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LETTER

Metformin's Enigma: Bridging Gaps in Research on Potential Benefits & Associated Risks - A Critical Plea for Comprehensive Investigation [Letter]

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Dear editor

Metformin, an extensively prescribed anti-hyperglycaemic and insulin sensitizing agent for T2DM, remains the first-choice medication for approximately 150 million people as of 2022.[1] Its usage extends beyond type 2 diabetes to prediabetes, insulin resistance, and PCOS, owing to its off-patent status, affordability, and compatibility with nearly all other diabetic medications.

However, its significance extends far beyond these attributes; it stands as a pharmaceutical marvel that has surpassed its initial purpose as a hypoglycaemic agent. Its putative benefits are manifold, encompassing the potential to mitigate aging, prolong lifespan, cardio protection, neuroprotection, inhibit cancer cell growth, and potentially guard against bacterial, viral, and malarial infections.[1] Yet, every pill has its pitfalls. The predominant side effects are dose-dependent, and GI related (including nausea, vomiting, bloating, and diarrhoea), as a consequence of which the patient compliance is strikingly deficient, falling well below expectations, estimated at just 5%[2]. According to a retrospective cohort study done in 2020, about one-third of patients initiating metformin discontinued within 12 months while less than half of all patients were adherent to the drug. GI intolerance and poor adherence are significant factors in the discontinuation of pharmacotherapy.[3] Chronic use of metformin has also been linked to vitamin B12 deficiency, with the prevalence rate varying between 6% to 50%.[4] Elevated metformin levels in individuals with reduced kidney or liver function, severe infection, or hypoperfusion can lead to metformin-associated lactic acidosis (MALA), a potentially fatal condition.[5] Concerns over reproductive health in males have also been raised due to preconception paternal metformin treatment, which is linked to increased rates of major birth defects, particularly genital defects in boys.[6] A study conducted in 2019 revealed that metformin leads to oxidative stress and two-generation endocrine disruption in O. Latipes (fish) which may have implications for humans as well.[7]

The discourse surrounding repurposing metformin remains ambiguous, especially when its mechanism is still debated, necessitating the need for rigorous clinical trials to ensure safety and tolerability.

While its effectiveness in T2DM management is well-documented, novel formulations should be explored to minimize gastrointestinal side effects and enhance therapeutic[1] adherence, such as extended-release formulations or combination therapies. Additionally, educating patients on medication adherence and strategies to manage gastrointestinal side effects can improve compliance. Interventions aimed at enhancing adherence to metformin therapy should be prioritized due to its critical role in optimizing therapeutic outcomes. Comprehensive research into metformin's pharmacological profile could reveal groundbreaking insights, potentially transforming medical practice.

Disclosure

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