Characterizing the dynamic interaction among gastric emptying, glucose absorption, and glycemic control in nondiabetic obese adults

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The effects of altered gastric emptying on glucose absorption and kinetics are not well understood in nondiabetic obese adults. The aim of this work was to develop a physiology-based model that can characterize and compare interactions among gastric emptying, glucose absorption, and glycemic control in nondiabetic obese and lean healthy adults. Dynamic glucose, insulin, and gastric emptying (measured with breath test) data from 12 nondiabetic obese and 12 lean healthy adults were available until 180 min after an oral glucose tolerance test (OGTT) with 10, 25, and 75 g of glucose. A physiology-based model was developed to characterize glucose kinetics applying nonlinear mixed-effects modeling with NONMEM7.3. Glucose kinetics after OGTT was described by a one-compartment model with an effect compartment to describe delayed insulin effects on glucose clearance. After the interactions between individual gastric emptying and glucose absorption profiles were accounted for, the glucose absorption rate was found to be similar in nondiabetic obese and lean controls. Baseline glucose concentration was estimated to be only marginally higher in nondiabetic obese subjects (4.9 vs. 5.2 mmol/L), whereas insulin-dependent glucose clearance in nondiabetic obese subjects was found to be cut in half compared with lean controls (0.052 vs. 0.029 l/min) and the insulin concentration associated with 50% of insulin-dependent glucose elimination rate was approximately twofold higher in nondiabetic obese subjects compared with lean controls (7.1 vs. 15.3 μU/ml). Physiology-based models can characterize and compare the dynamic interaction among gastric emptying, glucose absorption and glycemic control in populations of interest such as lean healthy and nondiabetic obese adults.

Obesity is a major health problem reaching epidemic proportions in adults as well as in the pediatric age group (43). This surge in obesity is very likely responsible for the recent increase in obesity-related comorbidities such as Type 2 diabetes mellitus (T2DM) (43). It is clinically relevant to understand glucose absorption and glycemic control in obese individuals before they develop a diabetic state.

Provocation experiments, such as an oral glucose tolerance test (OGTT), are widely used to study the regulation of glucose and insulin and thus to determine the diabetes status of an individual. However these tests lead to high variability in glucose concentrations that may be due to differences in gastric emptying rates. Horowitz et al. (17) showed that gastric emptying accounts for one-third of the variance in the postprandial glucose kinetics of healthy individuals. Further studies suggest that the dynamics of gastric emptying is altered in obese patients (18, 24, 28) affecting glucose absorption and postprandial glycemia (16, 27, 32, 40).

Gastric emptying can be measured using the [13C]sodium acetate breath test, established as an accurate, noninvasive method without radiation exposure and easy to use in clinical settings (6, 13). This test also presents the advantage of being a marker for both solid and liquid phases; therefore, it might be able to replace scintigraphy as the gold standard. The time required by the stomach to empty 50% of the ingested meal is commonly used as a reliable parameter to assess gastric emptying rate. Different mathematical methods have been developed to derive parameters based on gastric emptying curves from breath tests (21). However, these current available methods do not link individual dynamics of gastric emptying directly to individual glucose absorption profiles.

Advanced systems pharmacology and pharmacometric modeling approaches have been already applied to characterize drug effects on glycemic control in patients with T2DM (22, 29, 31, 45, 46). Cobelli et al. (7) developed the widely used oral minimal-model to describe plasma glucose and insulin data after OGTT. More mechanistic models, including physiological components, are also available. Jauslin (19) and Silber et al. (35, 37, 38) developed a complex semi-mechanistic model to characterize glucose and insulin kinetics after OGTT and intravenous glucose tolerance tests (IVGTT) in patients with T2DM. Silber et al. (36) applied an empirical flexible input model to describe absorption of glucose during OGTT in healthy adults. Recently, this model has been improved by Alskär et al. (1) by describing glucose absorption with a three-compartment model to represent the small intestine in patients with T2DM and healthy subjects. They also modeled the gastric emptying. In contrast to our study, these authors used gastric emptying data derived from an acetoniminophen absorption test, a suboptimal method based on the premise that...
the rate-limiting step of drug absorption is gastric emptying, since it is rapidly absorbed in the duodenum and not in the stomach (15). It should be noted that this test does not measure the rate of gastric emptying of a solid meal and results correlate primarily with emptying of the liquid phase (32). Since there is a weak correlation between scintigraphy and the acetaminophen absorption test, this acetaminophen-based method is not recommended as an alternative to scintigraphy or breath tests (32).

