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A Comparison of the Effects of the GLP-1 Analogue Liraglutide and Insulin Glargine on Endothelial Function and Metabolic Parameters: A Randomized, Controlled Trial Sapporo Athero-Incretin Study 2 (SAIS2).

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Abstract

Objective:

Glucagon-like peptide-1 (GLP-1) improves hyperglycemia, and it has been reported to have favorable effects on atherosclerosis. However, it has not been fully elucidated whether GLP-1 is able to improve endothelial function in patients with type 2 diabetes. Therefore, we investigated the efficacy of the GLP-1 analogue, liraglutide on endothelial function and glycemic metabolism compared with insulin glargine therapy.

Materials and Methods

In this multicenter, prospective randomized parallel-group comparison study, 31 diabetic outpatients (aged 60.3 ± 10.3 years with HbA1c levels of 8.6 ± 0.8 %) with current metformin and/or sulfonylurea treatment were enrolled and randomly assigned to receive liraglutide or glargine therapy once daily for 14 weeks. Flow mediated dilatation (FMD), a comprehensive panel of hemodynamic parameters (Task Force Monitor), and serum metabolic markers were assessed before and after the treatment period.

Results

A greater reduction (worsening) in %FMD was observed in the glargine group, although this change was not statistically different from the liraglutide group (liraglutide; 5.7 to 5.4 %, glargine 6.7 to 5.7 %). The augmentation index, C-peptide index, derivatives of reactive oxygen metabolites and BMI were significantly improved in the liraglutide group. Central systolic blood pressure and NT-proBNP also tended to be improved in the liraglutide-treated group, while improvements in HbA1c levels were similar between groups. Cardiac index, blood pressure and most other metabolic parameters were not different.

Conclusions

Regardless of glycemic improvement, early liraglutide therapy did not affect endothelial function but may provide favorable effects on beta-cell function and cardioprotection in type 2 diabetics without advanced atherosclerosis.

TRIAL REGISTRATION: UMIN Clinical Trials Registry System as trial ID UMIN000005331.

PMID: 26284918

Supplement:

Patients with type 2 diabetes mellitus are at a markedly higher risk of cardiovascular events compared with those without diabetes [1]. Although comprehensive care of risk factors of cardiovascular disease including not only glycemic control but also hypertension, hyperlipidemia and hyperuricemia, the rate of death is still higher in patients with diabetes [2]. Although several anti-diabetic chemical agents based on the patient's status are available, drugs which can suppress the risk of cardiovascular diseases are limited. For these reasons, anti-diabetic agents which possess anti-atherosclerotic effects would be beneficial.

Recently, one of the incretin drugs, glucagon-like peptide-1 (GLP-1) mimetics have been widely approved for the treatment of type 2 diabetes. These drugs not only improve glycated hemoglobin A1c (HbA1c) and glycemic control, but may also have anti-atherosclerotic and beta-cell protective effects. Although many *in vitro* and animal model experiments using GLP-1 mimetics have reported the protective effects on atherosclerosis, clinical evaluation focused on endothelial function, which has been reported to be an early stage of atherosclerosis, has not been elucidated. Therefore, using a multicenter, prospective, randomized parallel-group comparison study we aimed to evaluate the effects of the GLP-1 analogue, liraglutide, on endothelial function as assessed by flow mediated dilatation (FMD) in patients with type 2 diabetes.

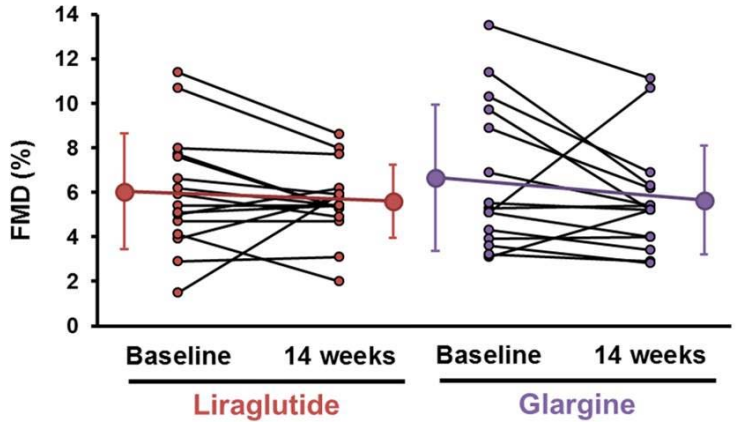

Figure 1. Comparison of individual changes of flow mediated dilatation (FMD) before and after administration of liraglutide and glargine. White circles are mean ± SD.

