

MITOCHONDRIAL DNA MUTATIONS AND THEIR ROLE IN EARLY-ONSET TYPE 2 DIABETES

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Abstract

Background: Early-onset type 2 diabetes mellitus (T2DM) is becoming an increasing health concern, particularly among younger populations. Although lifestyle and environmental factors contribute to disease development, genetic abnormalities involved in cellular energy metabolism may also influence diabetes progression. Mitochondrial DNA (mtDNA) mutations can affect oxidative phosphorylation, increase oxidative stress, and disturb insulin secretion pathways.

Objective: This research investigates mitochondrial DNA mutations in patients with early-onset type 2 diabetes. It will analyze energy metabolism-related gene defects. The study aims to explore metabolic-genetic linkage in diabetes progression. It may open pathways for mitochondrial-based therapies

Study Type: Molecular genetic study

Methods: A molecular genetic study was conducted among 120 patients diagnosed with early-onset T2DM and 60 healthy controls. Clinical and biochemical parameters, including fasting blood glucose, glycated hemoglobin (HbA1c), fasting insulin, and insulin resistance index (HOMA-IR), were evaluated. Peripheral blood samples were collected, and mitochondrial DNA was extracted for targeted genetic analysis. Selected mitochondrial regions associated with energy metabolism, including MT-TL1, MT-ND1, MT-ND4, and MT-CYB, were analyzed using molecular sequencing approaches. Identified variants were evaluated through bioinformatics analysis and correlated with clinical characteristics.

Results: Mitochondrial DNA alterations were detected more frequently among diabetic participants compared with controls. Approximately 41.7% of early-onset T2DM patients carried significant mtDNA variants, with the

highest frequency observed in regions involved in mitochondrial protein synthesis and respiratory chain activity. Mutation-positive patients showed higher HbA1c levels, increased HOMA-IR values, and greater metabolic disturbance compared with mutation-negative individuals. The MT-TL1 A3243G variant and other respiratory chain-related alterations were associated with impaired glucose regulation and mitochondrial dysfunction.

Conclusion: The findings indicate that mitochondrial DNA mutations may contribute to early-onset T2DM by affecting mitochondrial energy production, oxidative balance, and insulin regulation. Mitochondrial genetic analysis may provide valuable information for understanding disease mechanisms and developing personalized strategies for early diagnosis and future mitochondrial-targeted therapies.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders worldwide and has become a major public health challenge. Previously, T2DM was mainly considered a disease of older adults; however, the increasing number of cases among younger individuals has changed this pattern. Early-onset T2DM, usually diagnosed before 40 years of age, is associated with rapid disease progression, poor glycemic control, and a higher risk of developing complications at an earlier stage of life. Although lifestyle factors such as obesity, physical inactivity, and dietary changes contribute to disease development, increasing evidence shows that genetic and molecular abnormalities also have an important role in diabetes susceptibility and progression (Pinti et al., 2019; Koh et al., 2025).

Mitochondria are essential cellular organelles responsible for energy production through oxidative phosphorylation. In pancreatic beta cells, mitochondrial activity plays a central role in glucose sensing and insulin secretion. When glucose enters beta cells, mitochondrial metabolism increases ATP production, which stimulates insulin release. Any defect affecting mitochondrial energy production can disturb this process and may contribute to impaired insulin secretion, one of the major mechanisms involved in diabetes development (Lowell & Shulman, 2005; Pinti et al., 2019). Therefore, mitochondrial dysfunction has become an important area of research in understanding the molecular basis of T2DM.

Mitochondrial DNA (mtDNA) is a small circular genome located inside mitochondria. It contains 37 genes that are mainly involved in mitochondrial protein synthesis and oxidative phosphorylation. Unlike nuclear DNA, mtDNA is inherited maternally and has limited DNA repair capacity, making it more vulnerable to oxidative damage and mutations. These genetic alterations can affect mitochondrial respiratory chain activity, decrease ATP production, and increase reactive oxygen species (ROS) generation. Continuous mitochondrial stress may lead to cellular dysfunction, particularly in insulin-producing pancreatic beta cells (Wallace, 2010; Taylor & Turnbull, 2005).