The objective of our work was to further enhance existing physiology-based, mathematical models by characterizing and comparing interactions among gastric emptying, measured with the breath test, glucose absorption, and glycemic control after oral glucose administration in nondiabetic obese adults and lean healthy controls.

MATERIALS AND METHODS

Analysis Data Set

Data from a randomized, double-blind, parallel-group study conducted in the Phase 1 Research Unit of the University Hospital of Basel, in Switzerland, were available (27). The main objective of this study was to analyze the different parameters regulating blood glucose concentrations in response to increasing oral glucose loads in nondiabetic obese subjects and lean controls. The study was conducted in accordance with the Declaration of Helsinki and the protocol was submitted and approved by the Local Research and Ethics Committee in Basel [Ethikkommission Nordwest–und Zentralschweiz (EKNZ): 298/12] and registered at ClinicalTrials.gov (NCT01875575). All patients gave written informed consent. After an overnight fast, OGTTs were performed on each study participant. They received, on three separate occasions (at least 3 days apart), one of the following glucose solutions in random order: 10, 25, and 75 g glucose dissolved in 300 ml tap water, with 50 mg [13C]sodium acetate for determining gastric emptying. This study was also designed to investigate oral glucose loads in postoperative patients after gastric bypass. In these patients, OGTT greater than 75 g can induce severe side effects (e.g., dumping syndrome); for this reason, higher glucose doses than 75 g were not evaluated (10).

Glucose, insulin, gastric emptying, and other characteristics, such as incretin hormones [glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)] and C peptide, a byproduct of insulin production, were measured in each individual. GIP and GLP-1 are the two primary incretin hormones secreted from the intestine on ingestion of glucose or nutrients to stimulate insulin secretion from pancreatic β-cells. GIP enhances postprandial GLP-1 response, while GLP-1 suppresses glucagon secretion (34). In glucose homeostasis, GIP and GLP-1 effects overlap, for example, they both regulate the biosynthesis and secretion of insulin in a glucose-dependent fashion and inhibit gastric emptying (9, 25, 34, 39). Insulin resistance was also assessed based on the homeostasis model assessment (HOMA-IR) index using the following formula: HOMA-IR = (fasting glucose × fasting insulin)/22.5 (26).

Blood glucose concentrations were measured by a commercially available glucose oxidase-method (Bayer Consumer Care, Basel, Switzerland).

Gastric emptying rate was determined with the [13C3]sodium acetate breath test (6, 13). Test solutions were labeled with 50 mg of [13C3]sodium acetate, an isotope absorbed readily in the proximal small intestine and then transported to the liver where it is metabolized to [13CO2], which is then exhaled rapidly (13). At fixed time intervals, end-expiratory breath sample bags were taken into 100-ml foil bags. The [13C] exhalation was determined by nondispersive infrared spectroscopy using an isotope ratio mass spectrophotometer (IRIS; Wagner Analysen Technik, Bremen, Germany) and expressed as the relative difference (δ%) from the universal reference standard (carbon from Pee Dee Belemnite limestone). [13C] enrichment was defined as the difference between preprandial [13C] exhalation and postprandial [13C] exhalation at defined time points, δ% over basal (DOB, %). δ-values were converted into atom percent excess and then into percentage of administered dose of [13C] excreted per hour (%dose/h (%)). In this last conversion, the individual CO2 production was calculated as followed: 300 mmol/h × body surface area; body surface area was calculated with the formula of Haycock et al. (14). Blood samples and gastric emptying rates were collected at the following time points after OGTT: 0, 15, 30, 45, 60, 90, 120, and 180 min.

