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Mitochondria in Metabolic Syndromes

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MITOCHONDRIA IN CELLULAR METABOLISM AND METABOLIC SYNDROME

Metabolic syndrome (MS) is a cluster of metabolic and cardiovascular disorders (CVD), characterized by abdominal obesity, insulin resistance (IR), hyperglycemia, atherogenic dyslipidemia and hypertension (HT) [1-3]. Several hundred million people throughout the world have the MS [4] and its prevalence is expected to increase further as the proportion of individuals above 65 years of age is projected to double globally within the next years [5]. The etiology of MS is multifaceted where the interaction of sedentary lifestyle, unhealthy diet, obesity, genes and many other risk factors are reported [4-7]. Among the various factors, obesity, particularly abdominal obesity, is found to be the main underlying risk factor for the MS, accompanied with varying degrees and numbers of other risk factors [7]. The increasing prevalence of obesity and the MS is alarming as they increase the risk of type 2 diabetes (T2D) [8,9], coronary heart disease (CHD), CVD and premature mortality [10]. Nearly 200 million people around the world have diabetes and the prevalence is estimated to double by 2030 [11] with the maximum number having T2D.

Defective cell metabolism is considered as the main culprits of the syndrome [12] due to the imbalance between nutrient intake and its utilization for energy. Mitochondria are highly dynamic organelles which supplies energy to the cell in the form of ATP by converting nutrients

through cellular respiration [13]. In brief, the TCA cycle of mitochondria generates redox energy in the forms of NADH and $FADH_2$ by breaking down the organic substances. Mitochondrial protein complexes further converts the redox energy into chemical energy in the form of ATP; thereby meet the energy requirement of cells and tissues. Mitochondria change its size, shape, location and number according to the energy requirement of cells.

When this highly regulated process gets deregulated, there is a disturbance of the body's normal energetic regulation. Thereby the cells are exposed to misregulated excess supply of energy and damaging ROS contributing to organ damage. These maladies have been described in various metabolic pathologies [abdominal obesity, dyslipidemia, HT, hyperglycemia, prothrombotic and proinflammatory conditions] [12,14]. This group of abnormalities recognizes IR as the intrinsic and common mechanism [15]. Because IR alters various metabolic processes such as increased gluconeogenesis in liver, decreased glucose disposal in the muscle, endothelial dysfunction in the arteries and increased release of free fatty acid (FFA) from adipose tissue [14]. Elevated levels of fatty acids in the peripheral circulation further decrease the sensitivity of muscle to insulin [16].

An overabundance of circulating free fatty acids (FFA) following impaired insulin sensitivity leads to a compensatory increased production of insulin thus leading to hyperinsulinemia to maintain euglycemia [14]. The failure in the compensatory mechanism results in hyperglycemia. Moreover, under IR condition, muscle is overloaded with lipid; hence some of the excess fatty acids are diverted to the liver, which promotes the development of fatty liver and dyslipidemia [17]. Therefore, individuals with either of the MS gradually develop T2D and CVD. Genetic factors, oxidative stress, mitochondrial biogenesis and aging are reported to affect the mitochondrial function, leading to IR following obesity and its associated pathological conditions [18-20] such as MS, T2D and its complications and cardiovascular complications [21-23]. However, it is still not clear whether mitochondrial dysfunction is the primary cause or it is the secondary effect of the MS. In this chapter, the possible role of mitochondrial dysfunction in the development of metabolic diseases is discussed in detail with emphasize on diabetes and its complication, non alcoholic fatty liver disease (NAFLD) and other possible manifestations.

METABOLIC SYNDROME AND MITOCHONDRIAL DYSFUNCTION

Diabetes

Diabetes mellitus (DM) is a metabolic-cum-vascular syndrome of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [24]. Worldwide, its prevalence is increasing at an alarming rate. By 2030, 552 million adults are estimated to have either types of diabetes [25,26]. Increased rate of morbidity, mortality and their associated economic burden makes it one of the major health problems in the society.