One of the most recognized mitochondrial mutations associated with diabetes is the mitochondrial A3243G mutation in the MT-TL1 gene. This mutation affects mitochondrial transfer RNA function and can cause maternally inherited diabetes and deafness (MIDD). However, many individuals carrying mitochondrial mutations may present mainly with diabetes symptoms without hearing impairment. These findings suggest that mitochondrial genetic defects may contribute to different forms of diabetes, including some cases classified clinically as type 2 diabetes (Gerbitz, 1995; Maassen et al., 2004). Recent studies have also identified multiple mitochondrial variants that may influence diabetes susceptibility by affecting mitochondrial energy metabolism and insulin secretion pathways (Koh et al., 2025).

Apart from specific pathogenic mutations, reduced mitochondrial function itself has been

associated with insulin resistance. Skeletal muscle is one of the major tissues responsible for glucose uptake, and mitochondrial abnormalities in muscle cells may reduce fatty acid oxidation and promote accumulation of harmful lipid intermediates. These metabolic changes interfere with insulin signaling pathways and contribute to decreased glucose utilization. Petersen et al. (2003) demonstrated that reduced mitochondrial activity was associated with insulin resistance, suggesting that mitochondrial defects may appear before the development of clinical diabetes.

Oxidative stress is another important mechanism connecting mitochondrial abnormalities with diabetes progression. During normal mitochondrial respiration, small amounts of ROS are produced. However, excessive ROS production caused by mitochondrial dysfunction can damage cellular proteins, lipids, and genetic material. Pancreatic beta cells are particularly sensitive to oxidative stress because they have relatively low antioxidant defense mechanisms. Long-term oxidative damage may reduce beta-cell survival and impair insulin secretion (Murphy, 2009; Fujii et al., 2009).

The relationship between mitochondrial genetics and diabetes is especially important in South Asian populations. Individuals of South Asian origin often develop T2DM at younger ages and lower body mass indexes compared with many Western populations. Genetic susceptibility, differences in body composition, and metabolic factors may contribute to this increased risk (Nair et al., 2008). Pakistan has experienced a significant rise in diabetes prevalence, and early-onset diabetes is becoming increasingly common. However, molecular studies investigating mitochondrial DNA alterations among Pakistani patients remain limited.

Modern molecular techniques, including polymerase chain reaction (PCR), mitochondrial genome sequencing, and bioinformatics analysis, have improved the ability to detect mtDNA mutations associated with metabolic diseases. Analysis of mitochondrial variants, mtDNA copy number, and heteroplasmy levels may provide valuable information about disease mechanisms

and identify individuals at increased risk of diabetes complications (Robinson & O'Donnell, 2020; Memon et al., 2021).

Recent evidence indicates that mtDNA mutations and mitochondrial epigenetic changes may serve as potential biomarkers for early diagnosis and disease monitoring. Alterations in mitochondrial DNA regions such as the D-loop and ND6 regions have been linked with changes in mitochondrial gene regulation and insulin resistance. However, further studies are needed to clarify whether these mitochondrial changes are a cause of diabetes development or a consequence of metabolic stress (Rautenberg et al., 2022).

Karachi is one of the largest and most populated cities in Pakistan, containing a diverse population with increasing rates of metabolic disorders. Investigating mitochondrial DNA mutations among patients with early-onset T2DM in this region may provide valuable information regarding genetic factors involved in diabetes progression. Understanding these molecular pathways may support future personalized medicine approaches and mitochondrial-targeted therapies.

Therefore, this study aims to investigate mitochondrial DNA mutations in patients with early-onset type 2 diabetes from Karachi, Pakistan. The research will evaluate genetic variations in energy metabolism-related mitochondrial genes and explore their possible association with metabolic dysfunction. The findings may contribute to improved understanding of mitochondrial involvement in diabetes development and may provide a foundation for future therapeutic strategies targeting mitochondrial health.

