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PHARMACOLOGICAL APPROACHES TARGETTING INFLAMMATORY PATHWAY OF CARDIOVASCULAR COMORBIDITIES

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Abstract:

Cardiovascular event is the general term used to indicate numerous heart diseases which are related to fat deposition and arthrosclerosis which accounts for higher mortality rates. Co-occurrence of obesity, hyperglycemia and cardiovascular disease is the major health concern resulting in increased mortality. It is well known that obesity leads to cardiovascular mortality independent of other factors. Obesity activates JNK pathway through inflammatory response which is the hallmark of insulin resistance. Hyperglycemia and obesity promotes systemic inflammation. Inflammatory response remains the key factor for initiation and progression of cardiovascular disease and co morbid conditions. Hence focusing on the inflammatory mediator pathway will guide in individualizing therapeutic regimen to alleviate the disease. Existing hyperlipidiemic drugs HMG CoA Reductase inhibitors, Peroxisome proliferator activated receptors and Fibrates, Cholesterol absorption inhibitors and synthetic hypoglycemic agents GLP-1 agonist, Biguanide, DPP-4 inhibitors are focused in management because of their anti-inflammatory and insulin sensitizing mechanism which has positive impact on patient's life.

Keywords: *Arthrosclerosis, Cardiovascular disease, Inflammation, Insulin resistance, Obesity.*

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INTRODUCTION:

Cardiovascular disease are the leading cause of mortality accounting for about 17.9 million deaths every year globally of which more than 75% are observed in low and middle income countries.[1] Myocardial infarction and stroke are recognized as major complications of cardiovascular disease.[2] Insulin resistance and obesity are the most common hypothesis in describing the pathophysiology of cardiovascular events. Obesity defined as the body mass index greater than 30kg/m has direct relationship with cardiovascular disease and enhances production of inflammatory mediators. Obese condition contributes to hyperinsulinemia by elevating insulin secretion as a result of excess free fatty acid circulation. This affects JNK pathway leading to serine phosphorylation of insulin substrate resulting in insulin resistance.[3] Free fatty acid enhance inflammatory response producing abundance of triglycerides, very low density lipoproteins and leptin thus contributing to cardiovascular events.[4,5] Inflammation of the vessel is recognized to play the vital role in rupture of plaques in addition to that of initiation and progression of cardiovascular disease. Insulin resistance enhances release of pro coagulant factors by their mechanism of endothelial dysfunction that result in platelet aggregation.[6] Serine phosphorylation of IRS-1 is induced by c-Jun NH_2-terminal kinase (JNK) that is activated by hypoxia, and oxidative stress in addition to that of stress-activated protein kinases.[7] Serine phosphorylation of IRS diminish tyrosine phosphorylation which inhibit insulin signaling progressing to insulin resistance.[8] Inhibition of insulin signaling by serine phosphorylation of IRS-1 occurs either by intercession with insulin receptor or by increased IRS-1 degeneration.[9]

