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Glucagon-Like Peptide 1 Induces Natriuresis in Healthy Subjects and in Insulin-Resistant Obese Men

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Glucagon-like peptide-1-(7–36)-amide (GLP-1) is involved in satiety control and glucose homeostasis. Animal studies suggest a physiological role for GLP-1 in water and salt homeostasis. This study's aim was to define the effects of GLP-1 on water and sodium excretion in both healthy and obese men.

Fifteen healthy subjects and 16 obese men (mean body mass index, 36 kg/m^2) were examined in a double-blind, placebo-controlled, crossover study to demonstrate the effects of a 3-h infusion of GLP-1 on urinary sodium excretion, urinary output, and the glomerular filtration rate after an iv 9.9-g salt load.

Infusion of GLP-1 evoked a dose-dependent increase in urinary sodium excretion in healthy subjects (from 74 ± 8 to 143 ± 18 mmol/180 min, $P = 0.0013$). In obese men, there was a significant increase in urinary sodium excretion (from 59 to 96 mmol/180 min, $P = 0.015$), a decrease in urinary H^+ secretion (from 1.1 to 0.3 pmol/180 min, $P = 0.013$), and a 6% decrease in the glomerular filtration rate (from 151 ± 8 to 142 ± 8 ml/min, $P = 0.022$).

Intravenous infusions of GLP-1 enhance sodium excretion, reduce H^+ secretion, and reduce glomerular hyperfiltration in obese men. These findings suggest an action at the proximal renal tubule and a potential renoprotective effect. (*J Clin Endocrinol Metab* 89: 3055–3061, 2004)

EPIDEMIOLOGICAL STUDIES INDICATE that the prevalence of obesity in the United States and other Western countries has been steadily rising over the past two decades, a trend that has been linked to changing dietary habits and lifestyle (1–3). Obesity is associated with a high prevalence of hypertension, dyslipidemia, cardiovascular disease, diabetes mellitus, and other chronic diseases (4). The annual number of deaths attributable to obesity in the United States has been estimated to be 280,000–325,000 (5).

One of the major factors responsible for obesity-associated morbidity and mortality is an elevated blood pressure. The pathogenesis of obesity-induced hypertension has not been elucidated. Glomerular hyperfiltration and increased sodium reabsorption in the kidney have been demonstrated previously in obese patients and animals (6, 7). The authors of these studies suggest a putative factor in obese patients (*e.g.* hyperinsulinemia, the renin angiotensin system, the sympathetic nervous system, or an increase in renal interstitial pressure) as being responsible for an enhanced salt reabsorption in the proximal tubule and the loop of Henle. The consequence of enhanced salt reabsorption is an increase in blood pressure due to extracellular volume expansion. Elevated salt reabsorption at a segment proximal to the macula densa would reduce sodium chloride delivery to the macula densa and initiate a rise in the glomerular filtration rate (GFR) through tubulo-glomerular feedback. An elevated GFR would tend to return distal sodium delivery to normal. In fact, a few studies in humans have shown that obese patients have an increased GFR (8, 9). Another study has clearly demonstrated that nondiabetic, nonhypertensive obese people have an elevated GFR (10).

The pro-glucagon-derived glucagon-like peptide-1-(7–36) amide (GLP-1) is a gastrointestinal hormone that is released in response to the presence of food in the distal small intestine (11, 12). Its physiological effects include a glucose-dependent insulinotropic action on pancreatic β-cells and inhibition of gastric emptying. The latter effect can be interpreted as being part of the ileal brake mechanism, an endocrine feedback loop that becomes activated when nutrients are present in the ileum (12, 13). Furthermore, it has been suggested that GLP-1 plays a physiological regulatory role in controlling appetite and energy intake in normal volunteers and in patients with type 2 diabetes mellitus (14–16). As a result of its biological effects, GLP-1 is currently being considered as a potential therapeutic agent for the treatment of hyperglycemia associated with type 2 diabetes mellitus (17–19).

In previous studies related to the role of GLP-1 in regulating food intake, we have observed a significant reduction of water intake after administration of GLP-1 (15). This ob-

Abbreviations: AUC, Area under the curve; CH_2O, free water clearance; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1-(7–36)-amide; HOMA, homeostasis model assessment; IR, insulin resistance; PRA, plasma renin activity; TcH_2O, free water reabsorption.

