Adiponectin, Diabetes and Coronary Artery Disease

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Perspective

White adipose tissue is an active endocrine gland communicates with the brain and the peripheral tissue including pancreatic beta cell through adipocytokines [1]. Examples of adipokines are; acylation stimulating protein (ASP), adiponectin, adipsin, angiotensinogen, bone morphogenic protein (BMP), estrogen, insulin-like growth factor-1 (IGF-1), various IGF binding proteins, interleukins (ILs), leptin, monocyte chemoattractant protein 1 (MCP-1), plasminogen activator I (PAI-1), resistin, TNF-alpha, transforming growth factor-beta (TGF-beta) and various prostaglandins [2-8] (Figure 1).
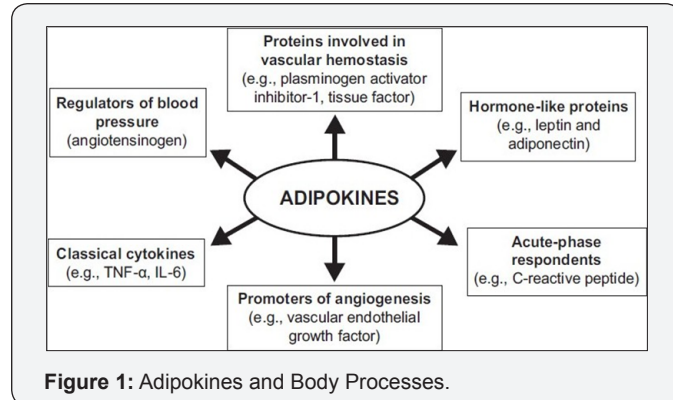

Figure 1: Adipokines and Body Processes.

Adipokines influence many physiological and metabolic processes, such as lipid metabolism, haemostasis, appetite and energy balance, immunity, insulin sensitivity, angiogenesis, inflammation and blood pressure regulation. Adiponectin and leptin are the most studied adipocytokines. Over 90% of adipokines are reported to be produced by the stromal-vascular cells. Different regions of white adipose tissue seem to secrete different adipokines [9,10]. For example, subcutaneous fat depot is reported to secrete leptin and visceral adipose tissue IL-6. Secretory products of visceral adipose tissue are reported to be six adipokines, three chemokines (growth-related oncogen factor, RANTES, macrophage inflammatory protein-1), one interleukin (IL-7), one tissue inhibitor of metalloproteinases (TIMP-1), and one growth factor (thrombopoietin)[11] It is also suggested that size of the adipocytes influence adipokine secretion. Hypertrophied adipocytes in obesity secrete less adiponectin and more in lean subjects with small sized adipocytes [12]. This could form the basis for the association of adipocyte size to obesity-related complications, such as insulin resistance and the increased risk for coronary heart disease [13] (Figure 2).
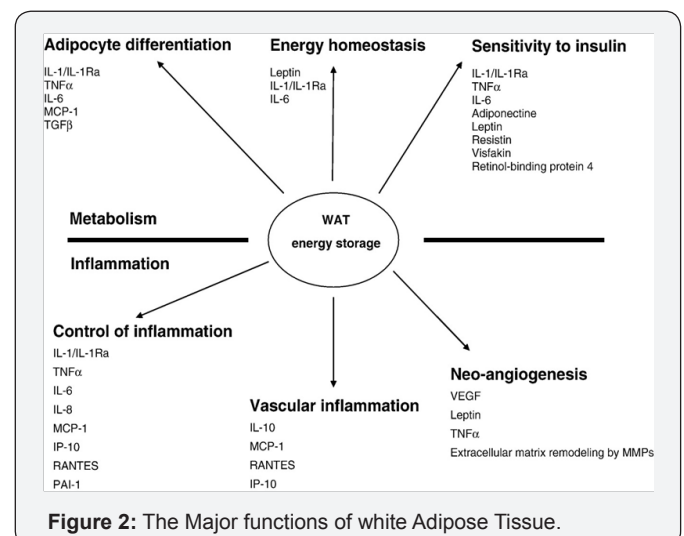

