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Mitochondrial Diabetes Mellitus Type 2 and its association with SNPs

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A kind of diabetes called diabetes mellitus is brought on by prolonged high blood sugar levels. It comes in Type-1, Type-2, and Type-3 varieties. Diabetes mellitus, which is more frequent in adults and obese persons, is brought on by cells that do not respond to insulin. Typically, oral drugs are suggested for the treatment of this kind of diabetes. The center of a cell's power is its mitochondria. Single Nucleotide Polymorphisms are markers that assist in identifying the specific regions of a genome that are indicative of Diabetes. Diabetes is associated with the A3243G mutation, ND1 T3394C mutation, and rRNa mutations found in the mitochondria of people who have been diagnosed with the disease. The investigation of mutations analysis and mitochondrial diabetes is provided below in detail.

Keywords: Mitochondria, Diabetes; Hyperglycemia, Single nucleotide polymorphism, Mitochondrial Diabetes; A3243G mutation and ND1 T3394C mutation

INTRODUCTION

In eukaryotic cells, powerhouses are specialized organelles that participate in the oxidative expulsion of nutrients. According to evolutionary theory, endosymbiosis with pro-eukaryotic cells is the mechanism through which mitochondria descended from bacteria. Mitochondria have their genome. Humans have circular molecules of mitochondrial DNA, which has 16.569 base pairs. DNA is present in numerous copies within a mitochondrion. Additionally, thousands of mitochondria can be found in a single cell.

The production of mitochondrial proteins requires two rRNA and twenty-two tRNA, but oxidative phosphorylation requires 13 proteins, all of which are encoded by human mtDNA. Some other mitochondrial products are also coded for in the nuclear DNA. Numerous metabolic processes are going on inside the mitochondrion. Pyruvate, a byproduct of glycolytic flux, reaches the mitochondrion where it is further broken down by the citric acid cycle (Maassen et al. 2002).

Deoxidizing NADH and FADH2 to produce ATP is the consequence of the oxidative phosphorylation of ADP. Additionally, mitochondria participate in the oxidation of fatty acids, apoptosis, and the control of cytosolic calcium (Ca). Any alteration in mitochondrial function leads to mutations in the mtDNA. These mutations change the intracellular stores of substances that serve as signalling chemicals and have an impact on ATP generation (Rovira-Llopis et al. 2017).

If mitochondria or their functional deterioration happens, age-dependent insulin resistance is also changed. Under hyperglycemia, mitochondrial biogenesis aids in controlling energy balance and increases ROS generation via the respiratory chain. This is exacerbating the degenerative processes that result in diseases like nephropathy, retinopathy, and diabetic neuropathy. There are also some macro-vascular consequences, such as myocardial ischemia and stroke. In addition, to point mutations and deletions in mtDNA, ageing also affects how any cell functions (Lenaz, 1998).

The traits listed earlier suggest that mitochondria generally play a significant role in Type 2 diabetes mellitus and insulin resistance (Rovira-Llopis et al. 2017). This necessitates constant observation and management of mitochondrial function and quality. Additionally, it is proposed that the altered oxidative activity of mitochondria is the main risk factor for the development of T2DM (Patti et al. 2010).

The metabolic illness known as Diabetes Mellitus is characterized by elevated blood sugar levels. Increased hunger, thirst, and urination are typical symptoms. If untreated, diabetes can cause a variety of health problems. Serious long-term effects include heart disease, chronic renal disease, stroke, nerve damage, foot ulcers, vision damage, and cognitive impairment (Kitabchi et al. 2009). Three Greek words are the origin of hyperglycemia. Glyc stands for sugar, hyper for high, and haima for blood. In total, hyperglycemia is characterized by blood glucose levels that are higher than 120 mg/dL while fasting and 180 mg/dL two hours later (Mouri et al. 2022).

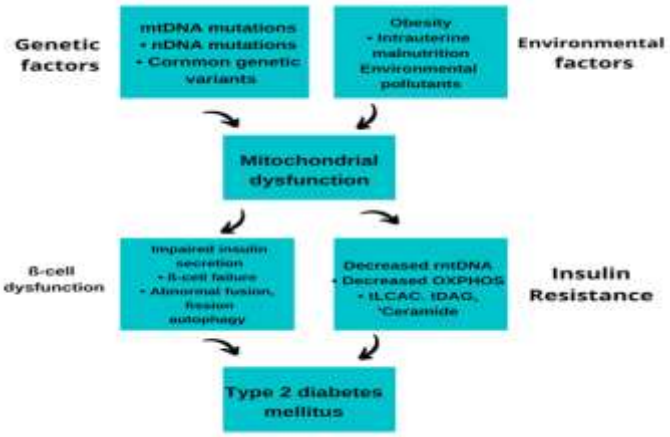

Figure 1: The layout of mitochondrial dysfunction.