Several subtypes of DM exist; as a clinical condition, DM is divided into Type 1 diabetes (T1D)

and Type 2 diabetes (T2D) on the basis of the management required to control glucose homeostasis. Among the different types, T2D is the most prevalent form accounting for 90 % of total diabetes cases [27]. The hallmark characteristic of T2D is the elevated levels of blood glucose caused by impaired insulin action and pancreatic insulin secretion. Besides, IR in insulin-sensitive tissues including hepatocytes, myocytes and adipocytes also plays major role in the pathophysiology of diabetes. Hyperglycemia resulting from the uncontrolled glucose regulation injures large and small blood vessel causing macrovascular (coronary artery disease (CAD), peripheral arterial disease (PAD) and cerebrovascular disease) and microvascular (nephropathy, neuropathy and retinopathy) complications respectively. At the time of diagnosis, almost all chronic T2D patients are reported to have either of these complications and are believed to be the major contributors for high morbidity and mortality among these patients. Though the diabetes and its associated complications arise from a complex set of factors such as life style, genetic predisposition etc., the impairment of mitochondrial function is identified to have intrinsic relationship with the various aspects of the pathogenesis of diabetes.

MITOCHONDRIAL (DYS) FUNCTION, INSULIN SECRETION AND SIGNALING

It is well known that the b-cells of pancreatic islets are the site for making and releasing insulin in response to changes in blood glucose levels. When the glucose transported across the cellular membrane by glucose transporters (GLUT-1), glycolysis transforms glucose to pyruvate, of which more than 90 % is shuttled into mitochondria. The ratio of ATP/ADP increases as processing of the glucose through glycolysis, TCA cycle and OXPHOS increases. This increase in ATP/ADP ratio causes the closure of ATP-sensitive K^+ channels, depolarizes the membranes and stimulates the opening of voltage-dependent Ca^{2+} channels with increased influx of Ca^{2+}. This increase in Ca^{2+} level in turn promotes the exocytosis of insulin, emphasizing the importance of ATP: ADP ratio for glucose stimulated insulin secretion (GSIS) [28] (Figure 1).

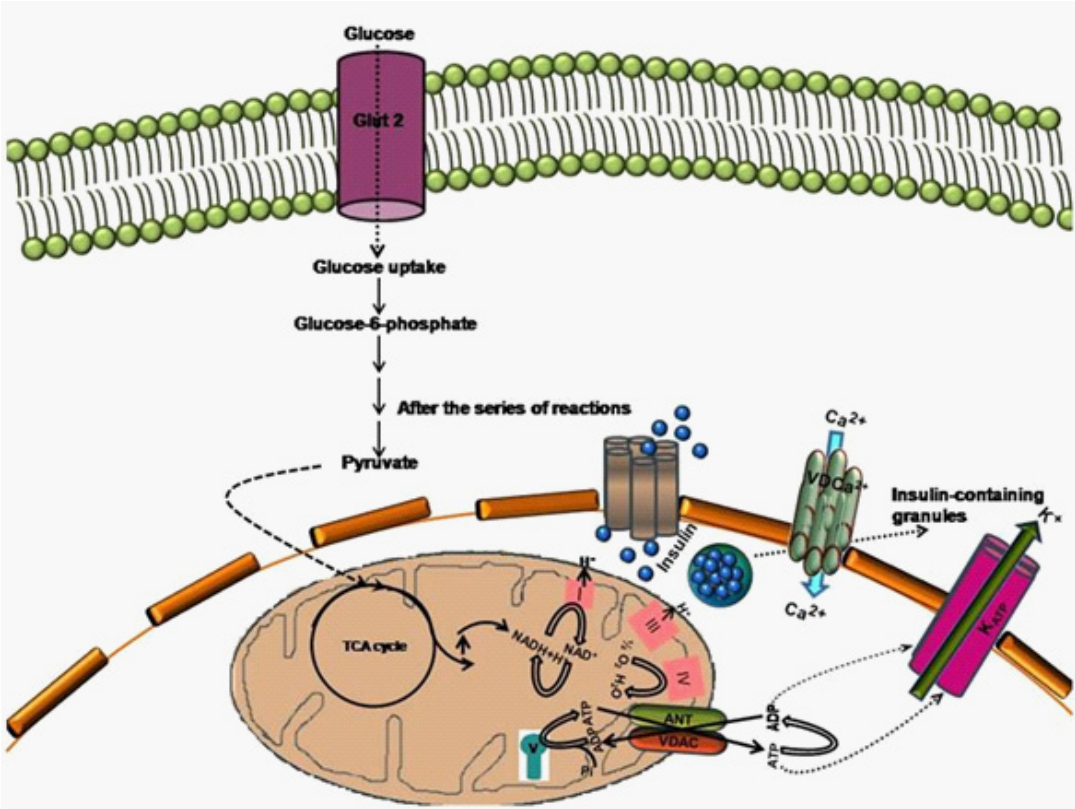

Figure 1: Association of mitochondrial ATP in the release of insulin from pancreas; Glut 2: Glucose transporters; Ca^{2+}: Calcium 2+; VD Ca^{2+}: voltage dependent calcium; TCA cycle: Tricarboxylic acid cycle; ANT: adenine nucleotide translocator; K_{ATP}: ATP-sensitive K^{+}; VDAC: Voltage-dependent anion channel; ADP: Adenosine Diphosphate; ATP: Adenosine Triphosphate; NAD^{+}: Nicotinamide adenine dinucleotide.