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servation has been confirmed in moderately obese patients with type 2 diabetes mellitus (16). Also, preliminary data in rats suggest a role for GLP-1 in regulating water and salt homeostasis (20). On the basis of this information, the present study was designed to investigate, in a randomized, double-blind, crossover fashion, the effects of GLP-1 on urinary sodium and hydrogen ion excretion and on glomerular filtration in both healthy volunteers and obese patients.

Subjects and Methods

Subjects

Healthy subjects. Fifteen healthy males aged 25.5 ± 0.5 yr who had a normal body mass index of 22.1 ± 0.5 were recruited for the study.

Each volunteer provided written informed consent. The protocol had been previously approved by the Human Ethics Research Committees of the University Hospitals of Basel and Aarau, Switzerland. Before being enrolled in the study, participants were required to complete a medical interview, undergo a full physical examination, and participate in an initial laboratory screening. No subject was taking any medication or had a history of diabetes, hypertension, or kidney disease. Two subjects were excluded after the screening visit because of noncompliance with the study protocol.

Obese subjects. Sixteen obese males aged 44.6 ± 3.0 yr who had body mass index of 36.5 ± 1.2 were recruited for the study (Table 1). Each patient provided written informed consent. The protocol had been previously approved by the local Human Ethics Research Committee. Before being enrolled in the study, participants were required to complete a medical interview, undergo a full physical examination, and participate in an initial laboratory screening for type 2 diabetes mellitus. The screening included a full physical examination and an initial laboratory screening including urinalysis. Patients suffering from any heart disease, microalbuminuria, or proteinuria were excluded from the study. Two patients had previously diagnosed type two diabetes mellitus, one patient suffered from hypertension, and six patients had elevated plasma cholesterol levels. One patient was subsequently diagnosed with hypertension, and one patient was diagnosed with type 2 diabetes. Patients were kept on their daily medication throughout the study protocol.

TABLE 1. Demographic data at screening of 16 obese subjects

Characteristic	Value
Age (yr)	44.6 ± 3.0
BMI (kg/m^2)	36.5 ± 1.2
Waist circumference (cm)	122.6 ± 2.7
Systolic blood pressure (mm Hg)	132 ± 3
Diastolic blood pressure (mm Hg)	74 ± 2
Cholesterol (mmol/liter)	5.4 ± 0.2
Triglycerides (mmol/liter)	1.7 ± 0.1

BMI, Body mass index. Data are expressed as mean ± SEM.

Homeostasis model assessment (HOMA)

Insulin resistance (IR) was determined by the HOMA (21) as follows: HOMA-IR = fasting serum insulin ∗ fasting serum glucose/22.5, where insulin is expressed in μU/ml and glucose is expressed in mmol/liter (21). IR, as determined by this method, closely correlates with more complex techniques, such as the euglycemic clamp method (22).

The index of insulin secretion was calculated as follows: β-cell function = (20 × insulin)/(glucose − 3.5), where insulin is expressed in μU/ml and glucose is expressed in mmol/liter.

Protocols

Dose response to GLP-1 in healthy subjects. For the purpose of the study, placebo, GLP-1 0.375 pmol/kg·min, and GLP-1 1.5 pmol/kg·min were infused in a random order, with infusions being separated by at least 7 d. All solutions were administered with a concomitant iv saline load (Fig. 1).

On the day of each study, volunteers had fasted from 2400 h onward before coming to the research unit 8 h later. The fasting state was assessed in the morning by an ultrasound examination of the gallbladder. At 0800 h, volunteers emptied their bladders, and this was confirmed by ultrasound. Afterwards, subjects were maintained supine for the duration of the experiment to avoid activation of the renin-angiotensin system with exercise. Teflon catheters were placed into each forearm, one for infusions and one for blood sampling.

After the baseline blood sample was drawn, an iv infusion of hypertonic saline was started at a rate of 0.06 ml/kg·min for 2 h. Simultaneously, a second infusion of 0.9% saline containing albumin 0.5% (placebo) or one of the synthetic GLP-1 doses dissolved in 0.9% saline and 0.5% albumin was started and continued for 3 h. The three solutions were indistinguishable in appearance and were prepared by a pharmacist who was not directly involved in the study. The physician in charge was not aware of the respective treatment, thereby permitting a double-blind study design. During the first 2 h of each experiment, no fluid consumption was allowed; starting with the third hour, volunteers were allowed to drink water *ad libitum*. Food intake was not permitted. At the end of each 180-min investigation period, water intake and the quantity of urine (ml) were measured; bladder emptying was confirmed by ultrasound.

