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Title page

Title: Hormone-Substrate Changes with Exenatide Plus Dapagliflozin Versus Each Drug Alone: The Randomized, Active-Controlled DURATION-8 Study

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Short title: Hormone changes with Exenatide plus Dapagliflozin Therapy

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Abstract

Aim: In DURATION-8, the combination of once-weekly exenatide (EQW)+10 mg dapagliflozin (Dapa) in patients with type 2 diabetes poorly controlled with metformin reduced glycated hemoglobin levels and body weight (at weeks 28 and 52) compared with EQW+placebo (Plb) or Dapa+Plb. Here we determined the effects of individual and combined therapies on plasma insulin, glucagon, β-hydroxybutyrate (β-OH), and associated metabolites.

Materials and Methods: The study included 678 patients randomized 1:1:1 to EQW+Dapa, EQW+Plb, or Dapa+Plb. Plasma insulin and glucagon were measured at fasting and 2 hours after a mixed meal. Fasting plasma free fatty acids (FFA) and β-OH concentrations were measured.

Results: The fasting insulin-to-glucagon molar ratio (I/Glg) increased with EQW+Plb only; postprandial I/Glg increased in all groups but significantly more with EQW+Plb. β-OH, FFA, and glycerol concentrations showed a parallel response: larger increments with Dapa+Plb, larger decrements with EQW+Plb, and intermediate changes with EQW+Dapa. β-OH levels and I/Glg were inversely related to one another. Patients in the top quartile of β-OH changes from baseline (median [interquartile range]: +207[305] *vs*. −65[−154] µmol/L, $P<0.0001$) were more frequently treated with Dapa+Plb, had higher urine glucose-to-creatinine ratios, and lower fasting insulin (52[51] *vs*. 68[53] pmol/L, $P=0.0013$) and I/Glg (1.76[1.49] *vs*. 2.23[1.70] mol/mol, $P=0.0020$). Hematocrit increased only in the Dapa group.

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Conclusions: The EQW+Dapa combination abolished the Dapa-induced rise in β-OH, reduced the EQW-induced increase in I/Glg, maintained glycosuria, and increased hematocrit in patients with poorly controlled type 2 diabetes. The drug combination may preserve any putative benefits while mitigating the risk of ketoacidosis.

Trial registration: ClinicalTrials.gov NCT02229396.

Keywords: Combination therapy, Dapagliflozin, Exenatide, GLP-1 agonist, Glycaemic control, SGLT2 inhibitor

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Introduction

The use of a sodium-glucose co-transporter 2 (SGLT2) inhibitor (SGLT2i) in patients with type 2 diabetes (T2D) induces a sequence of metabolic and hormonal changes, culminating in enhanced ketogenesis and relative hyperketonemia.[1] Specifically, the carbohydrate deficit that follows from the inhibition of renal glucose reabsorption with an SGLT2i stimulates lipolysis and whole-body lipid oxidation while decreasing plasma insulin concentrations. Lower insulin concentrations along with increased plasma glucagon levels stimulate hepatic ketogenesis. As the liver cannot use ketones, circulating levels of β-hydroxybutyrate (β-OH) and acetoacetate rise to a variable extent.[2] This sequence of changes has been verified in several clinical studies of short duration.[3,4] The persistence over months of treatment, however, has not been examined. Ketones may act as a thrifty myocardial fuel in patients with compromised cardiac function,[5] thereby contributing to cardiovascular risk reduction. However, it has been argued that concomitant treatment with agents that stimulate insulin secretion, such as a glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA), would abolish the ketonaemic response to an SGLT2i. In both the Empagliflozin, Cardiovascular Outcomes Event Trial (EMPA-REG OUTCOME)[6] and the CANagliflozin cardioVascular Assessment Study (CANVAS) trials,[7] sensitivity analyses failed to show a signal that SGLT2i treatment as an add-on to insulin or insulin secretagogues (sulfonylureas and dipeptidyl peptidase-4 inhibitors) was associated with lower cardiovascular protection. Conversely, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, patients randomised to

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liraglutide, a GLP-1RA, did not use an SGLT2i; nevertheless, the results showed a degree of cardioprotection similar to that observed in EMPA-REG OUTCOME and CANVAS.[8]

In the DURATION-8 trial,[9,10] dapagliflozin, an SGLT2i, and exenatide once weekly (EQW), a GLP-1RA, were used alone and in combination in patients with T2D on stable metformin doses. After 28 weeks of treatment, the expected reductions in glycated haemoglobin (HbA_{1c}) levels and body weight were significantly larger in patients receiving the combination compared with those receiving either of the individual treatments, an effect that was maintained after 52 weeks of randomised treatment[10]. The large number of patients included in the study, the randomised design, and the blinded extension of up to 1 year presented a unique opportunity to test the effects of individual and combined therapy on circulating ketones and associated metabolites, thereby prompting the present study.