Released insulin interacts with γ-subunits of its receptor (IR) on cell membrane. In response to stimuli, tyrosine residues undergo autophosphorylation; thereby the IR acquires tyrosine kinase activity. This leads to phosphorylation of insulin-receptor substrate-1 (IRS-1), activating a downstream cascade leading to the activation of Akt and translocation of the glucose transporter type 4 (GLUT4) to the cell membrane. GLUT-4 fusion with the membrane results in glucose uptake by facilitated diffusion and meets the energy requirement of target cells including the liver and skeletal muscles [29]. During diabetes development, b-cells are exposed to varying levels of glucose; hence insulin release is based on the changes in blood glucose level. Under chronic diabetes, cells lose its sensitivity to insulin signaling and develop IR, thereby demanding b-cells to secrete more insulin to compensate the resistance and to maintain normal blood glucose levels. When more insulin is demanded, more glucose would flow into b-cells, generates higher levels of redox energy in the forms of NADH and $FADH_2$ through glycolysis and TCA cycle. Higher

electron transfer to the ETC cycle increases ATP production and alters the ratio of ATP/ADP. This in turn inhibits the closure of ATP-sensitive K^+ channels and results in hyperpolarization of mitochondrial membrane potential. The high electrochemical potential difference generated by the proton gradient partially inhibit the electron transport in Complex III, thereby accumulates electrons to coenzyme Q. This in turn drives partial reduction of O_2 to generate free radical anion superoxide [30] and exhibit various pathological conditions, confirming key role of IR in the pathophysiology of diabetes.

A large number of molecules have been associated with contributing to IR, among which fatty acid stand as prominent inhibitors of glucose uptake [31]. In skeletal muscle, increased levels of fatty acids in blood plasma results in increased intracellular acyl-CoA concentrations, which activating intracellular signal cascade ultimately ending with the suppression of insulin-dependent glucose transport [32]. Mitochondrial dysfunction is depicted to develop insulin resistance in 2 ways. a). Defects in mitochondrial β-oxidation due to the spontaneous mitochondrial DNA (mtDNA) mutations increases fatty acid level contributing to fatty acid- induced IR [33,34] b). Mutations increases ROS accumulation, impair the ATP generating ability of mitochondria leading to shortage of ATP availability for the transport of glucose and insulin. In addition to IR, pancreatic β-cell dysfunction (i.e. impaired insulin production) is also reported to contribute for the disease pathogenesis [18].

OXIDATIVE STRESS AND VASCULAR COMPLICATIONS

Oxidative stress in DM plays a key role in cellular injury leading to diabetes complications, both microvascular and macrovascular. During mitochondrial respiration, molecular oxygen plays a crucial role in the complete metabolism of glucose and other substrates for producing ATP. During this process, ~ 0.4 to 4 % of all oxygen consumed is converted to free radical superoxide ($^*O_2$-) and then to ROS and reactive nitrogen species (RNS) [35]. These radicals normally eliminated by the antioxidant defense system of the body such as SOD, GSH, GPX and catalase. Under hyperglycemic condition, free radical accumulation overwhelms defense system. The weakened defense system loses its ability to counteract the enhanced ROS generation and alters the balance between ROS and their antioxidant defense leading to the condition dominating oxidative stress [36,37]. ROS plays various regulatory roles in cells and serve as stimulatory signals of several genes and stimulates cell-cell adhesion, cell signalling and fibroblast proliferation and increase the expression of various antioxidant enzymes [38-40]. Hence certain amount of oxidative stress/ ROS is generally required for the normal metabolic processes. However uncontrolled production of ROS turn to become deleterious and cause several adverse effects. In case of diabetes, oxidative stress induces metabolic abnormalities leading to overproduction of mitochondrial superoxide in endothelial cells of both large and small vessels, as well as in the myocardium [41,42]. Oxidative stress acts as mediator of IR and its progression to glucose intolerance and installation of DM, subsequently favouring the appearance of atherosclerotic complications, and contributes to rise in many micro- and macrovascular complications [43].

