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Review Article……!!!

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DIETARY FRUCTOSE INDUCED METABOLIC SYNDROME

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ABSTRACT

Purpose of review-Fructose is a commonly used sweetener associated with diets that increase the prevalence of metabolic syndrome (MS). Many studies assessed the effects of diets containing large amounts of fructose and suggested that fructose consumption tends to produce some metabolic alterations associated with MS including fatty liver, hypertension, insulin resistance and dyslipidemia. Fructose has been widely accepted as an animal model for MS that mimics the manifestations afflicting human subjects.

Recent finding-Recent study confirms link between fructose consumption and metabolic syndrome. Fructose consumption causes increase in plasma uric acid level, renin angiotensin level in hypertension and also causes many other problems in human and animals also. Fructose has also indirect effect on oxidative stress and inflammation. Human studies have demonstrated fructose's ability to change metabolic hormonal response.

Summary-There is much evidence from both animal and human study which states that fructose is highly lipogenic nutrient, when at high quantity it causes metabolic defects. This article will provide meaning of metabolic syndrome and mechanism of actions involved in that.

INTRODUCTION-

1.1. Metabolic Syndrome

Metabolic syndrome can be defined as a cluster of interrelated risk factors that are associated with an increased risk of diabetes and cardiovascular disease. [1] It is estimated that around 20-25 per cent of the world's adult population have the metabolic syndrome and they are three times as likely to have a heart attack or stroke compared with people without the syndrome. In addition, people with metabolic syndrome have a fivefold greater risk of developing type-2 diabetes.[2] Type-2 diabetes, which accounts for 90% of all diabetes, has become one of the major causes of premature illness and death, mainly through the increased risk of CVD which is responsible for up to 80% of deaths.[3]

1.1.1. Diagnosis of Metabolic Syndrome

Worldwide, CVD continues to be the major cause of mortality and morbidity, with its incidence increasing alarmingly in the developing world. Diabetes is rising in tandem due to increasing obesity and decreasing physical activity and fuelling the increase in CVD. There has also been confusion between whether it is a disease, a pathophysiological construct, or a diagnostic tool or all three and indeed doubts have been expressed as to whether it exists at all. [7] At its simplest, it is a cluster of interrelated risk factors for CVD and diabetes, which coincide more often than by chance alone. We would stress that the metabolic syndrome is an evolving concept, which does indeed have a clinical role and has stimulated much interest in the pathological basis of the cluster.

Modern interest in the clustering of cardiovascular and diabetes risk factors started with the epochal paper of Reaven in 1988. He described 'syndrome X' as a clustering of hyperinsulinemia, hyperglycemia, hypertension, raised very–low-density lipoprotein-triglycerides, and low levels of HDL-C with the suggestion that insulin resistance was the underlying etiological factor. Importantly he also suggested that changes in non-esterified fatty acids played a pivotal role in the interaction between hyperinsulinemia, glucose intolerance, and insulin resistance. He showed that insulin resistance correlated with each of the other factors and suggested that people with this cluster were at an increased risk of CVD. [1]

A range of new names have been applied to the cluster including metabolic syndrome, metabolic syndrome X, cardiovascular metabolic syndrome, chronic cardiovascular risk factor clustering syndrome, plurimetabolic syndrome, dysmetabolic syndrome, cardio metabolic syndrome and

"deadly quartet" as well as insulin resistance syndrome. [8] In general, metabolic syndrome became the accepted term and tended to be favored over insulin resistance syndrome as it carried fewer connotation of etiology. There were however no agreed major components or cut-off points for those components with most authors using their own arbitrary cut-off points. This led a World Health Organization (WHO) consultation group to attempt to produce a working definition. [1, 9]

Abnormalities associated with insulin resistance

- Raised blood pressure
- Dysglycaemia
- Hyperuricemia
- Dyslipidemia
  - Increased VLDL-triglycerides
  - Low HDL-cholesterol
  - Increased small dense LDL particles
- Endothelial dysfunction
  - Increased levels of adhesion molecules
  - Decreased endothelial-dependent vasodilatation
- Hypercoagulability
  - Increased PAI-1
  - Increased Fibrinogen

The premise for the WHO effort in defining the metabolic syndrome was the lack of any international definition. They carefully stated that their new definition did not imply causality and should be viewed as a starting point, a working definition to allow comparisons and further work and to be improved upon when more information was available. [10] In particular, they felt that data were needed to support the relative importance of each component.