Materials and Methods

This 52-week, double-blind, parallel-group, randomised, active-controlled, phase 3 study (NCT02229396) was carried out at 109 sites across 6 countries from 2014 to 2016. The study design consisted of a screening visit and a 1-week placebo (Plb) lead-in before randomisation. Eligible participants were aged 18 years or older with T2D and had inadequate glycaemic control (HbA_{1c} = 64–108 mmol/mol [8.0%–12.0%] inclusive at screening) despite at least 2 months of treatment with a stable metformin dosage (≥ 1.5 g/day). Patients who received any glucose-lowering drugs other than metformin for more than 14 days in the 12 weeks before enrollment were excluded.

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Patients were centrally randomised (1:1:1) *via* an interactive voice and web-response system to receive EQW 2 mg with once-daily dapagliflozin 10 mg (EQW + Dapa group), EQW with once-daily oral Plb tablets (EQW + Plb group), or Dapa with once-weekly injections of Plb microspheres (Dapa + Plb group), on top of their existing metformin regimen. Patients, investigators, and data analysts were blinded to treatment assignment. Plb was supplied as oral tablets matching those of Dapa, or as powder along with prefilled syringes of diluent as a suspension for injections matching those provided for EQW. Results for the primary endpoint (namely, change in HbA_{1c} levels from baseline to weeks 28 and 52) and secondary glycaemic endpoints (the proportion of patients achieving an HbA_{1c} target of less than 53 mmol/mol [< 7.0%] at weeks 28 and 52, and a change in fasting plasma glucose and 2-hour postprandial glucose levels from baseline to weeks 28 and 52) have been published previously, as have results on all the safety variables.[9,10]

Fasting plasma glucose was measured after an overnight fast; postprandial glucose was measured 2 hours following ingestion of a standardized liquid meal of defined nutrient content (Ensure Plus [Abbott Nutrition, Abbott Park, IL, USA] or a regional equivalent). Plasma insulin (Chemiluminescence Access on plasma [Beckman Coulter, Brea, CL, USA]) and glucagon concentrations (Radioimmunoassay [MilliporeSigma, Burlington, MA, USA]) were measured in fasting and 2-hour postprandial blood samples; plasma glucose, free fatty acids (FFA), β-OH, glycerol, and lactate were measured in fasting blood samples by standard enzymatic techniques; urinary glucose-to-creatinine ratio (g/g) was determined on spot urine samples using standard enzymatic techniques. For all measurements, samples were analysed at baseline (ie, at randomisation), 28 weeks, and 52 weeks. An insulin-to-glucagon molar

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concentration ratio (I/Glg; mol/mol) was calculated from both the fasting and the postprandial measurements.

The study protocol was approved by the Institutional Review Boards and Ethics Committees at each site and carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines**.** All patients provided written informed consent prior to their inclusion in the study.

Statistical Methods: For this *post hoc* analysis, we used all available data from all participants regardless of rescue therapy. Data are summarised as mean ± standard deviation (SD) or, for variables with a skewed distribution, as median and interquartile range [IQR]*. Time courses were tested by multivariate analysis of variance (MANOVA) for repeated measures; *P* values for time, treatment, and their interaction are reported. Changes from baseline across treatment group were analysed by analysis of variance (ANOVA) for repeated measures with adjustment for baseline value. Within-group paired comparisons were carried out by the Wilcoxon signed-rank test. For statistical analyses, variables with a skewed distribution were log-transformed. Univariate and multivariate linear regressions were carried out by standard methods. Data analyses were performed using JMP® 7.0 (SAS Institute Inc., 2007); $P \leq 0.05$ was considered statistically significant.

Results

In the entire study cohort (n = 678), 52% of the patients were female, mean age was 54 ± 10 years, duration of diabetes was 6 [7] years, mean body mass index (BMI) was 32.7 ± 6.3

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kg/m^2, mean HbA_{1c} levels were 9.3% ± 1.1% (78 ± 9 mmol/mol), and baseline urine glucose-to-creatinine ratio was 0.3 [3.0] g/g; these clinical characteristics were balanced across the 3 treatment groups.

Over 1 year of treatment, the levels of HbA_{1c} and fasting and postprandial glucose decreased in all the 3 treatment groups but significantly more with EQW + Dapa than with either treatment alone, as previously reported[9,10]. Fasting and postprandial plasma insulin concentrations increased with EQW alone, whereas fasting plasma glucagon concentrations decreased slightly in all the 3 groups; postprandial glucagon levels were maintained with Dapa alone and declined in the other 2 groups (**Table 1**). Consequently, the fasting I/Glg increased in the EQW group only. Compared with baseline, the corresponding postprandial I/Glg increased in all the 3 groups but significantly more in the EQW alone group. Of note, weight loss was greater with EQW + Dapa than with either treatment alone at week 28 and did not change at week 52 (**Table 1**), an extent and time course similar to that observed in longer-term trials of empagliflozin[6] and canagliflozin,[7] or liraglutide.[8] The individual treatments, however, were associated with weaker weight loss as compared with previous trials,[6-8] possibly because the patients in DURATION-8 had worse glycaemic control at baseline[9].

