

## Mitochondrial Dysfunction Linked with Fructose Induced Insulin Resistance

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### Abstract

### Review Article

Insulin resistance (IR) is considered to be the primary pathogenesis that introduces Type 2 diabetes mellitus (T2DM) and is often associated with cardiovascular disease including hypertension, dyslipidemia, polycystic ovary syndrome, non-alcoholic fatty liver disease, and certain forms of cancer and sleep apnoea. Insulin resistance (IR), mostly driven by an imbalance between intake and utilization of metabolic substrates such as carbohydrates and lipids persist a prominent hallmark of the metabolic syndrome. Mitochondria are considered to be essential in glucose and lipid metabolism to generate energy in cells. Thus, when nutrient oxidation is inefficient, the ratio of ATP generation/oxygen consumption is low, which leads to an enlarged production of superoxide anions. The formation of reactive oxygen species (ROS) may have maladaptive outcomes which augment the rate of mutagenesis and stimulate proinflammatory processes. In addition to ROS production, decrease in mitochondrial biogenesis, reduced mitochondrial protein content and decrease in activity of the complexes of the electron transport chain (ETC) all contribute to mitochondrial dysfunction. These factors are also responsible to cause insulin resistance in insulin target tissues. Thereby, mitochondrial dysfunction has been involved in the development of IR. Mutually, these observations proposed that mitochondrial dysfunction may be a central organelle which is associated with insulin resistance and associated complications. In this review, we discuss mechanisms of mitochondrial dysfunction associated to the pathophysiology of insulin resistance.

**Keywords:** Mitochondrial dysfunction, insulin resistance, fructose.

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## INTRODUCTION

Insulin resistance (IR), mostly driven by an imbalance between intake and utilization of metabolic substrates such as carbohydrates and lipids, persists to be a prominent hallmark of the metabolic syndrome [1]. Globally, a quarter of adult population is being affected and has fallen target to IR [2]. The IR is a primary pathogenesis which often introduces type-II diabetes, cardiovascular and metabolic disorders with increased risk of morbidity and mortality [3].

The consequences of IR are disruption of glucose uptake in peripheral tissues, impaired glucose tolerance, suppression of glycogen synthesis, dyslipidemia, hyperandrogenism, hyperuricemia and endothelial dysfunction [4].

Fructose or fruit sugar has been identified as the most harmful of all the sugars, especially with regard to the pathogenesis of type 2 diabetes and obesity [5]. Over the years, high fructose consumption has been associated with development of IR, obesity, metabolic syndrome, leptin resistance, dyslipidemia, hypertension, and hyperuricemia in both humans and

rodents [6-9]. In fact, dietary fructose intake has escalated considerably in the last decades due to increase in the consumption of pre-packaged foods, soft drinks and juice beverages containing sucrose or high-fructose corn syrup [10, 11].

In particular, chronic dietary overload with fructose and saturated fatty acids enhance the accumulation of lipid metabolites and oxidative stress in liver [12-14]. Increased lipogenesis with decreased fatty acid  $\beta$ -oxidation leads to the accumulation of triglycerides in hepatocytes, which, combined with increased levels of reactive oxygen species, contributes to IR [15]. The mitochondrial dysfunction produces reactive oxygen species (ROS) which is frequently reported to be increased in the pathophysiology of IR. The excessive ROS production impairs the activities of respiratory chain complexes and thus decreases the oxidative functions of the mitochondria [16].

### Insulin Resistance

Insulin Resistance (IR) is a pathological condition which indicate the inefficiency of insulin to evoke a hormonal response in insulin dependent cells to

conduct glucose and lipid metabolism [17]. The IR is associated with insulin sensitivity in insulin dependent tissues [18]. It is the pre-diabetic state which reduces glucose tolerance and leads to dyslipidemia, pro-inflammatory and hypoxic state [19]. The actions of IR results in impairment of phosphorylation signalling pathway of the skeletal muscle adipose tissue which reduces GLUT-4 expression and translocation and causes disruption in glucose uptake. In the liver, IR endorses gluconeogenesis and suppresses glycogen synthesis [20, 21]. Moreover, IR is considered to be the primary pathogenesis that introduces Type 2 diabetes mellitus (T2DM) [22] and is often associated with cardiovascular disease, essential hypertension, dyslipidemia, polycystic ovary syndrome, non-alcoholic fatty liver disease, certain forms of cancer and sleep apnoea [23, 24].

