Chronic GLP1 therapy reduces postprandial IL6 in obese humans with prediabetes

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Single-dose glucagon-like peptide 1 (GLP1) therapy increases postprandial plasma IL6 levels in prediabetic, obese humans. GLP1-IL6 interactions underly multiple antidiabetic effects, but these may differ after acute versus chronic therapy. This study examines postprandial effects of GLP1 after chronic therapy. Seven humans (six Black) with prediabetes and obesity completed 6 weeks of exenatide extended release therapy. Then subjects returned for pre- and post-meal measurements of plasma IL6, GLP1, glucagon, and related inflammatory markers. Weight, which was measured before and after therapy, did not change. Plasma IL6 decreased from baseline to postmeal state ($P = 0.016$), with decreases in free fatty acids ($P < 0.001$) and increases in insulin ($P = 0.002$), glucose ($P < 0.0001$), triglycerides ($P = 0.0178$), and glucagon ($P = 0.018$). Baseline GLP1 levels matched 6 weeks of therapy. The fall in postprandial plasma IL6, which contrasts with the increase after acute therapy, highlights the need for more investigation regarding the mechanisms of acute versus chronic GLP1-IL6 signaling.

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Introduction

Interleukin-6 (IL6) impacts the pathogenesis of insulin resistance and obesity, but its effects are incompletely understood. IL6 promotes both pro- and anti-inflammatory actions in mice and humans [1]. Specific actions of IL6 differ in transient versus chronic inflammatory settings [2].

Glucagon-like peptide 1 (GLP1) is an incretin hormone largely known for its beneficial antidiabetic and antiobesity properties. GLP1 analogs lower blood glucose and weight while conferring cardiovascular protection [3]. The interplay between IL6 and GLP1 may differ in the chronic versus acute setting, suggesting different mechanistic pathways [4–6].

Our recent randomized controlled trial (RCT) in prediabetic, obese humans showed that single-dose GLP1 analog therapy, versus placebo, increased plasma postprandial IL6 [7]. Similar acute meal challenges (comparable to the study's placebo arm) do not increase IL6 [8,9]. However, the effects of chronic GLP1 therapy on inflammation and circulating IL6 remain unknown.

We now report an extension of our prior RCT to investigate the postprandial inflammatory effects of chronic GLP-1 therapy in prediabetic, obese humans.

Methods

The protocol conformed to the Declaration of Helsinki and was approved by the Committee for the Protection of Human Subjects at The University of Texas (UT) Health Science Center at Houston. All subjects gave written informed consent. Exenatide extended release (ER) is indicated for the treatment of type 2 diabetes and was used off-label in this study.

Human subjects

Eligible subjects were men and women, ages 30 to 70 years, with prediabetes (as defined by American Diabetes Association) [10] and BMI of 30-35 mg/kg^2 (±1 mg/kg^2). Women of childbearing age agreed to a nonhormonal pregnancy prevention method. On screening, the following laboratory values were required: hematocrit ≥ 34%, serum creatinine < 1.5 mg/dl in men and 1.4 mg/dl in women, AST < 2.5 times upper limit of normal (ULN), ALT < 2.5 times ULN, and alkaline phosphatase

< 2.5 times ULN. Subjects were excluded for the use of non-statin lipid-lowering medications, metformin, DPP-IV inhibitors, GLP1 analogs, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, thiazolidinediones, insulin, sulfonylureas, corticosteroids, hormone replacement therapy, and/or immunosuppressive therapy during the 3 months prior to study initiation. NSAIDs and antioxidant vitamins were discontinued 1 week prior to study start. Statins, ACE inhibitors, and angiotensin-receptor blockers were allowed at stable doses for at least the prior 3 months and for the duration of the study. Other exclusions were significant cardiac, hepatic, or renal disease, current tobacco use, active malignancy, diabetes mellitus, acute infectious conditions, prior history of pancreatitis, prior history of medullary thyroid cancer, and prior history of multiple endocrine neoplasia 2 (MEN2). Pregnant and breastfeeding women were excluded. Full inclusion and exclusion criteria were described previously [7,11].

Clinical study protocol

After completing the aforementioned RCT [7], eight of the participating subjects joined this nonblinded extension study. The subjects self-administered exenatide ER 2 mg subcutaneously weekly for 6 weeks. Prior to beginning medication, a study physician provided education on home dosing and administration. Notably, exenatide ER reaches steady state concentration in 6 weeks [12].

Approximately 1 week after the final dose, each subject returned to the Clinical Research Unit (CRU) at 0800 after an overnight fast. All exenatide ER pens were returned to the investigators to verify adherence. An intravenous catheter was placed in a stable vein in an upper extremity. At 1100, subject began eating a standardized high-carbohydrate, high-fat test meal described previously [11]. Venous blood was collected prior to meal and 2 hours postmeal.

Plasma measurements

Plasma IL6 was determined by an ELISA kit (R&D Systems, Inc, Minneapolis, MN). Plasma total GLP1 was measured by an ELISA kit (EMD Millipore Co., St. Louis, MO). Plasma glucagon was assessed by an ELISA kit (R&D Systems, Inc, Minneapolis, MN). All other plasma measurements were described previously [11].