Fasting plasma β-OH, FFA, and glycerol concentrations showed a parallel behavior over time: larger decrements in the EQW alone group, larger increments in the Dapa alone group, and intermediate changes in the combination group. Plasma lactate concentrations decreased in all groups to a similar extent (**Table 2**). In the whole cohort, fasting β-OH and FFA levels at baseline were well correlated with one another in a direct fashion (**Fig. 1**). Furthermore, in

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the combined Dapa groups, β-OH at week 52 was also directly related to the urine glucose-to-creatinine ratio ($P = 0.0035$). The changes from baseline in fasting β-OH at weeks 28 and 52 were opposite with Dapa alone *vs* EQW alone, and the changes in the combination group were intermediate (**Fig. 2**). Likewise, the fasting and postprandial I/Glg showed no change from baseline with Dapa alone, large increments with EQW alone, and intermediate increases with the combination. In addition, in this analysis, values of both fasting and postprandial I/Glg were significantly higher at week 52 than at week 28 (**Fig. 3**). In the whole cohort, fasting β-OH levels and I/Glg at baseline were inversely related to one another; though statistically significant, the association was weak (**Fig. 1**).

Glycosuria and haematocrit increased and BMI decreased in the groups receiving Dapa *vs* EQW alone (**Table 1**). Serum low-density lipoprotein (LDL)-cholesterol increased slightly, and serum triglycerides decreased in all the 3 groups, whereas high-density lipoprotein (HDL)-cholesterol increased with Dapa alone (data not shown).

Because of the skewed distribution of plasma β-OH concentrations, we analyzed the percentage of β-OH values in the top quartile of all available fasting plasma β-OH measurements (*i.e.*, ≥ 442 μmol/L, n = 1711) by week and treatment group. As shown in **Fig. S1**, there were significantly more values falling into the top quartile in the Dapa group than in the EQW alone group, particularly at week 52 (35% *vs* 18%).

As expected, patients in the top quartile of changes in β-OH levels from baseline to week 28 were more frequently treated with Dapa alone and had higher urine glucose-to-creatinine ratios. The clinical phenotype of these patients showed lower baseline BMI, fasting insulin, I/Glg, lactate, and HDL-cholesterol (**Table S1**).

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Rescue treatment with insulin was used – at the discretion of the investigators – in 26% of the whole cohort, similarly in the 3 treatment arms. Patients receiving rescue insulin treatment had longer baseline diabetes duration, higher HbA_{1c} and fasting glucose, lower postprandial insulin concentrations and insulin/glucagon concentration ratio (**Table S2**). Nonetheless, the pattern of changes in glucose and metabolites over time and across treatment was similar to that of the whole cohort (**Table S3**) as were the changes from baseline in plasma ß-OH and FFA levels (**Fig. S2**).

Discussion

The present study confirms that Dapa causes an increase in fasting β-OH levels (similar to other SGLT2i) and also shows that this increase (+41% ± 26%) persists essentially unchanged for up to 1 year, accompanied by parallel increments in plasma FFA concentrations. Of note is that the increments in β-OH had a skewed distribution, with ~30% of the on-treatment values falling into the top quartile of the distribution of all baseline β-OH measurements (**Fig. S1**), and 10% of the values exceeding a concentration of 1 mmol/L. The other major finding is that although 1-year treatment with EQW suppressed plasma β-OH and FFA concentrations, EQW + Dapa prevented only the rise in fasting β-OH and FFA levels seen with Dapa alone, resulting in values that were almost exactly intermediate between those of the two drugs alone. With regard to the hormonal background, the changes in both fasting and postprandial I/Glg matched the changes in β-OH in an inverse fashion: higher values were coupled with lower β-OH and FFA changes across the treatment groups and time. These

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results align with the physiological paradigm of SGLT2 inhibition: the glycosuria-induced drop in plasma glucose levels leads to decreased insulin release, enhanced lipolysis, and increased FFA delivery to tissues and ketogenesis.[1] The concomitant increase in glucagon release, persistent though mild, assists in sustaining ketogenesis in the liver and, possibly, in the kidneys. It is remarkable that treatment with EQW alone increased the I/Glg (fasting and postprandial) significantly more at week 52 than at week 28 (**Fig. 3**), indicating some strengthening of insulin stimulation and/or glucagon suppression. Nevertheless, EQW + Dapa did not result in a significantly stronger suppression of β-OH levels at week 52 compared with week 28 (**Fig. 2 and Table 2**). These data suggest that, with SGLT2 inhibition, fasting ketogenesis is somewhat reinforced over time.

Of additional interest is that the hematocrit increased similarly with Dapa alone (by 4% ± 8% and by 4% ± 7% above baseline at week 28 and week 52, respectively, $P < 0.04$ for the paired difference) and in combination with EQW (by 3% ± 8% and 5% ± 8% at the 2 time-points, respectively, $P < 0.001$) *vs* with EQW alone (−2% ± 6% and −1% ± 6%, at the 2 time-points, respectively, $P < 0.001$). Furthermore, in the whole dataset, changes in hematocrit were directly related to the urine glucose-to-creatinine ratio at both follow-up examinations ($P < 0.0001$ for both).