After starting the hypertonic saline infusion, volunteers scored their subjective feelings of thirst on visual analog scales at 30-min intervals throughout the experiments, with values ranging from 0–100 mm. A score near 0 mm (at the left) for thirst indicated the subject was not thirsty

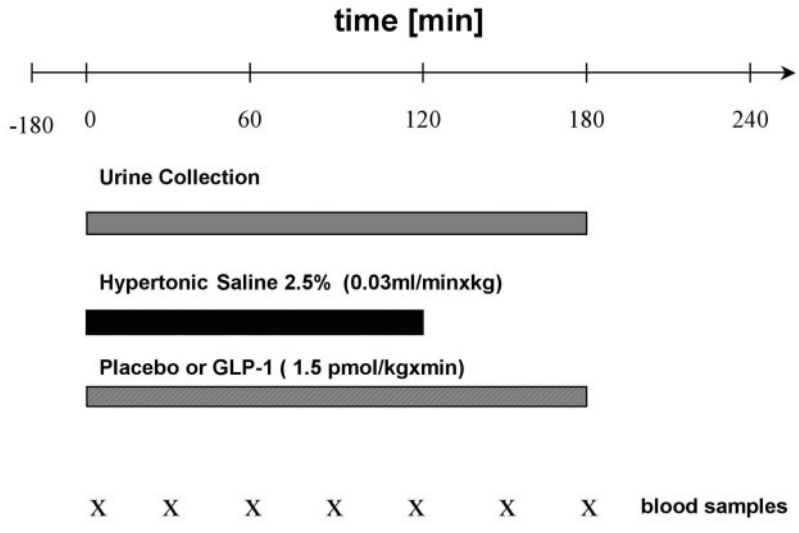

FIG. 1. Urine period: urine was collected over 180 min. Hypertonic saline: infusion with 2.5% saline was done at a rate of 0.03 ml/kg·min. Placebo or GLP-1: infusion of placebo or GLP-1 (0.375 and 1.5 pmol/kg·min in the group of healthy subjects; and only the 1.5-pmol/kg·min dose in the group of obese subjects). Drinking time: volunteers were allowed to drink during 1 h (after stopping hypertonic saline infusion between minutes 120 and 180). Blood samples: time points of blood sampling during experiment. Visual analog scale for thirst (time point of measurement).

at all, and a score near 100 mm (at the right) indicated he was maximally thirsty. This scale has been described and validated elsewhere (17). Adverse effects were assessed by the attending physician through close observation of the participants.

Effect of GLP-1 in obese subjects. The experimental procedure was similar to the design depicted in Fig. 1 with the exception that only one dose of GLP-1 (1.5 pmol/kg·min) was infused. Treatments were given in random order, with infusions being separated by at least 7 d. All solutions were administered with a concomitant iv saline load (Fig. 1).

On the day of each study, patients had fasted from 2400 h onward before coming to the research unit 8 h later. The fasting state was assessed in the morning by an ultrasound examination of the gallbladder. At 0800 h, the patients emptied their bladders, which was confirmed by ultrasound. Afterwards, to avoid additional, nonstandardized activation of the renin-angiotensin system, subjects were maintained supine for the duration of the experiment. Teflon catheters were placed into each forearm, one for infusions and one for blood sampling. After the baseline blood sample was taken, an iv infusion of hypertonic saline (2.5% NaCl) was started at a rate of 0.03 ml/kg·min for 2 h. The total salt load was 9.9 ± 0.3 g, which represents the daily salt load in a liberal Western diet. Simultaneously, a second infusion of 0.9% saline containing 0.5% albumin (placebo) or 0.9% saline plus synthetic GLP-1 (for an infusion rate of 1.5 pmol/kg·min) was started and continued for 3 h (infusion rate 50 ml/h). The additional salt load through the peptide/placebo infusion was equal for both treatments and was approximately 1.35 g NaCl.

During the whole experiment, free fluid consumption was allowed. Food intake was not permitted. At the end of each 180-min investigation period, water intake and the quantity of voided urine (ml) were measured, and bladder emptying was again confirmed by ultrasound. Adverse effects were assessed by the attending physician through close observation of the participants and by questioning.

