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RESPONSE TO LETTER

Response to Comment to the Article "Are There Differences in Gut Microbiome in Patients with Type 2 Diabetes Treated by Metformin or Metformin and Insulin?" [Response To Letter]

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Dear editor

Various patients with type 2 diabetes mellitus (T2DM) need alternative types of treatments. The mainstream strategy for T2DM treatment mainly includes the administration of oral hypoglycemic drugs and/or injectable agents like insulin secretagogues. In our research we investigated head-to-head gut microbiome in the T2DM patients with long duration of treatment by the most traditional type – metformin group or metformin+insulin group. Adding next oral hypoglycemic agents or insulin is intended to delay diabetic complications and improve outcomes. Study has revealed low richness and diversity of gut microbiota in those with long treatment with metformin or metformin+insulin with no differences between groups.

We have read the letter by Panjaitan et al regarding our article with interest and appreciate the criticisms and comments expressed. The letter brings the opportunity to further discuss the merits and limitations of our study. We respond to some doubts and questions. Moreover this leads us to propose international studies with a carefully selected group in the field of patients and drugs used so far and extending them to further hypoglycemic agents and various types of insulin in the area of gut microbiota investigation.

In response to Panjaitan et al, the aim of our study was to compare gut microbiome in type 2 diabetes mellitus (T2DM) patients using the most traditional strategy of treatment for the disease (metformin or metformin+insulin) for a long time (treatment duration 5–10 years).[1] The gut microbiome is mutable over time, depending on the health and disease, environment, diet and lifestyle, and, in those with disease, the used strategy of treatment (agents).[2]

In the meantime the novel therapeutic strategies for T2DM have been blooming, such as injectable drugs: glucagon-like peptide-1 (GLP-1) receptor agonists and/or oral hypoglycemic agents: sodium-dependent glucose transporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. Still, we have also "old" antidiabetic drugs such as sulfonylureas, thiazolidinediones, and α-glucosidase inhibitors. In the introduction of our manuscript we mentioned pharmacomicrobiomics – the branch of medicine that investigates the interactions between the microbiome and drugs.[3] All oral hypoglycemic agents and novel-like insulin secretagogues through different pathomechanisms may influence the gut microbiome – summarized in Table 1. Thus, we focused only on the metformin and metformin+insulin model of treatment. The investigation was carried out as a head-to-head study with comparison of two different types of treatment. We did not find any significant difference in the gut microbiome between the studied groups, neither in richness nor in diversity. At present, as we stated in the limitation of the study, due to the small number of patients, we cannot perform multiple regression analysis and answer why and how there were no differences of insulin influence on gut microbiome.[4]

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Table 1 Pathomechanisms Which through Oral Hypoglycemic Agents, Insulin and Novel-like Insulin Secretagouges Have Influence on the Gut Microbiome[4,5]

Agents Used to Treat Diabetes	Pathomechanism Which Influences Gut Microbiome
Biguanides (Metformin)	Improves gut energy metabolism. Increases the production of short-chain fatty acids. Regulates bile acid metabolism. Decreases intestinal inflammation through reduction in lipids absorption and lipopolysaccharides production. Regulates metabolism of metalloproteins or metal transporters.
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Decreases intestinal inflammation through reduction of Toll-like receptor ligands and cytokine expression. Exerts immunomodulatory effects. Increases the production of short-chain fatty acids.
Sodium-dependent glucose transporter-2 (SGLT-2) inhibitors	Increases the production of short-chain fatty acids.
Thiazolidinediones	Improves gut energy metabolism. Decreases intestinal inflammation by the influence on the expression of immune gene markers.
Sulfonylureas	Potential effect on gut energy metabolism.
α-Glucosidase inhibitors	Increases the production of short-chain fatty acids. Regulates bile acid metabolism. Inhibits microbial α-glucosidases.
Glucagon-like peptide-1 (GLP-1) receptor agonists	Improves gut energy metabolism. Increases the production of short-chain fatty acids.
Insulin	Improves gut energy metabolism.

In addition, we did not distinguish the type of insulin: long-acting, intermediate, short-acting, rapid-acting, mixed. Yet, it opens up new possibilities for further studies of the gut microbiome.

Moreover we did not extend our study to the other T2DM treatment models, neither administered as oral hypoglycemic drugs nor as injectable agents like insulin secretagogues. It brings the opportunity to design novel models of the investigation by international teams.

Furthermore, we did not investigate the management of lifestyle and diet as these areas were unfortunately poorly documented and quantitated in the clinical data for that long time. Hopefully, study of the relationship between the age, sex, anthropometric measurements, comorbidities, diet, lifestyle and different administered antidiabetic drugs may be performed as multi-arm multi-stage clinical trial in the international group in the future.

Actually, all these T2DM patients must be managed using the established methods.

Author Contributions

SDG and MMW went through the discussion letter and analyzed the data. SDG designed, answered, and wrote the original letter draft. EF, MP, and AW recommended required corrections, AW produced Table 1, and SDG and MMW carried out necessary revision for improvement of the manuscript accordingly.

Disclosure

The authors report no conflict of interest regarding this communication.

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