These findings bear some relevance to potential mechanisms explaining the cardiovascular outcomes of SGLT2i trials,[6,7] as SGLT2-induced hyperketonaemia has been hypothesised to provide metabolic relief to a failing heart.[5] The current results demonstrate that *initial* association of a GLP-1RA (an insulin secretagogue) with an SGLT2i prevents the rise in plasma ketones seen with Dapa alone. Whether the same would occur if SGLT2

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inhibition were to be added to an *existing* regimen of insulin secretagogues remains to be established. At present, the degree of chronic hyperketonaemia necessary and sufficient to activate this putative metabolic mechanism remains undefined. Conversely, an increased haematocrit reflects both a diuretic effect and an improved oxygen-carrying capacity of blood[1,5]; the present data demonstrate that GLP-1 agonism does not inhibit the rise in hematocrit elicited by SGLT2 inhibition. Therefore, in high-risk patients, the combination of SGLT2 inhibition and GLP-1 agonism may enhance cardioprotection by adding a potential anti-atherosclerotic activity of a GLP-1RA[8,11] to the persistent haemodynamic changes.[12]

Use of an SGLT2i has been associated with cases of ketoacidosis both in patients with type 1 diabetes and T2D, especially if on insulin treatment.[13-17] It, therefore, was of particular interest to try and identify any baseline patient characteristics, clinical or metabolic, that might predict an exaggerated rise in ketonaemia after initiation of treatment with Dapa. In the present cohort of patients with poorly controlled T2D, patients in the top 25% of β-OH changes at 28 weeks were in the combined Dapa groups *vs* the EQW group (82% *vs* 64%, respectively), as expected. However, 25 patients (18%) in this higher β-OH-response category were found in the EQW group, indicating that a rise in ketones can occur even in patients treated with an insulin secretagogue. The phenotype of patients in the higher β-OH-response category included relative hypoinsulinaemia and better hepatic insulin sensitivity (as indexed by HOMA-IR); the strongest single predictor was fasting plasma insulin concentration. Of further note is that half of the patients in the top quartile of β-OH changes at week 28 were in the top quartile of β-OH changes at week 52, indicating a tendency to ketosis that is consistent over time. Even more stringently, the 18 patients in whom β-OH

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levels at 28 weeks exceeded ≥ 1 mmol/L (median: 1.35 mmol/L, range: 1.01–3.58; 89% in the combined Dapa groups) had fasting plasma insulin levels that were half those of all the other patients in the study (38 [27] *vs* 65 [55] pmol/L, $P = 0.0005$). Notably, there were no cases of diabetic ketoacidosis in either of the Dapa groups in DURATION-8; there was a single case of diabetic ketoacidosis in the EQW alone group.

In conclusion, combining Dapa with EQW in poorly controlled T2D abolishes the rise in ketonaemia seen with Dapa alone but maintains a higher ketonaemia than that achieved with EQW alone. Low fasting plasma insulin concentrations are predictive of higher on-treatment ketonaemia, in line with the established concept that insulin is a potent suppressor of ketogenesis. β-OH values in the millimolar range occasionally develop in patients with T2D (3% in this cohort), implying a risk of progression to ketoacidosis; simultaneous treatment with EQW mitigates this risk.

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Conflict of Interest:

E.F. has served as an ad hoc consultant and occasional speaker for Boehringer Ingelheim, Merck & Co., Sanofi, Eli Lilly & Co., Johnson & Johnson, AstraZeneca, and Novo Nordisk, and has received research grants from Eli Lilly & Co. and Boehringer Ingelheim. S.B. has no conflict of interest to disclose. J.P.F. has received research support from AbbVie, Akcea, Allergan, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cirius, Cymabay, Elcelyx, Eli Lilly, Enanta, Genentech, Intercept, IONIS, Janssen, Johnson & Johnson, Lexicon, Ligand, Madrigal, Merck, Mylan, NGM, Novartis, Novo Nordisk, Pfizer, Sanofi, Theracos, and vTv Therapeutics; has participated in scientific advisory boards for and received consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, Novo Nordisk, Sanofi, and Theracos; and is involved in speaker bureaus for Merck and Sanofi. C.G. has participated in scientific advisory boards and received consulting fees from Astra Zeneca, Boehringer Ingelheim, Egis, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Zentiva. E.H. and E.R. are employees of AstraZeneca. S.A.J. is a consultant for AstraZeneca, Eli Lilly, and Janssen. R.A.D. has received research support from Bristol-Myers Squibb, Boehringer Ingelheim, Takeda, and

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An abstract on this study was presented at the 77th Scientific Sessions, American Diabetes Association at San Diego, California, in 2017.

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Author contributions

E.F. researched data and wrote the manuscript. S.B. researched data and reviewed/edited the manuscript. J.P.F., C.G., and S.A.J. researched data and contributed to the discussion and reviewed/edited the manuscript. E.H., E.R., and R.A.D. contributed to the discussion and reviewed/edited the manuscript. All authors take responsibility of the content of the article.

Data Sharing and Data Accessibility

Additional data can be found in the 2016 and 2018 publications of the DURATION-8 study.[9,10] Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Legends to the figures

Figure 1. Relationship between fasting β-OH and FFA (*top panel*) concentrations or the fasting I/Glg ratio (*bottom panel*).

β-OH, β-hydroxybutyrate; FFA, free fatty acids; I/Glg, insulin-to-glucagon molar ratio.