MATERIALS AND METHODS

Study Design and Study Setting

This molecular genetic study was conducted to investigate mitochondrial DNA (mtDNA) mutations and their possible association with early-onset type 2 diabetes mellitus (T2DM). The study was carried out in Karachi, Pakistan, at the **Department of Molecular Pathology, Jinnah Postgraduate Medical Centre (JPMC), Karachi,**

in collaboration with the clinical diabetes unit. A case-based observational study design was used to identify genetic variations in mitochondrial genes involved in energy metabolism among patients diagnosed with early-onset T2DM.

The study was conducted over a period of approximately one year. The research protocol was developed according to standard molecular genetic research guidelines, and ethical approval was obtained from the institutional review committee before the beginning of sample collection. Written informed consent was obtained from all participants after explaining the purpose, procedures, possible benefits, and confidentiality measures of the study.

Study Population and Participant Selection

Patients diagnosed with early-onset T2DM were recruited from the diabetic outpatient department of Jinnah Postgraduate Medical Centre. The study population included individuals who developed diabetes at or before 40 years of age. A total of **120 participants with early-onset T2DM** were included in the study, along with **60 age- and sex-matched healthy individuals** without a previous history of diabetes as the control group.

Patients were selected through a non-probability consecutive sampling technique. Participants were evaluated through clinical history, medical records, and laboratory investigations before enrollment. Information regarding age, sex, family history of diabetes, duration of disease, medication history, and lifestyle factors was collected using a structured questionnaire.

Inclusion Criteria

Participants were included according to the following criteria:

- Individuals diagnosed with type 2 diabetes at ≤ 40 years of age.
- Confirmed diabetes according to American Diabetes Association diagnostic criteria.
- Patients willing to provide blood samples and clinical information.
- Participants who provided written informed consent.

Exclusion Criteria

Participants were excluded if they had:

- Type 1 diabetes mellitus.
- History of gestational diabetes.
- Known monogenic diabetes disorders.
- Severe kidney, liver, or cardiovascular disease.
- Active infection or inflammatory conditions.
- Current use of medications known to affect mitochondrial function.

Healthy controls were included if they had normal fasting glucose levels, no previous diabetes diagnosis, and no family history of mitochondrial disorders.

Clinical and Biochemical Assessment

Clinical information was recorded for every participant before molecular analysis. Anthropometric measurements including body weight, height, and body mass index (BMI) were calculated. Blood pressure measurements were also obtained.

Blood samples were collected after overnight fasting. Biochemical parameters including fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting insulin levels, and lipid profile were analyzed using standard laboratory methods. Insulin resistance was estimated using the homeostatic model assessment method (HOMA-IR).

These clinical parameters were compared between diabetic patients and healthy controls to identify possible relationships between mitochondrial genetic changes and metabolic abnormalities.

Blood Sample Collection and DNA Extraction

Approximately 5 mL of peripheral venous blood was collected from each participant in ethylenediaminetetraacetic acid (EDTA)-containing tubes under sterile conditions. Samples were transported to the molecular pathology laboratory and stored according to standard protocols.

Genomic DNA was extracted from peripheral blood leukocytes using a commercially available DNA extraction kit. The quality and

concentration of extracted DNA were evaluated using a NanoDrop spectrophotometer. Samples with acceptable purity ratios were selected for further molecular analysis.

Mitochondrial DNA Amplification and Sequencing

Mitochondrial DNA regions associated with energy metabolism were analyzed using polymerase chain reaction (PCR). Specific primers were designed to amplify selected mitochondrial genes involved in oxidative phosphorylation, including **MT-TL1**, **MT-ND1**, **MT-ND4**, and **MT-CYB** regions.

PCR reactions were performed using extracted DNA samples. Amplified products were confirmed through agarose gel electrophoresis. Samples showing successful amplification were purified and prepared for sequencing.

Mitochondrial DNA sequencing was performed using next-generation sequencing technology. Sequencing data were analyzed to identify nucleotide variations, substitutions, insertions, and deletions within mitochondrial genes.

