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Fibroblast Growth Factor-21 Is Not Suitable as a Biomarker for Diagnosing Mitochondrial Disorders

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In a recent article Morovat et al. claimed that elevated serum levels of fibroblast growth factor-21 (FGF21) could serve as a biomarker for the detection of mitochondrial disorders (MIDs) manifesting with myopathy [1]. We have the following comments and concerns.

In chapter 3.2 the authors mention that the diagnosis of a MID was established upon mtDNA data in 104 patients. However, in their further statements it turned out that only 89 patients had a confirmed genetic diagnosis (mtDNA point mutations, n=40, nDNA mutations, n=32), single mtDNA deletions, n=17) [1]. The discrepancy requires an explanation. How was the diagnosis established in the remaining patients?

Since FGF21 serum levels may be influenced by various modifying factors, we should be informed if follow investigations were carried out and if FGF21 serum levels changed with the progression of the disease. We should be also informed if FGF21 serum levels correlated with the severity of the MID. Furthermore, it would be interesting to know if FGF21 serum levels were elevated in asymptomatic mutation carriers.

Since drugs may potentially influence serum levels of FGF21, it should be mentioned which drugs the included patients were taking. MID patients usually take drugs for epilepsy, Parkinson's disease, arrhythmias, arterial hypertension, hormone deficiency, muscle cramps, osteoporosis, or dystonia [2]. Were there any indications that the medication these 104 patients were taking influenced the FGF21 serum levels?

Since drugs are eliminated via the kidneys or the liver, we should be informed if FGF21 serum levels increased or decreased in relation to liver or kidney functions.

Since FGF21 is mainly produced in the skeletal muscle, it would be interesting to know how many of the included patients had involvement of these organs and if affection increased or decreased serum FGF21 levels.

It is not comprehensible why the parents of the index cases were classified as non-mitochondrial. It is well established that 75 percent of the MIDs due to mtDNA point mutations are maternally inherited [3]. In how many of the index cases was the MID inherited from the mother? In how many of the included cases were the mother clinically affected?

A main disadvantage of the study is that serum FGF21 levels were not useful as a biomarker of MIDs in patients without a myopathy. Since there are a number of MIDs which do not

manifest with myopathy [4,5], FGF21 levels may not serve as a biomarker for MIDs without affection of the muscles.

Since FGF levels may increase with stress, diabetes, obesity, steatosis hepatitis, or metabolic syndrome [1], it would be interesting to know if MIDs associated with any of these conditions had higher FGF21 levels than MID patients without these abnormalities. Were MID patients with these conditions excluded from the study?

Overall, this interesting study could be more meaningful if the points raised above were carefully addressed. The best biomarkers suggesting a MID are still the individual and family history and the phenotype.

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Both authors contributed equally.

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