Submission of Revised Manuscript No. 46593 (Crosstalk between gut microbiota and anti-diabetic drug action) for publication in World Journal of Diabetes.

We thank the reviewers for their comments and the Editorial Board for the decision to revise our manuscript entitled “Crosstalk between gut microbiota and anti-diabetic drug action”. We are pleased to submit the revised version according to the reviewer and editor suggestions that we believe have improved our manuscript.

The authors are very appreciated for reviewer’s comments about the article. The manuscript was corrected as appropriate. All changes are highlighted.

This manuscript has been read and approved by all contributing authors. All the authors declare that there are no financial or other relationships that might lead to a conflict of interest.
We are looking forward to hearing from you at your earliest possible convenience and hope that the revised manuscript is now acceptable for publication in “World Journal of Diabetes”.

Yours sincerely,
Dr Nazarii Kobyliak

Nevertheless, the increase of intestinal Firmicutes/Bacteroidetes ratio are observed in both obesity and energy-rich diets in humans and animal models [5,9,10]. ……..The bacterial phylotypes found to be correlated with weight and were associated with phyla Firmicutes (two families and 11 genera), Bacteroidetes (one family and two genera) and Tenericutes (one family and one genus) [3,13]. Among them five genera affiliated with an increase in weight which were *Erysipelotrichaceae Incertae Sedis, Marvinbryantia, Roseburia, Candidatus Arthromitus, and Parabacteroides* [3,13]. The phylotypes associated with a weight loss were the genera *Lactobacillus, Turicibacter, Anaerostipes, Coprococcus, Blautia, Oscillibacter and Clostridium* [3,13]. ……

…….Moreover, T2D patient treated with metformin can improve the lipid levels, which contributes to the reduction of chronic micro- and macrovascular complications. Most of metformin pleiotropic effects predetermined by adenosine monophosphate–activated protein kinase (AMPK) activation in the skeletal muscle and the liver [29].

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The number of positive connections among microbial genera, especially those within Proteobacteria and Firmicutes, increased after 2 months of metformin treatment [33]. Than after 4 months of treatment with metformin significantly larger increases in fecal concentrations of lactate and a trend toward a larger increase in fecal concentrations of succinate were revealed [33].

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The prominent mechanisms for this cardiovascular protective function are only partially understood, but they can be attributed to the ability of acarbose to neutralize oxidative stress by increasing H2 production in the GI tract [38,41]. …… Zhang *et al* [38] compared treatment for T2D with acarbose and metformin and showed that both treatments notably increased GLP-1 concentration and decreased glucagon after 24 weeks.

Acarbose is effective in lowering blood glucose level in patients with T2D by delaying the digestion of complex carbohydrates through the inhibition of pancreatic α-amylase and a variety of α-glucosides [38].

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GLP-1 after release can affect afferent neurons innervating the gastrointestinal tract which signal to the caudal brainstem or enteric neurons, and/or they can enter the circulation to functionate centrally, or on peripheral targets, to regulate metabolic disorders [60,64].

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GUT MICROBIOTA AS A TREATMENT OPTION FOR T2D: FUTURE PERSPECTIVES

Over the past 10 years, an increasing body of literature has suggested that gut microbiota play a crucial role in the host immune system, modulation of inflammatory processes, extraction of energy from the host diet and alterations of human gene expression and considered to make an important impact on obesity/IR development. Several mechanisms that contribute to explaining the link between altered gut microbiota and pathogenesis of IR are described [7]. They control the fermentation and absorption of dietary polysaccharides to produce SCFA, which may explain their importance in the regulation of fat accumulation. SCFA can stimulate the secretion of GLP-1 and GLP-2, thus increasing insulin and adiponectin expression, might contribute to the enhanced insulin sensitivity, and pancreatic ß-cells proliferation [104,105]. Another mechanism by which the microbiome may contribute to IR is compromised gut barrier function with an increased intestinal permeability, accumulation of LPS and metabolic endotoxemia development of [106].

Lactobacillus and *Bifidobacterium* are commonly used as probiotics and most studied strains in the treatment and prevention of obesity-associated disorders [15]. Moreover, several potential bacterial candidates, such as *Saccharomyces cerevisiae var. boulardii, Parabacteroides goldsteinii, Enterobacter halii* or *Akkermansia muciniphila*, have been identified and innovative mechanisms of action overriding their beneficial effects for IR/obesity have been elucidated [107,108].

The abundance of *Akkermansia muciniphila*, which is a mucin-degrading bacterium that resides in the mucus layer, decreased in obese/T2D and inversely correlates with body weight in both rodents and humans [34]. Metformin treatment [35,36], consumption of oligofructose [109], dietary concord grape polyphenols [110], gastric bypass surgery in humans [111] and mice [112] leads to a marked increase in *A. muciniphila* abundance with

subsequent weight loss and reversed metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and IR [34].

F. prausnitzii plays an important role in preserving the gut barrier and controlling inflammation and T2D progression [113]. A traditional Chinese berberine-containing herbal formula given to T2D patients [113,114] changed the gut microbiota by increasing *F. prausnitzii*, which was negatively correlated with fasting blood glucose, HbA1c and postprandial blood glucose levels, and positively correlated with homoeostasis model assessment of beta-cell function (HOMA-B).

Parabacteroides goldsteinii, a commensal bacterium whose level was reduced in HFD-fed mice. Oral treatment of HFD-fed mice with live *P. goldsteinii* reduced obesity and was associated with increased adipose tissue thermogenesis, enhanced intestinal integrity and reduced levels of inflammation and insulin resistance [107].

Identifying the most important microbiota-related metabolic pathways could lead to the development of integrated strategies using new prebiotics or beneficial bacterial strains to prevent and treat these metabolic disorders in the near future [113].

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