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Effect of short-acting exenatide administered three times daily on markers of cardiovascular disease in type 1 diabetes: A randomized double-blind placebo-controlled trial

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Abstract
Aims: To investigate the effect of adding the short-acting glucagon-like peptide 1 receptor agonist (GLP-1RA) exenatide to insulin treatment on markers of cardiovascular risk in type 1 diabetes.

Materials and methods: In a randomized, double-blind, parallel-group trial, 108 individuals with type 1 diabetes aged ≥18 years on multiple daily injection therapy with a body mass index >22.0 kg/m² and glycated haemoglobin concentration of 59 to 88 mmol/mol (7.5%−10.0%) were randomized (1:1) to preprandial subcutaneous injection of 10 μg exenatide (Byetta®) or placebo three times daily over 26 weeks as add-on treatment to existing insulin therapy. Reported markers of cardiovascular risk were secondary endpoints and were analyzed in a baseline-adjusted linear mixed model in the intention-to-treat population. The primary results of this study, the MAG1C (Meal-time Administration of exenatide for Glycaemic control in type 1 diabetes Cases) trial, were previously reported.

Results: Exenatide changed total fat mass by −2.6 kg (95% confidence interval [CI] −3.6; −1.6; P < 0.0001) and lean body mass by −1.1 kg (95% CI −1.9; −0.4; P = 0.01) compared with placebo, as assessed by dual-energy X-ray absorptiometry. Fat mass reductions were similar for central and peripheral fat mass. Exenatide did not change levels of interleukin-2 or -6; tumour necrosis factor-α; C-reactive protein; N-terminal prohormone of brain natriuretic peptide; or 8-oxo-7,8-dihydroguanosine

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1 | INTRODUCTION

In type 1 diabetes, cardiovascular disease reduces mean average life expectancy by up to 11 years for men and 13 years for women.\(^5\) Strict glycaemic control through insulin therapy reduces the risk of microvascular and macrovascular complications\(^5-8\) but promotes body weight gain, thus contributing to the growing burden of overweight and obesity in people with type 1 diabetes.\(^4\) Also in type 1 diabetes, weight gain promotes risk of metabolic syndrome and cardiovascular disease.\(^5-7\) Consequently, with fewer than half of patients meeting their recommended glycaemic target,\(^9\) the focus of effective treatment of type 1 diabetes is on both glycaemic control and reduction of cardiovascular disease risk. Glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) add-on treatment to insulin control and reduction of cardiovascular disease risk. Glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) add-on treatment to insulin control and reduction of cardiovascular disease risk. Glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) add-on treatment to insulin control and reduction of cardiovascular disease risk. Glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) add-on treatment to insulin control and reduction of cardiovascular disease risk.

Conclusions: Exenatide added to insulin therapy in type 1 diabetes for 26 weeks resulted in body weight loss primarily from fat mass reduction, but had no effect on biomarkers of cardiovascular disease risk.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The MAG1C trial was a 26-week, randomized, double-blind, placebo-controlled, phase 2a clinical trial, testing the efficacy and safety of 10 μg short-acting exenatide administered three times daily as preprandial injections 1 hour of before breakfast, lunch and dinner as add-on treatment to multiple daily injection therapy in type 1 diabetes (www.clinicaltrials.gov, NCT03017352). As previously described,\(^13\) the MAG1C trial was conducted at the Steno Diabetes Center Copenhagen (Gentofte, Denmark); participants were recruited from outpatient clinics in the Capital Region of Denmark. Eligible participants were aged ≥ 18 years with type 1 diabetes (according to World Health Organization criteria) for ≥ 1 year, had a body mass index (BMI) > 22.0 kg/m\(^2\) and an HbA1c of 59 to 88 mmol/mol (7.5%–10.0%). The main exclusion criteria were insulin pump treatment, hypoglycaemia unawareness, diabetic gastroparesis, compromised kidney function and untreated proliferative retinopathy.\(^16\) The Danish Medicines Agency (EudraCT no. 2016-001365-92) and the Regional Scientific Ethics Committee of the Capital Region of Denmark (H-16034515) approved the trial, it was registered at the Danish Data Protection Agency and surveyed and guided by the Good Clinical Practice Unit for university hospitals associated with University of Copenhagen. All participants provided written informed consent.

