Int. j. adv. multidisc. res. stud. 2026; 6(3):516-517

Received: 26-04-2026
Accepted: 06-05-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

ATP Concentration in Serum and Urine in Mitochondrial Diabetes Depends not only on the Specific Mutation, but also on Numerous other Factors

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Letter to the Editor

We read with interest the article by Maksum *et al*. on the relationship between mtDNA mutations and serum/urine ATP levels in 30 patients with mitochondrial diabetes and 30 patients with non-mitochondrial diabetes [1]. Serum ATP levels were reduced in both groups, but no significant difference was found between the groups [1]. The presence of an mtDNA mutation was associated with reduced ATP levels [1]. The study is interesting, but leaves some questions unanswered.

First, serum or urine ATP concentrations depend not only on the specific mtDNA gene defect and its heteroplasmy, but also on numerous other factors that must be included in the analysis before definitive conclusions can be drawn. Factors influencing ATP concentrations include age, sex, phenotypic severity, muscle mass, physical condition, haplotype, mtDNA copy number, mitonuclear interactions, tissue distribution of the variant, polymorphisms in nuclear genes involved in mitochondrial function, replication, and morphology, comorbidities, concomitant medication, oxygen availability, and the quality of diabetes control [2]. There is also evidence that ATP production is subject to diurnal variations [3]. Until these influencing factors are taken into account, the reported results may be unreliable.

The second point is that the patient selection criteria for ATP measurement are narrow, and there is a possibility that many patients with mitochondrial disorder (MID) were missed. Selecting patients with diabetes, maternal inheritance, neuromuscular disease, a BMI < 25, and the absence of ketoacidosis may result in numerous patients with mitochondrial diabetes, who may also carry an mtDNA variant, being excluded. Why were such narrow inclusion criteria chosen? The phenotypic spectrum of m.3243A>G carriers is much broader and can range from asymptomatic conditions to severe and fatal multisystem diseases [4]. To increase the suitability of the study, it is recommended to broaden the inclusion criteria to include patients with diabetes and multisystem diseases, which is typically seen in patients with MID. Furthermore, only 25% of mtDNA variants occur sporadically and therefore do not follow a maternal inheritance pattern. For this reason, the criterion of "maternal inheritance" can lead to non-inherited mitochondrial diseases being overlooked.

Third, it was not reported how many patients with diabetes were screened for possible mitochondrial diabetes and how many were excluded to form the cohort of 30 patients with mitochondrial diabetes [1].

Fourth, the introduction mentions that patients with and without mitochondrial dysfunction were included [1]. However, it was not specified how the mitochondrial dysfunction was detected. It can be detected clinically, immunohistologically, biochemically, or genetically. Mitochondrial dysfunction does not necessarily mean MID, as it can be secondary and not caused by a pathogenic mtDNA variant.

Finally, the sentence in the introduction, “Mitochondrial DNA is associated with a variety of diseases, including mitochondrial diseases,” is unclear [1]. What other diseases besides MIDs can be caused by mtDNA mutations? Pathogenic mtDNA variants usually occur together with symptomatic MIDs, unless they are initially asymptomatic [5].

Overall, a reduction in serum or urine ATP levels is not uncommon in carriers of pathogenic mtDNA variants; however, several other causes must be ruled out before a reduction in ATP levels can be attributed to the underlying genetic defect.

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. xx: contributed to literature search, discussion, correction, and final approval.

Acknowledgements: None.

Keywords: mtDNA, m.3243A>G, Mitochondrial Diabetes, ATP, Heteroplasmy

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