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CHAPTER

Mitochondria as a New Target for Managing Diabetic Complications

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ABSTRACT

Diabetes mellitus (DM) is a serious chronic noncommunicable disease (NCD) now being considered as one of the largest global health crises. Management of diabetes and its complications is focused on controlling the blood glucose levels by various nonpharmacological and pharmacological strategies, but still control of blood glucose may not prevent and decrease complications of diabetes, suggesting to search for new strategies and focus on the target to alleviation of root cause of diabetes rather than symptomatic approach. Mitochondria are known as the powerhouses of the cell and have been extensively studied and implicated as an important factor in pathogenesis, development, progression, and complications of type 2 diabetes mellitus (T2DM). Different types of mitochondrial dysfunction have been implicated in pathogenesis of T2DM which has led to research into the role of mitochondrial dysfunction in insulin resistance, diabetes, and its complications. Interventions influencing mitochondria in diabetes include dietary interventions, exercise, pharmacological agents like metformin, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, or gliflozins and a few novel therapeutic approaches targeting mitochondria has been explored. This chapter explores new insights into the role of mitochondria in pathogenesis of diabetes and managing complications of diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a serious chronic noncommunicable disease (NCD), presently being considered as one of the largest global health crises with 11.4% Indian prevalence of diabetes and 15.3% prediabetes, more importantly >50% people being unaware of their diabetic status predisposing them to increased incidence of complications of diabetes and mortality.

Interplay of various environmental and genetic factors in DM can result in progressive loss of β-cell function and/or mass or insulin resistance (IR) clinically resulting in hyperglycemia and risk of developing chronic complications of DM for which the progression rates may differ. Type 2 diabetes mellitus (T2DM) comprise about 90% of total diabetic cases.

Triumvirate hypothesis explains the pathogenesis of T2DM involving three organs dysfunction, the pancreas with decreased insulin secretion/sensitivity, liver with increased hepatic glucose production, and muscles with decreased glucose uptake leading to hyperglycemia. Later hypothesis included adipose tissue, gut, kidney, α-cells of pancreas, and nervous system. Chronic complications associated with T2DM have been classified into macrovascular complications including cardiovascular, cerebrovascular, and peripheral vascular diseases whereas microvascular complications include neuropathy, nephropathy, and retinopathy.

MITOCHONDRIA AND TYPE 2 DIABETES MELLITUS

Mitochondria are known as the powerhouses of the cell and have been extensively studied and implicated as an important factor in pathogenesis, development, progression, and complications of T2DM, now being considered as an important target for lifestyle and pharmacological interventions. Mitochondria play a

pivotal role in cellular energy metabolism, oxidative phosphorylation (OXPHOS), β-oxidation of fatty acids, and adenosine triphosphate (ATP) production making mitochondria essential for glucose and lipid metabolism including the cellular redox state with production and clearance of reactive oxygen species (ROS), calcium homeostasis, substrate metabolism, and apoptosis.

Different types of mitochondrial dysfunction have been implicated in pathogenesis of T2DM including decreased mitochondrial content, mitochondrial dysbiogenesis, impaired mitochondrial function causing intracellular accumulation of lipids and increased ROS production as a potential cause of IR, β-cell dysfunction, and diabetes complications. A vicious cycle is created with association of T2DM, IR, and mitochondrial dysfunction. Human studies investigating mitochondria in liver, skeletal muscle, and blood cells have shown that in diabetic patients, mitochondrial function is impacted but may be with different tissue-specific mechanisms.

In DM, mitochondrial function has been extensively studied in skeletal muscle, and found an undeniable relationship between mitochondrial dysfunction, T2DM, and IR may be due to intrinsic mitochondrial dysfunction or reduced mitochondrial content, accumulation of intramuscular fat, and lipid products like diacylglycerol and ceramides responsible for inhibition of insulin signaling by activating novel protein kinases C (PKC). Another hypothesis proposed that impaired oxygen supply to the skeletal muscle is responsible for suboptimal muscle mitochondrial function rather than intrinsic impairment of mitochondrial oxidative function. Increased production of ROS because of mitochondrial dysfunction further accentuates muscle dysfunction in DM.