Statistical analyses

For this pilot study, all outcomes at two different times were compared by Wilcoxon signed-rank test. The primary outcome was plasma IL6, with related metabolic markers as secondary outcomes. All analyses were performed in SAS 9.4 software (Cary, NC) and Stata/IC 13.1 (StataCorp).

Table 1 Baseline clinical characteristics of study participants

Variable	$n = 7$
Ethnicity (Caucasian/Black/Hispanic/Pacific Islander)	0/6/1/0
Sex (M/F)	4/3
Age (years)	51 ± 4
Weight (kg)	96.8 ± 4.1
BMI (kg/m^2)	33.3 ± 0.6
SBP (mm Hg)	140 ± 9
DBP (mm Hg)	84 ± 3
Fasting glucose (mg/dl)	89 ± 2
Fasting insulin (mIU/L)	6.5 ± 0.9
HOMA-IR	1.18 ± 0.22
Hemoglobin A1c (%)	6.01 ± 0.08
Triglycerides (mg/dl)	105 ± 11
Total cholesterol (mg/dl)	190 ± 18
HDL cholesterol (mg/dl)	53 ± 3
LDL cholesterol (mg/dl)	116 ± 17
AST (units/L)	21 ± 3
ALT (units/L)	23 ± 6
Creatinine (mg/dl)	1.04 ± 0.07
Hemoglobin (g/dl)	14.0 ± 0.5
Platelets (×10^9/L)	228 ± 15

Data for ethnicity and sex are presented as absolute numbers. All other data are presented as mean ± SEM.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Results

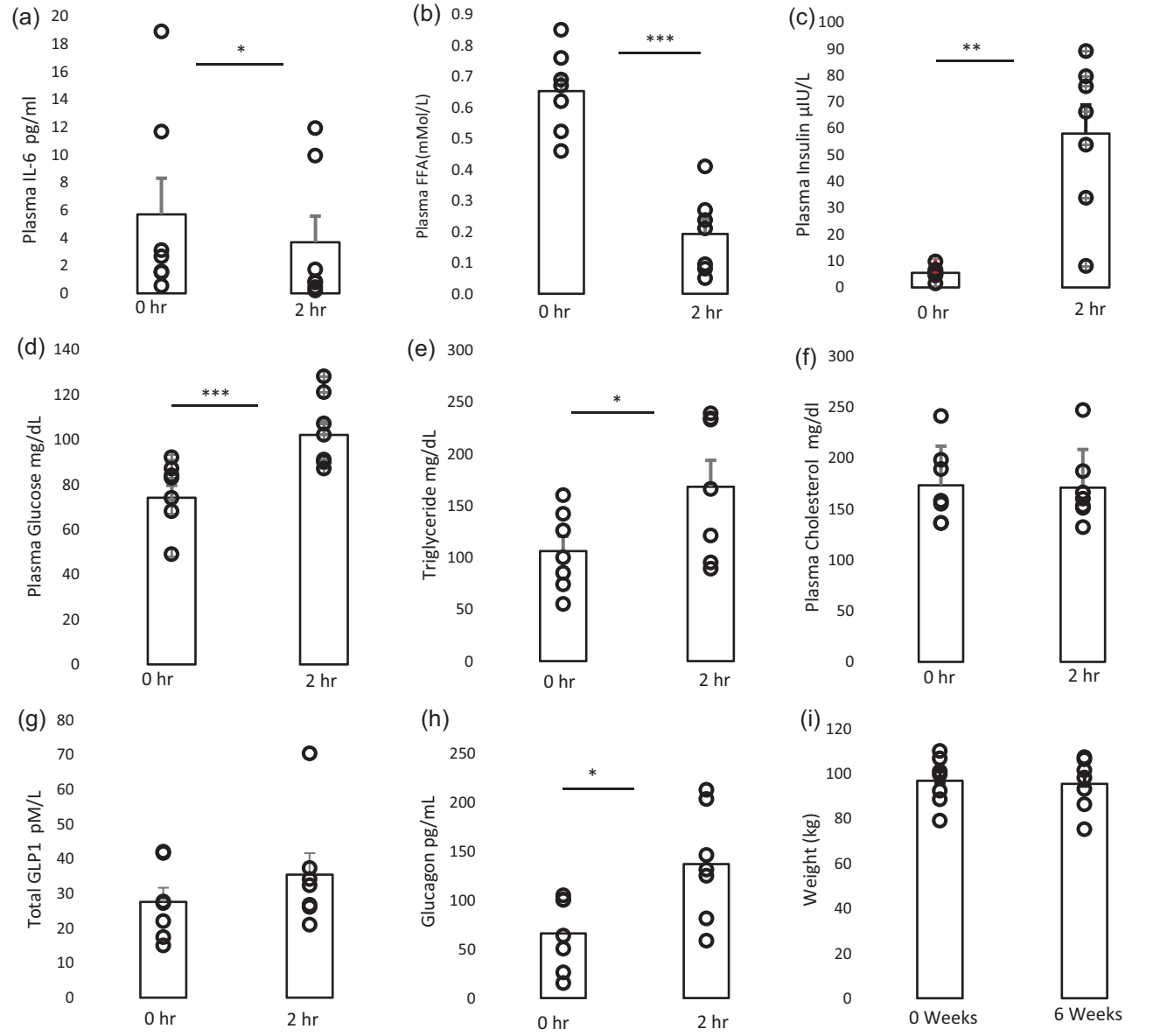
Seven of eight subjects completed the study. One withdrew due to severe nausea. Subjects were predominantly obese and Black, with near-equal numbers of males and females (Table 1). Two subjects had hypertension and were treated with a stable dose of either ACE-I or ARB. Four subjects had hyperlipidemia, one of which was treated with a stable dose of statin and three received no medication. There were no other relevant comorbidities per medical history.