Materials

Synthetic human GLP-1 was obtained from Bachem (Bubendorf, Switzerland). The peptide content was used in the calculation of the doses infused. The infusions were prepared by the University of Basel Hospital Pharmacy (Basel, Switzerland) according to good manufacturing practice criteria. The solutions were tested for sterility and pyrogenicity.

Glucose, electrolyte, pH, osmolality, and renin analyses and measurement of glomerular filtration, solute clearance, and solute-free water reabsorption

At the start of the study and subsequently in 30-min intervals, blood samples were drawn for glucose, sodium, osmolality, creatinine, vasopressin, renin activity, angiotensin II, and aldosterone determinations (Fig. 1). Sodium, chloride, H^+, and calcium excretion, osmolality, and creatinine were measured in the urine collected during 180 min. Glomerular filtration was assessed by creatinine clearance and solute clearance by the osmolal clearance.

Creatinine clearance was calculated using the following formula: $C_{cr} = U_{cr} \times V/P_{cr}$, where C_{cr} is creatinine clearance, U_{cr} is urine creatinine concentration, V is the urine volume collected during 180 min, and P_{cr} is plasma creatinine concentration.

Using the same formula, osmolal clearance was calculated using urine and plasma osmolality.

Free water reabsorption (TcH_2O) was determined using the following formula, which considers plasma and urine osmolality: $TcH_2O = V(Uosm/Posm - 1)$, where V is urine volume expressed in liters, Uosm is urine osmolality, and Posm is plasma osmolality.

Glucose concentrations were measured with the hexokinase method. Electrolyte concentrations in heparin plasma and in urine were measured on an automated analyser (Dimension RXL; DADE-BEHRING Corp, Wilmington, DE), following the manufacturer's instructions, using an ion-selective electrode method. pH was measured immediately from urine samples using an autoanalyzer (ABL 700; Radiometer, Copenhagen, Denmark). Plasma and urine osmolality were determined with an osmometer (OM802; Vogel Corp., Bern, Switzerland) using the freezing point method. Insulin was determined by RIA using a commercially available kit (Schering Schweiz AG, Baar, Switzerland) with a detection limit of 2.0 μIU/ml. Plasma renin activity (PRA) was measured by RIA (DSL-25100; Diagnostic Systems Laboratories, Inc., Webster, TX). Inter- and intraassay coefficients of variation were 3.0 and 4.3%, respectively, with a detection limit of 1.8 pg/ml. Plasma concentrations of aldosterone were determined using a commercially available, solid-phase RIA (Diagnostic Products Corporation, Los Angeles, CA). Inter- and intraassay coefficients of variation at 140 pg/ml were 6.9 and 5.5%, respectively, with a detection limit of 16 pg/ml.

Laboratory analyses

At the beginning of the study and at 30-min intervals, blood samples were drawn for glucose, sodium, osmolality, renin activity, angiotensin II, and aldosterone determinations (Fig. 1). Sodium excretion, osmolality, pH, and creatinine were measured in the urine collected at the end of 180 min.

Glucose concentrations were measured with the hexokinase method. Sodium concentrations in plasma and in urine were measured on an automated analyzer (DADEBEHRING Corp.), following the manufacturer's instructions, using an ion-selective electrode method. Osmolality in plasma and urine were determined on an osmometer (OM802; Vogel Corp.) using the freezing point method.

PRA was measured by RIA (Diagnostic Systems Laboratories). Inter- and intraassay coefficients of variation were 3.0 and 4.3%, respectively, with a detection limit of 1.8 pg/ml. Angiotensin II was measured by RIA (double-antibody RIA; Bühlmann Laboratories AG, Allschwil, Switzerland) with a detection limit of 0.7 pg/ml and a coefficient of variation of 6%. Plasma concentrations of aldosterone were determined using a commercially available, solid-phase RIA (Diagnostic Products Corporation). Inter- and intraassay coefficients of variation at 140 pg/ml were 6.9 and 5.5%, respectively, with a detection limit of 16 pg/ml.

Calculations

Solute-free or free water clearance (CH_2O) was assessed according to the following: $CH_2O = V \times (1 - Uosm/Posm)$, where V is urine volume, and Uosm and Posm are osmolality in urine and plasma, respectively. The TcH_2O by the kidneys is inversely related to the CH_2O and, therefore, can be estimated as follows: $TcH_2O = -CH_2O$.