2-Type2

Table 1: Types of Diabetes.

TYPE1	TYPE2	TYPE3 (GESTATIONAL)
Pancreatic dysfunction (Devendra et al. 2004).	Insulin Malfunctioning (Kharroubi et al. 2015).	Pregnant women have a history of sugar (Metzger et al. 2008).
Autoimmune reaction in β-cells (Daneman, 2006).	Cells don't react (Halban et al. 2014)	Pre-pregnancy enhanced blood glucose (Galtier, 2010).
In adolescence or throughout childhood (Dabelea et al. 2014).	In obese (Dabelea et al. 2014).	Post Pregnancy normal blood level of glucose (Sacks, 2014).
Controlled with insulin (Galtier, 2010).	Oral drugs are taken to treat (Ginsberg et al. 1975).	Risk for Whole life (Starikov et al. 2014).

2. Mitochondrial diabetes

2.1 History:

Diabetes Mellitus is one of the oldest illnesses that humans have ever known. An Egyptian newspaper published the first account of it 3000 years ago. Late in the 1930s, the distinction between types of diabetes became obvious. The first metabolic condition, type 2 Diabetes Mellitus, was recognized in 1988. Type 2 is a tradition that does not depend on insulin and is identified by insulin resistance aversion, relative insulin insufficiency and hyperglycemia. It develops because of interactions between environmental, behavioural, and genetic factors (Olokoba et al. 2012). The diagnosis of mitochondria-related diabetes mellitus (DM) is thought to occur later, in the fourth decade of life (Karaa et al. 2015).

When a patient has DM-type, they are more prone to have short- and long-term health problems, which may lead to an early death. It has been demonstrated that higher rates of morbidity and mortality in undeveloped countries like Africa are significantly influenced by the accidental development and delayed detection of this kind of DM (Olokoba et al. 2012). Hyper-glycoma levels in type 2 can cause carbohydrate oxidation that produces NADH and pyruvate. Additionally, Complexes I and III in the mitochondria emit ROS. Different antioxidant mechanisms, including uncoupling protein-1 (UCP-1) or manganese superoxide dismutase (SOD), are activated in certain conditions to prevent the generation of ROS, decrease the development of glycation end products, or activate nuclear factor kappa beta (NF-B). This prevents the development of a chronic pro-inflammatory state (Kiritoshi et al. 2003).

As soon as the pancreas cell obtains blood glucose, the plasma membrane becomes depolarized due to an increased ATP-to-ADP ratio, which causes it to block the ATP-sensitive K channel. Calcium enters the body because of the voltage-sensitive calcium channel opening (Starikov et al. 2014). The plasma membranes of granules holding insulin fuse in response to a rise in calcium concentration, causing the release of insulin. An impaired mitochondrial activity in any of the routes can lead to impaired insulin secretion and T2DM (Ashcroft et al. 1994).

Type 2 accounts for 90% of all diabetes cases. Insulin is available in the blood, but a person with T2DM is unable to respond to it, which is known as insulin-resistant diabetes. To maintain glucose homeostasis in an insulin-resistant state, insulin levels first rise. This increase is managed and brought about to reduce the insulin production that leads to type-2 diabetes. Most of the time, it affects persons over the age of 45. However, due to a sedentary lifestyle, an increase in obesity, physical inactivity, and calorie-rich meals, children, adolescents, and younger people are now also diagnosed with T2DM (Sharma, 2015; Y. Zheng et al. 2018).