PATHOPHYSIOLOGY

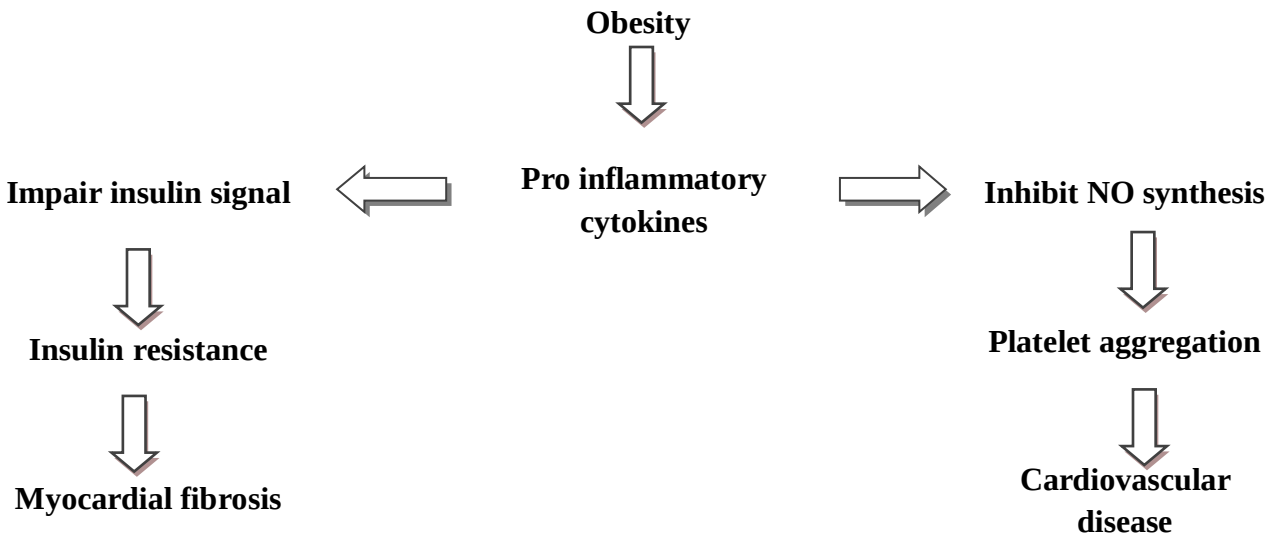

Fig 1: A brief pathway of co-morbid conditions in cardiovascular events

Inflammatory pathway

CRP is the biomarker in progress of cardiovascular disease and act as primary inflammatory factor in induction of type 2 diabetes mellitus. Concentration of CRP is enhanced by obesity.[10] CRP contribute to platelet aggregation by inhibiting nitric oxide synthesis whereby initiating the metabolic syndrome.[11] C-Reactive Protein alters insulin receptor substrate and spleen tyrosine kinase which eventually impair insulin signaling and resulting in type 2 diabetes mellitus.[12]

C-Reactive Protein enhance IL 6 which is strongly bound to insulin resistance by inhibiting insulin mediated glucose uptake and can be determined as an exasperate factor in initiation and progression of metabolic syndrome. IL-6 that in due course results in reduced level high density lipoprotein and raised triglyceride level contributing to cardiovascular diseases.[13,14]

Interleukin 18 level elevates with acute hyperglycemic condition through oxidative stress mechanism play a key role in immune responses.[15] Over time this results in insulin resistance and induces atherosclerotic plaque.[16] Higher concentration of IL 18 is observed to cause arterial stiffness which emerge as future risk of cardiovascular mortality. IL 18 contributes to metabolic syndrome by inhibiting fibrous cap formation and rupture through production of interferon gamma.[17] IL-18 is a pro inflammatory cytokine activate Nuclear Factor – kappa B cell pathway[18] which control genes involved in pathology of arthrosclerosis.

PHARMACOLOGICAL APPROACHES

HMG CoA Reductase inhibitors:

Statins with its pleiotropic effect stabilize atherosclerotic plaques, improves endothelial regulation, inhibits inflammatory response along with its lipid lowering activity.[19,20] Statins have shown to exerts its action in hypertension by reducing systolic blood pressure by 3-5mmHg and diastolic blood pressure by 1-3mmHg. Rosuvastatin shows about 45% reduction in cardiovascular events and 44% reduction in mortality rate.[21,22] Other statins including simvastatin, lovastatin and atorvastatin are beneficial in controlling cardiovascular events associated with co morbidities where lovastatin achieved its action by reducing high sensitive CRP >1mg/L.[23]

Table 1: Statin's therapy.[24-28]

Drug	Dose	MOA	Effect
Rosuvastatin	10mg/day	Decrease hepatic sterol synthesis	Reduce serum concentration of total cholesterol and LDL
Simvastatin	20mg/day	Elevate HDL and decrease LDL concentration	Prevent atherosclerotic plaque formation
Lovastatin	20mg/day	Decrease hsCRP concentration	Prevent atherosclerotic plaque formation
Atorvastatin	10mg/day	Decrease production of cholesterol in liver	Alleviate total cholesterol concentration

Peroxisome proliferator activated receptors and Fibrates:

PPAR's works effective in reducing risk of MI in patients with insulin resistance. PPAR activation is beneficial on regulation of endothelial functions and vessel wall inflammation.[29] Gemfibrozil is used to decrease the risk of major cardiovascular events by 22%. Gemfibrozil 600mg is effective in patient with hyperlipidemia exerting its action by stimulating oxidation of free fatty acids and reducing the expression of Apo lipoprotein C-III.[30] Alleviating Apo lipoprotein in turn decreases the serum concentration of VLDL.[31] PPAR works to suppress the concentration of CRP thus contributing its antagonist action towards cardiovascular events.[32]

Fibrates

Fibrates being peroxisome proliferator activated receptors agonist binds to PPAR alpha and enhance fatty acid and lipid metabolism along with synthesis of Apo proteins thus reducing triglyceride concentration and normalizing atherogenic lipid profile. Fibrates are associated with reduction of inflammatory factors IL 6. Reduction in cardiovascular morbidity is observed by using fibrates combined with statins in people with insulin resistance and obesity.[33, 34]

Cholesterol absorption inhibitors:

Cholesterol absorption inhibitors reduce cholesterol absorption in small intestine thus alleviate the level of cholesterol delivered to liver. Ezetimibe acts by diminishing the absorption of dietary and biliary cholesterol in the intestine by binding and inhibiting the Niemann- Pick C1 Like1protein. 10mg/day of Ezetimibe shows 20-25% reduction in LDL concentration along with decrease in triglyceride and Apo B levels. It is either prescribed as monotherapy or used in combination with simvastatin.[35]

Anti-inflammatory properties of existing synthetic anti-diabetic drugs have been focused for betterment of patient's life. They play the key role in regularizing hyperglycemic condition and suppress the progress of cardiovascular events through insulin sensitizing and anti-inflammatory mechanisms. PPARs, GLP-1 agonist, Biguanide, DPP-4 inhibitors were observed to exert anti-inflammatory properties.[36]

Biguanide:

Metformin works by inhibiting mitochondrial respiratory chain in liver which activates fuel sensing enzyme AMPK thus enhancing insulin sensitivity.

Metformin also improves lipid liver metabolism oxidizing fatty acids accumulated in liver thus rectifying dyslipidemia.[37] Metformin improves endothelial functions by regulating oxidative stress thus reducing the risk of cardiovascular events. It reduces LDL concentrations by activating AMPK which in turn inhibits alpha dicarbonyl mediated modification of Apolipoprotein.[38]

GLP 1 receptor agonist:

Exenatide plays a vital role in enhancing alleviating HbA1C as well as reduction in BMI over prolong therapy. 10 mcg Exenatide administered by subcutaneous route either as monotherapy or in addition with metformin and long-acting insulin results in fall of TNF α and IL 1 concentrations.[39]

Dipeptidyl peptidase-4 inhibitors:

Sitagliptin exerts its action by suppressing TNF α concentration and JNK pathway. Dipeptidyl peptidase-4 inhibitors were observed to reduce the progress of cardiovascular events by alleviating CRP concentration.[40]

IMPACT OF TARGETTING INFLAMMATORY PATHWAY

Concentrating on inflammation may help in alleviating complications of disease. Autoimmune conditions like rheumatoid arthritis and many more can be prevented on targeting TNF α levels. Demylination of central nervous system is the foremost result of excess IL-6 which in turn leads to multiple sclerosis. This can be avoided by appropriate therapy targeting the inflammatory pathway.

CONCLUSION:

Cardiovascular disease accounts for higher mortality rates. Excessive obesity remains the foremost risk factor of development of cardiovascular disease by enhancing the mediators involved in the progress. Medications like steroids, life style including sleep apnea trigger the mechanism. Co morbid conditions occurring in cardiovascular event make management and prevention challenging. Inflammatory response remains the key factor for initiation and progression of cardiovascular disease and co morbid conditions. Hence focusing on the inflammatory mediator pathway will guide in individualizing therapeutic regimen to alleviate the disease. This has positive impact on patient's life. Life style changes to reduce body weight, pharmacological therapy focusing on inflammatory pathway in addition to regulation of hyperlipidiemic condition prevent progress of cardiovascular events and mortality.

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