Figure 2. Changes from baseline in fasting plasma β-OH (*top panel*) and FFA (*bottom panel*) concentrations are plotted (mean ± SEM) by week and treatment.

β-OH, β-hydroxybutyrate; Dapa, dapagliflozin; EQW, exenatide once weekly; FFA, free fatty acids; Plb, placebo. *$P < 0.0001$ for the effect of treatment.

Figure 3. Changes from baseline in fasting (*top panel*) and postprandial (*bottom panel*) plasma I/Glg are plotted (mean ± SEM) by week and treatment. Dapa, dapagliflozin; EQW, exenatide once weekly; I/Glg, insulin-to-glucagon molar ratio; Plb, placebo. °$P < 0.0001$ for the effect of treatment; $^{§}P = 0.0103$ and $^{\#}P = 0.0004$ for the difference between week 28 and week 52.

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Table 1. Fasting and Postprandial Metabolic Variables by Time and Treatment[†]

	Baseline	28 Weeks	52 Weeks	P^{*}	P^{**}	P^{***}
BMI (kg/m^2)	(n = 678)	(n = 595)	(n = 546)	<0.0001	0.3140	<0.0001
Dapa + Plb	33.0 ± 6.1	32.2 ± 5.9	32.2 ± 5.8			
EQW + Plb	32.1 ± 5.9	31.5 ± 5.5	31.7 ± 5.4			
EQW + Dapa	33.3 ± 6.8	32.0 ± 6.2	32.2 ± 6.1			
HbA_{1c} (%)	(n = 658)	(n = 673)	(n = 673)	<0.0001	0.3140	<0.0001
Dapa + Plb	9.3 ± 1.0	7.8 ± 1.2	7.9 ± 1.1			
EQW + Plb	9.3 ± 1.1	7.6 ± 1.3	7.7 ± 1.3			
EQW + Dapa	9.3 ± 1.1	7.3 ± 1.3	7.5 ± 1.3			
Hematocrit (%)	(n = 677)	(n = 592)	(n = 537)	<0.0001	0.0141	<0.0001
Dapa + Plb	42.0 ± 3.5	43.5 ± 4.1	43.8 ± 4.0			
EQW + Plb	42.3 ± 3.9	41.5 ± 4.0	42.2 ± 3.8			
EQW + Dapa	41.7 ± 3.9	43.0 ± 3.9	43.8 ± 4.4			
Urine G/creatinine (g/g)	(n = 607)	(n = 540)	(n = 499)	<0.0001	0.0001	<0.0001
Dapa + Plb	0.3 [3]	27 [33]	22 [29]			
EQW + Plb	0.2 [3]	0.1 [0.1]	0.1 [0.1]			
EQW + Dapa	0.3 [3]	20 [24]	21 [24]			
Fasting I (pmol/L)	(n = 678)	(n = 570)	(n = 472)	0.0068	0.0681	<0.0001
Dapa + Plb	65 [61]	55 [56]	65 [55]			
EQW + Plb	65 [53]	76 [69]	81 [88]			
EQW + Dapa	60 [60]	59 [66]	64 [57]			
Fasting Glg (pmol/L)	(n = 672)	(n = 616)	(n = 622)	<0.0001	0.1413	0.7763
Dapa + Plb	31 [12]	30 [13]	29 [13]			
EQW + Plb	29 [10]	28 [10]	27 [10]			
EQW + Dapa	29 [12]	28 [15]	27 [12]			
Fasting I/Glg (mol/mol)	(n = 655)	(n = 604)	(n = 618)	<0.0001	0.0070	<0.0001
Dapa + Plb	2.12 [1.67]	1.95 [1.58]	2.21 [1.79]			
EQW + Plb	2.17 [1.74]	2.52 [2.52]	2.73 [3.05]			
EQW + Dapa	2.10 [1.99]	1.88 [2.12]	2.22 [2.36]			
Postprandial I (pmol/L)	(n = 658)	(n = 587)	(n = 603)	0.0003	0.1528	0.0001
Dapa + Plb	170 [186]	156 [165]	161 [173]			
EQW + Plb	151 [167]	198 [220]	205 [213]			
EQW + Dapa	151 [189]	176 [168]	168 [209]			
Postprandial Glg (pmol/L)	(n = 672)	(n = 600)	(n = 607)	<0.0001	0.0172	0.0613
Dapa + Plb	32 [10]	33 [14]	32 [14]			
EQW + Plb	31 [10]	30 [12]	29 [13]			
EQW + Dapa	31 [12]	29 [12]	29 [12]			
Postprandial I/Glg (mol/mol)	(n = 656)	(n = 584)	(n = 602)	<0.0001	0.0194	<0.0001
Dapa + Plb	5.10 [6.16]	4.64 [5.43]	5.25 [5.57]			
EQW + Plb	4.79 [5.34]	6.58 [7.69]	6.78 [7.80]			
EQW + Dapa	4.86 [5.27]	5.67 [5.59]	5.76 [8.20]			

[†]Values are mean ± SD or median [IQR].

$^{*}P$ = time, $^{**}P$ = treatment, $^{***}P$ = time × treatment.