2.2 | Randomization and blinding

Details about randomization and blinding were reported previously.\(^13\) In short, a computer-generated randomization list (50 exenatide; 50 placebo) was made by a third party not involved in the trial and a further
eight slots (four exenatide; four placebo) were added during the trial because of a larger-than-expected dropout rate. Participants were consecutively allocated on a 1:1 ratio to 10 μg short-acting exenatide (Byetta®; AstraZeneca, Cambridge, UK) or placebo (an indistinguishable liquid placebo formulation) by two other persons not involved in the trial. Participants and study staff were masked to treatment allocation. During the trial, as participants were enrolled consecutively, two other individuals who were not involved in the trial consecutively allocated participants to treatment groups from the randomisation list. The study drug package numbers were given to study staff who double-checked these with the actual packages. The packages were given to study participants. Both study staff and participants were masked to treatment allocation. All study drug pens and cartridges were indistinguishable. All statistical analyses were done by individuals masked to treatment allocation.

2.3 | Procedures and measurements

Four visits were planned at weeks 0 (randomization), 4, 12 and 26 (end-of-treatment), with fasting from 10:00 PM the night before. Body composition was measured by whole-body dual-energy X-ray absorptiometry (DXA) scans at weeks 0 and 26 using a Hologic Discovery QDR series 82 800 Apex 3.3 scanner (Hologic Canada ULC, Mississauga, Canada). At weeks 0, 12 and 26, BMI, waist circumference, hip circumference and waist: hip ratio were measured by study staff. Fasting blood samples were drawn at weeks 0, 4, 12 and 26, and morning spot urine samples were collected at weeks 0, 12 and 26 for storage in a biobank at −80°C. From these stored samples, the following biomarkers were analysed after study completion: plasma levels of IL-2, IL-6 and TNF-α were analysed by multiplex sandwich electrochemiluminescence immunoassays using a V-PLEX Custom Human Cytokine kit (Meso Scale Diagnostics, Rockville, Maryland). CRP was quantified in plasma by a high-sensitivity latex-enhanced immunoturbidimetric assay for the Atellica CH 930 analyser (Siemens Healthcare Diagnostics Inc., Tarrytown, New York). NT-proBNP in plasma was analysed using a Roche NT-proBNP device (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). 8-oxodG and 8-oxoGuo were analysed in spot urine samples using ultra-performance liquid chromatography tandem mass spectrometry, as described elsewhere, and adjusted to urine creatinine.