The study included 31 participates (aged 60.3 ± 10.3 years with HbA1c levels of 8.6 ± 0.8%) who were randomly treated with either GLP-1 analogue liraglutide or insulin glargine for 14 weeks. The participants did not suffer from severe atherosclerosis and their baseline FMD showed mild impairment. At the end of the study period, both treatments resulted in a reduction (worsening) in %FMD. The changes were not statistically different between the two groups (Figure 1), even after adjusting for baseline FMD measurements. In addition, using another evaluation method for endothelial function, the Endo-PAT, showed that the reactive hyperemia index also produced the same results.

Despite these data that indicated GLP-1 mimetics did not improve endothelial function after long term administration, our secondary analysis confirmed that liraglutide did possess not only potent hypoglycemic action but also cardioprotective effects (Figure 2). In the liraglutide treated group, systemic atherosclerosis assessed by the augmentation index was significantly improved and surrogate markers such as NT-pro BNP and centric systemic blood pressure, which reflect cardiac load, tended to be lower. A recent study demonstrated that vascular smooth muscles, but not endothelial cells, possess GLP-1 receptor [3]. Nevertheless, the presence or absence of GLP-1 receptor on endothelial cells has not yet been fully elucidated [4]. Moreover, a recent meta-analysis also revealed that only acute, but not chronic, GLP-1 based therapy affected FMD favorably [5].

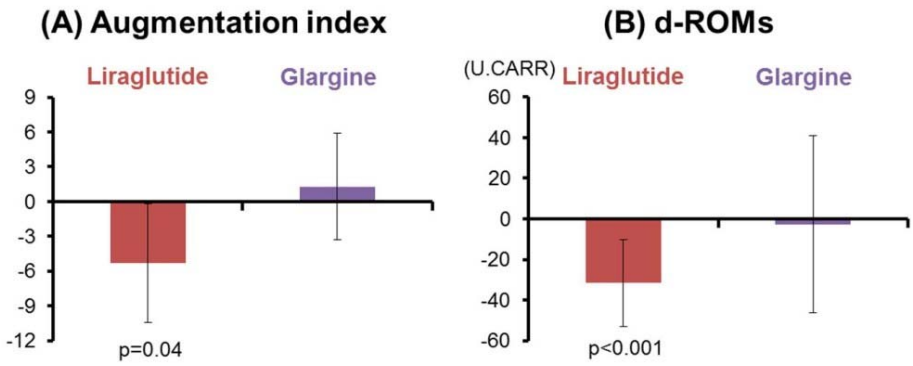

Figure 2. Comparison of changes in the augmentation index and d-ROMs after treatment in each group. Data are expressed as the least square means and 95% confidence interval.

Many studies have demonstrated a protective effect of liraglutide on pancreatic beta cells, but little is known about its *in vivo* effects on the beta cells, especially compared with that of insulin glargine. Our study results showed that improvement of beta cell function (C-peptide index) was observed only in the liraglutide treatment group. However, glycemic control was improved to the same degree in both groups. We assume that one of the factors that might be associated with these effects was the reduction of oxidative stress observed in the liraglutide treated group. Both endothelial cells and pancreatic islets are known to be sensitive to oxidative stress, especially the latter that possess a relatively low expression of oxidative enzymes such as superoxide dismutase, catalase and glutathione peroxidase [6]. Reduction of oxidative stress may, in part, contribute to the protection of both cardiovascular and pancreatic beta cells (Figure 3).

One of the strengths of our study was the procedure used for FMD measurement. Calculated %FMD is known to be affected by many confounding factors, for example baseline FMD, measurement skills of technicians, patients' background, conditions such as air temperature and mental/physical stresses, and medications such as angiotensin II receptor blockers, statins and some anti-diabetic agents. Our study strictly controlled these factors and all FMD measurements were made by the same well-quantified technician that was blinded to the treatment group.

In summary, these results imply that parenteral GLP-1 therapy is not enough to restore impaired endothelial cell function at least for the duration of this study period.

Importance of this study: This is the first report of a direct comparison between liraglutide and glargine on endothelial function. Our study clearly suggested that long term administration of liraglutide does not improve endothelial function, but protective effects on cardiovascular and beta-cell function have been confirmed.

