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Consider Sitagliptin for Worsening Heart Failure in m.3243A>G Related Dilated Cardiomyopathy

Josef Finsterer
MD, PhD, Neurology & Neurophysiology Center, Vienna, Austria, ORCID: 0000-0003-2839-7305

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LETTER TO THE EDITOR

We read with interest the article by Hiruma, *et al*., about a 64-year-old female with maternally inherited diabetes and deafness (MIDD) due to the variant m.3243A>G [Hiruma, T. *et al*., 2023]. The patient underwent a transcatheter edge-to-edge repair with the MitraClip system using two devices in the middle segment of the anterior and posterior leaflets for mitral regurgitation and severe heart failure (EF 29%) and contraindications to surgery [Hiruma, T. *et al*., 2023]. The intervention reduced mitral regurgitation without any cardiovascular events during a 2-year follow-up, but EF decreased to 26% [Hiruma, T. *et al*., 2023]. The work is compelling, but some points should be discussed.

We disagree with the diagnosis of MIDD [Hiruma, T. *et al*., 2023]. MIDD is characterised by diabetes and deafness alone, but the index patient also suffered from dilated cardiomyopathy, renal insufficiency, hepatopathy, and presumably short stature (BMI: 15.6kg/m2). Therefore, the diagnosis should be changed to MIDD plus or non-syndromic mitochondrial disorder. MIDD plus is common and can occasionally be associated with dilated cardiomyopathy or heart failure [Seiler, F. *et al*., 2023]. In addition to diabetes, hypoacusis, and cardiomyopathy, the index patient presented also with hepatopathy (elevated transaminases), renal insufficiency, and short stature. Prospective instrumental studies are required to evaluate the patient for subclinical involvement of the brain, endocrine organs, and eyes, Serum and cerebrospinal fluid lactate should be measured. In this context, the HbA1c value at admission is also missing to assess whether the diabetes was well controlled and whether the renal failure was due to diabetic nephropathy or a true phenotypic manifestation of the mutation. Kidney involvement is common in m.3243A>G carriers [Di Toro, A. *et al*., 2022]. It should also be clarified whether elevated liver transaminases were due to liver congestion due to right heart failure, to muscle involvement, or to the mutation.

A second point to discuss is that heteroplasmy rates of the m.3243A>G variant have not been reported in any of the clinically affected tissues (e.g. myocardium). Knowledge of mutational load is crucial as it can determine disease progression and is essential for genetic counselling. There is also no mention whether the mtDNA copy number was normal or reduced and which haplotype the patient belonged to.

The third point to discuss is that sitagliptin has not been considered a cause of heart failure. Sitagliptin has been found to increase the risk of congestive heart failure, particularly at high doses or in renal failure, as in the index case, [Muanda, F. T. *et al*., 2020]. A meta-analysis reported that DPP-4 inhibitors generally cause sympathetic activation as a class effect and therefore increase the risk of heart failure [Sano, M, 2019].

It should also be explained what was the rationale for administering taurine in such a high dose. The standard daily dose is 1000mg/d.

Overall, the study has limitations which challenge the results' interpretation. Addressing these limitations could further strengthen and reinforce the statement of the study. Although transcatheter edge-to-edge repair with the MitraClip system seems to be a viable approach to treating mitral valve regurgitation, the underlying cause of mitral insufficiency, left ventricular heart failure, should also be optimally treated. This includes discontinuing any regularly administered medications that could potentially worsen heart failure.

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Ethical Compliance Statement: The authors confirm that the approval of an institutional review board or patient consent was not required for this work. We confirm that we have read the Journal's

***Corresponding Author:** Josef Finsterer

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position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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