Int. j. adv. multidisc. res. stud. 2026; 6(4):1523-1524

Received: 02-08-2026
Accepted: 12-08-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

Mitochondrial Diabetes is not Restricted to mtDNA Variants

[1] Josef Finsterer, [2] Sounira Mehri

[1] Neurology Department, Neurology & Neurophysiology Center, Vienna, Austria
[2] Laboratory of "Nutrition - Functional Food & Health", Faculty of Medicine, University of Monastir, Monastir, Tunisia

DOI: https://doi.org/10.62225/2583049X.2026.6.4.6772
Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Rindell *et al*. on a retrospective study of the clinical presentation, treatment, and epidemiology of mitochondrial diabetes (MDM) in the southwestern Finnish province [1]. Of the 17 patients identified, the mean age at diagnosis of MDM was 35 years, 82% had hearing loss, insulin was required on average 3.5 years after diagnosis, only one-third of the patients had an HbA1c value < 7%, and the prevalence of MDM was 2.7/100,000 [1]. The study is impressive, but some points warrant discussion.

The first point concerns the retrospective study design [1]. Retrospective studies have limited explanatory power [2]. Data quality is generally low, there are missing data, and causal relationships cannot be proven, only associations can be established. There is a susceptibility to memory and selection biases, difficulties in controlling confounding factors, and generally a lower level of evidence compared to prospective studies [2].

The second point concerns the definition of the term "mitochondrial diabetes" [1]. MDM should not only refer to diabetes in patients with mtDNA mutations, but also to patients with mitochondrial disease (MID) due to mutations in nuclear genes. MDM due to mutations in nuclear genes has been described in patients with mutations in POLG1, LARS2, TWNK (PEO1), and GLUT1 [3]. Why were patients with MDM due to mutations in nuclear genes excluded from the study? MDM should not be limited to diabetes in patients with mtDNA mutations, but should also include patients with nuclear mutations.

The third point is that determinants of phenotypic expression, such as heteroplasmy rate, mtDNA copy number, modification of mtDNA variants by nuclear genes, haplogroup, the random distribution of mutated and normal mtDNA during mitosis, the bottleneck effect during oogenesis, the accumulation of mtDNA variants with increasing age, environmental factors such as alcohol, smoking, mitochondrially toxic drugs, diet, toxins and physical activity, sex-specific penetrance, the effectiveness of mitochondrial quality control mechanisms, the ability to compensate for oxidative stress, metabolic status, the degree of inflammation and the amount of reactive oxygen species produced, were not included in the analysis [4]. As long as these influencing factors are not taken into account, the results remain unreliable.

The fourth point is that it is unclear how the prevalence of MDM could be calculated, given that diabetes patients are treated not only as inpatients but also as outpatients, MDM can also be caused by nuclear mutations, and there are not just one but more than ten hospitals in the district. Were data from other hospitals also included in the analysis? It should also be clarified why there is a discrepancy between the prevalence of the m.3243A>G variant in the district (4.2/100,000) and the prevalence of MDM at 2.7/100,000. Does this mean that only about half of the m.3243A>G carriers have developed MDM? There is evidence that the prevalence of MDM among m.3243A>G carriers is significantly higher, reaching 85–100% [5].

The fifth point concerns the lack of explanation regarding how nephropathy, as a distinct phenotypic feature, was differentiated from diabetic nephropathy.

The sixth point concerns patient P16, who was treated with metformin [1]. Metformin is known to cause lactic acidosis [6]. What was the reason for administering metformin to patient P16? Did this patient die from lactic acidosis?

The final point concerns the patients who were not systematically investigated for multisystem disease. Since carriers of the m.3243A>G mutation typically suffer not only from MDM and hypoacusis, but also exhibit multisystem disease at the onset or during progression, it is crucial for treatment and prognosis to identify, as early as possible, which other organs are also affected.

Declarations

Ethical Approval: Not applicable.

Consent to Participation: Not applicable.

Consent for Publication: Not applicable.

Funding: None received.

Availability of Data and Material: All data are available from the corresponding author.

Completing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution: JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval. SM: contributed to literature search, discussion, correction, and final approval.

Acknowledgements: None.

Keywords: mtDNA, m.3243A>G, Diabetes, MELAS, Mitochondrial Disorder

References

1. Rindell N, Immonen H, Martikainen MH. Prevalence and treatment of mitochondrial diabetes in Southwest Finland. J Diabetes Metab Disord, Jun 5, 2026; 25(1):154. Doi: 10.1007/s40200-026-01964-x
2. Talari K, Goyal M. Retrospective studies - utility and caveats. J R Coll Physicians Edinb, Dec 2020; 50(4):398-402. Doi: 10.4997/JRCPE.2020.409
3. Koh MX, Simpson T, Zain SM, Ayub Q, Cheah HL, Pan Y, *et al*. Mitochondrial DNA Mutations and Epigenetic Regulation in Type 2 Diabetes Mellitus Development. Br J Biomed Sci, Nov 27, 2025; 82:15375. Doi: 10.3389/bjbs.2025.15375
4. Cicchinelli M, Primiano G, Servidei S, Ardito M, Percio A, Urbani A, *et al*. Resolving Phenotypic Variability in Mitochondrial Diseases: Preliminary Findings of a Proteomic Approach. Int J Mol Sci, Oct 5, 2024; 25(19):10731. Doi: 10.3390/ijms251910731
5. Langdahl JH, Frederiksen AL, Vissing J, Frost M, Yderstræde KB, Andersen PH. Mitochondrial mutation m.3243A>G associates with insulin resistance in non-diabetic carriers. Endocr Connect, Jul 2019; 8(7):829-837. Doi: 10.1530/EC-19-0118
6. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism, Feb 2016; 65(2):20-29. Doi: 10.1016/j.metabol.2015.10.014