2.4 | Statistical analysis

All reported outcomes in the present study were prespecified secondary endpoints, except for 8-oxodG and 8-oxoGuo, which were added as secondary endpoints after study commencement but prior to trial end. The sample size of the study population (n = 100) was based on a presumed 9mmol/mol (0.8%) standard deviation and enabled detection of an end-of-treatment difference between groups in HbA1c of 6 mmol/mol (0.5%) with 80% power and a 5% significance level. However, a bigger-than-expected dropout of 23 individuals (17 from the exenatide group, six from the placebo group) required an additional eight participants. Following study completion and analysis of arginine-stimulated serum C-peptide levels, participants with abnormally high C-peptide levels had their medical history and patient record closely reviewed. This resulted in two participants with exenatide (one was a dropout) and one participant with placebo being withdrawn from the statistical analysis due to reclassification of diagnosis to type 2 diabetes. In total, 105 participants were included in the statistical analyses. Baseline continuous data are means with standard deviation, medians with minimum and maximum range or, for categorical variables, numbers with percentage. Continuous data not normally distributed were log-transformed. For efficacy analysis, we used a baseline-adjusted linear mixed model based on a likelihood ratio test, with visit, treatment and their interaction as fixed factors and a random effect on participant level in the intention-to-treat population. Maximum likelihood estimation was used for missing data handling (equivalent to multiple imputation). As sensitivity analysis, all endpoints were compared with an unstructured covariance pattern. For the additional post hoc analysis of 8-oxodG and 8-oxoGuo, to avoid bias of weight changes during the study that may impact urine creatinine levels used to assess these biomarkers, we applied a model that estimates 24-hour excretion rates of 8-oxodG and 8-oxoGuo. Also post hoc, we stratified participants at baseline into cardiovascular risk categories of very high risk (risk of cardiovascular death ≥10% within 10 years), high risk (risk of cardiovascular death 5%–10% within 10 years) and moderate risk (lower than high risk) as defined by the European Society of Cardiology. In addition, post hoc, we used the “Steno Type 1 Diabetes Risk Engine” (https://steno.shinyapps.io/T1RiskEngine/) for a risk stratification that resembles clinical practice at the study site. This risk stratification stratifies patients into high-risk (10-year cardiovascular risk ≥20%), moderate-risk (10%–20%) or low-risk categories (<10%). As we report only secondary endpoints, P values were not used for assessing statistical significance. However, all reported P values were adjusted for multiple testing. R statistical software package (version 3.4.1) was used for all statistical analyses. Figures were designed using GraphPad Prism (version 8.0.2.263).

3 | RESULTS

3.1 | Study population

As previously described, the included participants were, on average, middle-aged with longstanding type 1 diabetes, had moderate glycemic dysregulation and were overweight, with total insulin requirements of 60 U/d and the majority were men (Table 1). Cardiovascular disease risk factors were evenly distributed between groups except for smoking, physical exercise level and diagnosis of simplex retinopathy (Table 1). When stratified into cardiovascular risk categories according to the European Society of Cardiology, in the exenatide group, 54% of participants were at very high risk, 21% at high risk and 25% at moderate risk. In the placebo group, 41% of participants were at very high risk, 19% at high risk and 40% at moderate risk (Table 1). For cardiovascular risk, as stratified by the "Steno Type 1 Diabetes Risk Engine", 40% of exenatide-treated participants were at high risk, 37% at moderate risk and 23% at low risk. With placebo treatment, 38% were at high risk, 38% at moderate risk and 25% at low risk (Table 1).
Body composition

After 26 weeks, exenatide caused marked reductions in BMI, waist circumference and hip circumference (Table 2). Evaluated from DXA scans, exenatide changed total fat mass by −2.6 kg (95% CI −3.6 to −1.6; P < 0.0001) and lean + bone mineral content body mass by −1.1 kg (95% CI −1.9 to −0.4; P = 0.01) as compared with placebo (Figure 1). The fat mass loss was reflected in substantial reductions of total fat mass (%), fat mass index (kg/m²), android fat mass and gynoid fat mass. Waist: hip ratio, measures of central and peripheral fat mass distribution and android/gynoid ratio were unchanged (Table 2).

Biomarkers

8-oxoGuo, a marker of RNA oxidation, and 8-oxodG, a marker of DNA oxidation, both increased over time, and exenatide caused a slight elevation as compared with placebo at end-of-treatment. However, this between-group difference diminished when applying a model that...
Table 2