### Hepatic Insulin Resistance

The liver is a central metabolic organ for regulating glucose and lipid homeostasis, as well as conform the energy needs in response to different metabolic stresses [25]. Hepatocytes are responsible for the major physiologic and metabolic functions of the liver [26]. Insulin is the only hormone that reduces blood glucose and is important for *in vivo* metabolism of carbohydrates and lipids [27]. During the progression from a fasted state to a fed state, the elevated blood glucose triggers the insulin secretion and promotes glycogen synthesis and lipogenesis but suppresses gluconeogenesis in the liver, thereby sustaining the normal range of blood glucose levels *in vivo* [28]. Impairments in insulin signalling in hepatocytes could lead to disruptions in intermediary metabolism that contribute to lipid accumulation in these cells [29]. The hepatic insulin resistance (HepIR) is considered to be an essential factor in the development of fasting hyperglycemia [30]. The HepIR is associated with obesity and metabolic syndrome which is mediated by raised hepatic influx of free fatty acids (FFAs), giving rise to increased levels of diacylglycerol (DAG) [31]. Increased hepatic DAGs activate protein kinase C $\epsilon$  (PKC $\epsilon$ ) [32], which impairs the tyrosine kinase activity of the insulin receptor by inhibiting phosphorylation of the insulin receptor (Fig 2.2) [33]. Therefore, accumulation of intrahepatic DAG and activation of PKC $\epsilon$  supports the translational relevance of the mechanism of HepIR [34]. The impaired liver insulin receptor kinase (IRK) activity proposed IRK regulation as a pathophysiological mechanism for HepIR [33]. However, selective HepIR is characterized by inadequate suppression of hepatic gluconeogenesis, reduced glycogen synthesis, and increased lipid accumulation [35].

### Fructose and Insulin Resistance

For thousands of year, the consumption of fructose by humans was measured to 16-20g/day and mainly acquired from fresh fruits, berries, honey and root vegetables. As a result of westernization of diets,

the consumption of fructose has now elevated to around 85-100g/day [6]. Fructose-rich diet constitutes diet-induced insulin resistance, linked with hyperinsulinemia, glucose intolerance, hypertriglyceridemia, as well as inflammation and oxidative stress (OS) in different tissues [36]. Collective information has exposed that the elevated consumption of fructose parallels the increase in obesity, metabolic syndrome and nonalcoholic fatty liver disease (NAFLD) [37]. Fructose retains no functional service in the body and its destructive effects on hepatic metabolic milieu are above those produced by glucose [19].

The fructose is readily absorbed and metabolised completely in the liver, which synthesizes both fructose-specific (GLUT5) and glucose-fructose (GLUT2) membrane transporter proteins as well as a set of three specific fructose metabolizing enzymes i.e., ketohexokinase C, aldolase B and triokinase [38]. Fructose, unlike glucose, is unable to trigger the insulin secretion from the pancreatic beta cells [39]. The acute hepatic fructose metabolism immediately results in the availability of *de novo lipogenesis* (DNL) substrate, and acute fructose ingestion may broadly indicate the rise in plasma triglyceride levels [40]. The escalated intake of fructose-rich diet such as soda, beverages, cakes, pastries, breakfast cereal is now positively associated with the onset of HepIR [41].

Hepatic fructolysis commences with the phosphorylation of fructose to fructose-1-phosphate by ketohexokinase. Fructolysis bypasses the rate-limiting steps of glycolysis and is therefore much faster [34]. This may explain the depletion of adenosine triphosphate (ATP) associated with fructose metabolism [42]. The conversion of fructose into fructose-1-phosphate irregularly provide glycerol phosphate and acyl coenzyme A [43]. The liver FFAs undergo mitochondrial  $\beta$ -oxidation or are esterified into triglycerides that accumulate as cytoplasmic fat deposits or interact with cholesterol esters, phospholipids and apolipoprotein B (ApoB) and microsomal triglyceride transfer protein (MTP) and secreted as very low density lipoprotein (VLDL) (Fig 2.3) [15]. The elevated VLDL secretion can result in chain reactions in other lipoproteins and lipids, such as low density lipoprotein (LDL). A hypertriglyceridemic effect is seen, presumably due to hepatic overproduction of VLDL and induction of lipogenic enzymes *via* dietary fructose [6]. Therefore, fructose is an immensely potent inducer of *de novo lipogenesis* that shows reduction in hepatic insulin sensitivity and increases the formation of VLDL [44].

The over-load of fructose increases hepatic metabolic burden, stimulating the overproduction of acetyl-CoA in mitochondria. Finally, an excess of acyl-CoA leads to abnormal production of leptin [45], inhibits hepatic lipid  $\beta$ -oxidation, and increases the

formation of reactive oxygen species (ROS), causing mitochondrial dysfunction [44].

### **Mitochondria: A Cellular Organelle**

Mitochondria are cellular organelles that carry intense metabolic machinery which mediates the transformation of multiple metabolic substrates to adenosine triphosphate (ATP), which produce energy for most cellular functions [46]. The mitochondria play a crucial role in generation of energy and responsiveness to nutrient availability by conducting mitochondrial oxidative phosphorylation (OXPHOS) and fatty acid oxidation [47].

The chief role of mitochondria, cellular respiration, is consecutively associated with various processes, including formation of reactive oxygen species (ROS), generation of ATP,  $\beta$ -oxidation and processing of acetyl-CoA, produced from fatty acids (FAs), oxidation of substrate through the tricarboxylic acid (TCA) cycle and activities of mitochondrial electron transport chain (ETC) complexes [48, 49]. The hepatocytes are rich in mitochondria due to their significant role in metabolism [50].