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Abbreviations: BMI, body mass index; Dapa, dapagliflozin; EQW, exenatide once weekly; Glg, glucagon; HbA_{1c}, glycated hemoglobin; I, insulin; I/Glg, insulin-to-glucagon molar ratio; IQR, interquartile range; Plb, placebo; SD, standard deviation.

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Table 2. Metabolite Concentrations by Time and Treatment[†]

	Baseline	28 Weeks	52 Weeks	P^{*}	P^{**}	P^{***}
Fasting glucose (mmol/L)	(n = 678)	(n = 678)	(n = 678)	<0.0001	0.0332	<0.0001
Dapa + Plb	10.8 ± 2.6	8.2 ± 2.3	8.4 ± 2.4			
EQW + Plb	10.6 ± 2.8	8.2 ± 2.5	8.2 ± 2.6			
EQW + Dapa	11.0 ± 3.0	7.4 ± 2.1	7.5 ± 2.5			
Postprandial glucose (mmol/L)	(n = 676)	(n = 608)	(n = 609)	<0.0001	0.0035	<0.0001
Dapa + Plb	14.6 ± 3.4	11.4 ± 3.1	11.6 ± 3.3			
EQW + Plb	14.9 ± 3.7	11.3 ± 3.2	11.5 ± 3.4			
EQW + Dapa	15.1 ± 3.7	9.9 ± 2.7	10.3 ± 3.0			
β-OH (µmol/L)	(n = 668)	(n = 568)	(n = 470)	0.0051	0.1597	<0.0001
Dapa + Plb	350 ± 183	448 ± 481	449 ± 367			
EQW + Plb	430 ± 232	351 ± 162	323 ± 176			
EQW + Dapa	402 ± 182	402 ± 227	377 ± 220			
FFA (µmol/L)	(n = 666)	(n = 570)	(n = 472)	0.2944	0.0695	0.0002
Dapa + Plb	500 ± 224	537 ± 217	553 ± 215			
EQW + Plb	587 ± 232	539 ± 199	534 ± 232			
EQW + Dapa	571 ± 220	559 ± 231	565 ± 229			
Glycerol (µmol/L)	(n = 621)	(n = 528)	(n = 441)	<0.0001	0.0716	0.0008
Dapa + Plb	70 ± 45	72 ± 36	70 ± 38			
EQW + Plb	75 ± 41	65 ± 33	65 ± 36			
EQW + Dapa	78 ± 44	73 ± 54	75 ± 43			
Lactate (mmol/L)	(n = 666)	(n = 563)	(n = 460)	<0.0001	0.9855	0.3722
Dapa + Plb	2.34 ± 1.16	2.24 ± 1.14	2.14 ± 1.02			
EQW + Plb	2.43 ± 1.08	2.24 ± 1.08	2.05 ± 0.75			
EQW + Dapa	2.34 ± 1.11	2.20 ± 1.05	2.00 ± 0.80			

[†]Values are mean ± SD.

$^{*}P$ = time, $^{**}P$ = treatment, $^{***}P$ = time × treatment by MANOVA for repeated measures.

Abbreviations: β-OH, β-hydroxybutyrate; Dapa, dapagliflozin; EQW, exenatide once weekly; FFA, free fatty acids; MANOVA, multivariate analysis of variance; Plb, placebo; SD, standard deviation.

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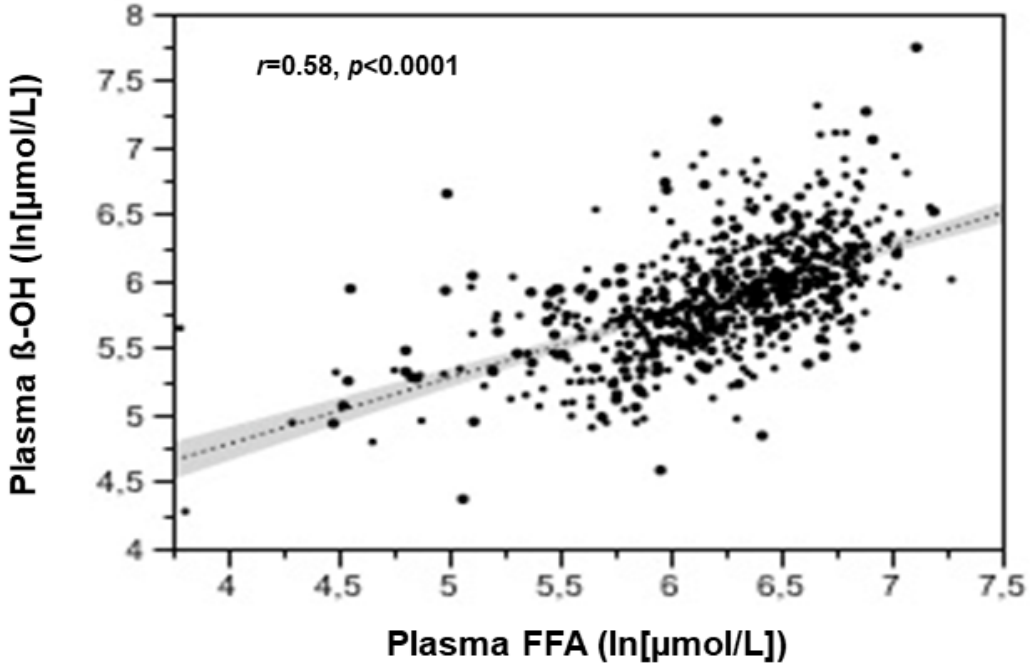

