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Evidence level for effectiveness of glucagon-like peptide-1 receptor agonists respectively sodium glucose co-transporter-2 inhibitors for mitochondrial diabetes is low

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1 LETTER TO THE EDITOR

We read with interest the article by Yeung et al. about three patients with a multisystem mitochondrial disorder (MID) due to the variant m.3243A>G with heteroplasmy rates (HPRs) of 60% (patient-1), 30% (patient-2), and 10% (patient-3) in blood lymphocytes respectively who were successfully treated for mitochondrial diabetes (MTDM) with the glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide (patient-1) respectively the sodium glucose co-transporter-2 inhibitor (SGLT-2i) empaglifozin (patient-2, patient-3) [1]. The authors concluded from this case series that providers should be encouraged to prioritise GLP-1 RA respectively SGLT-2i for the treatment of MTDM [1]. We have the following comments and concerns.

From three cases it is not justified to encourage providers to prioritise GLP-1 RA respectively SGLT-2i for the treatment of MTDM. Only one patient received a GLP-1 RA and only two patients received a SGLT-2i. Currently, it is unknown if these compounds exhibit any long-term side effects in MID patients, if their effect depends on haplotypes, HPRs, mtDNA copy number, or if these compounds are mitochondrion-toxic. The authors contradict oneself when stating on the other hand that the effect of GLP-1 RA and SGLT-2i on MTDM has yet to be fully explored.

Since a number of MIDs goes along with vomiting, poor appetite, nausea, dysphagia, gastroparesis, gastro-intestinal pseudoobstruction, diarrhoea, or constipation consecutively reducing appetite and thus body weight [2], since GLP-1 RA cause transient vomiting, nausea, or diarrhoea in 50% of the non-MID patients receiving these drugs, and since GLP-1 RA reduce appetite as well [3], these compounds should not be applied in MID patients with gastro-intestinal involvement and low body weight.

Gastro-intestinal involvement has not only been reported in patients with MIDD, MELAS, MERRF, KSS, MNGIE, PS and CPEO, but also in Leigh syndrome, various mtDNA depletion syndromes, PCH, and particularly in non-syndromic MIDs [2].

We do not agree with the proposal to treat MTDM with metformin. Metformin is a biguanide with lactic acidosis as one of the side effects. Since many of the MIDs go along with transient or permanent lactic acidosis [4], application of metformin may either trigger the occurrence of lactic acidosis or may worsen lactic acidosis in MIDs with already known elevated serum lactate. Thus, metformin should not be given in MID patients with known elevated serum or CSF lactate or to MID patients with a syndrome known to manifest with lactic acidosis.

We do not agree with the statement that evidence is lacking for the effectiveness of supplementary therapy in MIDs [1]. From idebenone it is well-known that it is beneficial to many patients with LHON. From coenzyme-Q it is known that it is highly effective in primary coenzyme-Q deficiency. Thiamine and biotin are highly effective in patients carrying *SLC19A3* variants. Enzyme replacement therapy can be beneficial to MNGIE patients.

MID patients may not only present with growth hormone deficiency leading to short stature since childhood, but with hypopituitarism with reduced TSH, ACTH, LH, FSH, or

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oxytocin production. The empty sella syndrome can be frequently found in MID patients and indicates hypotrophy of the pituitary gland. Hypoaldosteronism is also a frequent endocrine manifestation of MIDs. Since MIDs are associated with an increased risk of developing neoplasms [5], one should keep in mind that hormone producing tumours may occur in MID patients.

Missing in the report is the medication the three patients were receiving in addition to the anti-diabetic regimen. Knowing the entire current medication is crucial for assessing if any drug interactions occurred.

In conclusion, the interesting case series has a number of shortcomings, which need to be addressed before drawing conclusion as those provided. Randomised controlled trials are required to assess the effects and side effects of GLP-1 RA and SGLT-2i in MTDM patients and long-term, observational studies are required to assess the long-term effect of these compounds.

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