Plasma IL6 decreased from baseline to 2 hours postmeal (5.7 ± 2.6 to 3.7 ± 1.9 pg/ml, $P = 0.016$). Free fatty acids (FFA) also decreased postmeal (0.65 ± 0.05 to 0.19 ± 0.05 mMol/L, $P < 0.001$), with increases in plasma insulin (5.5 ± 0.9 to 58 ± 10.8 mIU/L, $P = 0.002$), plasma glucose (77 ± 6 to 104 ± 6 mg/dl, $P < 0.0001$), triglycerides (106 ± 14 to 168 ± 26 mg/dl, $P = 0.0178$), and plasma glucagon (66.0 ± 14.1 to 137.2 ± 21.7 pg/ml, $P = 0.018$). Compared to prior literature, this study's baseline total GLP1 level measured as expected after 6 weeks of exenatide ER therapy [12] and showed a non-statistically significant postprandial increase (27.6 ± 4.1 to 35.4 ± 6.2 pM/L, $P = 0.1763$) at the expected magnitude [13]. No significant changes were seen with total cholesterol. As seen in a prior study [14], our data showed that 6 weeks of exenatide ER therapy did not change weight (Fig. 1).

Discussion

In contrast to findings seen after acute GLP1 therapy in a prior study [7], we show for the first time that chronic GLP1 therapy decreases postprandial plasma IL6 in insulin-resistant humans. Subjects completed 6 weeks of chronic GLP1 therapy prior to postprandial challenge. As

Fig. 1



The postprandial effect of 6 weeks of exenatide ER on plasma IL-6 (a), plasma FFA (b), plasma insulin (c), plasma glucose (d), plasma triglycerides (e), total cholesterol (f), plasma total GLP-1 (g), and plasma glucagon (h) before and after meal challenge, and weight (i) before and after treatment. The data are mean ± SEM. n = 7 *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

expected, 6 weeks of therapy did not change weight [14]. A small increase in GLP1 was seen after the meal. The expected changes in postprandial FFA, insulin, glucose, and glucagon were observed [15,16]. While glucagon increase was observed, the magnitude was likely blunted by GLP1 [16].

GLP1-IL6 interactions represent a novel area of investigation. We recently demonstrated that 1) GLP1 analogs activate human monocytes to secrete IL6, 2) GLP1 analogs acutely increase systemic IL6 circulation in humans, and 3) GLP1-IL6 axis induces adipose tissue browning in rodent models [7]. The type of tissue secreting IL6 may influence a pro- or anti-inflammatory effect [17]. Numerous tissues express IL6 receptor, which binds IL6 via canonical and/or trans-signaling [1].

The mechanism of IL6 induction by chronic GLP1 analog therapy remains unknown. A murine study shows the PKA/CREB pathway may play an important role in IL6 reduction in cartilage [18]. More studies are warranted in other tissues.

There are important limitations to these findings. The study focuses on IL6 changes in the postprandial state

and does not address the fasting state. A comparison to acute postprandial state (i.e. after single dose of GLP1 treatment, and no prior therapy) can be made with our previous study [7]. A larger study examining postprandial GLP1-IL6 effects in human adipose, muscle, and soft tissues following chronic therapy is necessary to delineate novel mechanisms. Notably, chronic exenatide ER also slows gastric emptying [16], but at a magnitude less than acute exenatide [7]. The postprandial insulin, glucose, and FFA findings in this study, when compared to our prior study with acute exenatide [7], reflect less gastric emptying activity.

Notably, the majority of study subjects were Black (4 females and 2 males). African Americans, particularly females, generally exhibit higher baseline IL6 levels [19,20] and greater increases in postprandial inflammatory responses than matched Caucasian individuals [21,22]. African American women also generally have less visceral fat but more insulin resistance than Caucasian women [23]. Hence, ethnicity may potentially impact IL6 response.

The unexpected fall in postprandial plasma IL6 after chronic GLP1 calls for further investigation of the mechanisms underlying acute versus chronic GLP1-IL6 signaling.

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Previous presentation: A small portion of this work was presented in abstract form only at the American Diabetes Association Scientific Sessions 2017.

Conflicts of interest

There are no conflicts of interest.

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