1.1.2. WHO Criteria for Diagnosis of Metabolic Syndrome

World Health Organization criteria for the metabolic syndrome.

Essential component: Impaired glucose regulation or diabetes and/or insulin resistance (under hyperinsulinemia conditions, glucose uptake below lowest quartile for background population)

Plus two of the following:

- Raised arterial pressure (> 140/90 mmHg)
- Raised plasma triglycerides (> 1.7 mmol/L; 150 mg/dL) and/or low HDL-cholesterol (<0.9 mmol/L; 35 mg/dL in men: <1.0 mmol/L, 39 mg/dL in women)
- Central obesity (males: waist-to-hip ratio >0.90; females: waist-to-hip ratio > 0.85) and/or BMI > 30 kg/m2
- Microalbuminuria (urinary albumin excretion rate > 20 g/min or albumin : creatinine ratio > 30 mg/g)

1. Dietary Fructose and Hypertension-

Fructose consumption is able to produce these effects because fructose is more lipogenic than glucose and usually causes greater elevations of triglycerides, which, in turn, increases intramyocellular triglyceridecontent in the skeletal muscle, causing insulin resistance.

Interestingly, diets with normal levels of NaCl but high in fructose (around 60% of calories) will also increase blood pressure and produce signs of kidney damage in both Sprague-Dawley and Wistar rats. Such high fructose diets also cause IR (see section on high fructose diets) and this may in fact have a role in causing the hypertension. [9]

Mechanism of Action-

Since endothelial dysfunction is a hallmark of insulin resistance, it was interesting to find that vasorelaxation of arterial rings in response to acetylcholine, a process that is mediated by nitric oxide (NO), was blocked by uric acid. Thus uric acid-induced endothelial dysfunction with impaired NO production may participate in the development of insulin resistance in fructose-fed rats. On the other hand, renal arteriolar damage, glomerular hypertension, and cortical vasoconstriction have also been reported to be induced by Hyperuricemia.[6]

Roberts et al. demonstrated that NAD (P) Hoxidases, a major source of vascular O2•− production, are stronglyinvolved in impaired vascular function in the thoracic aorta of rats fed a diet enriched with sugar and fat. Delbosc et al.suggested thatO2 •− production was a key event in the initiation and the development of the cardiovascular complications associated with IR in fructose-fed rats. [7]

Inhibition of the renin-angiotensin system (RAS) has been consistently demonstrated to reduce MS. However, there has been no direct comparison among different pharmacological modes of inhibiting the RAS concerning their effects on MS.

It has been suggested that activation of the renin–angiotensin system (RAS) is a common feature in patients with MS (Rongetal, 2010). In addition to the exacerbation of hypertension, RAS has beenimplicatedintheetiologyofobesityandinsulinresistance,providingapivotallinkamongallalterationsoftheMSconcerning fatty liver,diabetesandhypertension (Boustanyetal, 2004). Nevertheless,multiplelinesofevidenceindicatethatinhibition of RASimprovesinsulinsensitivityindependentofchangesin blood pressure (Shiuchi etal, 2004; Morietal, 2007). Inrodents, pharmacological orgeneticdisruptionofRASpreventsweight gain, promotesinsulinsensitivityandrelieveshypertension. [8]

2. Dietary fructose and Dyslipidaemia

Dyslipidemia is the disorders of lipid and lipoprotein metabolism in individuals with insulin resistance. The most common characteristics of lipid disorders in insulin-resistant individuals are elevations of triglycerides and low levels of high-density lipoprotein (HDL)-cholesterol. The increase in triglyceride-rich remnant particles in the postprandial state in patients with metabolic syndrome could play a major role in development of atherosclerosis and subsequent cardiovascular disease. The dyslipidemia is a central player in the development of atherosclerosis in the setting of insulin resistance and other components of the metabolic syndrome. Elevated triglycerides levels and decreased HDL-C levels are included in the criteria for the diagnosis of the metabolic syndrome according to the WHO definitions. As already discussed, these lipid abnormalities are recognized as risk factors for atherosclerotic CVD.More than half of the patients diagnosed with the metabolic syndrome have elevated LDL.

Mechanism of Action

Insulin resistance is central to the dyslipidemia of metabolic syndrome. In the presence of insulin resistance there is an increased flux of free fatty acids from adipose tissue to the liver, as a result of decreased inhibition of the hormone-sensitive lipase. Fatty acids stimulate increased hepatic production and secretion of very low-density lipoprotein (VLDL), which is also increased by insulin resistance and hyperinsulinemia.

