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CORONARY ARTERY DISEASE WITH PROSPECT OF FIBROBLAST GROWTH FACTOR-23 AND VARIOUS OTHER FACTORS -A NOVEL REVIEW PART I.

Medical Science

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ABSTRACT

Cardiovascular disease is one of the major cause of death in worldwide. Obesity, hypertension, dyslipidemia, hyperuricemia and changes in lifestyle are the major causes attributed to Coronary Artery Disease (CAD). Various factors play a role in Coronary Artery Disease like Insulin, Vitamin-D, Calcium, Phosphorous, and FGF-23 levels in blood. The present review for the simplicity is divided into three parts and present part explains the coronary artery disease, atherosclerotic initiation, Insulin and Insulin resistance.

KEYWORDS

Coronary Artery Disease, Atherosclerotic Initiation, And Insulin Resistance.

INTRODUCTION

FGF-23 normally inhibit reabsorption of renal phosphate and parathormone secretion with a subsequent decrease in circulating blood levels of 1, 25-dihydroxy vitamin D[1] (Activated Vit-D). Parathyroid hormone activated vitamin D, secreted klotho, glucocorticoids, calcium, phosphate, leptin and glucocorticoid[2] are said to be regulates the secretion and maintenance of FGF-23. The FGF-23 is found to be related to insulin resistance and fat metabolism, there by suggests a relation with cardiometabolic syndrome[3-6]. Insulin sensitivity or resistance is closely related to Metabolic Syndrome (MS) and the major manifestation of MS is coronary artery disease (CAD).

CORONARY ARTERY DISEASE (CAD):

As the name suggest it refers to the thickening of inner layer of artery and accumulation of the lipid and it is the leading cause of death in developed countries. Epicardial coronary arteries are the most commonly site involved.

The genetic factor as a risk in atherosclerotic plaque are not completely known[7]. Hypercholesterolemia, hypertension, low HDL level, Diabetes mellitus, increased levels of lipoprotein, obesity, cigarette smoking, infection and physical inactivity can be considered as the environmental risk factors[8]. These factors cause disturbance in the normal endothelial function. Vascular endothelial dysfunction and their interaction with the blood platelets and monocytes lead to accumulation of abnormal fat, cells and debris in sub intimal layer leads to formation of atherosclerotic plaque. This lead to reduction in cross sectional area of artery at that segment.

ATHEROSCLEROSIS INITIATION:

Accumulation of lipoprotein and its modification:

Atherosclerotic lesion at the initial level is represented as "Fatty Streak." This is due to the focal lipoprotein accumulation at the intimal layer of artery. As the intima layer consists of smooth muscle cell remnants in extracellular matrix and covered by vascular endothelial cells, which is in single layer.

Leukocyte recruitment and foam cell formation:

Oxidative – modification hypothesis[9] suggest that firstly LDL accumulates at extracellular levels of subendothelial spaces of arteries which mildly oxidised to form minimally modified LDL. This inturn leads to production of granulocyte, macrophages, and monocyte chemotactic protein I by local vascular cells. As a result, monocyte recruitment and macrophage differentiation in arterial walls leading to further peroxidation of LDL. Now macrophages take up the completely oxidized LDL to form foam cells[9,10].

INITIATION:

Accumulation of lipoprotein and its modification: The intimal layer of arteries in normal human adult contains some resident smooth muscle cells embedded in extracellular matrix and is covered with single layer of vascular endothelial cells. The initial lesion of atherosclerosis is represented by "Fatty streak". The formation of these early lesion may be due focal lipoprotein accumulation in the intimal layer of the artery.

Leukocyte recruitment and foam cell formation: According to the oxidative – modification hypothesis[9], initially LDL accumulates in the extracellular subendothelial space of arteries and with accumulation of resident vascular cells, is mildly oxidised to form minimally modified LDL. This in turn produces monocyte chemotactic protein I by local vascular cells, granulocyte and macrophages colony stimulating factor, which stimulate monocyte recruitment and macrophage differentiation in arterial walls (9) leading to further peroxidation of LDL now the completely oxidized LDL is taken up by the macrophages to form foam cells[9,10].