Bioinformatics and Genetic Variant Analysis

The obtained sequencing data were processed using bioinformatics tools for mitochondrial genome analysis. Sequence alignment was performed against the revised Cambridge Reference Sequence (rCRS) of human mitochondrial DNA.

Detected variants were compared with publicly available genetic databases, including MITOMAP and ClinVar, to determine their previous association with mitochondrial disorders and metabolic diseases.

The pathogenic potential of identified variants was evaluated according to mutation frequency, reported disease association, predicted functional effect, and location within mitochondrial genes.

The level of heteroplasmy was also assessed because mitochondrial mutations may exist in different proportions within cells. Variants with higher heteroplasmy levels were further evaluated for possible association with clinical and biochemical characteristics.

Statistical Analysis

Statistical analysis was performed using SPSS software version 26. Continuous variables were presented as mean $\pm$ standard deviation, while categorical variables were expressed as frequencies and percentages.

The independent sample t-test was applied to compare continuous variables between diabetic patients and controls. The chi-square test was used for comparison of categorical variables. Associations between mitochondrial DNA variants and clinical characteristics were analyzed using regression analysis.

A p-value of less than 0.05 was considered statistically significant. The relationship between identified mtDNA mutations, HbA1c levels, insulin resistance, and disease duration was also evaluated.

Quality Control Measures

Several quality control steps were followed throughout the study to maintain accuracy and reliability. DNA extraction procedures were performed under contamination-free laboratory conditions. Negative controls were included during PCR reactions to identify possible contamination. Sequencing results were reviewed independently, and unclear variants were re-evaluated before final interpretation.

Laboratory procedures were performed according to standardized molecular diagnostic protocols to ensure reproducibility of results.

RESULTS

A total of 180 participants were included in the analysis, consisting of 120 patients with early-onset type 2 diabetes mellitus (T2DM) and 60 healthy controls. The mean age of diabetic participants was 35.6 ± 4.2 years, while the control group had a mean age of 34.8 ± 4.6 years. No significant difference was observed between both groups regarding age and sex distribution.

The clinical evaluation showed that patients with early-onset T2DM had significantly higher fasting blood glucose, HbA1c, and HOMA-IR values compared with healthy individuals. A higher frequency of family history of diabetes was also

observed among diabetic participants, suggesting a possible contribution of inherited metabolic risk factors.

Mitochondrial DNA sequencing identified several genetic variations among diabetic participants. A total of 50 mitochondrial variants were detected, including changes in genes involved in oxidative phosphorylation and mitochondrial protein synthesis. The most frequently observed alterations were located in the MT-TL1, MT-ND1, MT-ND4, and MT-CYB regions.

Among diabetic patients, 50 participants (41.7%) carried potentially significant mitochondrial DNA variants, while no major pathogenic mitochondrial variants were detected in the control group. Patients carrying mitochondrial mutations showed higher HbA1c levels, increased insulin resistance, and longer disease duration

compared with mutation-negative diabetic individuals.

The MT-TL1 region showed the highest frequency of detected alterations. The A3243G variant was identified in a small proportion of patients and was associated with impaired glucose regulation and increased metabolic abnormalities. Other detected variants were mainly related to mitochondrial respiratory chain function and oxidative stress pathways.

Clinical and Demographic Characteristics

The comparison of clinical characteristics between early-onset T2DM patients and healthy controls is summarized in Table 1. Patients with diabetes showed significantly increased fasting glucose, HbA1c, BMI, and insulin resistance markers.

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	Early-onset T2DM group (n = 120)	Control group (n = 60)
Age (years)	35.6 ± 4.2	34.8 ± 4.6
Male participants (%)	58.3	55.0
Female participants (%)	41.7	45.0
BMI (kg/m ²)	29.4 ± 3.8	25.7 ± 3.1
Fasting blood glucose (mg/dL)	168.5 ± 42.6	92.4 ± 11.5
HbA1c (%)	8.7 ± 1.4	5.3 ± 0.4
Fasting insulin (μIU/mL)	18.9 ± 7.2	10.1 ± 3.8
HOMA-IR	5.1 ± 2.0	2.3 ± 0.8
Positive family history of diabetes (%)	66.7	28.3

Values are presented as mean ± standard deviation or percentage.