Twelve lean healthy and twelve nondiabetic obese subjects were recruited for the study. Study subjects were classified based on their body mass index (BMI): nondiabetic obese subjects had a BMI value greater than 30 kg/m2, whereas lean healthy subjects had a BMI value between 18 and 25 kg/m2 (43). The study had the following inclusion criteria: age between 18 and 50 yr, female and male, normal eating habits, stable body weight for at least 3 mo. Exclusion criteria were: diabetes mellitus, smoking, substance abuse, regular intake of medication (except oral contraceptives), medical or psychiatric illness, and history of gastrointestinal disorders. Subjects with a BMI between 25 and 30 kg/m2 were not included in this study.

For our model-based analysis, we created two different analysis data sets: 1) independence of occasions was assumed and each “individual + glucose dose occasion” combination was treated as separate study individual; and 2) data from all glucose dose occasions was pooled at the individual level.

Model Development

A mathematical, physiology-based semi-mechanistic model, defined as a compartmental model with minimal physiological components, was developed to describe interactions among dynamics of gastric emptying, glucose absorption, and glycemic control.

Glucose kinetics after OGTT was characterized by compartment(s) where glucose is kinetically homogeneous and instantaneously well mixed. One and two compartment models with first-order glucose absorption and elimination rates were tested. Addition of an endogenous glucose production rate was investigated to account for glucose-neogenesis by organs such as liver. Different methods were evaluated to handle baseline glucose concentrations, e.g., models using observed or estimating baseline values, with or without interindividual variability (8).

Physiological components such as insulin kinetics and dynamic gastric emptying rates were included in the structural part of the model. As insulin inhibits hepatic glucose production and stimulates glucose utilization by peripheral tissues, the effect of observed insulin profiles was tested on both glucose production and clearance in the model. In addition, the effect of glucose on its own production was evaluated in various feedback models (11, 47). Observed C-peptide data as well as insulin over C-peptide ratio were also tested in models.

Individual observed gastric emptying rates were added as a time-varying covariate on glucose absorption rates. Further individual GIP and GLP-1 kinetics were tested in addition to and in place of gastric emptying effects on glucose absorption rates.

Different relationships between gastric emptying and glucose absorption rates and between insulin or glucose and glucose production and elimination rates were considered: linear, exponential, power, and saturable functions with and without sigmoidal coefficients (41). Addition of an effect compartment was tested to describe a delay before the action of gastric emptying, insulin, or glucose on model parameters.

To estimate population average parameters and their interindividual and residual variability, a population analysis was performed using a nonlinear mixed-effects modeling approach (35). Once structural and statistical components of the model were developed, indi-
concentration; V, volume of distribution; GL0, baseline glucose concentration; CL, insulin-independent glucose clearance; CLIns, insulin-dependent glucose clearance; InsE, insulin concentration in the effect compartment; Ins50, insulin concentration from the effect compartment associated with 50% of CLIns/V; Hill coefficient determining the steepness of the insulin-clearance relationship.

RESULTS

Analysis Data Set

Considering each “individual + glucose dose occasion” as one study individual, data from 72 “study subjects” were available: 12 nondiabetic obese adults at 3 occasions, resulting in 36 studied obese subjects, and 12 lean healthy adults at 3 occasions, resulting in 36 studied lean controls.

Gastric emptying rates were not assessed in lean healthy subjects receiving 75 g OGTT. Data from two previous trials performed by our group following the same protocol and using the same equipment for measurement of gastric emptying were included (12, 42). Twenty lean subjects receiving 75 g glucose were used to input median gastric emptying profiles in the study cohort. This resulted in 160 observations of gastric emptying rates with median [minimum-maximum] values of 15 %dose/h [11-21] at 30 min and 14 %dose/h [9-19] at 120 min.

Dynamic data of glucose, insulin, incretin hormones (GIP and GLP-1), C-peptide and gastric emptying from 36 nondiabetic obese (BMI median [minimum-maximum]: 38 kg/m² [31-48]) and 36 lean healthy (BMI: 22 kg/m² [19-25]) adults were available until 180 min after OGTT. Key characteristics of studied individuals and key measurements are summarized in Table 1. Mean glucose and insulin concentrations were higher in obese adults as compared with those in lean adults. Several individuals showed multiple peaks in their gastric emptying and glucose profiles. A majority of individuals had their glucose levels falling below baseline value (i.e., glucose level before oral glucose administration) 1-2 h after oral glucose administration. This interesting observation required incorporation of time-dependent components in the physiologically-based model as explained in the next section.

