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Allelic Variant in the Glucagon-Like Peptide 1 Receptor Gene Associated with Greater Effect of Liraglutide and Exenatide on Gastric Emptying: A Pilot Pharmacogenetics Study

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Abstract

Background—Weight loss in response to the long-acting GLP-1 receptor (GLP1R) analog, liraglutide, is correlated with delay in gastric emptying (GE). The aim of this pilot study was to assess whether specific genetic variants in *GLP1R* or *TCF7L2* are associated with delayed GE and weight loss in obese patients treated with liraglutide or the short-acting GLP-1 agonist, exenatide.

Methods—We evaluated in obese individuals the associations of genetic variations of *GLP1R* (rs6923761) and *TCF7L2* (rs7903146) on GE $T_{1/2}$ and weight from two trials that evaluated separately exenatide, 5µg BID for 30 days, or liraglutide, 3mg daily for 5 weeks. Data were analyzed using the dominant genetic model and intention to treat analysis.

Key Results—There was a significant correlation between changes in weight and GE $T_{1/2}$ ($r_s = -0.382$, $p=0.004$). *GLP1R* rs6923761 minor allele A (AA_AG) carriers who received either exenatide or liraglutide had greater delay in GE $T_{1/2}$ relative to baseline [117.9±27.5 (SEM) minutes and 128.9±38.32 minutes] compared to GG genotype (95.8±30.4 minutes and 61.4±21.4 minutes, respectively) ($p=0.11$). There was a nonsignificant difference in weight loss based on *GLP1R* rs6923761 genotype after 5 weeks of treatment. There were no significant correlations with *TCF7L2* (rs7903146) genotype.

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Conclusions & Inferences—The minor A allele of *GLP1R* (rs6923761) is associated with greater delay in GE $T_{1/2}$ in response to liraglutide and exenatide. These studies provide data to plan pharmacogenetics testing of the hypothesis that *GLP1R* (rs6923761) influences weight loss in response to GLP1R agonists.

Abbreviated Abstract

The minor A allele of GLP1R (rs6923761) is associated with greater delay in gastric emptying $T_{1/2}$ in response to liraglutide and exenatide. These studies provide data to plan pharmacogenetics testing of the hypothesis that GLP1R (rs6923761) influences weight loss in response to GLP1R agonists.

Keywords

glucagon-like peptide 1 receptor; rs6923761; liraglutide; gastric emptying; obesity

INTRODUCTION

A subset of obese individuals has significantly increased calorie intake, larger fasting gastric volume, and accelerated gastric emptying of solids¹. Glucagon-like peptide 1 (GLP-1) is a hormone secreted by the enteroendocrine intestinal L cells; GLP-1 results in insulin secretion, glucagon inhibition², and inhibition of gastric emptying³⁴. Morbidly obese patients (BMI=42±4 kg/m²) had faster gastric emptying and lower GLP-1 levels compared to normal weight controls⁵; this was replicated among overweight and obese class I or class II/III individuals¹. There is also evidence of variation in GLP-1 secretion in obesity after oral and small intestinal nutrient administration⁶; the precise mechanism(s) associated with this difference is unclear. GLP-1 receptor (GLP1R) agonists include short-acting, such as exenatide, and long-acting analogs, such as liraglutide. Participants treated with liraglutide experienced average weight loss of 8% after 6 months of treatment, with >10% body weight loss in 33% of participants; factors associated with greater weight loss are unclear⁷.

In a randomized, placebo-controlled trial of liraglutide, 3.0mg daily, in obese individuals, we recently reported that liraglutide delayed gastric emptying, and this was associated with weight loss with liraglutide over a 16-week treatment period⁸. Similarly, in a prior randomized, placebo-controlled trial of exenatide, 5µg BID for 30 days, obese participants

developed significant delay in gastric emptying, with non-significant higher weight loss with exenatide than placebo ($p=0.23$)⁹. Studies with liraglutide have shown that ~15% of patients lose >15% of body weight, and this is maintained over 1 or 3 years⁷. The reason(s) for the marked variation of weight loss in response to liraglutide treatment is unclear.

Our hypothesis was that the effect of GLP-1 agonists, such as exenatide and liraglutide, on weight loss may be affected by genetic variances of the *GLPIR* gene or the *TCF7L2* gene. The rationale for selecting these genes and single nucleotide polymorphisms (SNP) is provided in the methods section. The aim of this pilot study was to assess whether specific genetic variants in *GLPIR* (rs6923761) or *TCF7L2* (rs7903146) are associated with prolongation of gastric emptying and weight loss in obese patients treated with exenatide or liraglutide.