Studies showed that calcification of arteries causes CAD[11]. It involves following pathogenesis inflammation, endothelial dysfunction[12], smooth muscle cell (SMC) proliferation, oxidation of β lipoprotein, calcification, which can represent a vigorous instead of a dystrophic process[13] and fibrosis of arteries[14]. Initial calcium deposits can be tiny aggregates and later giant nodules in vascular walls. Coronary artery calcium score is detected by computed tomography [15].

Coronary angiography is used in diagnosis of CAD, ischaemic cardiomyopathy, coronary disease, patients with angina, cardiac failure, for revascularization procedure, patients with aortic stenosis, or mitral valve disease. Also indicated to rule out luminal stenosis in stable patients with suspected coronary artery stenosis; in patients with acute chest pain and to rule out stenosis in noncoronary cardiac surgery [16].

Non-obstructive atherosclerosis was associated increased risk of cardiac events such as myocardial infarction (MI) and other cardiac complication. Angiography detects narrowed or blocked boold vessels. Patients were considered as having normal, non-obstructive CAD. Non-obstructive CAD had an association with risk of MI[17].

INSULIN

Control of glucose metabolism is mainly done by Insulin**.** Beta cells of islets of Langerhans of pancreas synthesizes Insulin. Initially it's synthesized as pre-proinsulin which is a single chain of 86 amino acid (a.a) precursor. Proinsulin is formed by removal of amino terminal signal peptide by proteolytic process. Proinsulin is cleaved to form C-peptide, which is an internal 31- residue fragment. A (21 a.a) chain and B (30a.a) chains of insulin that are connected by disulphide bonds.

The C-peptide and matured insulin are co-secreted from secretary granules in the beta cells. Nowadays human insulin is produced by recombinant DNA technology [18]. A series of regulatory steps stimulate insulin secretion by the beta cell of pancreas, if any abnormality in glucose like Diabetes mellitus is detected. It begins with transport into the beta cells by GLUT2 glucose transport [19]. Phosphorylation of glucose by glucokinase is rate limiting step to control glucose by insulin secretion, once insulin is secreted half of it is removed and degraded by liver. The binding of unextracted insulin to its receptor stimulates intrinsic tyrosine kinase activity in target cell, which leads autophosphorylation of receptor and collection of intracellular signal molecule.

These and other proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions. This results in metabolic and mitogenic effects of insulin. Insulin mainly acts on heart, liver,

muscles and adipose tissue. Insulin regulates carbohydrate, lipid and protein metabolism and promote cell division and growth. Insulin exerts anabolic effects on fat by inhibiting synthesis of the hormone sensitive triacylglycerol lipase of adipocytes.

Insulin sensitivity of target tissue is decreased with high insulin level which down regulates the number of insulin receptors on the target cell membrane. Insulin decreases formation of glucose from glycogen and increases glucose utilization thereby leading to low blood glucose level [20].

Insulin resistance (IR): When body cells do not respond to insulin lead to insulin resistance. IR describes an impaired biological response to insulin [21-23]. IR can be due to disturbance at different sites of receptors[20]. IR is not just a defect in glucose uptake however is a multifarious disorder related with coronary artery disease. IR played a greater role in progression of CAD [24,25]. It's related to cardiometabolic syndrome that incorporates hyperglycemia, central obesity, dyslipidemia and atherosclerosis [26]. Obesity and insulin resistance interact leading to impaired vascular function and are related to endothelial dysfunction, increased intima media thickness of arteries, and increased vascular stiffness [27].

Diabetic patients exhibit high risk obstructive atherosclerosis leading to endothelial and vascular smooth muscle dysfunction.28 The Insulin Resistant Atherosclerosis Study (IRAS) [29] and others have shown that insulin resistant is associated atherosclerosis [30], outlined by the thickening of tunica intima- media carotid arteries. The role of inflammation in pathogenesis of CVD is well known. Inflammation contributes to all phases of atherosclerosis [31]. A report from the Third National Health and Nutrition Examination Survey said that increased levels of inflammatory markers such as CRP and fibrinogen were positively and independently associated with insulin resistance [32]. Underlying mechanisms for the risk factor role of IR are not fully known. Previous evidence-based study says that severity of CAD is foreseen by measuring insulin resistance in type 2 diabetes mellitus [33].

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