2.2. Insulin resistance

Since the 1990s, mitochondrial dysfunction in diabetes mellitus type 2 has been linked to insulin resistance. To bolster this theory, research was done on the association between the number of mtDNA copies in peripheral blood cells and other metabolic pathway anomalies. Based on the population prospective cohort, it

was found that those who developed type 2 diabetes during a follow-up of two years had significantly fewer peripheral blood leukocytes carrying the mtDNA gene (Song et al. 2015). It was shown that mtDNA copy number was significantly linked with insulin sensitivity in another sample of non-diabetic offspring of T2DM patients (Singh et al. 2007). Additionally, it was established that the mtDNA copy number was adversely connected with the weight-to-hip ratio, blood pressure, and fasting blood sugar (Song et al. 2015). Sadly, additional groups did not consistently confirm similar findings. One of the main critiques of our findings was that the number of mtDNA copies in peripheral blood cells would not accurately reflect the mitochondrial activity of insulin target cells (Vidal-Puig et al. 2000; Weng et al. 2009).

2.3 Involvement of beta cells in the development of T2D:

The most widely recognized theory now is that Diabetes mellitus type 2 develops prematurely because of beta cell malfunction (Esser et al. 2020; Haythorne et al. 2019). However, the physiological and molecular mechanisms behind beta cell malfunction and its primary cause are still unknown. What happened initially is the main question. Studies support the theory by showing that beta cell metabolic changes and diminished mitochondrial activity have been seen in islets obtained from type 2, models of animal diabetes, human islets, and beta cell lines resistant to high blood glucose levels (Prasun, 2020; Weksler-Zangen et al. 2013). Additionally, as shown in research that shows drug use affects the MRC, causes mutations, and depletes the mitochondrial genome, impaired mitochondrial function lowers GSIS (Fex et al. 2018; J. Hou et al. 2017).

However, increased ROS generation that results in cell damage can also be connected to faulty electron transport chain performance. In the case of insulin resistance, overstimulation of the beta cell has proposed as the first point of commencing the harmful process of beta cell malfunction (Göhring et al. 2014; Segerstolpe et al. 2016). In a mouse model of diabetes mellitus type 2 that does not exhibit insulin resistance, it has been proposed that a potential decrease in islet-Cox activity may be the underlying cause of beta cell failure (Aharon-Hananel et al. 2022; Weksler-Zangen et al. 2013).

3 Single nucleotide polymorphism

In genetics, a single-nucleotide polymorphism is a change of a single nucleotide at a particular position in the genome. Even though some definitions require the replacement to be present in a sizeable fraction of the population (like 1% or more) (Lang, 1999; Sherry et al. 1999), many publications do not employ this frequency criterion. For instance, the majority of individuals may have the G nucleotide at a certain base location in the human genome, whereas just a tiny portion of individuals may have the A. The two possible nucleotide variations, G or A, are known as the alleles for this position, indicating that an SNP exists there (Monga et al. 2017).

Figure 2: Alternation in a single nucleotide at a specific location.

3.1 Etiology of diabetic pathophysiology i.e. A3243G mutation:

Over the last decade, several genetic mutations with a high carrying risk for the genes connected to diabetes have been found. Diabetes and deafness are two instances of monogenetic conditions that are together referred to as "maternally inherited." Maturity-onset diabetes of the young (MODY), one of several kinds of mitochondrial diabetes, accounts for a relatively tiny percentage of all occurrences of diabetes (Maassen, 2004; Stride et al. 2002; Van den Ouweland et al. 1992).

Further findings suggest that organisms with the A3243G mutation lead to glucose stimulation have fallen in pancreatic insulin production. A high glucose clamp on 92 IGT patients with a setting of 10 mmol/L. In population studies on glucose intolerance conducted in the Netherlands and Hoorn, these people were taken an IGT diagnosis based on the results of two swiftly performed oral glucose tolerance tests (OGTTs). It was found that the A3243G mutation was present in two different individuals (Van den Ouweland et al. 1992).

Both A3243G carriers had higher insulin sensitivity than non-carriers and didn't have IGT when insulin sensitivity was checked as the difference between the glucose disposal rate at ten mmol/l glucose and the ambient insulin levels. 25 individuals with the A3243G mutation who didn't have diabetes using the OGTT. These individuals' gender, age, and body mass index were matched to those of the carriers. There were no noticeable changes in the levels of glucose, insulin, C-peptide, or

glucagon following the administration of the 75 g glucose load. According to these findings, the A3243G mutation had no obvious effects before the discovery of glucose (Maassen, 2002).

