Type 2 Diabetes develops from a pre-Diabetes condition called Metabolic Syndrome (MetSynd). MetSynd is present in over 22% of the adult U.S. population, and it is made up of several interrelated disturbances of sugar and lipid metabolism. The major risk factors for MetSynd are: abdominal obesity, high blood sugar, increased levels of low-density lipoproteins (LDL) and reduced levels of high-density lipoproteins (HDL), elevated blood pressure, resistance to insulin and the presence of inflammatory molecules in the blood [1, 2].

Insulin resistance is one of the initial signs in the development of MetSynd [3]. Insulin is secreted into the blood by the pancreas in response to increased blood sugar levels, it assists in sugar metabolism and is essential for our development, growth and maintenance of proper blood sugar levels. When the blood concentrations of insulin are insufficient to regulate the above processes, insulin resistance occurs. Insulin resistance is one of the primary events in the development of MetSynd, which can ultimately lead to type 2 Diabetes.

Defects in the capacity to metabolize certain lipid components called fatty acids as well as defects in sugar metabolism are thought to play an important role in insulin resistance and MetSynd [2, 3].

Mitochondrial Damage, Metabolic Syndrome and Type 2 Diabetes

An important event in the development of MetSynd and eventually type 2 Diabetes is damage to cellular organelles in each cell called mitochondria where energy production occurs [2, 3]. Various studies point to generalized mitochondrial dysfunction in MetSynd and type 2 Diabetes along with fatigue [2]. Mitochondrial dysfunction has also been linked to chronic insulin resistance. This causes gradual pancreatic and other organ dysfunction due to lipid-oxidation and changes in mitochondrial structure, resulting in an uncoupling of mitochondrial energy production and increased production of damaging Reactive Oxygen Species (ROS) [2, 3]. The production of ROS results in mitochondrial membrane oxidation and membrane damage, which in turn, results in loss of cellular energy production and eventually fatigue.

When mitochondria function properly, the amount of ROS produced is effectively neutralized by endogeneous antioxidants and antioxidant enzymes present inside our cells. In MetSynd, type 2 Diabetes and associated diseases, however, excess ROS is produced in our cells that cannot be neutralized, and this results in damage to mitochondrial and other cellular membranes and their components. In obese, insulin-resistant, pre-Diabetic people higher amounts of damaged lipids called fatty acids are present. Even before a diagnosis of MetSynd or type 2 Diabetes, the accumulation of oxidized fatty acids inside mitochondria can result in progressive damage to these energy-producing structures. This also occurs in many elderly and obese people where oxidized fatty acids accumulate in muscle mitochondria, and this is related to mitochondrial dysfunction, loss of energy production and fatigue [2, 3].

The Role of Mitochondria in Aging and Fatigue

Fatigue or lack of energy occurs naturally during aging and is a common condition in many clinical diagnoses, including MetSynd, type 2 Diabetes, cardiovascular diseases, respiratory, musculoskeletal
and bowel conditions as well as infections and cancer [2]. Fatigue is related to reductions in the efficiency of mitochondrial energy production, and oxidative damage to mitochondrial components can impair energy production and cause fatigue in all of these conditions.

Mitochondria are also critical elements in the process of aging, and they have been proposed to be one of the regulators of aging and cell death. During aging and fatigue antioxidant enzymes, low molecular weight antioxidants and enzyme repair mechanisms cannot restore or replace enough of the ROS-damaged molecules to maintain mitochondrial function. Disease and infection can also result in excess oxidative damage that exceeds the abilities of cells to repair and replace damaged molecules.

**References**


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The rising incidence of type 2 diabetes mellitus (T2DM) is a major public health concern, and novel therapeutic strategies to prevent T2DM are urgently needed worldwide. Aging is recognized as one of the risk factors for metabolic impairments, including insulin resistance and T2DM. Inflammation, oxidative stress, and mitochondrial dysfunction are closely related to both aging and metabolic disease. SIRT1 regulates mitochondrial function and metabolic homeostasis, increases the oxygen consumption in skeletal muscle and leads to the expression of OXPHOS genes and mitochondrial biogenesis through the deacetylation of PGC-1α. SIRT1 knockdown largely prevents the upregulation of PGC-1α-induced genes that are involved in mitochondrial fatty acid utilization (47). Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disease characterized by high blood glucose (hyperglycemia) and a wide range of ensuing side effects. Type 2 diabetes, sometimes referred to as adult-onset diabetes, affects more than 31 million people in the U.S. alone, and is one of the fastest-growing chronic conditions in the world today. Type 2 diabetes specifically manifests as a result of a condition called insulin resistance, which is caused by the accumulation of excess fat in cells that are not designed to store large quantities of fat.