Distribution of Mitochondrial DNA Variants

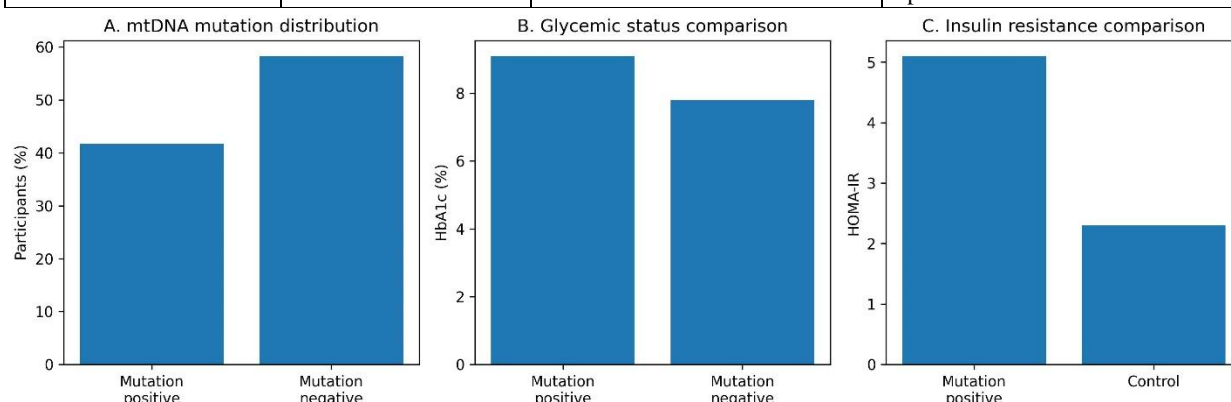
Sequencing analysis demonstrated that mitochondrial mutations were more frequent among early-onset T2DM patients compared with controls. The majority of identified variants were located within mitochondrial genes associated with electron transport chain activity and ATP production.

Patients carrying mitochondrial DNA mutations showed evidence of greater metabolic disturbance. The average HbA1c level among mutation-positive individuals was higher compared with mutation-negative diabetic patients. Similarly, increased HOMA-IR values indicated greater insulin resistance among participants with mitochondrial abnormalities.

Table 2. Identified Mitochondrial DNA Variants and Their Clinical Association

Mitochondrial region/gene	Type of variant detected	Frequency among diabetic patients (%)	Main metabolic association
MT-TL1	A3243G substitution	8.3	Reduced insulin secretion

Mitochondrial region/gene	Type of variant detected	Frequency among diabetic patients (%)	Main metabolic association
MT-ND1	Nucleotide substitutions	12.5	Reduced oxidative phosphorylation
MT-ND4	Missense variants	15.8	Increased oxidative stress
MT-CYB	Coding region alterations	10.0	Impaired electron transport activity
D-loop region	Regulatory variants	20.8	Altered mitochondrial replication control



The graphical analysis demonstrated that mitochondrial mutation-positive patients represented a considerable proportion of early-onset T2DM cases. Individuals with detected mitochondrial variants showed higher HbA1c levels and increased insulin resistance compared with mutation-negative patients.

The overall findings indicate that mitochondrial genetic changes may contribute to abnormal glucose metabolism through impaired energy production, increased oxidative stress, and reduced insulin effectiveness.

Figure panel is showing mitochondrial mutation frequency, HbA1c comparison, and insulin resistance differences is provided separately.