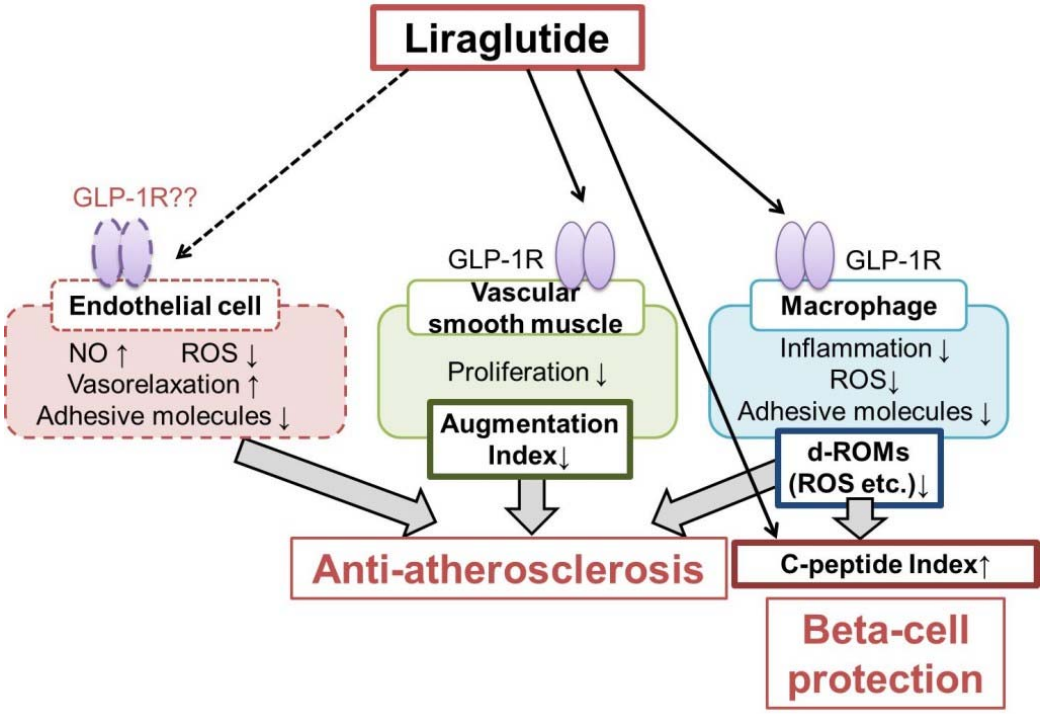

Figure 3. Based on the literature and our study, the figure shows the assumed protective mechanism for the effects of liraglutide on atherosclerosis and pancreatic beta cells.

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References

1. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22. Epub 2010/07/09. doi: 10.1016/s0140-6736(10)60484-9. PubMed PMID: 20609967; PubMed Central PMCID: PMCPmc2904878.
2. Lind M, Garcia-Rodriguez LA, Booth GL, Cea-Soriano L, Shah BR, Ekeroth G, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. Diabetologia. 2013;56(12):2601-8. Epub 2013/10/12. doi: 10.1007/s00125-013-3063-1. PubMed PMID: 24114114.
3. Pyke C, Heller RS, Kirk RK, Orskov C, Reedtz-Runge S, Kaastrup P, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology. 2014;155(4):1280-90. Epub 2014/01/29. doi: 10.1210/en.2013-1934. PubMed PMID: 24467746.
4. Lovshin J, Cherney D. GLP-1R Agonists and Endothelial Dysfunction: More Than Just Glucose Lowering? Diabetes. 2015;64(7):2319-21. Epub 2015/06/25. doi: 10.2337/db15-0366. PubMed PMID: 26106189.
5. Song X, Jia H, Jiang Y, Wang L, Zhang Y, Mu Y, et al. Anti-atherosclerotic effects of the glucagon-like peptide-1 (GLP-1) based therapies in patients with type 2 Diabetes Mellitus: A meta-analysis. Scientific reports. 2015;5:10202. Epub 2015/06/27. doi: 10.1038/srep10202. PubMed PMID: 26111974; PubMed Central PMCID: PMCPmc4481643.
6. Grankvist K, Marklund SL, Taljedal IB. CuZn-superoxide dismutase, Mn-superoxide dismutase, catalase and glutathione peroxidase in pancreatic islets and other tissues in the mouse. The Biochemical journal. 1981;199(2):393-8. Epub 1981/11/01. PubMed PMID: 7041886; PubMed Central PMCID: PMCPmc1163382.

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