MATERIALS AND METHODS

Overall Design of Trial, Participants, and Treatment

We evaluated the genetic variations of *GLPIR* and *TCF7L2* from two different published studies^{8,9} involving single-center, double-blinded, placebo-controlled, randomized clinical trials: the first (ClinicalTrials.gov #NCT02160990) utilized exenatide, 5µg BID administered for 30 days, in 20 obese individuals with rapid gastric emptying of solids (GE $T_{1/2}$ <90 min)⁹, and the second (ClinicalTrials.gov #NCT02647944) studied liraglutide, 3mg/day, administered over 16 weeks in 40 obese individuals with normal or accelerated gastric emptying of solids⁸. Further details of these trials are provided in the relevant publications and in Figures 1A and 1B.

Gastric Emptying Measurement

Both studies utilized the same 296kcal test meal and scintigraphic method to measure gastric emptying. Details are available elsewhere^{8,9,10,11}.

Rationale for Selection of Genes and SNPs

GLPIR is the therapeutic target of GLP-1 and its agonists, such as exenatide, and analogs, such as liraglutide. Genetic variants in *GLPIR* have been associated with altered *GLPIR* function¹². Of these SNPs, *GLPIR* (rs6923761) is the most frequent missense variant that has been studied in obesity and type 2 diabetes¹³. In prior studies in the same geographic region, a genetic evaluation of *GLPIR* (rs6923761) demonstrated that 51 patients (56.7%) had GG genotype and 39 (43.3%) had either AA or AG genotypes. Based on an analysis using a dominant genetic model in 90 overweight patients with type 2 diabetes, participants with the variant A allele (AA_AG) demonstrated greater effects on body mass index (BMI), body weight, and fat mass in response to liraglutide, 1.8mg/day, than participants carrying only the G allele (GG)¹³.

TCF7L2 is involved in the secretion of GLP-1 from enteroendocrine L cells and, therefore, it impacts the levels of endogenous GLP-1. *TCF7L2* (rs7903146) gene variants have been associated with defects in insulin secretion and type 2 diabetes^{14–16}. In a study by Vazquez-Roque et al., reduced fasting gastric volume and more rapid gastric emptying of liquids were

associated with the T allele of the *TCF7L2* (rs7903146) gene¹⁷. Accelerated gastric emptying is associated with obesity¹. Based on a similar population of 3,609 participants, *TCF7L2* (rs7903146) allelic frequency consisted of 53.4% with CC and 46.6% with TT_CT¹⁸.

Genotyping *GLP1R* rs6923761 and *TCF7L2* rs7903146

DNA was extracted from venous blood, and candidate genotype analysis was conducted on stored DNA by established PCR-based methods using TaqMan® SNP Genotyping Assays rs6923761 [*GLP-1* (catalog no. C_25615272_20)] and rs7903146 [*TCF7L2* (catalog no. C_29347861_10)] (Applied Biosystems, Foster City, CA) in accordance with the manufacturer's instructions. Following polymerase chain reaction amplification, end reactions were analyzed with an ABI ViiA-7 Real-Time PCR System using QuantStudio™ Real-Time PCR software (Applied Biosystems, Foster City, CA).

Statistical Analysis

The genes were grouped into dominant (AA) and minor alleles (Aa/aa) based on reported prevalence in the population from the NCBI database¹⁹. We used an intention to treat analysis with multiple imputations for any missing data. Our major outcomes were the changes in gastric emptying and weight loss at 5 weeks for liraglutide and at 30 days for exenatide studies. First, we combined data from the two studies to assess effects of GLP-1 agonist or analog versus placebo.

In the genotype by treatment analysis, data from the two studies were assessed using three groups (liraglutide, exenatide, and the combined placebo group). Transformation to rank scale was used for change in weight (*TCF7L2*), but not for *GLP1*. For post-gastric emptying (e.g. GE T_{1/2} at 30 days), a proportional hazards regression analysis was used to accommodate “censored” values. Analyses of the “interaction effects” of treatment by genotype were used for both changes in weight and GE T_{1/2}. Data were reported as mean ± standard error of the mean (SEM).

