cardiac muscle contractility, hypertrophy, fibrosis, apoptosis, and metabolism (26,27). Leptin also affects blood pressure, sympathetic nervous system (SNS) activation, insulin resistance, platelet aggregation and pro-inflammatory processes. Different studies have shown a positive correlation between circulating leptin levels and blood pressure, suggesting that leptin could act as a hypertensive molecule (28).

Long term administration of leptin increase heart rate and mean arterial blood pressure via the sympathetic nervous

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system and catecholamines (29). Another mechanism described in the development of hypertension by leptin is by decreased diuresis and increased sodium reuptake in the kidneys (30). Some of the cardio-protective effects of leptin such as reduced extent of myocardial infarction (MI) and protection against reperfusion damage by local autocrine effects and also anti-lipotoxic effects are probably mediated through nitric oxide (NO) (31,32). Hyperleptinemia in the general population is associated with atherosclerosis, hypertension and the metabolic syndrome with an increased risk of myocardial infarction and stroke independent of obesity status and cardiovascular risk factors (29,33). Leptin induces autophagy in cardiac cells, but its importance needs to be further investigated (34).

Adiponectin

Adiponectin is mainly produced by SAT and it affects energy expenditure and food intake regulation (8,35). Adiponectin levels are decreased in obesity and correlate negatively with BMI, glycemia and circulating insulin levels (35). Adiponectin has also been implicated in the protection against endoplasmic reticulum stress in the heart (36).

Low adiponectin level is associated with aortic vasodilatation dysfunction, endothelial dysfunction and hypertension through various mechanisms involving hyperactivity of the renin-angiotensin-aldosterone and sympathetic nervous system, endothelial dysfunction and impaired renal pressure natriuresis (21,24). Serum adiponectin concentrations are markedly decreased in diabetic patients with coronary heart disease (37,38). Adiponectin has a role in cardiac remodeling by limiting the extent of cardiac hypertrophy and it protects against ischemia/reperfusion injury (10,31,37). However, despite its well documented cardio-metabolic benefits, high levels of circulating adiponectin have been shown to be associated with increased risk of atrial fibrillation in the elderly people aged over 70 years (39).

Adiponectin is considered an anti-atherosclerotic factor that inhibits proliferation and migration of smooth muscle cells, inhibits the conversion of macrophages into foam cells, suppresses the production of reactive oxygen species (ROS) and increases the production of nitric oxide (NO) by decreasing macrophage TNF-α production (21). Some studies have demonstrated an inverse relationship between adiponectin levels and inf- lammatory markers including CRP (21). Adiponectin levels are positively associated with HDL, negatively with TAG. Hypo-adiponectinemia has been detected in patients with angiographically confirmed coronary atherosclerosis and acute coronary syndrome with relevance to severity of coronary artery disease and the risk of myocardial infarction and the risk of MI (31,40). It is logical that hypo-adiponectinemia should be associated with hypertension in obese individuals. One study however, has shown that hypo-adiponectinemia can lead to the development of hypertension in lean people as well (41). Another interesting observation is that of elevated levels of adiponectin in patients with chronic heart failure. Several explanations for this have been offered and one of them could be resistance to adiponectin (42).

At the present time, adiponectin cannot be regarded as a predictor of cardiovascular diseases. The reason for this may be due to different effects of individual forms of adiponectin (a low molecular weight (LMW) and a high molecular weight form (HMW) on the cardiovascular system. Research suggests that the protective subtype is the HMW adiponectin. In contrast, LMW adiponectin has damaging and pro-inflammatory effects and possibly increases insulin resistance. It is therefore appropriate to measure the ratio of HMW adiponectin to total adiponectin (43).

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Resistin

In humans, resistin is produced by pre-adipocytes and macrophages. Lower resistin levels are reported in VAT of genetically obese rats in comparison with lean rats. Mice lacking the resistin gene have lower fasting glucose levels and a better glucose tolerance and insulin sensibility while resistin over-expression is associated with insulin resistance and dyslipidemia (31,44).

Resistin exerts its actions on cardiovascular system mainly through the interaction with other adipokines such as adiponectin or leptin. There appears to be a both direct and reciprocal effect between resistin and adiponectin on endothelial cells inflammation. Resistin induces the expression of adhesion molecules while adiponectin inhibits resistin action (31). Higher levels of plasma resistin correlate with pro-atherogenic inflammatory markers, increased cardiovascular risk, unstable angina, poor prognosis in coronary artery disease, T2DM and metabolic syndrome (31,45). Increased content of resistin in EAT of patients with advanced coronary atherosclerosis and history of myocardial infarction has been reported (46).

Visfatin

VAT secretes more visfatin than SAT. In general, visfatin may have a role in the pathogenesis of diabetes mellitus, obesity, dyslipidemia, hypertension, renal failure and atherosclerosis (47). Substantial clinical evidence supports the role of visfatin as a potential marker of inflammation and endothelial dysfunction in both metabolic disease (48) and in patients with acute coronary syndrome (49).