Mitochondrial abnormalities in liver lead to IR and influence glucose homeostasis in liver by affecting various pathways of glucose metabolism including glycogenesis, glycogenolysis, glycolysis, and gluconeogenesis. Cellular subcompartment essential for lipid metabolism, the mitochondrial-associated endoplasmic reticulum membranes (MAMs) is upregulated in hepatic IR and mitochondrial abnormalities are responsible for increased hepatocellular lipid content that is nonalcoholic fatty liver (NAFL), often progresses to nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), which play an important role in the development of IR and fatty liver disease in diabetes and more importantly may even precede the manifestation of T2DM.

A research paper that aimed to study mitochondrial parameters like mitochondrial mass, membrane potential, and superoxide production in peripheral blood mononuclear cells (PBMCs) of T2DM patients showed more spherical smaller mitochondria with reduced total mitochondrial mass, increased mitochondrial superoxide production, and mitochondrial membrane potential. Another study done in diabetic patients assessed platelet mitochondria showing reduced oxygen consumption and oxygen-dependent ATP synthesis, induction of mitochondrial antioxidant enzymes, and upregulation of oxidative stress. Evidence showed higher maximal oxygen consumption in PBMCs from patients of DM is consistent with higher ROS production suggesting relationship between mitochondrial and vascular smooth muscle cell dysfunction. Evidence suggests that sirtuin (silent mating-type information regulation 2 homolog) 1 (SIRT1) stimulates pancreatic β-cells to secret insulin and decreases oxidative stress. SIRT1 in muscle and liver activates peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) to stimulate mitochondrial biogenesis making sirtuin-activating compounds, novel agents for prevention, and management of DM and its complications.

Mitochondrial dysfunction also affects other tissues implicated in pathogenesis as well as complications of diabetes.

MITOCHONDRIA AND COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

Presently, management of diabetes is focused on controlling the blood glucose levels to prevent and decrease complications of diabetes, but complications develop even with tight control of diabetes suggesting focus on the target to alleviation of root cause of diabetes rather than symptomatic approach. This has led to research into the role of mitochondrial dysfunction in IR and DM and its complications.

In development of diabetic complications, complex relationship between chronic hyperglycemia-induced over production of ROS, diminished antioxidant defense, IR, and mitochondrial dysfunction, where one factor influences the other and vice versa. That is why focus is being shifting to "mitochondrial medicine," that is interventions to stimulate mitochondrial biogenesis, metabolism, and/or reduce mitochondrial dysfunction to ameliorate IR and prevent or reduce complications of DM.

A study reviewed the role of mitochondria in complication of diabetes and indicated that mitochondria dysfunction or damage could be important in development of complications like cardiomyopathy, nephropathy, neuropathy, and retinopathy. Evidence showed dramatic dysfunction in the inner mitochondrial membrane potential, mitochondrial superoxide production, mitochondrial mass leading to endothelial dysfunction. Main reason for coronary arteries dysfunction was suggested to be the increased ROS production resulting

in superoxide dismutase 2 (SOD2), a key mitochondrial antioxidant enzyme ubiquitination and reduction of mitochondrial SOD2 expression.

Retinopathy was suggested to be caused by activation of Rac GTPases of the Rho family, Rac1, the intracellular signal transducers (RAC1)—NOX2, an isoform of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase signaling in retinal cells leading to increase of ROS production in the cytosol and subsequent mitochondrial damage.

Another study showed reduced expression of organic anion transporter 1 (OAT1) and OAT3, confirmed by reduction of PGC-1α production and mitochondrial DNA in patients with diabetic nephropathy.

Mitochondria and diabetes have a very complex relationship with reciprocal interaction and causation makes a vicious cycle.

INTERVENTIONS INFLUENCING MITOCHONDRIA IN DIABETES

Dietary Interventions

In spite of paucity of evidence, nutritional interventions like caloric restriction, reducing consumption of fats especially long-chain saturated fatty acids, increased intake of omega-3 polyunsaturated fatty acids (PUFAs), intermittent fasting, food nutraceuticals, bioactive food derivatives, coenzyme Q10, resveratrol, and quercetin are emerging as promising nutritional interventions to boost mitochondrial function and biogenesis to ameliorate or prevent the metabolic dysfunctions because of mitochondrial dysfunction. Calorie restriction is known to prevent and reverse IR mainly through SIRT, a family of NAD^+-dependent deacetylases, playing main role in mediating the effect on mitochondrial function. Mitochondrial function not only improve by direct scavenging of ROS with food bioactive derivatives and interventions but also protect mitochondria from oxidative damage, modulate mitochondria function, and biogenesis by activating intracellular signaling pathways including 5′ adenosine monophosphate-activated protein kinase (AMPK), SIRT1, and nuclear respiratory factor 1 (NRF-1) making these an attractive nutritional interventions for mitochondrial and metabolic health. Despite these advances in understanding the role of nutrition in mitochondrial function, dietary interventions to restore mitochondrial dysfunction remain to be elucidated.