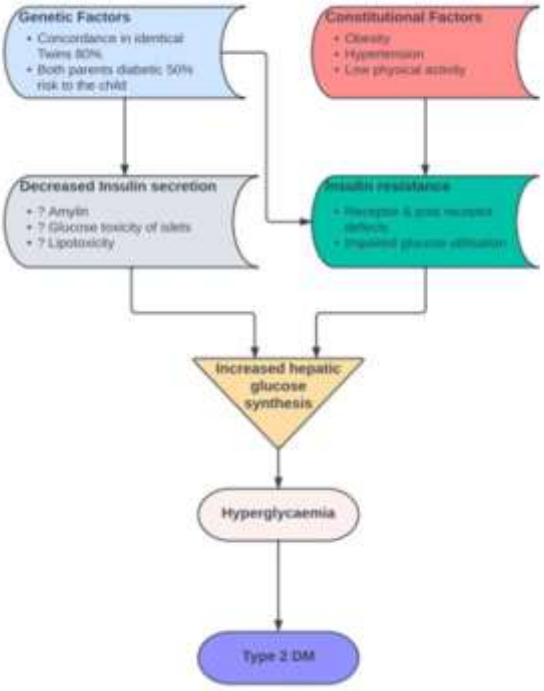

Figure3: Flowchart of the pathophysiological mechanisms leading to diabetes

3.2 Clinical presentation of A3243G mutation:

For patients who exhibit characteristics similar to type 2 phenotypes, sulfonylurea or diet are two viable therapies. Due to the potential for lactic acidosis, metformin is not recommended. Since insulinogenic steadily gets worse over time, most people will need insulin therapy for diabetes diagnosis. The hetero-plasmic mtDNA, which includes mitochondrial DNA with the wild-type and without the mutation, has the A3243G mutation in the patient cells (Lee et al. 1998; Wallace, 1999). Numerous additional mtDNA mutations have also been demonstrated to be related to mitochondrial diabetes, even though the mtDNA mutation A3243G has been associated with the illness. The average age at which MD induced by the A3243G mutation emerges in 38 years, despite the large range of starting ages. The penetrance of this mutation is virtually 100% because almost all the carrier's acquired diabetes or IGT before they were 70. Depending on the degree of insulinpenia, type 1 or type 2 diabetes might occur (Maassen, 2002; Wallace, 1992).

3.3. Age-dependent beta cells in A3243G mutation:

Non-diabetic bearers of the A3243G mutation release usual levels of C-peptide and insulin following an OGTT. The ability to maintain glucose homeostasis diminishes with ageing. Insulin resistance does not appear to be the primary underlying reason. The decrease in insulin synthesis brought on by glucose appears to have a considerable impact. On the other hand, nonprogressive diabetes usually appears rather early in life in people with glucokinase mutations. Ageing does not increase in the heteroplasmy for the A3243G mutation, so other involving must be at work if there is a time-dependent loss in-cell function. Even though increasing age-related cell loss now looks to be a plausible contributing factor, these reasons are yet unclear. Apoptosis and maybe also pancreatic cell differentiation are influenced by the amount of ROS. Pancreatic cells have a weak potential for regeneration. As a result, when cell loss increases whether, by apoptosis or necrosis, there won't be enough of them to replace those lost. Increased mitochondrial membrane potential appears to favour ROS production. protein release Faulty mice demonstrate that this condition is brought on by low amounts of uncoupling proteins (Duchen, 1999).

The mitochondrial membrane's potential is what most the glucose is used for. A Ca influx in mitochondria is brought on by the increase in cytosolic Ca in the interim. There, calcium limits the citric acid cycle (Laybutt et al. 2003). As a result, NADH-FADH2 production increases, increasing the amount of membrane potential that accumulates across the inner membrane of mitochondria. ADP is typically utilized to reduce the membrane potential while ATP is being produced. However, when ADP regeneration is at its peak and attenuating the mitochondria under hyperglycemic circumstances, the mitochondrial membrane potential rises and ROS production rises. Pancreatic beta cells lose their differentiation as a result, and they also become less sensitive to glucose (Bakker et al. 2001). The effectiveness of the adenine nucleotide translator, which interferes with the exchange of ADP for ATP between the cytosol and mitochondrial membrane, also indicates the accessibility of ADP (Anello et al. 2005).