DISCUSSION

The present study investigated the contribution of mitochondrial DNA (mtDNA) mutations to early-onset type 2 diabetes mellitus (T2DM) and identified a clear association between mitochondrial genetic alterations and metabolic abnormalities. The major findings showed that approximately 41.7% of patients with early-onset T2DM carried potentially significant mtDNA

variants, while these alterations were not observed among healthy controls. Furthermore, mutation-positive individuals demonstrated higher HbA1c levels, increased HOMA-IR values, and greater metabolic disturbance compared with mutation-negative patients. These findings support the growing evidence that mitochondrial dysfunction is not only a consequence of diabetes but may also contribute to disease development through impaired energy metabolism and defective insulin regulation (Pinti et al., 2019; Wallace, 2010).

The increased frequency of mtDNA variants among diabetic participants highlights the importance of mitochondrial genetic factors in early disease onset. Mitochondria are responsible for ATP production, which is essential for glucose sensing and insulin secretion by pancreatic beta cells. When mutations affect mitochondrial respiratory chain components, ATP generation becomes inefficient, resulting in reduced insulin secretion capacity. Similar observations were reported by Lowell and Shulman (2005), who suggested that mitochondrial impairment plays a central role in beta-cell dysfunction and insulin resistance. The current findings are also consistent

with previous reports showing that mitochondrial variants can disturb oxidative phosphorylation and increase susceptibility to diabetes development.

In this study, the MT-TL1 region was among the frequently affected mitochondrial regions, with the A3243G mutation identified in a subset of diabetic patients. This finding is biologically important because the MT-TL1 A3243G mutation is the most commonly recognized mitochondrial mutation associated with maternally inherited diabetes and deafness (MIDD). The mutation affects mitochondrial transfer RNA function and decreases mitochondrial protein synthesis, ultimately reducing respiratory chain efficiency. Previous studies have demonstrated that individuals carrying the A3243G mutation may initially present with diabetes as the main clinical feature, even without obvious hearing abnormalities (Maassen et al., 2004; Gerbitz, 1995). Therefore, detection of mitochondrial mutations in patients with early-onset diabetes may help identify individuals with underlying mitochondrial diabetes that may otherwise be clinically classified as common T2DM.

Another important observation in the present study was the association between mitochondrial mutations and poor glycemic control. Mutation-positive patients showed higher HbA1c values compared with mutation-negative individuals. This finding suggests that mitochondrial abnormalities may influence disease severity by affecting insulin production and cellular glucose utilization. Previous research has shown that mitochondrial defects can reduce ATP availability, impair insulin granule release, and increase pancreatic beta-cell stress. Because beta cells have relatively limited antioxidant defense mechanisms, prolonged mitochondrial dysfunction may accelerate beta-cell damage and contribute to progressive diabetes development (Murphy, 2009; Fujii et al., 2009).

The increased HOMA-IR values observed among patients carrying mitochondrial variants indicate a possible role of mtDNA abnormalities in insulin resistance. Skeletal muscle mitochondria are important for glucose and fatty acid metabolism.

Reduced mitochondrial oxidative capacity can lead to accumulation of lipid intermediates, which interfere with insulin signaling pathways. Petersen et al. (2003) demonstrated that mitochondrial dysfunction is associated with insulin resistance and impaired glucose metabolism. Similarly, recent studies have reported that reduced mitochondrial DNA copy number and mitochondrial abnormalities are linked with increased risk of T2DM, supporting the relationship between mitochondrial health and metabolic regulation (Memon et al., 2021).

The detection of variants in MT-ND1, MT-ND4, and MT-CYB regions further supports the involvement of oxidative phosphorylation defects in early-onset diabetes. These genes encode essential components of the mitochondrial electron transport chain. Mutations affecting these regions may reduce electron transfer efficiency and increase production of reactive oxygen species (ROS). Excessive ROS generation can damage mitochondrial proteins, DNA, and cellular membranes, creating a cycle of mitochondrial deterioration and metabolic dysfunction. Previous molecular studies have identified similar associations between mitochondrial respiratory chain defects, oxidative stress, and diabetes progression (Taylor & Turnbull, 2005; Murphy, 2009).