MACROVASCULAR COMPLICATIONS

The central pathological mechanism in diabetic macrovasculature is the process of atherosclerosis leading to narrowing of arterial walls throughout the body. Though diabetes is an independent risk factor for atherosclerosis, association between these two is profound. However, HT and hyperlipidemia of abnormal glucose metabolism, endothelial dysfunction resulting from the high levels of circulating glucose and lipids and the inflammation provoked by macrophages and T-cells mediated immune responses are implicated in the pathogenesis of atherosclerosis and vascular disease [44,45]. These changes in turn lead to chronic cardiovascular complications such as cerebrovascular disease, CAD ultimately ending with heart failure and PAD. In contrast to macro vascular complications, a variety of cellular and molecular mechanisms are contributing to microvascular disease in diabetes. Small vessels throughout the body are affected by diabetes including those in the eye, kidney, brain, heart and peripheral vasculature leading to various complications. Pathological role of each of these complications are summarized in the following sections.

Cerebrovascular Diseases

Cerebrovascular disease is an important cause of disability in diabetes, leading to sudden death. Compared to nondiabetic individuals, diabetic patients are having at least twice the risk for stroke, earlier onset of symptoms, and worse functional outcomes. Approximately 20 % of diabetic patients are dying from stroke, leaving similar number of patients' remains with neurological deficits, making it one of the leading causes of death in diabetes population [46]. Besides diabetes, diabetes mediated CAD, myocardial infarction (MI) and atrial fibrillation are also found to play a significant role in the development of cerebral embolism. Several subtypes of cerebrovascular diseases are present in diabetes patients such as lacunar infarcts, ischemic stroke, transient ischemic attacks (TIA), extracranial and intracranial carotid stenosis. Among these types, lacunar infarcts are the main subtypes as it occludes the penetrating arteries involved in supplying blood to the deep structures of brain. Ischemic stroke is caused by occlusion of the large cerebral vessels and transient ischemic attacks (TIA) are found in a smaller percentage compared to lacunar infarcts. Extracranial and intracranial carotid stenoses are found in up to 30% of strokes. Lesions are mostly located on the intracranial vessels, affecting the middle cerebral artery. Their severity is positively correlated with lipid disorders [47]. Indeed, all these types affect the cerebrovasculature in a similar manner but, the exact mechanism is poorly elucidated. All these subtypes are unifying in the mechanism it affects neurons and glial cells, increasing intracellular acidosis during diabetes. This increased intracellular acidosis affects neuron and glial cell during an ischemic event [48] and induces intracellular damage by generating ROS, disrupting intracellular signaling, and by activating DNA-splitting enzymes (Siesjo et al., 1995). Under elevated glucose, it affects cerebral blood flow and at its extremes affects overall oxidative metabolism of the brain, leading to the generation of ROS and induce neuronal cell death. This suggests the pathological role of hyperglycemia for the development of fatal and nonfatal stroke [49].

Coronary Artery Disease (CAD)

Among the cardiovascular complications, CAD is one of the most severe, long-term and life threatening complications frequently diagnosed in diabetic patients. Two- to four folds increase in the incidence of CAD is reported in diabetes patients, particularly in T2D, CAD is found to be the most common cause of death [50]. It has a complex etiopathogenesis and a multifactorial origin relating both genetic and environmental factors, modulating risk of the disease both individually and through interaction [51]. The effects of these factors are mediated through cardiovascular risk factors. Various epidemiologic studies had also consistently reported the severity of diabetes and its progression into CAD [52-54].

CAD is a complex chronic inflammatory disease, characterized by remodeling and narrowing of the coronary arteries supplying oxygen to the heart. It has varied clinical manifestations, including stable angina, acute coronary syndrome and sudden cardiac death [55]. Similar to cerebrovascular disease, atherosclerosis is the main etiopathogenic process causing CAD and its progression is related to interplay between environmental and genetic factors. Although clinical ischemic cardiovascular events usually appear at the later ages in the patients, CAD starts early in life, even during fetal development [56]. The clinical manifestations and the severity of CAD vary based on the age, disease duration and the levels of biochemical markers [57]. Although the common risk factor of CAD among diabetes patients is accounted by the presence of diabetes associated cerebrovascular diseases risk factors such as hyperlipidemia, HT and smoking, a substantial proportion remains to be explained [58]. Because, CAD is often found asymptomatic [59] and the increased rate of mortality was observed in the patients with silent CAD [60]. A deleterious effect of the diabetic state on vascular and endothelial function seems to be important because of its ability to increase the potential for vasoconstriction and thrombosis [61].