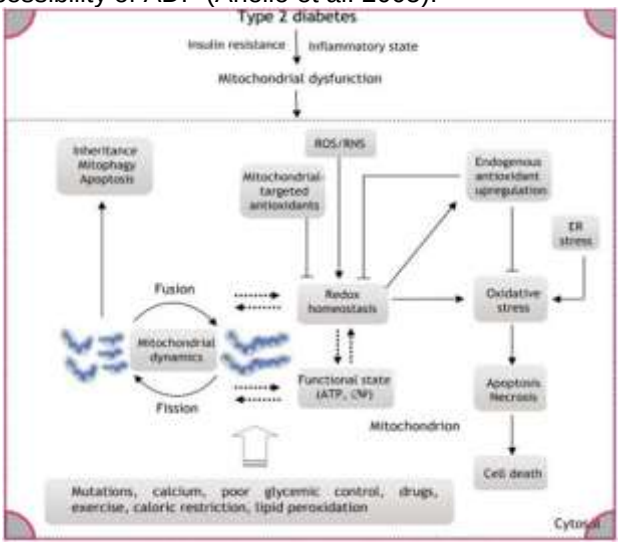

Figure 4: Deterioration of Beta-cells

Increased amounts of fatty acid-CoA esters, a condition that is probably present in obese individuals, appear to decrease the efficiency of adenine nucleotide translation, favouring the generation of ROS. Understanding the Glucotoxicity and lipotoxicity of -cells is made easier by this procedure (Haythorne et al. 2019; Kytövuori et al. 2016).

4. Vascular dynamics

The vascular effects of mitochondrial diabetes are significantly influenced by mitochondrial dynamics. Type 2 diabetes has been associated with alterations in mtDNA. Insulin secretion is under the control of mitochondria. The newly discovered mutation m.8561 C>G, which is linked to hypogonadotropic hypogonadism and diabetes mellitus, has been reported to be nurtured by 6–8 subunits of MT-ATP (Hoeks et al. 2006). The amount of insulin produced by the beta cells that make it regulates insulin levels. As a result, high glucose levels in cells lead to oxidative phosphorylation, which increases the ATP–ADP ratio and blocks K+ channels that can ionize the cell membrane and boost Ca2+ concentration in the cells. Insulin can enter circulation by maintaining a healthy blood glucose level (Diaz-Morales et al. 2016).

Insulin resistance and mitochondrial dysfunction are frequent indicators of type 2 diabetes (Kelley et al. 2002). Elevated lipid peroxidases in skeletal muscles and impaired mitochondrial activity are exclusive to individuals with insulin resistance (Mootha et al. 2003). Downregulation of genes involved in oxidative phosphorylation and mitochondrial biogenesis is connected to type 2 diabetes (Heinonen et al. 2015). When lean co-twins and obese people are compared, it is demonstrated that the global expressional pathways of oxidative pathways, as well as the mtDNA, mtDNA-dependent system of translation and protein translational system in the oxidative phosphorylation machine, are all down-regulated. The obesity level, insulin resistance, tricarboxylic acid cycle, and inflammatory cytokines have also been shown to have reduced (Apostolova et al. 2015). Type 2 diabetes has enhanced insulin sensitivity and mitochondrial function when combined with exercise, resveratrol, antioxidants that impact the mitochondria, and calorie restriction (A. Li et al. 2016). For example, it has been discovered that metformin and resveratrol are beneficial because they safeguard the mitochondria's integrity by inhibiting DRP1 activity and stop NLRP3 from activating inflammasomes by lowering endoplasmic reticulum stress, protecting cell function during hyperglycemic times (Y. Hou et al. 2016; Sathananthan et al. 2015).

Finally, it has been demonstrated that people with type 2 diabetes benefit from calorie restriction. For instance, the study found that after 6 weeks, calorie restriction, lowering blood glucose levels when fasting, and endogenous glucose production enhanced the function of cells in diabetic patients (Cerqueira et al. 2016). Furthermore, it has been demonstrated that type 2 diabetes commonly changes hyperglycemia, poor mitochondrial oxygen consumption, and high palmitate block fusion (Morino et al. 2006).

5. Impaired muscular mitochondrial function

Myopathy is referred to as MELAS. Lactic acidosis, encephalopathy, and stroke-like symptoms. It is brought on by a mutation in the mtDNA that is inherited from the mother and causes abnormalities in cellular respiration. Diabetes caused by MELAS has been linked to inadequate insulin secretion because of -cell mitochondrial malfunction. Insulin-resistant populations have lower mitochondrial activity and higher levels of muscle and liver lipids (You et al. 2022).