Statistical analysis

Comparisons between the different infusion periods were made by ANOVA for repeated measurements or by paired *t* tests (two-tailed) as appropriate. Paired *t* tests were used when ANOVA was statistically significant using a Bonferroni correction. Otherwise, the Wilcoxon signed rank sum test was used. For all calculations, STATA software, version 6.0 for Windows 95/98 (Stata Corporation, College Station, Texas) was used. Unless otherwise noted, data are expressed as means ± SEM. A significance level of 5% was used throughout.

Results

Effect of GLP-1 on blood glucose, water intake, and thirst in healthy subjects

Figure 2A shows the physiological effect of GLP-1 on blood glucose. The graded doses of synthetic human GLP-1 reduced glucose concentrations and the glucose/time area under the curve (AUC) in a dose-dependent manner. Volunteers reduced water consumption by 15% during the infusion of the higher GLP-1 dose; however, the difference was not statistically significant ($P = 0.178$, ANOVA). Water ingestion was slightly reduced from 1405 ± 110 ml (placebo) to 1327 ± 95 ml (GLP-1 infusion rate of 0.375 pmol/kg·min) and, finally, to 1279 ± 78 ml. GLP-1 infusions did not have an influence on the visual thirst analog scales (data not shown).

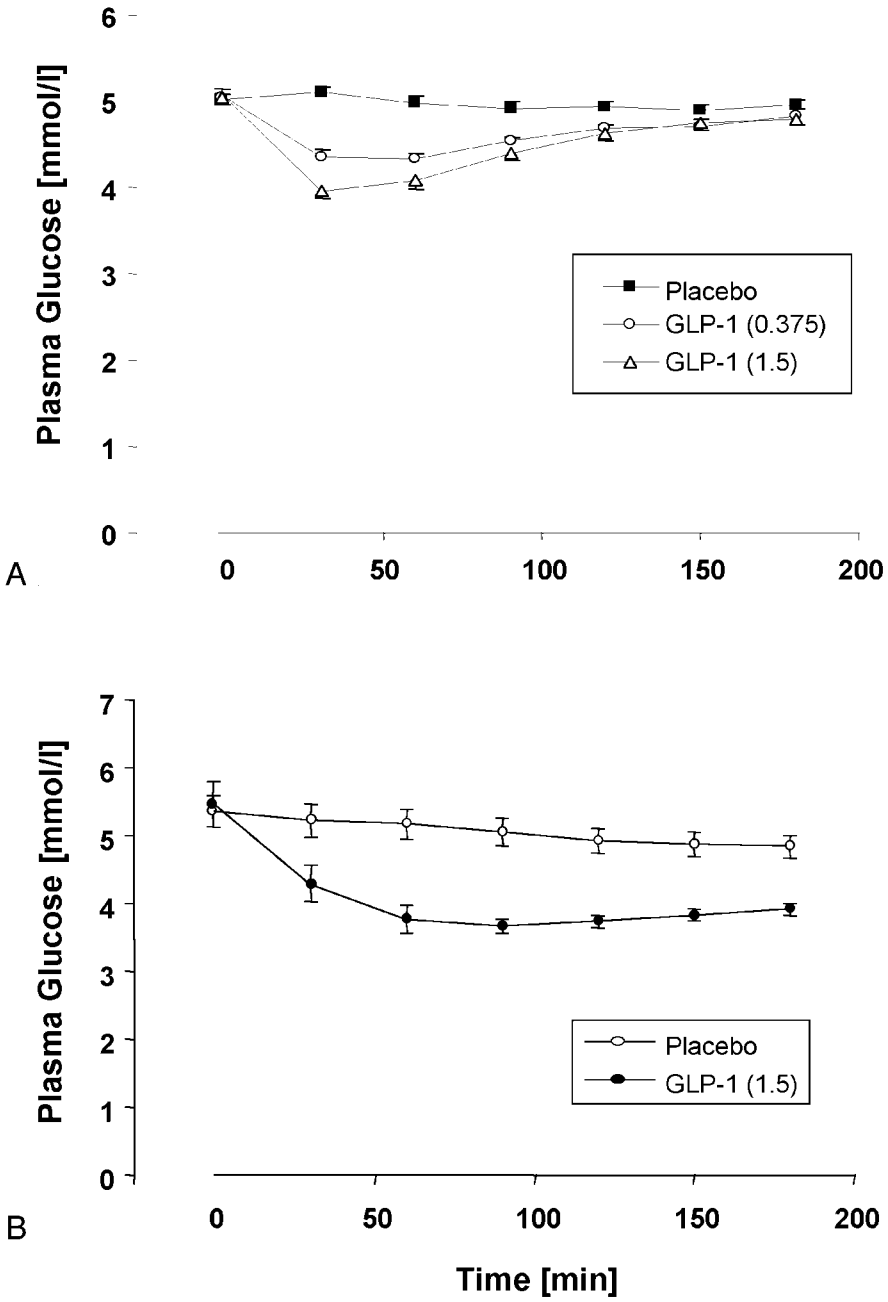

FIG. 2. Data are means (±SEM) of plasma glucose during treatment with GLP-1 and placebo (0.9% saline) in (A) healthy subjects and (B) obese persons.

Effects of GLP-1 on sodium, urine volume excretion, and water reabsorption in healthy subjects

Renal handling of sodium and free water. Sodium excretion increased from 74 ± 8 to 86 ± 9 and 143 ± 18 mmol (P = 0.0009, ANOVA), and fractional sodium excretion rose from 1.6 ± 0.2 to 1.7 ± 0.2 and 2.7 ± 0.3% (P = 0.0004, ANOVA) during the placebo, GLP-1 0.375 pmol/kg·min, and GLP-1 1.5 pmol/kg·min infusion periods, respectively. According to this pattern, osmolal