Peripheral Artery Disease (PAD)

Peripheral arterial disease (PAD) is characterized by occlusion of the lower-extremity arteries [62] resulting in functional impairments and disability [63]. PAD causes intermittent claudication and pain where claudication is defined as aching, and fatigue or discomfort in the lower extremities reproducible by exercise and relieved by rest [64]. Pain occurs in patients when they are at rest with critical limb ischemia in whom the resting metabolic needs of the tissue are not adequately met by the available blood supply. The abnormal metabolic state accompanied by increased level of blood glucose predisposes diabetic patients to PAD by changing the state of arterial structure and function [65]. The risk of development of PAD increases 15 times more in people with diabetes than without diabetes; in diabetes, PAD increases with age, duration of diabetes and presence of peripheral neuropathy (PN). Hence lower-extremity amputation is more common in diabetes with PAD than in people without diabetes but with PAD [66].

Various risk factors are associated with the development of PAD which includes hyperglycemia, HT, hyperlipidemia, smoking, tobacco use, obesity (ie, waist-to-hip ratio), elevated serum fibrinogen levels, history of cerebrovascular diseases and physical inactivity [67,68]. Among which, formation of atherosclerotic plaques at the branch points of arteries resulting from the disturbed blood flow on endothelial cells is found to be the major risk factor of PAD [69]. These plaques contain various inflammatory cells such as monocytes, macrophages, and lymphocytes in addition to a thrombogenic lipid core that is covered by a fibrous cap [70].

The "response-to-injury" theory is most widely accepted mechanism where the endothelial injury causes vascular inflammation and triggers a fibroproliferative response. Once the fibrous cap is disrupted, the resultant exposure of the prothrombogenic lipid core leads to thrombus formation followed by flow occlusion [69,70]. Other factors associated with this occlusive mechanism are impaired vasodilatation due to decreased levels of nitric oxide and aggravated vasoconstriction results from the increased expression of inflammatory factors, mainly thromboxane, serotonin, angiotensin II, endothelin, and norepinephrine [69,70].

MICRO VASCULAR COMPLICATIONS

Diabetic Retinopathy

Diabetic retinopathy (DR) severely affects the peripheral retina, the macula, or both and results in the visual disability and blindness in diabetes [71]. In spite of the remarkable development in the diagnosis and treatment of DR, it remains to be the leading cause of blindness in the diabetic patients. Total or partial loss of vision is observed in the DR condition as a result of retinal detachment, retinal vessel leakage and macular edema in these patients [72]. Depending on the presence/absence of abnormal new blood vessels, DR is classified into non-proliferative (NPDR) and proliferative (PDR) retinopathy [73]. NPDR is the indicative of the presence of progressive ischemia in the retina and is an important risk factor for the development of PDR and blindness. The well-known clinical features of NPDR include micro aneurysms, dot or blot haemorrhages, venous abnormalities, hard yellow exudates, intraretinal micro vascular abnormalities and cotton wool spots. PDR is characterized by the presence of neovascularization from retina, fibrous tissue, preretinal haemorrhage, vitreous haemorrhage, vitreoretinal traction and localized retinal detachment [74].

The earliest histological marker used to diagnose DR are the loss of pericytes involved in maintaining capillary tone (i.e., dilatation and constriction), capillary growth and protection against ROS damage [75,76]. The loss of pericytes in DR also interferes with capillary constriction thereby producing chronically dilated vessels, new capillary generation and normal homeostasis. Other micro vascular changes that occur with DR include capillary basement membrane thickening [77], increased permeability of endothelial cells and formation of micro aneurysms (i.e., weakening of vessel walls resulting in the projection of a balloon like sac) [78]. The common risk factors of DR include insulin signaling abnormalities, hyperglycemia, HT, hyperlipidemia and smoking. DR is found affecting 80 % of diabetes patients with 10 years of disease history [79].