Non esterified fatty acids (NEFA) are present in plasma primarily as the products of lipolysis of triglyceride stored in adipose tissue. They are the main substrates for energy metabolism in the

fasting state when insulin and glucose levels are relatively low. Circulating NEFA are also the major substrates for liver triglyceride synthesis. Increases in insulin concentrations such as occur in the fed state normally suppress plasma NEFA primarily by inhibiting hormone-sensitive lipase, the enzyme responsible for lipolysis.

Circulating NEFA are the major substrates for triglyceride synthesis in liver, and triglyceride synthesis and secretion are stimulated by increases in NEFA flux to the liver. Thus there is a direct relation between resistance to insulin suppression of NEFA and very low density (VLDL)-triglyceride synthesis and secretion.[10]

3. Dietary fructose and Hyperglycaemia (Diabetes)

In normal glucose homeostasis plasma glucose levels increase because the amount of glucose entering the circulation exceeds the amount of glucose leaving the circulation. In people with metabolic syndrome or Type-2 DM, excessive release of glucose into the circulation rather than reduction in removal of glucose is the primary problem. As glucose tolerance deteriorates, postprandial plasma glucose levels increase earlier and at a faster rate than fasting plasma glucose levels. [11]

High-fat-high-fructose diet (HFFD) induced hyperglycemia, manifested by a significant increase in the levels of glucose and glycogen as well as a-amylase activity when compared to normal rats. The administration of GPHs to HFFD-fed rats significantly decreased blood glucose and a-amylase activity and hepatic glycogen levels. By contrast, the UGP increased the glucose metabolic disorders in HFFD-fed rats. [9]

Mechanism of action

Normally after meal ingestion, release of glucose into plasma due to glycogenolysis and gluconeogenesis is markedly suppressed. Glycogenolysis is virtually completely suppressed, thereby permitting hepatic glycogen repletion. The gluconeogenic pathway remains operative, but in the postprandial state, more of the three-carbon precursors (lactate, alanine, pyruvate, and glycerol) are diverted into glycogen (indirect pathway) rather than into plasma glucose. As a consequence, most of the glucose entering the systemic circulation represents carbohydrate from the meal that has escaped initial liver sequestration (glycogen) or utilization (glycolysis), and to renal gluconeogenesis, which actually increases after meal ingestion. Regulation of postprandial glucose release is largely a function of changes in insulin and glucagon secretion, alterations in sympathetic nervous system activity, and the sensitivity of the liver and kidney to these factors.[7]

In people with metabolic syndrome or Type-2 DM, various abnormalities have been identified. First of all, suppression of glycogenolysis and gluconeogenesis is reduced, and there is increased hepatic glycogen cycling, so that early on more of the ingested glucose escapes hepatic sequestration and enters the systemic circulation. As a consequence, the overall release of glucose into the systemic circulation is increased, and net hepatic glycogen repletion is reduced.[10]

Although studies on the polyol pathway and nonenzymatic glycation remain inconclusive so far, more recent studies strongly point to a decisive role of the DAG-PKC pathway for the vascular complications associated with diabetes. Incubation of vascular tissue with high concentrations of glucose increases intracellular DAG levels, which ultimately lead to PKC activation. High glucose-induced endothelial dysfunction can be corrected with PKC inhibitors. These in vitro observations are supported by studies demonstrating that in vivo treatment with PKC inhibitors ameliorates vascular complications in diabetic rats. The mechanisms underlying PKC-mediated endothelial dysfunction remain poorly understood. In vitro experiments have shown that PKC mediated phosphorylation of nitric oxide synthase (NOS) III protein may reduce the activity of the enzyme. Stimulation of endothelial cells with phorbol esters (direct activators of PKC) or glucose increases the expression of NOS III. [12]

Glucose also greatly enhances endothelial superoxide production, leading to increased vascular formation of the nitric oxide (NO)/superoxide reaction product peroxynitrite. Peroxynitrite in turn has been recently shown to oxidize avidly tetrahydrobiopterin, an NOS III cofactor, to dihydrobiopterin.[16] Increased superoxide production in diabetes is not restricted to endothelial cells and was also demonstrated to be increased in the smooth muscle layer. Interestingly, adenoviral transfection of NOS III to diabetic vessels improved endothelial-dependent relaxations without altering superoxide production of vascular smooth muscle cells, an observation that may point to a significant contribution of dysfunctional NOS to endothelial dysfunction in diabetes.[14]