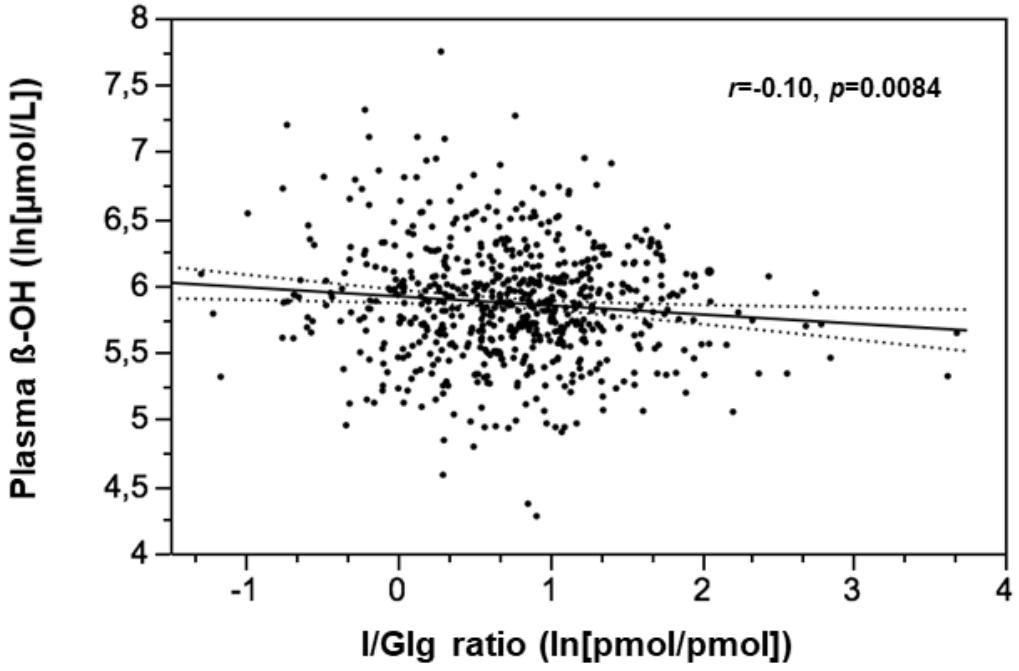

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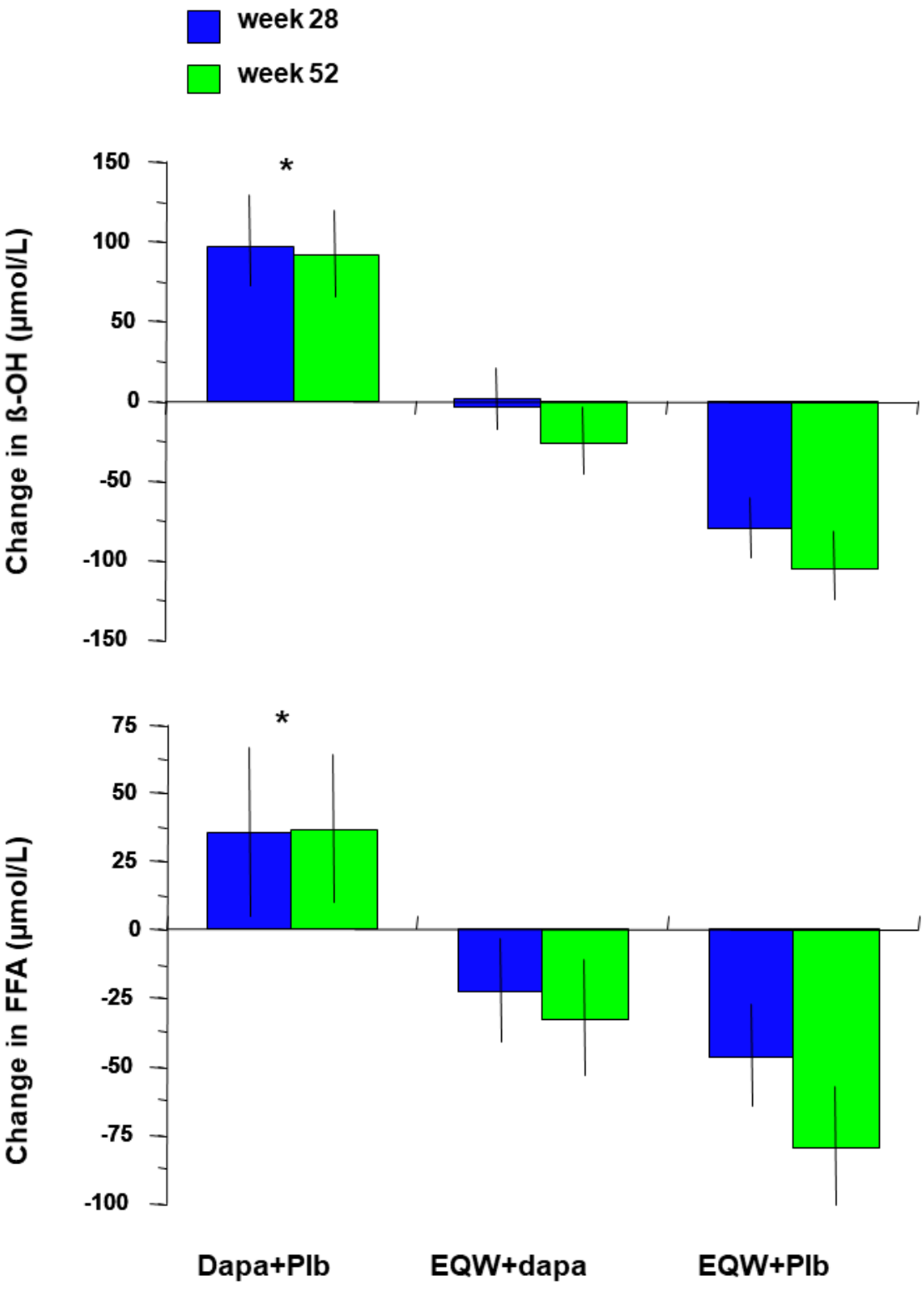