Diabetic Nephropathy

Diabetic nephropathy is estimated to affect 50 % of T2D and is one of the leading causes of end stage renal disease (ESRD) in both types of diabetes [80,81]. During its initial stage, increase in the size of kidney, glomeruli as well as glomerular filtration rate are identified. Under chronic condition, thickening of glomerular basement membranes, glomerular hyper filtration and mesangial extracellular matrix expansion are observed which results in the increased excretion of urinary albumin [82]. These characteristics changes ultimately progresses into glomerular and tubular sclerosis leading to renal failure [83]. Accumulation of ECM protein in the mesangial interstitial space is also found to have pathological role for the development of glomerulosclerosis in diabetic nephropathy [84]. When the kidney fail to filtrate, various proteins such as albumin starts leaking into the urine causing proteinuria and wastes such as uric acid, accumulates in the blood [85,86]. Therefore, elevated level of albumin and uric acid are the indicative of renal damage, hence serves as a clinical marker for the diagnosis of nephropathy in diabetes patients. The natural history of nephropathy in a patient is generally viewed as a descending path from normoalbuminuria to microalbuminuria, macroalbuminuria and eventually to ESRD [87]. In addition to the common risk factors such as hyperglycemia and HT, chronic inflammation and oxidative stress also found to have significant contribution in the pathology of diabetic nephropathy.

Diabetic Neuropathy (DN)

Diabetic neuropathy is one of the most prevalent and complicated conditions damaging every type of nerve fibre in the body such as sensory, autonomic and motor neurons. This suggest PN to be heterogeneous, hence patients are usually present themselves with diverse clinical symptoms to indicate the damage in their nervous system. Among the different types of neuropathies, chronic sensorimotor distal symmetric polyneuropathy and the autonomic neuropathies are common among the diabetes [88]. The incidence of neuropathy increases with duration of diabetes and poor glycemic control [89].

Under elevated level of blood glucose, patients usually present with unusual sensory symptoms, mainly in the lower limbs. Reduced nerve conduction velocity and increased resistance to ischemic conduction failure is also observed under neuropathic conditions. Approximately, 50 % of patients with either of the diabetes are found to have DN. Although the exact prevalence of this complication depends on the diagnostic criteria used to identify neuropathy, most studies suggest the history of chronic diabetes (either T1D or T2D) being the culprit for neuropathy development in these patients [90,91]. About 60 to 70 % of diabetes people are reported to have mild to severe forms of nervous system damage, resulting in impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, precursor for foot ulcers and other nerve problems [92].

PN is characterized by the presence of thickened axons progressing to its loss, thickened basement membrane, loss of pericytes and microfilaments and decreased capillary blood flow to C fibers, leading to decreased nerve perfusion and endoneurial hypoxia [93]. Hyperglycemia is found to impair the neuronal microvasculature through the abnormal initiation of signaling cascades [94], potentially leading to the demyelination. Hence, both nonvascular and vascular mechanisms of PN appear to be primarily related to the metabolic aspects (ie, hyperglycemia) of diabetes. Beside the common risk factors, cardiovascular diseases, severe ketoacidosis and microalbuminuria are found to be independent risk factor of PN. Compare to other complications of diabetes, DN accounts for hospitalization more frequently and also is the most frequent cause of non-traumatic amputation.

HYPERGLYCEMIA MEDIATED MITOCHONDRIAL ROS PRODUCTION AND VASCULAR COMPLICATIONS

All forms of diabetes are characterized by hyperglycemia and it damages tissue through 5 major mechanisms: 1. increased flux of glucose and other sugars through the polyol pathway; (2) increased intracellular formation of advanced glycation end products (AGEs); (3) increased expression of the receptor for AGEs (RAGEs) and its activating ligands; (4) activation of protein kinase C isoforms (PKC); and (5) over activation of the hexosamine pathway (UK Prospective Diabetes Study, 1998). Specific inhibitors of each of these pathways are found to ameliorate various diabetes-induced abnormalities in cell culture or animal models, but it has not been clear whether these processes are interconnected or mediated by a common mechanism [95-99]. Moreover, all of these pathways are rapidly getting corrected when normal blood glucose is restored, which makes the phenomenon of hyperglycemic memory conceptually difficult to explain. It has now been established that all of the 5 different pathogenic mechanisms are activated by a single upstream event: overproduction of superoxide by the mitochondrial ETC [100]. This excess superoxide anion radicals inhibit GAPDH (glyceraldehyde-3-phosphate dehydrogenase) leading to the subsequent accumulation of glycolysis intermediates by uncoupling with the flux of NADH from the hyperglycemia-enhanced glycolysis. The inhibition of GAPDH by hyperglycemia is the consequence of poly (ADP-ribosyl)ation of GAPDH by PARP [poly (ADP-ribose) polymerase], activated by DNA strand breaks produced by mitochondrial superoxide overproduction [100].