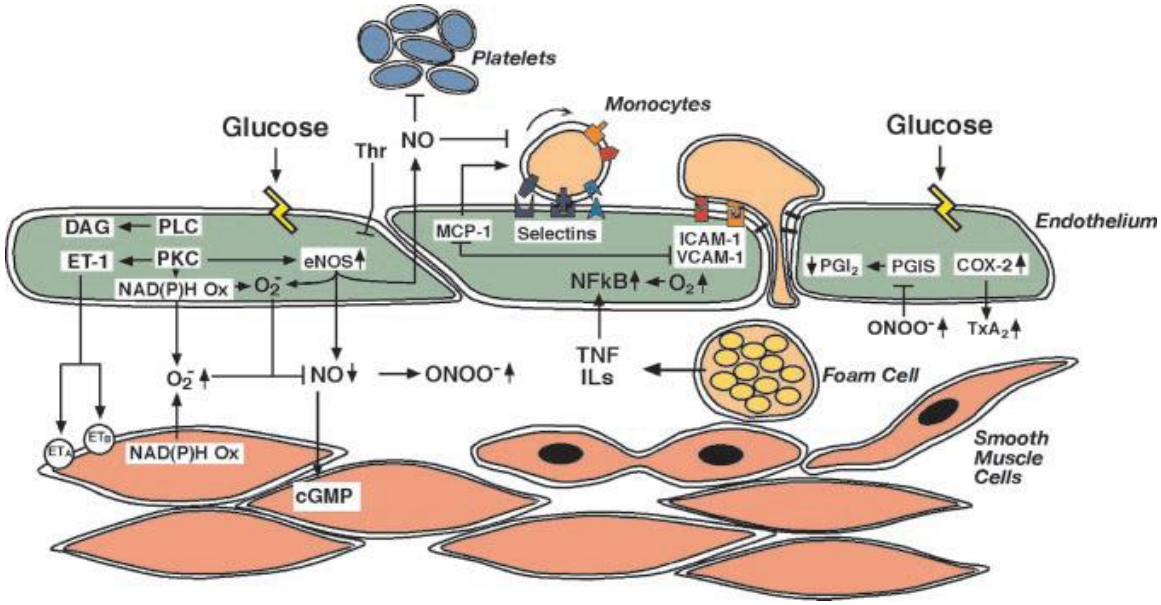

Fig 1. Hyperglycemia and endotheliumderived vasoactive substances. Hyperglycemia decreased the bioavailability of nitric oxide (NO) and prostacyclin (PGI2), and increased the synthesis of vasoconstrictor prostanoids and endothelin (ET-1) via multiple mechanisms, as discussed in the text. PLC indicates phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; eNOS, endothelial nitric oxide synthase; Thr, thrombin; NAD(P)H Ox, nicotinamide adenine dinucleotide phosphate oxidase; O_2^-, superoxide anion; $ONOO^-$, peroxynitrite; MCP-1, monocyte chemoattractant protein-1; NFκβ, nuclear factor kappa β; TNF, tumor necrosis factor; ILs, interleukins; and COX-2, cyclooxygenase-2.[13]

4. Dietary fructose and Inflammation

Fructosefeeding for 10 weeks caused oxidative stress, inflammation and insulin resistance.It is well established that inflammation plays a pivotalrole in the development of classical atherosclerosis, and theinhibition of the expression of adhesion molecules reducesthe plaque volume in animal models, probably by reducingthe recruitment of monocytes from the blood. Patientswith primary hyperglyceridemia display increased plasmalevels of intercellular adhesion molecule-1 (ICAM-1) andvascular cell adhesion molecule-1 (VCAM-1). Moreover,hyperglycemia induces the increased expression ofadhesion molecules in cultured endothelial cells. Thusit is tempting to speculate that the propensity to acceleratedlesion

formation in metabolic syndrome may involveincreased vascular inflammatory response. However, it isnot well known whether metabolic syndrome affects the expression of adhesion molecules in the arterial wall before the lesion formation. Animal studies have shown that high fructose feeding causes oxidative stress, low grade inflammation and altered lipid metabolism and play a majorrole in the genesis of insulin resistance. The development of insulin resistance leads to impairedinsulin signaling and reduced glucose uptake.[16]