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 12</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled group</strong></td>
<td><strong>Exenatide</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>Mean ETD</strong></td>
<td><strong>Mean ETD (95% CI) P value</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.3 (27.5; 29.2)</td>
<td>27.4 (26.5; 28.2)</td>
<td>28.5 (27.6; 29.4)</td>
</tr>
<tr>
<td><strong>Total fat mass, kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.9 (26.5; 27.8)</td>
<td>27.7 (26.8; 28.8)</td>
<td>28.0 (27.5; 28.5)</td>
</tr>
<tr>
<td><strong>Total fat mass, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>96.9 (94.3; 99.5)</td>
<td>97.7 (94.9; 100.6)</td>
<td>98.7 (95.9; 101.5)</td>
</tr>
<tr>
<td><strong>Fat mass index, kg/m²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.93 (0.91; 0.94)</td>
<td>0.94 (0.92; 0.96)</td>
<td>0.94 (0.92; 0.96)</td>
</tr>
<tr>
<td><strong>Trunk/limb fat mass ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.01 (0.96; 1.07)</td>
<td>1.00 (0.94; 1.05)</td>
<td>1.00 (0.94; 1.05)</td>
</tr>
<tr>
<td><strong>Trunk fat percentage/leg fat percentage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.97 (0.93; 1.01)</td>
<td>0.96 (0.92; 1.00)</td>
<td>0.96 (0.92; 1.00)</td>
</tr>
<tr>
<td><strong>Android fat mass, kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6 (2.4; 2.9)</td>
<td>2.3 (2.1; 2.4)</td>
<td>2.3 (2.1; 2.4)</td>
</tr>
<tr>
<td><strong>Gynoid fat mass, kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.7 (4.4; 5.0)</td>
<td>4.3 (4.0; 4.6)</td>
<td>4.3 (4.0; 4.6)</td>
</tr>
<tr>
<td><strong>Android/gynoid ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.06 (1.02; 1.10)</td>
<td>1.05 (1.00; 1.10)</td>
<td>1.05 (1.00; 1.10)</td>
</tr>
<tr>
<td><strong>Lean + BMC body mass (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60.2 (58.2; 62.2)</td>
<td>60.1 (58.1; 62.1)</td>
<td>60.0 (58.1; 62.0)</td>
</tr>
</tbody>
</table>

**Notes:** All reported outcomes were protocol-specified secondary endpoints except for 8-oxodG and 8-oxoGuo. As such, our findings cannot exclude an effect of short-acting exenatide on the distribution of central versus peripheral fat mass loss or plasma levels of IL-2, IL-6, TNF-α, hsCRP or NT-proBNP (Table 3). Of note, median hsCRP remained in the range of 1 to 2 mg/L at all time points. In addition, NT-proBNP stayed within normal range at all visits.

## 4 DISCUSSION

In this randomized, double-blind, placebo-controlled clinical trial, testing the efficacy of short-acting exenatide administered three times daily before breakfast, lunch and dinner added to insulin therapy in type 1 diabetes and in a study population with overall high risk of cardiovascular disease, exenatide elicited relevant body weight reductions mediated by greater reductions of fat mass as compared with lean mass and with equal reductions in centrally and peripherally located fat mass. Biomarkers related to cardiovascular disease risk showed no between-group differences. Measures of RNA and DNA oxidation increased over 26 weeks, and exenatide increased both markers as compared with placebo at end-of-treatment, but this increase diminished when corrected for changes in body weight.

### 4.1 Strengths and limitations

All reported outcomes were protocol-specified secondary endpoints except for 8-oxodG and 8-oxoGuo. As such, our findings cannot exclude an effect of short-acting exenatide on the distribution of central versus peripheral fat mass loss or plasma levels of IL-2, IL-6, TNF-α, hsCRP or NT-proBNP (Table 3). Of note, median hsCRP remained in the range of 1 to 2 mg/L at all time points. In addition, NT-proBNP stayed within normal range at all visits.