Besides mitochondrial uncoupling, several other mechanisms are also found to have association with the overproduction of superoxide under diabetic condition, such as auto-oxidation of glucose and nonenzymatic glycation [101], activation of NADPH oxidases and uncoupling of eNOS (endothelial NOS) [102-104] and impaired antioxidant status [105]. Under normal level of l-arginine, eNOS is known to synthesis NO, whereas under low level of l-arginine or cofactors, it leads to the generation of superoxide instead of NO. Superoxide is the initial oxygen free radical formed by the mitochondria, which is then converted to other more reactive species that damages cells in numerous ways [106] and affects many signaling pathways such as G-proteins, protein kinases, ion channels and transcription factors. ROS also modifies endothelial function through the peroxidation of membrane lipids, activation of NF-κβ and interference with the availability of NO [107]. All these reports reveal the overproduction of mitochondrial ROS during hyperglycemia and suggest its central role in the pathology of diabetes and its complications.

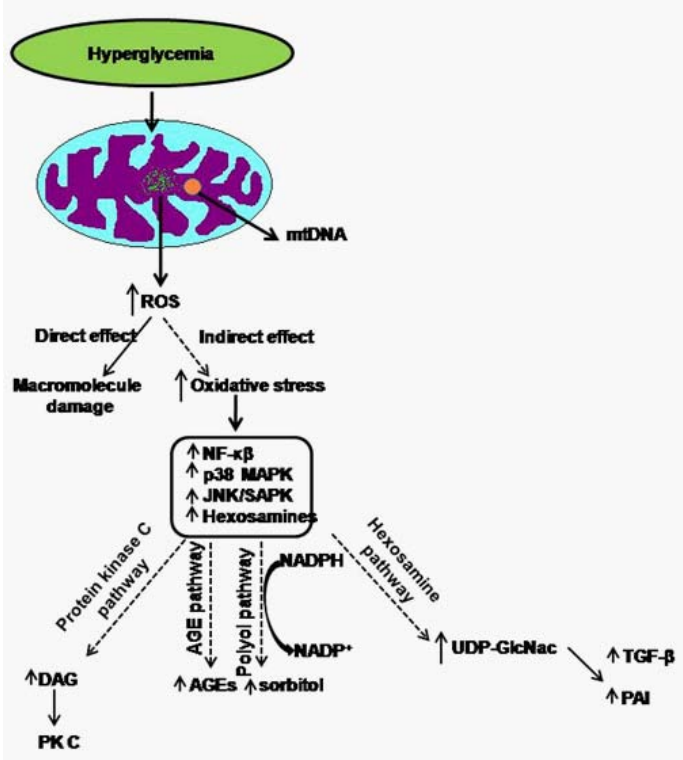

Figure 2: Hyperglycemia-mediated ROS generation and subsequent activation of pathological pathways; ROS: Reactive oxygen species; mtDNA: mitochondrial DNA; NF-κβ: Nuclear factor kappa and beta; p38-MAPK: *p38* mitogen-activated protein kinases; JNK/SAPK: c-Jun NH2-terminal kinase/Stress-activated protein kinase; AGE: Advanced glycation end product; DAG: diacylglycerol; PK C: Protein kinase C; UDP-GlcNac: Uridine diphosphate N-acetylglucosamine; TGF-β: Transforming growth factor beta; *PAI*: plasminogen activator inhibitor.

NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Non alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in adults [108] and is characterized by the presence of liver damage. In NAFLD, fat accumulation in liver exceeds 5 % of total liver weight [109]. The fatty liver results in steatohepatitis and further progress to cirrhosis and liver failure [110]. Insulin resistance due to defective metabolic activity under obesity, hyperglycemic and dyslipidemic conditions are found to have association with NAFLD. Hepatic IR impairs the ability of insulin to suppress hepatic glucose production leading to mild hyperglycemia to hyperinsulinemia (under stimulated insulin secretion) [108,111]. Moreover, IR in combination with excess adipose tissue, releases triacylglycerol (TAG) into circulation, a process normally suppressed by insulin through inhibition of hormone-sensitive lipase. Insulin normally inhibits VLDL production, especially apoB containing VLDL particles from the liver.

