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LETTER TO THE EDITOR

Response to 'comment on "associations of statin use with glycemic traits and incident type 2 diabetes"'

We welcome the comments on our article "Associations of statin use with glycemic traits and incident type 2 diabetes[1]" by Sansome DJ et al, which express the importance of bile acid (BA) as an important metabolic regulator in the association of statins and glycaemic control in type 2 diabetes (T2D).

As such, the authors highlighted the potential interactions of statins particularly at high doses in combination with glucose-lowering therapy, namely, metformin, which leads to impaired glycaemic control in patients with T2D. The effect of statins on regulating BA homoeostasis in patients with T2D has been shown by several studies.[2] It has been known that BA sequestrants may also reduce serum glucose in patients with T2D.[3] A recent meta-analysis of randomized controlled trials (RCT) suggests that BA intake substantially improves HbA1c and fasting glucose levels.[4]

In our study, we investigated the association of statin use in two ways, first cross-sectionally with glycaemic traits and second longitudinally with incident T2D, both among the general population, therefore free of diabetes at the time of statin use. As we described in the methods section of our manuscript, during follow-up, we classified each participant into current use, past use and never use of statins based on incident dates of T2D. From the date of baseline centre visit and during follow-up, prevalent and incident T2D cases were defined as a fasting serum glucose concentration of ≥7.0 mmol/L or the use of glucose-lowering medications. We excluded all prevalent T2D cases at baseline (n = 1165), and only individuals with available data on statin use and baseline glycaemic values (n = 9535) were included. Moreover, in a sensitivity analysis, we examined the association between statins and risk of incident T2D only in a subset of individuals (n = 6787) with normal baseline fasting glucose concentrations (<6.1 mmol/L) by excluding cases of impaired fasting glucose or prediabetes (n = 2748). Most importantly, to decrease the effect of reverse causality on our findings, we further investigated the association of cumulative statin use with incident T2D until one year before the onset of diabetes, where the results still showed significant associations. Therefore, the design of our study did not allow any possibility of including patients with diabetes before starting statins. This design per se does not allow using glucose-lowering medications either. Hence, there was no concurrent use of statins and metformin in our study population.

Theoretically, there are some potential underlying mechanisms for the effect of statins in a population free of diabetes as we highlighted the most important ones in our manuscript. We endorse other potential underlying mechanisms as we have recently provided evidence of DNA methylation as a possible mediator in the association of statin use and T2D.[5] Statins are widely prescribed to prevent cardiovascular diseases. However, yet there is no reliable biomarker to predict the diabetogenic effect on vulnerable patients. Complementary to genome-based studies, serum biomarkers discovery is an emerging technology platform that offers the next level of information needed to extend our pathophysiological insight into medication response to treatment. Since genes, RNAs and proteins converge onto the terminal downstream metabolome, metabolomics offers a rich source of information in a complex and convoluted presentation. The causal paths between different types, duration and dosages of statins, metabolites and incident T2D remain unclear, though the effect of statins on metabolites could also be explained by the altered gut microbiome. A shred of recent evidence suggests that the modulation of the gut microbiome by statins could partly explain the response to this medication.[6]

In conclusion, we believe that further efforts should disentangle the molecular effects of statin therapy on multiple metabolic pathways. Metabolomics together with multi-omics data, for example, gut microbiome, might provide new insights into statins mechanism of action and development of diabetogenic effects in the general population.

COMPETING INTERESTS

Fariba Ahmadizar and Bruno H. Stricker have no conflicts of interest directly relevant to the content of this response.

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