Mechanism of action

Several lines of evidence from in-vitro and in-vivo models have demonstrated that hyperglycemia and elevated plasma free fatty acids cause enhanced production of reactive oxygen species (ROS) which further triggers the production of pro-inflammatory cytokines such as TNF-α, IL6, IL1β, etc. The increased production of ROS leads to oxidative stress which further activates multiple stress sensitive kinases (NF-κB, p38 MAPK, JNK and ERK.). The activation of stress sensitive kinases and inflammatory cascades contribute to impaired insulin signaling. As a consequence, inactivation/inhibition of other substrates involved in the insulin signaling pathway like protein kinase B (PKB), IP3, Grb2 leads to reduced glucose uptake ultimately insulin resistance. Though several experimental evidence suggests that fructose consumption is associated with insulin resistance the possible mechanisms responsible for the same remain unclear. Hence, we investigated the mechanisms involved in the development of insulin resistance in the high fructose fed male Wistar rats.[16]

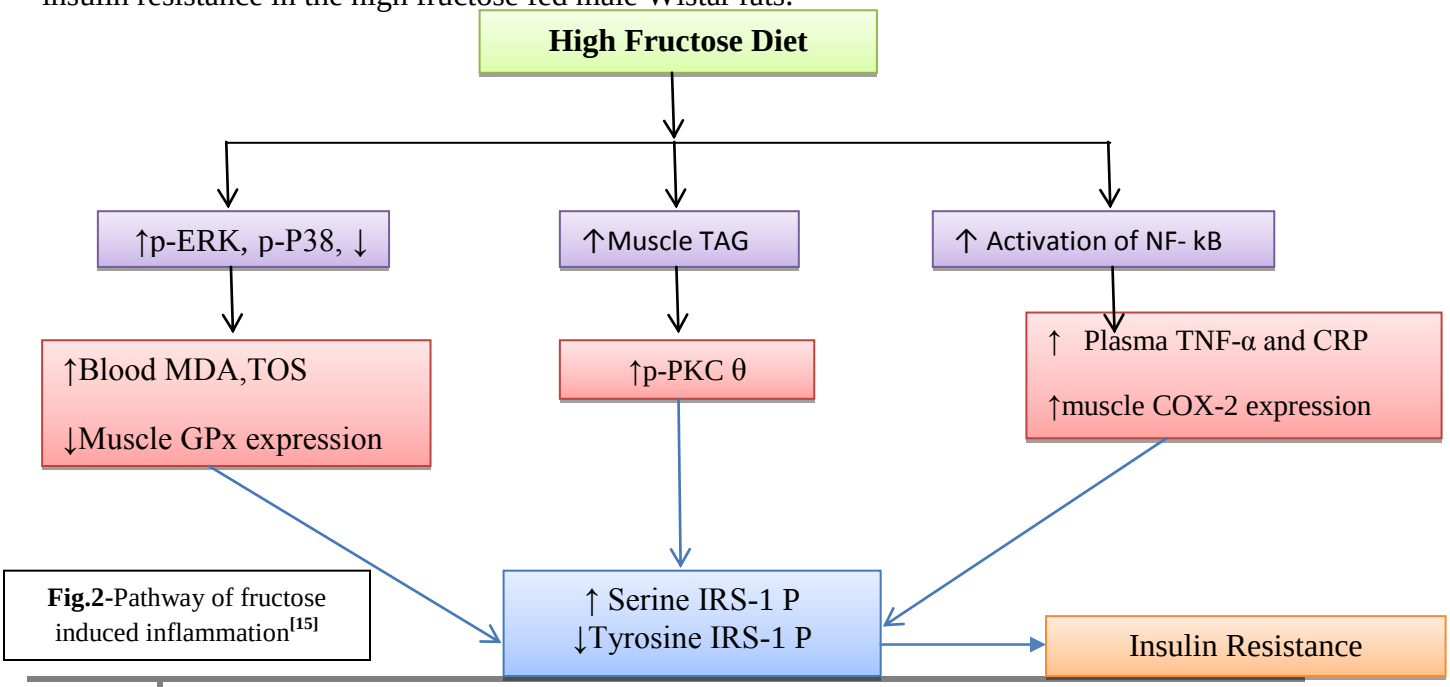

Fig.2-Pathway of fructose induced inflammation[15]

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