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**FIGURE 1** Efficacy of short-acting exenatide administered three times daily as compared with placebo in participants with type 1 diabetes. Change in mean body weight after 26 weeks stratified by fat mass and lean mass, as assessed by dual-energy X-ray absorptiometry scanning. Values are between-group mean differences with 95% confidence intervals or intra-group mean difference ± SEM from a linear mixed model incorporating baseline adjustment that handles missing data with maximum likelihood estimation (equal to multiple imputation) in the intention-to-treat population. ETD, estimated treatment difference.
Table 3

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2a pg/mL</td>
<td>0.15 (0.12; 0.19)</td>
<td>0.14 (0.11; 0.18)</td>
<td>0.14 (0.11; 0.19)</td>
<td>0.98 (0.69; 1.39); 0.96</td>
</tr>
<tr>
<td>IL-6a pg/mL</td>
<td>0.85 (0.76; 0.94)</td>
<td>0.93 (0.81; 1.07)</td>
<td>1.01 (0.88; 1.16)</td>
<td>0.92 (0.78; 1.09); 0.54</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1.62 (1.32; 2.00)</td>
<td>1.21 (0.94; 1.57)</td>
<td>1.61 (1.25; 2.06)</td>
<td>0.76 (0.57; 1.02; 0.51)</td>
</tr>
<tr>
<td>hsCRP</td>
<td>1.97 (1.86; 2.07)</td>
<td>2.01 (1.89; 2.14)</td>
<td>2.09 (1.96; 2.22)</td>
<td>0.94 (1.08; 1.26; 0.12)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>7.80 (7.12; 8.54)</td>
<td>7.38 (6.62; 8.19)</td>
<td>7.36 (6.62; 8.19)</td>
<td>1.00 (0.90; 1.12; 0.97)</td>
</tr>
<tr>
<td>8-oxoGuo/creatinine, nmol/mmol</td>
<td>1.83 (1.70; 1.97)</td>
<td>1.77 (1.65; 1.90)</td>
<td>0.06 (-0.10; 0.22; 0.69)</td>
<td>2.20 (1.91; 2.50)</td>
</tr>
<tr>
<td>8-oxodG/creatinine, nmol/mmol</td>
<td>1.46 (1.35; 1.58)</td>
<td>1.46 (1.35; 1.58)</td>
<td>0.21 (0.08; 0.34; 0.17)</td>
<td>1.80 (1.61; 2.00)</td>
</tr>
<tr>
<td>24-hour 8-oxoGuo, nmol/24 h</td>
<td>17.78 (16.65; 18.91)</td>
<td>19.24 (17.65; 20.84)</td>
<td>18.71 (17.24; 20.18)</td>
<td>0.53 (-0.13; 0.22; 0.42)</td>
</tr>
<tr>
<td>24-hour 8-oxodG, nmol/24 h</td>
<td>13.33 (12.29; 14.37)</td>
<td>13.33 (12.29; 14.37)</td>
<td>13.33 (12.29; 14.37)</td>
<td>0.17 (-0.19; 0.55)</td>
</tr>
</tbody>
</table>

**Abbreviations:** 8-oxodG, 8-oxo-7,8-dihydro-2'-deoxyguanosine; ETD, estimated treatment difference; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; TNF, tumour necrosis factor.

**Data notes:** Mean ± standard deviation, mean (95% CI); mean difference (95% CI); mean percentage difference (95% CI); 95% confidence intervals in brackets; relative difference of medians (95% CI) with P values.

**P values** represented. Finally, 26 weeks is a short period in which to conclude on possible changes in cardiovascular disease risk and, as the assessed endpoints are indirect markers of cardiovascular disease, it should be stressed that the reported findings should be interpreted with caution.