RESULTS

Disposition

Figure 1 shows the CONSORT flow charts and genotypes by treatment group for both exenatide and liraglutide studies. Genotyping for *GLP1R* rs6923761 was unavailable for one participant in the placebo group in the exenatide cohort. One participant in the liraglutide group refused genotyping. In our study, the overall allelic frequencies for *GLP1R* (GG 53.5%, AA_AG 46.5%) and *TCF7L2* (CC 55.9%, TT_CT 44.1%) were similar to those reported in the literature.

The baseline demographics in the three groups (placebo vs. liraglutide vs. exenatide) were not significantly different (Table 1). The mean baseline gastric emptying T_{1/2} for the 31 participants in the placebo arm was 103.7±6.2 (SEM) minutes and for the liraglutide group it was 121.2±58 minutes, which is consistent with the reported range for normal controls [median 120 minutes (5–95th percentile, 78.4–174)]²⁰. In the exenatide group, we had

preselected participants with accelerated gastric emptying (GE $T_{1/2}$ 82.4 ± 5.1 minutes). The effects of these GLP-1 agents are published elsewhere ^{8,9}. There was a significant correlation between the change in weight and gastric emptying at 30 days or 5 weeks ($r_s = -0.382$, $p = 0.004$) (Figure 2).

Effect of Genetic Variants on Gastric Emptying in Response to Exenatide and Liraglutide

Data obtained by subdividing the groups by *GLPIR* (rs6923761) and *TCF7L2* (rs7903146) genotypes are available in the Appendix table.

Within *GLPIR* (rs6923761), patients carrying the minor allele A (AA_AG) who received either exenatide or liraglutide had a numerically larger mean retardation in gastric emptying relative to baseline, 117.9 ± 27.5 minutes and 128.9 ± 38.3 minutes, respectively, compared to those with the dominant allele G (GG), 98.5 ± 30.4 minutes and 61.4 ± 21.4 minutes, respectively ($p = 0.11$). As seen in Figure 3A, the delay in gastric emptying was greatest in response to liraglutide in patients with the AA_AG genotype of *GLPIR* compared to the GG genotype. There was a nonsignificant mean change in weight (weight) at 5 weeks in the AA_AG group (-0.9 ± 0.5 kg in the exenatide group and -3.5 ± 0.6 kg in the liraglutide group) compared to the GG group (-1.9 ± 0.4 kg in the exenatide group and -3.0 ± 0.5 kg in the liraglutide group) ($p = 0.62$) (Figure 3B).

For the *TCF7L2* (rs7903146) genotype (major vs. minor allele), assessment, changes in gastric emptying at 5 weeks ($p = 0.93$) and weight loss at 5 weeks ($p = 0.72$) were not different. The box-and-whiskers plot (Figure 3B) highlights these results.

DISCUSSION

In this study, we evaluated the potential impact of functional genetic variants of *GLPIR* (rs6923761) and *TCF7L2* rs7903146 on the response to exenatide or liraglutide. Our data represent a 67.5 minute (~50%) difference in the mean change in gastric emptying in (AA_AG) and (GG) subgroups based on the *GLPIR* (rs6923761) variants on treatment with liraglutide. Hence, we observed a numerically greater delay in gastric emptying in carriers of the minor variant (AA_AG) of *GLPIR* (rs6923761) in response to liraglutide. Although this difference was not statistically significant, a mean difference of 65 minutes (and median 25 minutes) is biologically relevant from the perspective of the association of delayed gastric emptying with satiation and, therefore, caloric intake, since a 25 minute difference in gastric emptying $T_{1/2}$ would be associated with 80kcal greater calorie intake in a buffet meal or nutrient drink test ²³. There was also a greater delay in the change in gastric emptying in the AA_AG compared to the GG group for exenatide (mean difference, 19.4 min), but not to the same degree observed with liraglutide. Although we did not observe a substantial difference in weight loss at 5 weeks between AA-AG and GG *GLPIR* (rs6923761) genotype groups, this may reflect a type II error and the relatively short duration of the treatment trial.

Genetic variants of *GLP-IR* have been associated with changes in *GLPIR* function ¹², response to hypocaloric diets ²⁴, as well as response to treatment with liraglutide ^{13,25}. Specifically, the minor variant allele (A) of *GLPIR* (rs6923761) has been associated with better anthropometric parameters after a hypocaloric diet for 3 months ²⁶ and 9 months ²⁴

compared to a standard diet. A study by de Luis et al. in diabetic patients with obesity treated with liraglutide, 1.8mg/day, showed that the minor variant allele (A) carriers had a greater decrease in weight loss and fat mass¹³. Our study demonstrated a potential effect of genetic variability in *GLPIR* (rs6923761) on gastric emptying in response to treatment with liraglutide and provided pilot data for planning a future hypothesis-testing pharmacogenetics trial.