6. MitochondrialND1T3394Cmutation

The ND1 T3394C mutation is found in families that also contain a set of variants that are members of the mitochondrial haplogroups Y2 and m9a, according to an analysis of genes. The ND1 mRNA metabolism can fail because of the m.T3394C mutation, which is present at position 30 of tyrosine. This can eventually lead to mitochondrial malfunction. In addition, sequence analysis of individuals who are maternally linked identifies the m.A14693G mutation, which can occur in the tRNAglu T-C-loop at position 54 and is essential for forming the structure and stabilising the tRNA. Therefore, the m.A14693G mutation can impair tRNA metabolism. The mitochondrial malfunction brought on by the ND1 T3394C mutation makes it worse. The lack of functional mtDNA variations suggests that mitochondrial haplogroups may not be a key factor in displaying diabetes. This indicates that the development of matrilineal diabetes mellitus type 2 is not influenced by the mitochondrial ND1 T3394C mutation (Ding et al. 2022).

The respiratory chain is used by the mitochondria, which function as the cell's power plants, to oxidize reducing equivalents and produce ATP. The citric acid cycle, which also takes place inside the mitochondria, is where most of these reducing equivalents originate from. Circular DNA is present in human mitochondria, although it only contains the encoding information for a small portion of the mitochondrial components. Nuclear coding makes up the remaining mitochondrial components. The efficiency of the respiratory chain may be impacted by pathogenic mtDNA mutations, which will result in less ATP being generated. In addition to making ATP, mitochondria control the amounts of signalling substances like calcium and iron ions in the cytosol. The citric acid cycle and mitochondrial metabolism both regulate the concentration of metabolites that may serve as signalling molecules. Furthermore, two significant sources of reactive oxygen radicals are the respiratory chain and mitochondrion-associated monoamine oxidase. Thus, numerous cellular processes may become dysregulated because of mtDNA mutations. The clinical phenotype may be related to the

degree of balance in this deregulatory process (Maassen, 2002).

7. ATP6andND3genesrelatedto TDM2

There have been reports of type 2 diabetes in the Karaikudi people and changes in the mitochondrial NADH dehydrogenase gene. This study found rare mutations in people with maternally inherited peripheral neuropathy. Cytochrome-C activity, mitochondrial DNA state, and antioxidant status all fell as oxidative stress indicators increased. According to mtDNA studies, several mutations were discovered in different regions of the mitochondrial genome. But the following mutations were discovered: 9 base pair deletion; 10188A > G; 8597T > C; 8699T > C; and 8966T > C. Peripheral neuropathy and diabetes mellitus type 02 were both shown to be caused by maternally inherited mutations in the patient and its family (Yee et al. 2018).

8. Curative significance of mitochondrial diabetes

Diabetes Mellitus is not categorized as a traditional mitochondrial disease. The normal symptoms of stroke, encephalopathy, and lactic acidosis are absent. It is the most common inherited illness, though (Chow et al. 2017). Variations in the CXPHOS gene reduce insulin secretion and cause mitochondrial dysfunction in T2D (Olsson et al. 2011; Pullen et al. 2010). The homeostasis of pancreatic beta cells is coupled by OXPHOS, which necessitates the secretion of insulin for glucose metabolism. Through the housekeeping genes GSIS and OXPHOS, which are also prominent in cells, beta cells have a method to create ATP (Chow et al. 2017; Rutter et al. 2020). Although beta cell mitochondria have been defined, significant information is still lacking that suggests that the primary issue in DM type 2 is mitochondrial malfunction. According to research, diminished islet-COX activity is the primary cause of decreased GSIS in the pancreatic islets of CD rats (Gerbitz et al. 1995; Rutter et al. 2020; Thorrez et al. 2011).

In conclusion, diabetes mellitus type 2 is a mitochondrial illness since it depends on mitochondria. But whether it is a primary illness or not remains a dispute. It is a crucial component of mitochondrial pathological disorders that exhibit distinct clinical traits and issues that are not present in classical diabetes (Keidai et al. 2019). Therefore, it's crucial to evaluate patients and give them the right care. Metformin is the fundamental option of treatment for diabetes mellitus type 2; however, it is not advised owing to lactic acidosis risk (S. L. Zheng et al. 2018). Reduced islet-COX activity is the root cause of lower GSIS in the pancreatic islets of CD rats, according to a study (Gerbitz et al. 1995). As a result of its dependence on mitochondria, type 2 diabetes mellitus is a mitochondrial disease. However, there is disagreement over whether it is a primary illness. It is an essential part of mitochondrial pathological diseases, which differ from classical diabetes in that they show specific clinical features and problems. Therefore, it's essential to assess patients and provide them with the appropriate care. Although metformin is the primary option for treating diabetes mellitus type 2, it is not recommended because of the risk of lactic acidosis (S. L. Zheng et al. 2018).