### 4.2 Body composition

As evaluated by DXA scans, after 26 weeks, exenatide caused greater reductions in total fat mass as compared with total lean mass, whereas measures of central and peripheral fat mass loss were unchanged. Exenatide caused marked reductions of BMI, waist circumference and hip circumference but did not affect waist: hip ratio. To our knowledge, this is the first time the impact of GLP-1RA treatment on body composition has been assessed by DXA in type 1 diabetes. A small (n = 15) crossover study evaluating once-daily 1.8 mg liraglutide over 24 weeks as add-on treatment to insulin therapy in obese individuals reported reductions of fat mass of 3.8 kg and fat-free mass of 1.0 kg as assessed by bioimpedance analysis; reductions in BMI, waist circumference and hip circumference were similar to ours.25 Also, 4 weeks' treatment with short-acting exenatide or the short-acting GLP-1RA, lixisenatide, in small, mainly mechanistic studies reported BMI reductions of 0.5 to 1.0 kg/m² as compared with placebo.26–28 Likewise, in a 12-week randomized, double-blind, placebo-controlled clinical trial (n = 40), 1.2 mg liraglutide once daily reduced BMI by 1.0 kg/m².10 However, a 5kg/m² lower baseline BMI compared to our trial and only 12 weeks' intervention complicates comparisons. Taken together, our body composition results suggest that short-acting exenatide induces primarily fat-mass loss, but any particular effect on central obesity is unclear from the present data; possibly due to insufficient sample size. Notably, short-acting exenatide has a half-life of 2.4 hours and, thus, fluctuating plasma levels over the day could attenuate its impact on risk of cardiovascular disease as compared with more stable plasma levels of long-acting GLP-1RAs. Our study population of glycaemic dysregulated, normal-to-overweight/obese patients with longstanding type 1 diabetes represented an overall high-risk patient group of cardiovascular disease as assessed by two different cardiovascular risk stratification algorithms. However, a discrepancy between baseline risk of cardiovascular disease, as defined by the European Society of Cardiology,22 should be noted as opposed to a similar distribution of risk of cardiovascular disease as defined by “Steno Type 1 Diabetes Risk Engine”.23 We speculate this to be a chance finding as the majority of baseline covariates were evenly distributed between groups. Notably, our study population complicates generalizability as it consisted of Danish patients of white ethnicity, and male sex was overrepresented. Finally, 26 weeks is a short period in which to conclude on possible changes in cardiovascular disease risk and, as the assessed endpoints are indirect markers of cardiovascular disease, it should be stressed that the reported findings should be interpreted with caution.
exenatide seems to improve insulin sensitivity as assessed by the hyperinsulinaemic-euglycaemic clamp technique.29

4.3 | Biomarkers

In our study, exenatide elicited no changes in proinflammatory cytokines, TNF-α and IL-6, or acute phase reactant, CRP, after 26 weeks as compared with placebo. Interestingly, infusion of GLP-1 attenuated the rise of IL-6 during a hypoglycaemic clamp and a hyperglycaemic clamp as compared with placebo.30 In relation to these biomarkers and cardiovascular disease risk, a large, cross-sectional case–control study in type 1 diabetes (n = 543) reported that increased mean levels of CRP, IL-6 and TNF-α (in ranges comparable with our reported median values) were all strongly associated with the presence of cardiovascular disease in a crude model. When adjusted for age, sex, HbA1c, diabetes duration and systolic blood pressure, only CRP lost its association with cardiovascular disease.31 Also in a case–control study (n = 136), increased levels of a compound low-grade inflammation score (IL-6, CRP and soluble receptors 1 and 2 of TNF-α) were independently associated with arterial stiffness, a marker of cardiovascular disease, in men but not women with type 1 diabetes.32 Taken together, our median levels of IL-6, TNF-α and CRP remained constant during trial; and our median levels compared with reported means in other studies; and exenatide did not change any of these biomarkers as compared with placebo. Exenatide’s lack of effect on IL-6, TNF-α and CRP could be attributable to an overall low-grade inflammation status, as suggested by the median CRP levels in the average risk range of cardiovascular disease of 1–3 mg/L.33

Exenatide did not change relative median IL-2 levels as compared with placebo after 26 weeks in the present study. Interestingly, IL-2 stimulates regulatory T-cell activity, and reduced levels of regulatory T cells have recently been correlated with cardiovascular disease in type 1 diabetes.34 In contrast, elevated IL-2 levels have been linked to reduced progression of atherosclerosis in mouse models.35 We speculate that exenatide’s lack of effect on IL-2 plasma levels could be attributable to the low inflammation levels as indicated by TNF-α, IL-6 and CRP in the study population.