Exercise

Exercise or physical activity has numerous health benefits induced mainly by increased mitochondrial biogenesis and mitophagy. Insulin sensitivity in T2DM is increased by exercise, modulating the energy metabolism by stimulation of mitochondrial turnover, and biogenesis and induction of mitohormesis. Muscle contractions through molecular mechanisms induce an adaptive response in mitochondria leading to increased calcium concentration, increased AMP/ATP and NAD^+/NADH ratios, and activation of AMPK and mitochondrial biogenesis (PGC-1α). Evidence showed that low-intensity exercises in healthy sedentary subjects increased PBMCs ROUTINE mitochondrial respiration by 31%, LEAK mitochondrial respiration by 65%, and OXPHOS with fatty acid substrates-dependent respiration by 76%. More over twofold increase in lipolysis rate was observed and 57% more lipids were metabolized than during the incremental-load exercise. Irrespective of IR, high intensity interval exercise increased electron transfer (ET) capacity in muscle of T2DM patients as well as controls.

Pharmacological Therapy

Many conventional antidiabetic pharmacological agents have been reported to influence mitochondrial function.

Metformin, a biguanide, widely used for treatment of T2DM for decades but its molecular mechanism of action is still debated and multiple mechanisms of action have been suggested like AMPK, inhibition of mitochondrial respiratory chain [complex I (CI)], inhibition of glucagon-induced increase of cyclic adenosine monophosphate (cAMP) with decreased activation of protein kinase A (PKA), complex IV-mediated inhibition of glycerol-3-phosphate dehydrogenase 2 (GPD2) variant of mitochondrial GPD thus decreasing glycerol-derived hepatic gluconeogenesis and effect on gut microbiota. Insulin-sensitizing effect of metformin has multiple actions on tissues like liver, skeletal muscle, endothelium, adipose tissue and ovaries. Animal studies showed inhibition of mitochondrial glycerophosphate dehydrogenase causing altered redox state in primary rat hepatocytes, liver of metformin treated rats, and mouse hepatocytes. Another study showed that therapeutic concentrations of metformin caused increase in mitochondrial respiration, mitochondrial density, ATP production in hepatocytes, and CI activity in liver of high-fat fed mice, caused by AMPK-dependent mechanism. So metformin is being suggested to be an AMPK activator and respiratory CI inhibitor influencing mitochondrial function.

Thiazolidinediones (TZDs), glitazones, are antidiabetic drugs, peroxisome proliferator-activated receptor (PPAR) agonists acting on PPAR-γ, primarily in adipose tissue and also act as specific inhibitors of the mitochondrial pyruvate carrier (MPC). PPAR-γ regulates the transcription of many genes crucial for mitochondrial biogenesis

and function, while mitochondrial pyruvate uptake is required for efficient gluconeogenesis, but the potential influence of TZDs on mitochondrial function has been debated and explored.

Dipeptidyl peptidase-4 inhibitors inhibit DPP-4 activity in peripheral plasma, increase glucagon-like peptide-1 (GLP-1) and effectively treat T2DM and both have vasotropic effects and decrease diabetes-induced oxidative stress. DPP-4 inhibitor, sitagliptin, was shown to increases β-cell mass or islet angiogenesis by activating the transcription factor cAMP response element-binding protein (CREB), which plays a pivotal role in regulating PGC-1α, increases mitochondrial DNA expression and cytochrome c oxidase 1 (COX-1), COX-4, and mitochondria-specific proteins genes encoding. Evidence suggests that GLP-1 induced by DPP-4 inhibitors can activate adenylyl cyclase, a membrane-bound enzyme, promotes cAMP production by catalyzing the conversion of ATP to cAMP, and fosters PKA activation, which in turn induces serine phosphorylation of CREB.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, gliflozins, have been shown to inhibit CI respiration in primary mouse hepatocytes and to increase mitochondrial function and biogenesis in white adipose tissue of mice and also beneficial cardiovascular effect in diabetic animal models mediated through effect on mitochondrial number, size, and dynamics, but no data on in human regarding effect on mitochondrial respiration. Empagliflozin was shown to decrease diabetes-induced mitochondrial ROS, related to abnormal mitophagy in cultured renal proximal tubular cells.