Visfatin has a pro-inflammatory effect at vascular level and also an anti-inflammatory action via adipokines production, endothelial proliferation and angiogenesis (31,50). A positive correlation between circulating visfatin levels and HDL is suggested. However, visfatin expression is increased in macrophages from atherosclerotic plaques in patients with unstable atherosclerosis (51). On the other hand, visfatin induces endothelium vaso-relaxation by increasing nitric oxide production, and it has a protective effect of ischemia/ reperfusion injury by reducing the infarct area size (31). However, plasma visfatin levels were recently found to be associated with major adverse cardiovascular events in patients with acute ST-elevation myocardial infarction (STEMI) (49). This temporary increase in the visfatin concentration in the first week after STEMI and its correlation with an increase in cardiac enzymes might indicate that visfatin plasma level corresponds to the extent of myocardial disease (21).

Apelin

Apelin is produced by SAT, VAT and other tissues such as the brain, heart, lungs, vascular endothelium, gastrointestinal tract and kidneys (1,8,31,52,53). It improves glucose tolerance. Apelin injection reduces fat mass without modifying food intake, but promotes adiponectin secretion (53,54).

The therapeutic potential of apelin appears to be significant since it is considered as a cardio-protective factor, particularly in the treatment of heart failure and pulmonary hypertension. However, several studies have confirmed reduced levels of apelin in heart failure (55) whereas other studies have shown differing responses (56). Circulating apelin levels are low in paroxysmal supra-ventricular tachycardia, chronic heart failure and dyslipemic patients (24). An increased risk of recurrence of atrial fibrillation (AF) in subjects with lower levels of apelin is reported in a recent study (57). In those with high cholesterol, the therapeutic LDL reduction induces an increase in plasma apelin levels (31,58). Apelin exerts an anti-atherogenic effect and to prevent the formation of aortic aneurysms by

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reducing macrophage-induced inflammation in dyslipemic animal models (59). Apelin also induces angiogenesis and endothelium vaso-relaxation by increasing nitric oxide production, as well as protection against ischemia/reperfusion injury (31). Apelin gene therapy increases vascular density and alleviates diabetic cardio-myopathy in diabetic mice (60). Apelin falls early after myocardial infarction (MI). After a few days, its levels start rising again, but remain reduced until 24 weeks post-MI. Post-infarct treatment with apelin improves myocardial function by increasing neo-vascularization and over expression of angiogenic growth factors in rats and also increases cardiac contractility (61). Generally, levels of apelin are lower in subjects with coronary heart disease (CHD). In patients with unstable angina and myocardial infarction, apelin levels are lower than in patients with stable forms of CHD. Apelin levels are also negatively correlated with the severity of coronary stenoses (62).

Chemerin

Chemerin is produced by endothelial cells and both chemerin and its receptor are expressed in WAT and EAT. It attracts macrophages and dendritic cells to inflammatory areas (63). Chemerin secretion is promoted by pro-inflammatory cytokines that help in angiogenesis and vascular remodeling (63). Chemerin is proposed as a predictive marker of cardiovascular risk. It is increased by IL-1β and in obesity. Following bariatric surgery its circulating level is reduced (63). Its circulating levels correlate positively with the severity of coronary artery disease, dilated cardiomyopathy as well as with acute myocardial infarction. Chemerin expression in human aortic, coronary artery and periadventitial adipose tissues is positively correlated with the severity of atherosclerosis (64).

Chemerin levels also correlate positively with body mass index, blood pressure, serum LDL -cholesterol and triglycerides and negatively with serum HDL-cholesterol (65). Because of its chemotactic effects mediated reduction in NO production and negative effects on plasma lipids, chemerin is linked to progression of atherosclerosis (66).

Omentin

VAT secretes more omentin as compared to SAT and is also produced in EAT, intestines and endothelial cells (63). Omentin is decreased in obesity, and correlate positively with plasma adiponectin and LDL levels, and negatively with abdominal girth, BMI, and insulin resistance. It may also act as a vasodilator by inhibiting catecholamine-induced vasoconstriction and increasing nitric oxide production in endothelial cells (31). Omentin slows down the pathological process of myocardial hypertrophy and ameliorates acute ischemic injury by suppressing myocyte apoptosis. Decreased serum omentin-1 levels are associated with a poor cardiac outcome in patients with heart failure and are considered an independent risk factor for peripheral arterial disease and acute myocardial infarction (67).

AFABP

Adipocyte fatty-acid-binding protein (AFABP) levels positively correlate with metabolic and inflammatory cardiovascular risk factors, which include atherogenic dyslipidemia, hyperglycemia, hypertension and also some laboratory markers of inflammation (s-CRP and IL-6). A higher concentration of AFABP4 may predict increased risk of cardiovascular death, non-fatal myocardial infarction or stroke for people with pre-existing coronary heart disease (68).

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Fibroblast growth factor 21 (FGF21)

Increased level of FGF21 is associated with atherosclerosis, cardiac hypertrophy, coronary artery disease and diabetic cardiomyopathy (69). Experimentally induced myocardial hypertrophy or infarction leads to increased expression of FGF21 which might prevent further progression of myocardial damage (70).

Conclusion

It appears that in the near future, adipokines could find clinical use in two ways. Firstly, they could be a marker of a number of pathological conditions and diseases associated with obesity, metabolic syndrome and cardiovascular diseases. Low serum levels of cardio-protective adipokines or increased levels of pro-inflammatory adipokines might be useful biomarkers of different cardiovascular diseases. Currently, some promising ones are low values of cardio-protective omentin, increased levels of visfatin as markers of acute coronary syndrome and AFABP as a marker of metabolic syndrome. Despite the vigorous research in the field of adipokines, it may take some more time to very clearly establish the role of each adipokine in health and disease conditions.

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