Chapter 7

Effect of linagliptin on arterial \( ^{18}\text{F}-\)fluorodeoxyglucose positron emission tomography uptake
A randomized controlled trial (RELEASE)

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LETTER TO THE EDITOR

Dipeptidyl peptidase (DPP)-4 inhibitors are a class of oral antidiabetic agents of which favorable cardiovascular effects are suggested. For example, experimental studies have shown that DPP4-inhibitors reduce atherosclerotic plaque area and macrophage accumulation.\(^1\) However, there are no randomized controlled trials investigating these effects in humans. Arterial \(^{18}\text{F}\)-fluorodeoxyglucose (\(^{18}\text{F}\)-FDG) uptake on positron emission tomography (PET) is associated with macrophage infiltration and levels of inflammatory activity.\(^2\) Consequently, arterial \(^{18}\text{F}\)-FDG uptake represents a surrogate marker of arterial inflammation and is a potential target for therapy.

In this randomized controlled trial we assessed the effect of 26 week\(^{\prime}\) treatment with the DPP-4 inhibitor linagliptin on arterial \(^{18}\text{F}\)-FDG uptake in early type 2 diabetes subjects, without cardiovascular disease and naïve to antidiabetic treatment. A total of 45 type 2 diabetes subjects (median age 63 [interquartile range (IQR): 54 to 66] years, 61% men, mean glycosylated hemoglobin 6.3±0.4%, median body mass index 30.4 [IQR: 27.5 to 35.8] kg/m\(^2\), median high-sensitivity C-reactive protein 1.15 [IQR: 0.70 to 3.08] mg/L, use of a statin [55%]) were randomized (1:1) to once daily linagliptin 5 mg or placebo in a double-blind fashion (RELEASE study [\text{Off taRGet Effects of Linagliptin monothErapy on Arterial Stiffness in Early Diabetes}]; baseline data previously published\(^3\); 40 subjects completed the study. At baseline and at 26 weeks a whole body \(^{18}\text{F}\)-FDG-PET/low-dose computed tomography scan (Siemens Biograph 64 slice, Siemens Medical Systems, Knoxville, Tennessee) was performed. Image analyses are described in detail elsewhere.\(^3\) In brief, arterial \(^{18}\text{F}\)-FDG uptake was quantified as the prescan glucose-corrected maximal standardized uptake value as previously described\(^3,4\) and corrected for background activity (target-to-background ratio, [TBR]). TBRs were calculated for the carotid arteries, ascending aorta and aortic arch, descending and abdominal aorta, and iliac and femoral arteries, and then averaged for the total aortic tree (mean\(_{\text{TBR}}\)). Between-group differences were analyzed using a Student independent \(t\) test on the calculated deltas.

As expected, linagliptin decreased glycosylated hemoglobin (-0.4%; \(P<0.001\)), fasting plasma glucose (-0.7 mmol/L; \(P=0.002\)), and triglycerides (-0.49 mmol/L; \(P=0.019\)) as compared to placebo. The changes in body mass index, cholesterol, and high-sensitivity C-reactive protein did not differ significantly between groups. At 26 weeks, the decrease in mean\(_{\text{TBR}}\) under linagliptin exceeded that under placebo with 0.18 units (95% CI: 0.04 to 0.32; \(P=0.015\)) (Figure 1). No significant differences were found for the glucose-uncorrected mean\(_{\text{TBR}}\) (0.01 [95% CI: -0.08 to 0.09]; \(P=0.821\)).

This is the first randomized placebo-controlled trial that demonstrates that 26 weeks of treatment with linagliptin decreases arterial \(^{18}\text{F}\)-FDG uptake in subjects with early type 2 diabetes. Recently, \(^{18}\text{F}\)-FDG-PET/ computed tomography has been introduced as an imaging technique for assessment of atherosclerosis. Arterial \(^{18}\text{F}\)-FDG uptake is a marker of
inflammation and associated with future cardiovascular events. Therefore, arterial $^{18}$F-FDG uptake may potentially be used as a surrogate marker to evaluate protective cardiovascular effects. Our results add evidence to the hypothesis that linagliptin may have potentially favorable vascular effects, supporting observations from preclinical studies.

Despite the randomized controlled design, our study also has some limitations. First, we selected early stage diabetes subjects without cardiovascular disease and therefore our findings may not be extrapolated to subjects with longer diabetes duration or advanced atherosclerotic disease. Second, although background statin therapy was equally distributed among treatment groups and doses were stable throughout the study, it could have attenuated arterial $^{18}$F-FDG uptake, limiting the observed treatment effect. Third, our results could be influenced by the glucose-lowering effect, as glycaemic control is associated with arterial $^{18}$F-FDG uptake. However, because we adjusted for prescan glucose levels, the competitive effect of glucose and $^{18}$F-FDG is thought to be minimized.

In summary, 26 weeks of linagliptin decreases arterial $^{18}$F-FDG uptake in treatment-naive type 2 diabetes subjects, supporting earlier observations from (pre)clinical studies that DPP4-inhibitors may have favorable effects on atherosclerosis.

Figure 1 | Effect of Linagliptin on Arterial $^{18}$F-Fluorodeoxyglucose Uptake. In the linagliptin group, mean target-to-background ratio ($\text{mean TBR}$) changed from 2.12 (95% confidence interval [CI]: 1.99 to 2.26) to 2.00 (95% CI: 1.90 to 2.11) at 26 weeks and in the placebo group changed from 2.09 (95% CI: 1.96 to 2.21) to 2.15 (95% CI: 2.01 to 2.28), resulting in a placebo-corrected change of 0.18 units (95% CI: 0.04 to 0.32; $P=0.015$).
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