Plasma levels of NT-proBNP were stable during the study period, and exenatide elicited no changes as compared with placebo. Importantly, increased levels of NT-proBNP, as a marker of left ventricular dysfunction and, indirectly, coronary heart disease, have been found to correlate with cardiovascular disease in type 1 diabetes.36,37 Notably, our reported median levels were < 8 pmol/L (within normal range), limiting detection of an impact of short-acting exenatide on cardiovascular disease risk.

Oxidatively generated DNA and RNA modifications measured as urinary excretion of 8-oxodG and 8-oxoGuo increased from baseline until end-of-treatment. Exenatide increased both markers as compared with placebo after 26 weeks, but these between-group differences diminished in a model accounting for body weight changes. Interestingly, in type 2 diabetes, increased levels of 8-oxoGuo have been associated with increased risk of cardiovascular death,38 and GLP-1RA-mediated reductions of cardiovascular risk have been suggested to be partly mediated by reductions of oxidative stress.39 However, our results do not indicate a beneficial effect of short-acting exenatide on oxidative stress in patients with type 1 diabetes.

4.4 | Previously reported endpoints related to cardiovascular disease

Ambulatory blood pressure and heart rate, together with blood lipid levels, were previously reported but are of interest to the present discussion of short-acting exenatide’s impact on risk of cardiovascular disease in type 1 diabetes. Exenatide increased heart rate by 3.9 beats per minute (95% CI 0.5 to 7.2; P = 0.16) as compared with placebo after 26 weeks’ treatment. Exenatide did not change ambulatory blood pressure or blood lipid levels at end-of-treatment as compared with placebo.33

4.5 | Conclusions

Taken together, short-acting exenatide administered three times daily before breakfast, lunch and dinner as add-on treatment to multiple daily injection therapy in type 1 diabetes in a study population with overall high risk of cardiovascular disease resulted in clinically relevant reductions in body weight, primarily derived from a reduction of both central and peripheral fat mass. Exenatide did not affect low-grade inflammatory status as assessed by IL-2, IL-6, TNF-α and CRP, nor cardiac function as assessed by NT-proBNP. Finally, exenatide did not markedly impact DNA/RNA oxidation status assessed by 8-oxodG and 8-oxoGuo, respectively. To our knowledge, no previous study has investigated the effects of GLP-1RA treatment on any of these biomarkers related to cardiovascular disease in type 1 diabetes.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

N.J.J. has received a travel grant from AstraZeneca. T.F.D. has received lecture fees from Boehringer Ingelheim, Novo Nordisk and AstraZeneca, and research support from AstraZeneca and Novo Nordisk. A.B.L. has received lecture fees from Novo Nordisk, Astra Zeneca and Sanofi. C.S., J.P.G. and H.U.A. have nothing to disclose. E.L.L. and H.E.P. have received research funding from Boehringer Ingelheim. T.V. has served on scientific advisory panels and/or speakers’ bureaus or has served as a consultant to and/or received research support from AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Mundipharma, Novo Nordisk, Sanofi and SunPharma. H.U.A. owns stocks in Novo Nordisk, is on advisory boards for Novo Nordisk, Abbott and Astra Zeneca, and has received a lecture fee from Nordic Infucare. F.K.K. has served on scientific advisory panels and/or been part of speaker’s bureaus for, served as a consultant to and/or received research..
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AUTHOR CONTRIBUTIONS
N.J.J., T.F.D., A.L., T.V., H.U.A. and F.K.K. initiated and designed the trial. N.J.J., T.F.D., C.S., E.L.L., H.E.P., J.P.G., H.J.M. and H.U.A. participated in the data collection. N.J.J. performed the statistical analysis and wrote the first draft of the manuscript. All authors revised the manuscript for crucial intellectual content. N.J.J. and F.K.K. are the guarantors of this work and, as such, had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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