9. Type 2 diabetes mellitus and the number of copies of mtDNA

The blood mitochondrial DNA duplication rate (mtDNA-CN), which has been complicated by the pathophysiology of TDM2, can be used to treat mitochondrial malfunction. However, this is a limitation of the suggested experiments and Mendelian Randomization analysis. Multivariable multivariate regression analyses were used to evaluate the relationship between blood mtDNA-CN and TDM2, and bidirectional MR was used to investigate the relationship between these two variables and BMI (Reiling et al. 2010; Shan et al. 2022). 15,111 individuals in the age group follow-up of 11.87 years had TDM2. However, there was a lower chance of developing TDM2 among individuals with greater levels of mtDNA-CN. The data somewhat decreased and persisted even after being adjusted for BMI. It was discovered by cross-section analysis that lower BMI and increased mtDNA-CN were related. Blood mtDNA-CN and TDM2 or even BMI were not shown to be related. As a result, there is no correlation between high TDM2 and low blood mtDNA-CN (DeBarmore et al. 2020; Schaefer et al. 2013).

10. Type 2 diabetes and treatment

Type 2 diabetes mellitus, the most prevalent form of diabetes and metabolic disorder sickness, is defined by elevated levels of LDL cholesterol, triglycerides, and fatty acids as well as a disturbing calorie intake that leads to metabolic inflammation. The results of this metabolic stress include insulin endurance and abnormality of the islet beta cells. Healthcare is significantly burdened by patients who have insulin resistance and islet beta cell dysfunction because they are going to induce later-stage conditions like neuropathy, circulatory system diseases and nephropathy. Each T2DM therapy options include sulfonylureas, metformin, alpha-glucosidase inhibitors and meglitinides and these have disadvantages. For instance, metformin produced intestinal pain and reduced vitamin B12 absorption, but sulfonylureas induced high blood glucose and a decline in efficacy. The genesis of T2DM needs to be the subject of new mechanistic studies to address this problem and offer effective treatment approaches. Mitochondrial dynamics play a significant role in the onset of diabetes. Low ROS generation is what leads to mitochondrial dysfunction, even though type 2 diabetics also have high pyruvate levels and nonalcoholic steatohepatitis. A homeostatic mechanism that has persisted throughout evolution is autophagy. The availability of nutrients, cellular metabolism, energy level, oxidative situations, and the accumulation of undesirable proteins all have a substantial impact on autophagy (Yu et

al. 2018).

ATGs oversee tightly regulating the start, growth, and fusion of autophagosomes and lysosomes to form autolysosomes. Mammalian ATG genes are involved in around 30 distinct autophagy processes. when specific nutrients or metabolic products, such as glucose and amino acids, are not available in appropriate amounts. Initiation of autophagy occurs in the endoplasmic reticulum (Wang et al. 2022).

11. Future perspective

Mitochondria are extremely active organelles that are crucial for preserving homeostasis. This organelle control cellular homeostasis, and apoptosis, and they are the primary source of ROS in the body. Therefore, their capacity for employment is essential to their capacity for survival. In cases of insulin resistance in general and type 2, the processes of mitochondrial dynamics and biogenesis are impeded. To treat this group of age-related disorders, these pathways are therefore fascinating pharmaceutical possibilities (N. Li et al. 2008; Rachek et al. 2006).

CONCLUSION

To adapt to metabolic demands, mitochondria's dynamics, biogenesis, and mitophagy are all involved. Research on how mitochondrial dynamics impact food uptake and energy expenditure is still in its infancy. Furthermore, a reduction in autophagic flux and an increase in ROS production, overnutrition results in mitochondrial dysfunction and fragmentation. Both type 2 diabetes and insulin resistance have been linked to perturbations in mitochondrial dynamics. Additionally, we have investigated substances including S3, P110, and mdivi-1 that encourage mitochondrial fusion and prevent mitochondrial fission. The development and design of pharmacological therapies that target mitochondrial dynamics hold promise for advancements in the treatment of cardio-metabolic disorders, even though the molecular mechanisms underlying mitochondrial dynamics and their relationship to illnesses are still unknown.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors have equal contributions.

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