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COMMENTARY

Metformin Revisited

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The explosive increase in the prevalence of type 2 diabetes (T2D) in recent decades has been paralleled by an almost equally dramatic increase in the number of therapeutic agents available for treating this condition. However, in spite of the development of several new classes of antidiabetes agents in recent years, metformin remains the first-line pharmacotherapeutic option for most cases of T2D, as per most national and international guidelines.[1,2] It also finds use as an adjunct to insulin in gestational diabetes and diabetes complicating pregnancy.

In spite of wide clinical experience stretching back to the 1950s, the exact mechanism of action of biguanides in general (and metformin in particular) remains an enigma. It has been suggested that the drug ameliorates insulin resistance at the liver and to a lesser extent the skeletal muscle by interfering with the fuel-sensing mechanism of the cell, mediated by the enzyme cyclic adenosine monophosphate kinase.[3] Recent studies indicate that metformin noncompetitively inhibits the mitochondrial isoform of glycerophosphate dehydrogenase, leading to an alteration in the hepatocellular redox potential and, ultimately, a reduction in hepatic gluconeogenesis.[4]

Notwithstanding the uncertainty regarding its exact mode of action, there is international agreement that metformin is an extremely efficacious antidiabetes agent, with most studies reporting a reduction in glycated hemoglobin level of between 1% and 2% when this agent is used as monotherapy.[5] Metformin also has salutary effects on several other metabolic parameters, with studies reporting significant improvements in lipid profile, endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, and fat redistribution.[6] These pleiotropic effects of metformin most likely underlie its role in the reduction of risk of atherosclerotic cardiovascular disease. There has also been considerable interest in its antitumor effect, although the heterogeneity of cancer types and populations studied and the presence of comorbidities make it difficult to come to conclusions regarding its benefits in this respect.[7]

In this issue of *Diabetes Technology & Therapeutics*, Fan et al.[8] report on another fascinating aspect of metformin's action—its ability to inhibit the expression of fibroblast growth factor (FGF)-21 in patients with newly diagnosed T2D. FGF-21 belongs to the ''endocrine'' subfamily of FGFs, which lack a heparin-binding site and can be released freely into the circulation, thereby serving as markers of various disease processes. Earlier studies have shown increased levels of FGF-21 in patients with T2D, although whether this is a cause or consequence of diabetes remains to be elucidated.[9] As FGF-21 seems to work additively with insulin in increasing glucose uptake in adipocytes, the elevated levels of this protein seen in diabetes may represent compensation in the face of high levels of insulin resistance.[10] Levels of FGF-21 have also been shown to be elevated in other insulin-resistant states such as nonalcoholic fatty liver disease and are positively correlated with body mass index. Although it has not been shown whether the elevated levels of FGF-21 in diabetes are by themselves deleterious, novel therapeutic agents working as FGF-21-mimetics have shown promising metabolic benefits.[11]

In their study, Fan et al.[8] compared FGF-21 levels at baseline in 74 individuals with newly diagnosed T2D and 100 age- and sex-matched controls and assessed the effect of metformin monotherapy on FGF-21 levels in the former group after 12 weeks of therapy. Metformin, as expected, had significant beneficial effects on metabolic parameters such as blood glucose, hemoglobin A1c, and blood lipids, anthropometric indices such as weight, body mass index, and waist circumference, and inflammatory markers such as high-sensitivity C-reactive protein. Additionally, there was a significant reduction in FGF-21 levels after 12 weeks of treatment with metformin.

As discussed by the authors, the effect of metformin on FGF-21 in their study[8] is diametrically opposite to that reported in an earlier study, where metformin caused a dose-dependent increase in FGF-21 expression in rat and human hepatocytes.[12] The conclusion of the earlier study was that, as FGF-21 has been shown to normalize blood glucose levels in animal models of diabetes, part of the antidiabetes effect of metformin could be explained by its induction of FGF-21 expression in the liver. In the present study,[8] the direct effects of metformin of FGF-21 expression were perhaps overridden by its effects on ameliorating insulin resistance, thereby causing a fall in the compensatory high levels of FGF-21. It would be interesting to assess the effect of metformin on FGF-21 in those individuals who failed to show metabolic benefits with the drug, although a much larger sample size would admittedly be required in order to tease out such a subgroup. Although the reduction in FGF-21 levels was

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accompanied by a simultaneous amelioration of deranged glucose–lipid parameters, it is perhaps premature to conclude that lowering of FGF-21 levels can result in improvement of metabolic parameters; larger studies are required to test this hypothesis as well. This is all the more so in the context of beneficial effects attributed to FGF-21 in earlier studies.[10]

It is also interesting to note that the lowering of FGF-21 levels in the present study was more strongly correlated to reductions in glucose parameters than other metabolic indices. Other antidiabetes medications like glinides and thiazolidinediones (glitazones) have also been associated with lowering of FGF-21 levels, suggesting that a common pathway centered on correction of insulin resistance and hyperglycemia may be the causative mechanism. It is not clear why only 74 of the 226 T2D patients initially recruited into the study received metformin. It would be worthwhile assessing the changes in FGF-21 levels in those individuals with newly diagnosed T2D who were, for some reason, not prescribed metformin; this would help in elucidating whether the reduction in FGF-21 levels occurred as a result of glucose level lowering per se, or as part of a unique action of metformin. Although the levels of C-reactive protein were also decreased concordant with reduction of FGF-21 levels, no conclusion can be drawn from the data on whether FGF-21 actually alleviated inflammation; further studies are clearly needed in this area. It is also not clear what concomitant drugs (e.g., statins) were given to these 76 patients, as these could also have influenced FGF-21 and high-sensitivity C-reactive protein levels.

As reiterated by the authors,[8] a great deal remains to be learned about FGF-21. It is not known what its exact biological role is and what, if any, role it plays in the metabolic derangements leading to T2D. It is also not known whether persistently high levels of FGF-21 are associated with any deleterious effects with respect to long-term complications of T2D; however, until such data are available, the effect of metformin on lowering FGF-21 levels in T2D can be considered to represent yet another arrow in its already overflowing quiver of antidiabetes effects.

Author Disclosure Statement

No competing financial interests exist.

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