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Editorial

Microvascular and macrovascular effects of liraglutide

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Current management of type-2 diabetes (T2DM) has significantly changed with the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), since such therapeutic approaches have shown over the years a number of important extra-glycemic effects, covering the cardiometabolic risk of T2DM patients [1]. Liraglutide is the first GLP-1RA that showed cardiovascular benefit; indeed, the results of Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results-A Long Term Evaluation (LEADER) trial showed that liraglutide significantly reduced the rates of major adverse cardiovascular events in T2DM patients at elevated cardiovascular risk [2].

There is therefore great interest to fully assess the mechanisms underlying such beneficial vascular effects of liraglutide, and Suhrs et al. have performed a rather small but interesting study, in order to evaluate the effects of liraglutide on body weight and microvascular function in non-diabetic overweight women with coronary microvascular dysfunction [3]. The study is not randomized and placebo-controlled, and the authors considered it as a preliminary proof-of-concept study.

The protocol included a control period of 5 weeks followed by an intervention period with liraglutide (titrated up to 3 mg daily) for 12 weeks. Participants were investigated before and after the control period and again 1–2 weeks after the last liraglutide dose. The authors report that 29 patients completed the study, and treatment with liraglutide led to significant weight loss and lowering of blood pressure with no persistent improvement in coronary microvascular function.

This is an interesting study since the vascular effects of liraglutide have been evaluated in a cohort of non-diabetic patients. The primary endpoint was the change in coronary microvascular function, and it was not achieved, probably due to the unusual study design, since participants were investigated 1–2 weeks after the last injection of liraglutide, and therefore the direct effect of liraglutide on coronary microvascular function was not evaluated. Yet, the authors confirmed that liraglutide is able to reduce body weight and blood pressure independently of the presence of diabetes [4], and it has to be highlighted that such positive results have been achieved after a very short period of liraglutide administration, since the full dosage of 3.0 mg/daily was administered for only 8 weeks.

Since liraglutide has shown strong cardiovascular benefit, the interest for its microvascular and macrovascular effects is elevated, and the mechanisms involved for such cardiovascular benefit have not been fully elucidated so far [5]. We have performed in the last years several studies on the microvascular effects of GLP-1RAs, and liraglutide in particular, in order to contribute to the understanding on the potential mechanisms involved in the cardiometabolic benefit of some GLP-1 RAs.

We first reported that liraglutide significantly improved carotid intima-media thickness (cIMT) after just 4 months of treatment in T2DM patients [6], and then we have extended this observation in patients with the Metabolic Syndrome with a longer follow-up period [7]. More recently, we have reported at the last annual congress of the European Association for the Study of Diabetes in October 2018 that such beneficial microvascular effect by liraglutide can be seen up to 7 years of follow-up (manuscript submitted for publication).

Such a rapid and progressive improvement by liraglutide on cIMT has been linked to the rapid reduction in oxidative stress (and ultimately in oxidized small, dense LDL) found in patients with T2DM after just two months of liraglutide therapy [8]. A growing body of evidence suggests that liraglutide has a direct beneficial effect on atherosclerotic plaque formation and progression (as reviewed in [9]).

In conclusion, liraglutide has shown over the years a number of beneficial microvascular and macrovascular effects, highlighting the cardiometabolic role of this agent. It is therefore obvious that therapies with GLP-1RAs, and liraglutide in particular, have gained interest for cardiovascular beyond the presence of T2DM in itself, assessing, for instance, the microvascular and macrovascular effects in patients with obesity or type-1 diabetes [10]. Since the body of evidence is becoming very strong and consistent, we cannot exclude that in the future liraglutide and/or other GLP-1RAs may be prescribed as cardiometabolic drugs and not as anti-diabetic drugs only.

Conflict of interest

The authors report no conflict of interest. MR is currently Chief Medical and Scientific Advisor, Diabetes, Novo Nordisk Europe East and South. DC has been on Speakers Desk of Novo Nordisk. Yet, Novo

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Nordisk or other pharmaceutical companies had not been involved in the writing of the present article, which solely reports the views and opinions of the authors.

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