Insulin is the major hormone responsible for regulation of glucose homeostasis, and short-term insulin treatment has been shown in rat and human-cultured myotubes to acts on mitochondria by increasing coupling efficiency and decreasing LEAK respiration. Some studies show an increase of mitochondrial ATP production in vivo and ex vivo in muscle biopsies of humans. Insulin might be considered as an OXPHOS modulator for its effect on mitochondria with precise mechanisms still to be defined.

Other medication frequently used in diabetics and comorbidities of diabetes, like statins have been shown to influence mitochondrial function by inhibiting maximal OXPHOS capacity with CI and CII-linked substrates, may be as a consequence of reduced coenzyme Q10.

NOVEL THERAPEUTIC APPROACHES TARGETING MITOCHONDRIA

Mitochondria appear to be a valuable target for novel drugs development for treatment of diabetes, IR, and prevention of diabetic complications. Suggested potential pharmacological strategies targeting mitochondria are AMPK activator, respiratory CI inhibitor, MPC inhibitors, PPARs agonist, OXPHOS modulator, NAD^+ booster, mitochondrial permeability transition pore (mPTP) inhibitors, sirtuin-activating compounds (STACs), coenzyme Q10 analogs, ROS scavenger, and MAMs modulators. Some of these potential approaches are proven to be beneficial in human or animal studies or some are not yet tested in diabetes or IR, yet there is always ample space for novel drugs to be designed.

Exercise mimetics are substances that mimic the effects of exercise with a potential to act as a pharmacological supplement for exercise, especially in people who are unable to exercise due to various reasons. Evidence suggests that exercise mimetics act on the cellular level by increasing mitochondrial content, reducing oxidative stress, and activating fatty acid oxidation, etc.

Some of the most studied molecules are 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), metformin (AMPK activators), and GW501516 (PPAR agonist), whereas natural products present in certain foods include resveratrol, found in grapes and red wine, and epicatechin, present in cocoa and dark chocolate.

Imeglimin, a novel oral antidiabetic drug, called "glimins", the first of a new class of tetrahydrotriazine-containing molecules was introduced in Japan in 2021 based on results of the TIMES 1 (Trials of Imeglimin for Efficacy and Safety 1) study designed to confirm the efficacy, safety, and tolerability of imeglimin monotherapy in Japanese patients with T2DM. Imeglimin, a novel glucose-lowering drug, was shown to be efficient in lowering fasting glucose and HbA1c in streptozotocin-treated rats and in human subjects as monotherapy or in combination with other antidiabetic drugs with only few side effects. Imeglimin's dual effect, on both pancreas insulin secretion and insulin sensitivity in muscle and liver, makes it a unique potential candidate for T2DM management and the proposed mechanism of action on mitochondria in animal and human studies include inhibiting CI and restoring CIII function favoring CII-linked respiration resulting in increased fatty acid oxidation and decreased intrahepatic lipid accumulation, decreased ROS production, increase mitochondrial redox potential with OXPHOS modulating properties, possibly by CI inhibition, mPTP inhibition and antioxidant activity. A study in insulin-resistant rodents showed that imeglimin increased coronary artery endothelium-dependent relaxation, ameliorated cardiac dysfunction, decreased left ventricular (LV) end-diastolic pressure, and increased LV tissue perfusion those were associated with a decrease in LV ROS production. Imeglimin in a rodent model also decreased albuminuria and interstitial fibrosis.

CONCLUSION

Good glycemic control in diabetes is best for prevention, management, and control of complications of diabetes, but despite good glycemic control and meticulous treatment of diabetes, complications may still develop, stimulating research exploring new avenues to treat diabetes and prevent complications leading to investigation into the role of mitochondria in pathogenesis of diabetes, IR, and complications of diabetes. Mitochondria have been extensively studied in diabetes and are increasingly being recognized as an important factor in the causation, progression of diabetes, and its complications, thus considered to be a valuable target for mitochondrial specific interventions and novel drug development. Positive thing is that mitochondrial dysfunction can be improved by interventions, most importantly increasing physical activity and healthy diet along with conventional and mitochondrial targeted pharmacological interventions leading to improvement of metabolic health and prevention of diabetes, its treatment and its complications. Thus, the present chapter stresses on need for opening new avenues for the prevention and treatment of diabetes and its complications with a focus on associated mitochondrial dysfunction.

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