clearance increased from 4.45 ± 0.42 to 4.96 ± 0.29 and 7.11 ± 0.67 ml/min ($P < 0.0086$, ANOVA). Water reabsorption equalled 450 ± 56, 573 ± 34, and 747 ± 70 ml (P = 0.0158) with the infusions of placebo, GLP-1 0.375 pmol/kg·min, and GLP-1 1.5 pmol/kg·min, respectively. Urine volume increased from 360 ± 38 to 400 ± 28 and 639 ± 68 ml/3 h (P = 0.0009). Urine volume and sodium excretion changes by infused GLP-1 were dose dependent. The creatinine clearance did not change in healthy subjects under the experimental conditions (data not shown). Table 2 summarizes the results on urinary volume and electrolyte outputs.

Effects of GLP-1 on the renin-angiotensin-aldosterone axis

In healthy volunteers, increasing doses of GLP-1 did not affect the time course, the PRA, angiotensin II, or the aldosterone plasma concentrations. The AUCs are depicted in Table 3.

TABLE 2. Effect of GLP-1 on urine fluid and electrolyte output in healthy subjects

Parameter	Placebo	GLP-1		*P* (ANOVA)
		0.375 pmol/kg·min	1.5 pmol/kg·min	
Urine volume (ml/180 min)	360 ± 38	400 ± 28	639 ± 68	0.0009
Urine osmolality (mosmol/liter)	701 ± 59	746 ± 25	673 ± 28	0.2595
Sodium excretion (mmol/180 min)	74 ± 8	86 ± 9	143 ± 18	0.0013
Fractional excretion of sodium (%)	1.6 ± 0.2	1.7 ± 0.2	2.7 ± 0.3	0.0004

Data are mean values ± SEM. *P* values calculated using ANOVA for repeated measurements.

TABLE 3. Effect of different doses of GLP-1 on hormone responses of the renin-angiotensin-aldosterone system in healthy volunteers

Parameter	Placebo	GLP-1		*P* (ANOVA)
		0.375 pmol/kg·min	1.5 pmol/kg·min	
AUC aldosterone	17,490 ± 1,185	17,700 ± 1,302	17,562 ± 1,114	0.928
AUC renin	1,256 ± 150	1,319 ± 155	1,152 ± 81	0.316
AUC angiotensin II	860 ± 92	889 ± 122	729 ± 71	0.196

Data are mean values ± SEM of AUCs of the renin-angiotensin-aldosterone system. *P* values were calculated using ANOVA for repeated measurements. Units are expressed as pg*180 min.

