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RESPONSE TO LETTER

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

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Dear editor

We would like to thank the authors for showing interest in our article and appreciate the comments from Faiqa Iqbal, Zoha Haroon, Qirat Qasim from Zoha Haroon Shaheed Mohtarma Benazir Bhutto Medical College, Lyari, Karachi, Pakistan for our article titled " Metformin: A review of potential mechanism and therapeutic utility beyond diabetes".[1]

Our article was an attempt to extensively review and put together the existing evidence on the utility of metformin other than its most common use in diabetes.[1] The authors have rightly concorded with the pleiotropic effects of metformin mentioned in our review and have mentioned a few general adverse events associated with chronic use of metformin.

Concerning the first query, we agree with the fact that metformin is associated with low adherence rates as rightly mentioned in the literature.[2–4] The issue of adherence to antidiabetic medications or by enlarging any therapy for chronic diseases has always been a matter in question.[5] However, the literature reveals that using low-dose metformin and extended-release dosage forms has been found to improve adherence and decrease rates of discontinuation.[6] Therefore, using extended-release formulations can be a reasonable solution at present. Yet, trials need to be conducted to develop novel formulations of metformin with better tolerability to improve the compliance of patients in the long run.

Regarding the second observation with "chronic use of metformin has also been linked to vitamin B12 deficiency, with the prevalence rate varying between 6% to 50%", the research has indicated a correlation between metformin use and low levels of vitamin B12 in patients with diabetes mellitus type 2. The most widely acknowledged mechanism of metformin's influence on vitamin B12 level relates to the absorption process, wherein metformin interferes with the binding of the calcium-dependent Intrinsic Factor-vitamin B12 complex to the ileal cubilin receptor and antagonizes the calcium cation leading to reduced absorption. A higher dose of metformin prescribed for a prolonged period is the most common risk factor for B12 deficiency. Furthermore, there was a positive correlation between the risk of vitamin B12 insufficiency in diabetic patients taking metformin and male gender, chronic conditions such as type 2 diabetes itself, hyperlipidemia, coronary artery disease, polycystic ovarian disease (PCOD), and obesity.[7]

Therefore, it is advisable to check serum vitamin B12 levels in patients being treated with metformin who have symptoms suggestive of vitamin B12 deficiency along with periodic monitoring for patients with risk factors for vitamin B12 deficiency and should be given vitamin B12 supplementation.

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Concerning to the third observation regarding "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" it is noted that it is an uncommon but serious side effect of taking metformin. The primary causes of lactic acidosis are either excessive blood lactate generation or insufficient utilization of lactate by the liver. There are two forms of lactic acidosis: type A and B. Type A is typically associated with tissue hypoxia or global hypoperfusion, which can be observed in the presence of elevated anaerobic activity or circulatory collapse.[8] When there is no tissue hypoperfusion, type B lactic acidosis arises from a variety of causes, such as drug overuse like metformin, liver failure, cancer, and rare inherited enzyme defects.[8]

It is difficult to ascertain the actual prevalence of MALA since it encompasses a wide range of conditions, from acute metformin overdose in the absence of additional causative pathologies to accidental metformin use in patients who are severely ill. Furthermore, there is a weak association between pH, lactate, and metformin levels in the data, which raises questions about the diagnostic precision and causation of linking metformin overdose to metabolic acidosis and hyperlactatemia.[9–11] Due to the temporal nature of many MALA presentations, it's possible that metformin concentrations will not be determined until after corrective measures have improved lactate and acid-base indices, which will result in a poor association.[11] According to earlier research, there are 1 to 9 instances of MALA for every 100,000 individuals.[12]

Many conditions now precluding the use of metformin include liver disease, heart failure, age over 65, lung illness, use of intravenous contrast agents within 48 hours, and chronic renal disease (creatinine levels >1.5 mg/dL in men and >1.4 mg/dL in women).[11] Metformin uses carefully, taking into account contraindications might further reduce the incidence of MALA. However, these aspects have been briefly described in the introduction section of our published article.

The effect of metformin on preconceptional administration has been briefly explained in the "Metformin as an Endocrine Disruptor" section in our article and it states the effect of metformin on the male offspring which was associated with an increased risk of genital birth defects.[12] Similar effects were also observed in the preclinical studies where, as a result of metformin exposure with its probable endocrine disrupter activity to male fish from early to adult life stages, a decrease in fertility, decrease in overall size, and increase in intersex fishes were reported.[13–15] The above finding of metformin on males is based on an isolated cohort study and further large studies with long follow-ups need to be conducted in order to establish the definite causality.

Our review was mainly aimed at the diverse therapeutic utility and pleiotropic effects of metformin in depth in order to spark novel areas of research for its further usage in varied therapeutic domains. The analysis of adverse event was not the primary focus of the review because metformin is an age-old drug with extensive usage and established safety profile. However, we did mention the common and expected adverse events associated with it. The limitations of the therapy of metformin can be addressed by undertaking large clinical trials with longer follow-up and development of novel formulations with minimal adverse effects. Even though metformin has few shortcomings, yet taking note of the beneficial effects it exerts, the drug is a boon for a diverse patient population at large.

Disclosure

The authors report no conflicts of interest in this communication.

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