Elevated levels of VLDL and the defect in insulin suppression of VLDL production correlate with the amount of fat in the liver [112-113]. Lipids are taken up either by peripheral tissues or by the liver, where the lack of insulin sensitivity further promotes fatty acid synthesis, adding to the lipid overabundance, which in turn contributes to oxidative stress for the nonalcoholic steatohepatitis (NASH) progression. This explains the commonness of oxidative stress in developing metabolic diseases.

Similar to the mechanism explained in the previous section for T2D and its complications, mitochondria is observed to produce excess ROS when it crosses its ΔΨm threshold. The elevated ROS and free fatty acids from b-oxidation are found to have contribution with NAFLD development [114]. The elevated ROS acts in close proximity to their production and oxidizes proteins, lipids and DNA which in turn results in altered function. Besides, mitochondrial ROS is also found to modify its own protein complexes such as the ETC components thereby altering their function. This is seen in the patients who have progressed from NAFLD to NASH shown a reduced activity at all five ETC complexes [115], ultimately ending with impaired ATP production in these patients [116]. Moreover, morphological deformation of mitochondria is also reported in NAFLD patients where the mitochondria are found in round and swollen shape with the loss of discernable cristae structure instead of the mitochondria contained paracrystalline inclusion bodies [117]. Although the exact mechanism of ROS production from mitochondria is still the subject of investigation, its pathological role in defective mitochondrial activity in NAFLD is clear.

OTHER MANIFESTATIONS

Metabolic syndrome is associated with several other manifestations in addition to T2D and NAFLD. These include obstructive sleep apnea (OSA) and polycystic ovary syndrome (PCOS) where OSA is poorly recognized and metabolic derangements are associated with PCOS development. PCOS is the most common endocrine disorder of premenopausal women. It is characterized by chronic, hyperandrogenic oligoanovulation and oligoamenorrhea [118]. PCOS women are found to have IR, which is frequently exacerbated by obesity [119,120]. IR increases the plasma insulin concentration and suppresses the expression of IGF-1 binding protein. This in turn results in enhancement of pituitary luteinizing hormone (LH) response to LH-releasing hormone and potentiating its action in the ovarian theca and stroma by inhibiting androgen aromatization to estrogen in the granulose. These changes and the development of polycystic ovaries lead to ovarian hyperandrogenism, suppression of the mid cycle LH surge, ligoanovulation, stromal growth and accumulation of dysfunctional, cystic follicles in the ovaries [121-123].

Diagnosing PCOS at an early age has important implications, since the affected individuals are found to have a substantial risk for subsequent development of a number of metabolic (118,124] and cardiovascular [125-127] disorders. Particularly, women with PCOS are the

one with highest reported rates of early-onset impaired glucose tolerance, T2D [128,129] as well as an increase in risk for HT [130], dyslipidemia [131,132] coronary [131] and other vascular disorders [133-135]. Besides to this list of health risks, PCOS women are now appears to be present with OSA in a disproportionate number. Indeed, the risk for OSA is at least 5-fold higher and perhaps as much as 30-fold higher in PCOS [136], than in similarly obese women. Recent findings suggest the occurrence of two subtypes of PCOS viz. a. PCOS with OSA and b. PCOS without OSA. These subtypes are reported to have association with distinct metabolic and endocrine alterations. PCOS women with OSA are found to have higher risk for diabetes and cardiovascular disease than PCOS women without OSA [137]. Though the incidence of OSA is most common in middle aged, obese men [124] its prevalence is reported to increase significantly in the women receiving no gonadal hormone replacement therapy (men-to-women ratio, 1.4:1), after the menopause [129].

Hence, early diagnosis of PCOS has important implications in its treatment. In spite of the availability of many supporting evidences, the precise role of OSA as a cause of these metabolic and cardiovascular derangements is not fully understood.

SUMMARY

Worldwide, the prevalence of metabolic abnormalities is increasing at an alarming rate. Results of various studies implicated mitochondrial dysfunction for the various abnormalities of MS as it plays a vital role in cellular function and survival. To date, great advances have been made in mitochondrial biology and new treatments and therapies are under development to reestablish normal function of the organelles and restore cellular homeostasis. But, as mentioned in the chapter, it is not clear whether the mitochondrial dysfunction is a contributing factor of MS or is a consequence of MS. Hence, comprehensive research is needed to identify all possible risk factors to unravel the mechanism of MS and to develop effective therapeutic treatment.

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