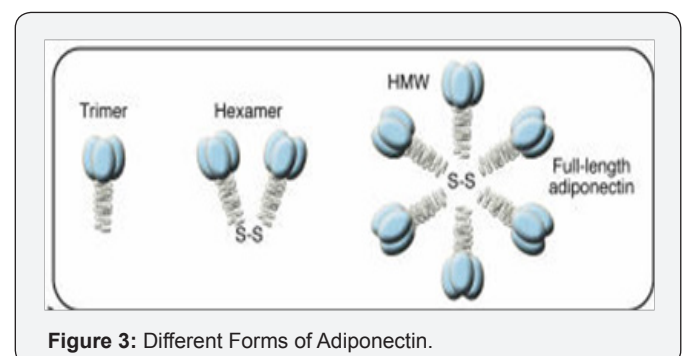**Figure 2:** The Major functions of white Adipose Tissue.

Figure 3: Different Forms of Adiponectin.

Of the major adipokines Adiponectin (APN) has a molecular weight of 30-kDA .It exists in many different forms. APN exists as a trimer, known as low molecular weight oligomers, a hexamer,

which consist of two trimers linked by a disulphide bond known as middle-molecular weight adiponectin, and a high molecular weight (HMW) multimer [14-17]. The relative distribution of adiponectin multimers seems to differ between the adipose tissue and the circulation. The larger HMW forms is dominating in plasma, [5] whereas the presence of the globular fragment in human plasma has been questioned [6,7] (Figure 3). APN is considered to be an important modulator of insulin sensitivity [8] and dyslipidemia [9]. AP is reported to be an anti-inflammatory marker which is shown to have an inverse relation with pro-inflammatory markers like fibrinogen, intracellular adhesion molecule-1, Eselectin, and C-reactive protein [10,11]. APN though structurally related to TNFα, increases insulin sensitivity particularly in the liver, promotes beta cell function and survival [12]. AP is shown to bind with its receptors in beta cells and may augment glucose induced insulin secretion [13]. It is considered to be a powerful anti-apoptotic molecule possibly through the activation of kinases which promote beta cell survival along with reducing the levels of ceramide and increasing the sphingosine-1-phosphate, one of the key anti- apoptotic metabolite [14]. APN is also reported to have a protective effect on coronary artery disease (CAD) evidenced by prospective studies indicating that higher adiponectin is associated with a decreased risk CAD in non diabetic subjects [15] type I diabetic subjects [16], type 2 diabetic men [17] and in end-stage renal disease patients [18].

APN appears to play an important role in the pathogenesis of type 2 diabetes. T2DM patients are reported to have reduced serum levels of APN compared to control subjects [19-21]. It is also observed that higher APN levels are associated with better lipid and glycemiccontrol inT2DM subjects [22,23]. Therefore it is assumed that APN could be a marker of insulin resistance and T2DM [24]. Adiponectin is widely regarded as an anti-atherogenic, antioxidant and anti-inflammatory molecule. However, adiponectin concentration is paradoxically increased in individuals with type 1 diabetes, in whom it is positively associated with adverse clinical outcomes [23]. There is now considerable body of evidence to suggest that there is link between visceral fat and CHD. That is why these molecules are collectively named as 'adipocytokines.' It is also known that 'visceral fat syndrome' may cause dysregulation of adipocytokines and clustering of other factors. A direct link has been established between visceral fat and CHD. It was named collectively as adipocyte-derived molecules as 'adipocytokines'. The 'visceral fat syndrome' accelerates atherosclerosis due to the dysregulation of adipocytokines and clustering of other coronary risk factors [25].

Circulating adiponectin is shown to accumulate where endothelial barrier is damaged, and has protective effects against almost the whole process of atherosclerosis [18].Therefore adiponectin and other adipokines do play a vital role in the metabolic processes of the body. APN's role in insulin action and insulin sensitivity needs more studies to bring out the beneficial effects of APN and its associated adipokines.

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