



Direct Healthcare Professional Communication

Aug 2025

Metformin- risk of lactic acidosis exacerbation and neurologic complications in patients with mitochondrial diseases as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome & Maternal inherited diabetes and deafness (MIDD)

Dear Healthcare Professional,

MAH, in agreement with the General Administration for Pharmaceutical Vigilance of the Central Administration for Pharmaceutical Care at The Egyptian Drug Authority, would like to inform you of the following:

Summary:

- Metformin is not recommended in patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD) due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.
 - In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.
 - Prior to initiating metformin, clinicians should meticulously inquire about a family history of diabetes, deafness, neurological disorders, or other symptoms suggestive of mitochondrial disease.
 - Maintain a high index of suspicion for mitochondrial disease in patients presenting with atypical diabetes (e.g., lean patients, early-onset diabetes with sensorineural hearing loss, or a family history of maternally inherited diabetes).
 - For the management of diabetes in these patients, alternative glucose-lowering agents that do not interfere with mitochondrial function should be considered and prioritized.
 - Careful patient evaluation and consideration of these risks are paramount to ensure patient safety and prevent severe adverse outcomes in this specific patient population.
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Background

Treatment of type 2 diabetes mellitus, particularly in overweight patients when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Metformin may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure

Metformin use in patients with MELAS syndrome or MIDD, both mitochondrial diseases, is generally discouraged due to the risk of exacerbating lactic acidosis and triggering neurological complications. These conditions, particularly MELAS, can manifest with stroke-like episodes and lactic acidosis, which can be worsened by metformin's mechanism of inhibiting mitochondrial function

Metformin's primary mechanism of action involves inhibiting mitochondrial respiration, specifically complex I of the electron transport chain in hepatocytes.

This effect can lead to increased lactate production (lactic acidosis) and potentially exacerbate mitochondrial dysfunction in individuals with pre-existing mitochondrial diseases like MELAS and MIDD.

While some studies have explored the potential use of metformin in MELAS and MIDD, the general consensus is to avoid it due to the high risk of adverse effects, according to the European Medicines Agency.

A new warning will be added to the local SMPCs concerning this risk

Overview of MELAS and MIDD

MELAS Syndrome (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes):

- MELAS is a mitochondrial disorder characterized by stroke-like episodes, lactic acidosis, and encephalopathy.
- It is often caused by a specific mutation in mitochondrial DNA (mtDNA), most commonly the m.3243A>G mutation.
- Metformin, a common diabetes medication, is known to inhibit mitochondrial function and can potentially trigger or worsen stroke-like episodes in individuals with MELAS

MIDD (Maternally Inherited Diabetes and Deafness):

- MIDD is another mitochondrial disorder that presents with diabetes and sensorineural hearing loss.
 - Like MELAS, MIDD is also frequently associated with the m.3243A>G mutation in mtDNA.
 - Metformin is generally avoided in MIDD patients due to the risk of lactic acidosis and potential for neurological complications.
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Reference

EMA: https://www.ema.europa.eu/en/documents/psusa/metformin-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable-implementation-psusa-00002001-202404_en.pdf

Call for reporting

Healthcare professionals are asked to report any suspected adverse reactions via the Egyptian reporting system:

Name: General Administration for Pharmaceutical Vigilance

Email: pv.followup@edaegypt.gov.eg

Online reporting: : <https://vigiflow-eforms.who-umc.org/eg/med>

QR Code:

Hotline: 15301