The inner mitochondrial membrane contains electron transport chain (ETC) which is composed of five multi-subunit enzyme complexes viz. I, II, III, IV and V [51]. The electrons provided through coenzymes, reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH<sub>2</sub>) in TCA cycle are obtained and transferred to components of ETC at complex I (NADH ubiquinone reductase) and complex II (Succinate dehydrogenase), and then successively to complex III (Ubiquinol-cytochrome c reductase), complex IV (Cytochrome c oxidase) and finally to oxygen through complex V (F<sub>0</sub>F<sub>1</sub> ATP synthase) [52]. The ETC transmit electrons derived from metabolic intermediates coupled with transfer of protons into the intermembrane space to generate the mitochondrial membrane potential which drives synthesis of ATP from adenosine diphosphate (ADP) and inorganic phosphate (Fig 2.4) [46].

### **Mitochondrial Dysfunction and Insulin Resistance**

Mitochondrial dysfunction has been involved in the development of IR. Impairment of insulin signalling is the major cause of IR which has been related to excessive production of reactive oxygen species (ROS). Insulin signaling is compromised by ROS through stimulating phosphorylation of the serine/threonine residues of insulin receptors and insulin receptor substrate-1/2 leading to a decline in their ability to recruit downstream signaling molecules [53]. Accumulation of hepatocellular lipids are thought to simultaneously accelerate mitochondrial fatty acid oxidation and the production of ROS, thereby promoting lipid peroxidation and destruction of mitochondrial DNA and proteins [54].

Oxidative stress impairs insulin signaling, which contributes to insulin resistance in T2DM. In insulin-resistant or diabetic states, in addition to hyperglycemia, other metabolites, including free fatty acids (FFAs) and certain cytokines, such as TNF- $\alpha$ , induce the overproduction of ROS from mitochondria [47]. Mitochondrial dysfunction can result from a decrease in mitochondrial biogenesis, reduced mitochondrial protein content and decrease in activity of the complexes of the ETC [55].

In a study, the results disclosed a significant reduction in protein expression levels of PGC-1 $\alpha$  and OXPHOS complexes (subunit CI-IV) with fatty liver. These results revealed that fatty liver exhibit a destruction in mitochondrial biogenesis and respiratory chain function, which additionally indicates hepatic mitochondrial dysfunction has mainly occurred [56].

After High fat diet (HFD) fed in rodents, the isolated mitochondria were analysed which discovered a reduction in respiratory capacity and amplification in oxidative stress [57- 59]. Similarly, mice with genetic obesity (db/db and ob/ob) have shown a decline in the activity of mitochondrial complexes (CI to CV) in isolated mitochondria [60, 61].

In recent studies, it was found that concentrations of a molecule called coenzyme Q (CoQ) which is an essential component of mitochondria in the production of ATP, were lower in mitochondria from insulin-resistant fat and muscle tissue [62]. The decrease in the activity of complex IV was the most definite succeeding in the reduction of cellular CoQ10 levels, with a decrease of 69 % compared to control [63].

Subsequent evaluation of OXPHOS activity, as measured by NADH:O<sub>2</sub> oxidoreductase activity (CI activity), determined a 40% reduction in T2DM patients [64].

Generation of ROS in mitochondria is intently associated with the defects in transportation of electron within the respiratory chain complex. The electron leak may responsible for the mitochondrial dysfunction and prevalent the oxidative stress (Fig 2.5) [65]. In any case, mitochondria are the main site for lipid oxidation which exhibit a relation between reduced FFA uptake, as well as diminished ATP generation and compromised activity of respiratory chain has been reported due to mitochondrial dysfunction [66, 58].

## **SUMMARY AND CONCLUSION**

Insulin resistance is a leading cause of metabolic disorders, including glucose intolerance, dyslipidemia, hyperuricemia, and hypertension [67].

Insulin promotes glucose disposal in skeletal muscles and adipose tissues whereas in the liver, suppresses gluconeogenesis and promotes glycogen

synthesis [17, 68]. When these tissues become insensitive to insulin action, glucose can no longer be absorbed but remains in the blood. At first, in the prediabetic state, the pancreatic beta cells increases insulin secretion to compensate for IR and to maintain a normal glucose homeostasis (compensatory hyperinsulinemia) [69].

Recent epidemiological and biochemical studies shows the emerging evidence which clearly suggest that enhanced dietary consumption of fructose is an important causative factor in the development of metabolic syndrome associated with type 2 diabetes [70, 71]. High-fructose feeding has been reported to induce IR in various experimental animal models [72].

The liver plays an integral role in lipid metabolism and is a key organ for the maintenance of systemic glucose homeostasis. In rodents, high-fat diet leads to obesity, insulin resistance, and hepatic steatosis with concomitant reductions in respiratory capacity and increased oxidative stress in liver mitochondria [57-59].

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