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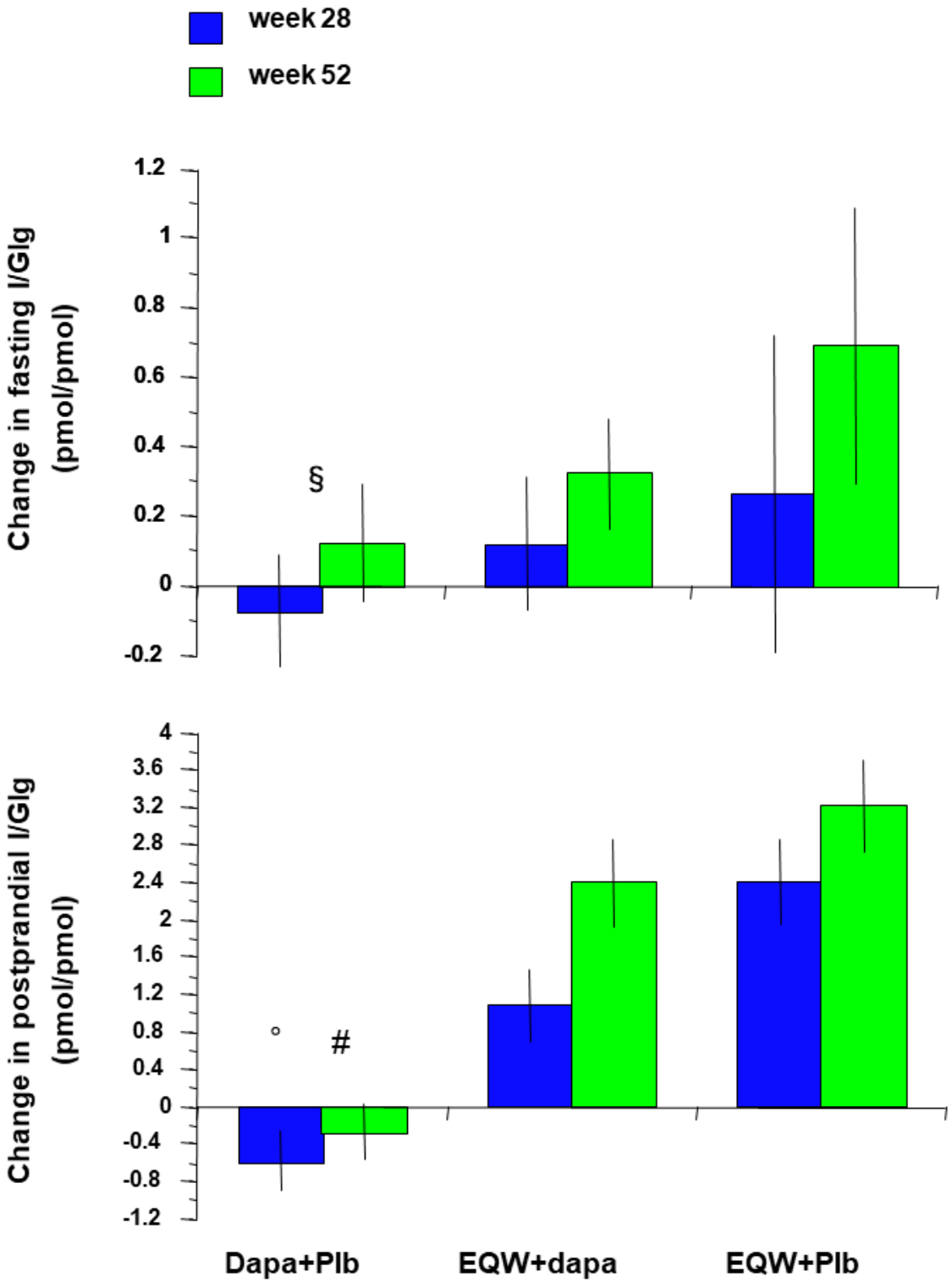

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