In this study, genotype variants in *TCF7L2* (rs7903146) gene were associated with no difference in the mean change in gastric emptying of solids in response to either exenatide or liraglutide. Similar to our findings, Vazquez-Roque et al. showed that there was no effect of genotype variants in *TCF7L2* (rs7903146) gene on gastric emptying of solids¹⁷.

Limitations

While we demonstrated a greater delay in gastric emptying in the minor variant allele (A) in *GLPIR* (rs6923761), our study was not powered to detect a pharmacogenetics association, and the observations were not statistically significant ($p=0.11$). Based on the minor allele (A) frequency of ~36% in the population¹⁹, which is similar to the minor allele frequency in our patient population, we used the current data and calculated that a future study would conservatively require 70 patients with the minor variant (AA_AG) and 160 patients with the dominant variant (GG) to detect the clinically important difference in the effect of liraglutide on gastric emptying of 25 minutes.

Lastly, the exenatide cohort was preselected for those with accelerated gastric emptying. In theory, these patients should have greater delay in gastric emptying after exposure to a GLP-1 agonist, but, in our cohort, the degree of change in gastric emptying among those with accelerated gastric emptying at baseline was similar to the delay observed in participants with normal gastric emptying at baseline.

In summary, the current pilot study supports the need for further studies to test the hypothesis that the minor variant allele (A) of *GLPIR* (rs6923761) plays a role in the response to GLP-1 agonists by delaying gastric emptying. This study also has provided the preliminary data on the coefficient of variation in responses in order to plan further evaluation of genetic variants of the *GLPIR* (rs6923761), gastric emptying and weight loss in response to both exenatide and liraglutide. We believe this could have important implications in patient selection of who will respond to the relatively expensive GLP-1 agonists, exenatide and liraglutide, based on *GLPIR* variants, supporting the general objective to provide individualized or precision medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- The aim of this pilot study was to explore whether specific genetic variants in *GLP1R* (rs6923761) or *TCF7L2* (rs7903146) are associated with prolongation of gastric emptying and weight loss in obese patients treated with GLP-1 agonists (liraglutide and exenatide).
- A allele of *GLP1R* (rs6923761) is associated with a greater delay in gastric emptying in response to treatment with GLP-1 agonists.
- This study has acquired pilot data to plan a future study to assess the effect of genetic variability in *GLP1R* (rs6923761) on gastric emptying and weight loss in response to treatment with GLP-1 agonists.

Figure 1.

Figure 1A. CONSORT flow chart of participants in the exenatide study

Figure 1B. CONSORT flow chart of participants in the liraglutide study

Figure 2.

Spearman correlation between change in weight (y axis) and change in gastric emptying (x axis) at 5 weeks. The orange circles represent participants who received liraglutide, and the blue circles those who received exenatide.

Figure 3.

Box plots comparing the changes in gastric emptying and weight loss at 5 weeks compared to baseline among the various genotypes and drug vs. placebo.

A. Effects of liraglutide vs. placebo on gastric emptying at 5 weeks based on genetic variants of *GLP1 R* (rs6923761) and *TCF7L2* (rs7903146) genes. Note that the median prolongation

of GE $T_{1/2}$ was 80.0 (48.0, 211.0) in the AA_AG genotype and 55.5 (24.0, 105.0) in the GG genotype group for *GLP-1 R* (rs6923761).

B. Effects of liraglutide vs. placebo on weight loss at 5 weeks based on genetic variants of *GLP1R* (rs6923761) and *TCF7L2* (rs7903146) genes. There were no significant associations of genotypes tested with weight loss.

Table 1

Demographics of participants in the studies, with participants in the two trials assigned to placebo grouped together

Mean $\pm$ SEM	<i>Drug</i>		<i>Placebo</i> (n=31)
	Liraglutide (n=18)	Exenatide (n=10)	
Gender (% Female)	89 %	60 %	80.6 %
Age (years)	41.4 $\pm$ 2.6	39.0 $\pm$ 3.6	38.4 $\pm$ 2.2
Baseline BMI (Kg/m ²)	37.4 $\pm$ 1.0	34.6 $\pm$ 0.9	35.7 $\pm$ 0.7