TABLE 4. Insulin resistance in 16 obese subjects

Insulin resistance data	Obese subjects
Diabetes mellitus (%)	25
IR-HOMA (mU·mmol/liter^2)	8.2 ± 0.9
Index of insulin secretion (%)	544 ± 167
Plasma glucose (mmol/liter)	5.5 ± 0.3
Plasma insulin (mU/ml)	33.8 ± 3.0

Data are mean values ± SEM at study entry.

Glucose tolerance and IR in the obese population

The diagnosis of type 2 diabetes mellitus was made in 25% of the patients (n = 4) based on abnormalities in glucose tolerance (Table 4).b Of these patients, two were on diet therapy alone, one was using a combination of sulfonylureas and metformin, and one was on a combination of thiazolidindiones and metformin; none was on insulin therapy. There was a family history of diabetes in one subject, and 31% of patients had first-degree relatives with diabetes.

IR data are presented in Table 4. IR as defined by HOMA was present in all nondiabetic patients (Table 4).

Effect of GLP-1 on blood glucose and plasma insulin

Figure 2B depicts the well-known effect of GLP-1 on blood glucose, an effect that is similar in both the obese and healthy volunteers. Synthetic human GLP-1 reduced glucose concentrations and the glucose AUC ($P = 0.0001$). Insulin release was slightly stimulated during GLP-1 administration, as shown by an increase in the insulin/time AUC (data not shown; $P = 0.006$), thereby confirming the peptide's well-known insulin-releasing property.

Renal effects of GLP-1

Glomerular filtration and urine volume. The effect of GLP-1 on creatinine clearance is shown in Fig. 3. GLP-1 decreased creatinine clearance from (mean ± SD) 151 ± 8 to 142 ± 8 ml/min ($P = 0.022$). In contrast to the decline in creatinine clearance, patients showed a higher urine output with GLP-1; urine volume increased from 343 ± 35 to 454 ± 62 ml ($P = 0.028$, paired *t* test) during the collection period of 180 min.

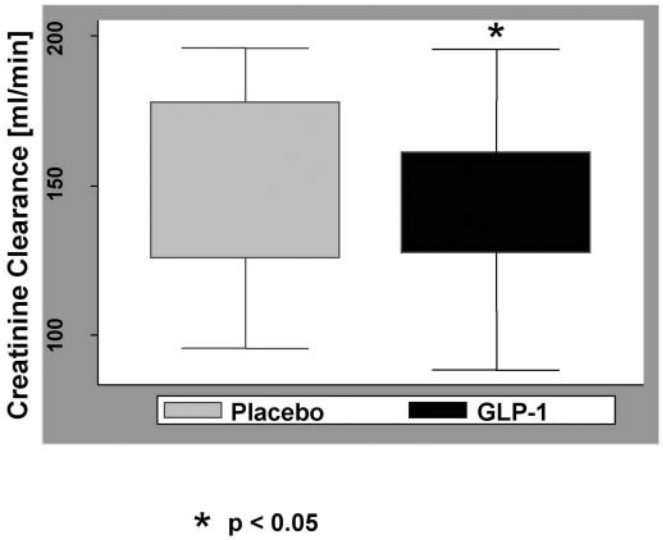

FIG. 3. Data are presented with box-whisker plots. With GLP-1 infusion, the GFR decreased from 151 ml/min (placebo) to 142 ml/min (GLP-1; *, $P = 0.022$, paired *t* test) in obese persons.

This improvement was achieved with enhanced solute excretion as shown by an increase in the osmolal clearance, an increase in sodium, chloride, and calcium excretion, and an increase in tubular water reabsorption.

Renal handling of solutes and water. Osmolal clearance rose from 3.8 ± 0.3 to 4.8 ± 0.5 ml/min ($P = 0.023$). Figure 4 shows the effects of the GLP-1 infusion on sodium and chloride excretion. Sodium excretion increased by 60% ($P = 0.015$), and fractional sodium excretion rose from 1.4 ± 0.1 to 2.3 ± 0.3% ($P = 0.003$). Similarly, chloride excretion improved by 44% ($P = 0.011$). Calcium excretion increased by 60% ($P = 0.011$; Fig. 4C), whereas hydrogen excretion was dramatically reduced by 75% ($P = 0.013$; Fig. 4D). Potassium excretion, on the other hand, did not change under treatment with GLP-1 compared with placebo; potassium excretion reached 23.4 ± 1.4 mmol with GLP-1 and 21.6 ± 1.7 mmol with placebo ($P = 0.24$).

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