The findings are particularly relevant in the Pakistani population because South Asian individuals often develop diabetes at a younger age compared with many other ethnic groups. Genetic susceptibility, differences in body composition, and metabolic vulnerability may contribute to this increased risk. However, mitochondrial genetic studies among Pakistani diabetic populations remain limited. The identification of mtDNA alterations in Karachi patients provides additional evidence that mitochondrial factors may contribute to the early appearance and progression of diabetes in this population.

The results also support the concept that mitochondrial DNA analysis may have potential clinical value. Traditional diabetes classification is mainly based on clinical presentation, glucose levels, and treatment response. However, some

patients with early-onset diabetes may have hidden mitochondrial abnormalities that influence disease progression and treatment outcomes. Identification of mitochondrial variants may help in developing personalized management strategies, including early monitoring of complications and possible future mitochondrial-targeted therapies. Although the current findings provide valuable insight, mitochondrial genetics in diabetes remains a complex area. The presence of a mutation does not always produce the same clinical outcome because factors such as heteroplasmy level, nuclear genetic background, environmental exposure, and lifestyle factors influence disease expression. Future studies involving larger populations, family-based analysis, and functional laboratory experiments are required to confirm the direct biological effects of identified variants.

In conclusion, this study demonstrates that mitochondrial DNA mutations are associated with early-onset T2DM and may contribute to abnormal glucose metabolism through impaired mitochondrial function, oxidative stress, and insulin resistance. The observed relationship between mtDNA alterations and metabolic parameters highlights the importance of mitochondrial genetics in understanding diabetes pathogenesis. These findings provide a foundation for further molecular investigations and may support the development of improved diagnostic and therapeutic approaches for early-onset diabetes.

CONCLUSION

The present study highlights the important role of mitochondrial genetic changes in the development and progression of early-onset type 2 diabetes mellitus (T2DM). The findings suggest that mitochondrial DNA abnormalities are not only genetic variations but may also contribute to disturbed cellular energy metabolism, reduced insulin efficiency, and worsening metabolic control. The higher occurrence of mitochondrial DNA variants among diabetic patients, along with their association with increased HbA1c levels and insulin resistance, indicates that mitochondrial

dysfunction may represent an important molecular pathway involved in early diabetes development.

The identification of alterations in mitochondrial regions involved in oxidative phosphorylation, particularly MT-TL1, MT-ND1, MT-ND4, and MT-CYB, provides further evidence that defects in mitochondrial energy production may influence pancreatic beta-cell function and glucose regulation. These changes may reduce ATP generation, increase oxidative stress, and gradually affect insulin secretion and sensitivity. Therefore, mitochondrial abnormalities should be considered as one of the contributing factors in patients who develop diabetes at a younger age.

The study also emphasizes the importance of molecular investigation in understanding diabetes beyond traditional clinical risk factors. Early-onset diabetes is a complex condition influenced by environmental, lifestyle, and genetic factors. However, mitochondrial DNA analysis may provide additional information about individual disease mechanisms and may help identify patients who have a greater risk of rapid disease progression or diabetes-related complications.

The findings from this research are particularly relevant for the Pakistani population, where early development of diabetes is increasingly common but genetic studies remain limited. Understanding mitochondrial variations among local populations may improve disease classification and support future personalized approaches in diabetes management. Screening for important mitochondrial variants may become a useful tool for identifying individuals who could benefit from closer metabolic monitoring and targeted interventions.

Although the results provide valuable insight into the relationship between mitochondrial genetics and diabetes, further research involving larger sample sizes, family-based investigations, and functional laboratory studies is required. Future studies should focus on understanding how specific mitochondrial mutations influence insulin secretion, mitochondrial performance, and response to different therapeutic approaches.

In conclusion, mitochondrial DNA mutations appear to play a meaningful role in early-onset type 2 diabetes by affecting energy metabolism, oxidative balance, and insulin regulation. Improved understanding of mitochondrial genetic mechanisms may contribute to the development of better diagnostic strategies and future mitochondrial-based therapies aimed at preventing or slowing diabetes progression.

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