Final Model

Structural components of the final model. The final structural model is composed of three compartments. The first compartment, A, corresponds to the absorption of oral glucose in the gut. The second compartment, Gluc, represents the glucose kinetics with its production and elimination rates. An additional compartment was added to characterize the delayed insulin effect (InsE) on glucose elimination (Fig. 1).

Glucose kinetics after OGTT with 10, 25, or 75 g of glucose was characterized by a kinetic one-compartment model with first-order glucose absorption and elimination rates. Individual

Fig. 1. Structural components of the final model to characterize interactions among gastric emptying, glucose absorption and glycemic control in nondiabetic obese and lean healthy adults. The blue bubble corresponds to observed insulin kinetics, gray bubble to observed gastric emptying profiles, and pink bubbles to the population effect of obese vs. lean. CMT: compartment; K, glucose absorption rate; Gast, observed dynamic gastric emptying rates; EXPOGast, effect of gastric emptying rate on K, A, amount of glucose after ingestion; Kprod, glucose endogenous production rate; Ins: observed dynamic insulin data; Gluc, glucose concentration; V, volume of distribution; GL0, baseline glucose concentration; CL, insulin-independent glucose clearance; CLIns, insulin-dependent glucose clearance; InsE, insulin concentration in the effect compartment; Ins50, insulin concentration from the effect compartment associated with 50% of CLIns/V; H, Hill coefficient determining the steepness of the insulin-clearance relationship; K1E, equilibration rate constant of the insulin effect compartment.
Table 1. **Key characteristics and measurements of healthy lean and non-diabetic obese studied adults**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lean Adults</th>
<th>Obese Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studied individuals</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Number of observations</td>
<td>323</td>
<td>323</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22 [19–25]</td>
<td>38 [31–48]</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Glucose doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 g</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>25 g</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>75 g</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Characteristics per doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline glucose, mmol/l</td>
<td>4.9 [4.3–5.5]</td>
<td>5.2 [4.7–5.6]</td>
</tr>
<tr>
<td>Glucose at 30 min, mmol/l</td>
<td>6.1 [4.7–7.4]</td>
<td>6.4 [5.4–6.9]</td>
</tr>
<tr>
<td>Glucose at 120 min, mmol/l</td>
<td>4.8 [4.3–5.2]</td>
<td>4.9 [4.7–5.3]</td>
</tr>
<tr>
<td>Baseline insulin, μU/ml</td>
<td>4.3 [2.5–6.9]</td>
<td>3.5 [2.4–8.1]</td>
</tr>
<tr>
<td>Insulin at 30 min, μU/ml</td>
<td>9.2 [5.9–15.2]</td>
<td>33.7 [9.9–85.7]</td>
</tr>
<tr>
<td>Insulin at 120 min, μU/ml</td>
<td>2.4 [2.0–7.0]</td>
<td>18.0 [2.2–40.9]</td>
</tr>
<tr>
<td>Gastric emptying at 30 min, %dose/h</td>
<td>31.8 [26.6–39.7]</td>
<td>15.1*</td>
</tr>
<tr>
<td>Gastric emptying at 120 min, %dose/h</td>
<td>11.3 [9.4–13.9]</td>
<td>26.8 [21.9–38.0]</td>
</tr>
<tr>
<td>T50% gastric emptying, h</td>
<td>59 [49–79]</td>
<td>120.0 [120.0–185.7]</td>
</tr>
<tr>
<td>Baseline GIP, pg/ml</td>
<td>120.0 [120.0–375.9]</td>
<td>120.0 [120.0–167.2]</td>
</tr>
<tr>
<td>GIP at 30 min, pg/ml</td>
<td>202.3 [120.0–429.1]</td>
<td>429.8 [272.0–755.1]</td>
</tr>
<tr>
<td>GIP at 120 min, pg/ml</td>
<td>120.0 [120.0–383.6]</td>
<td>120.0 [120.0–167.2]</td>
</tr>
<tr>
<td>Baseline GLP-1, pg/ml</td>
<td>10.5 [4.5–41.0]</td>
<td>15.5 [6.7–35.2]</td>
</tr>
<tr>
<td>GLP-1 at 30 min, pg/ml</td>
<td>12.0 [5.0–30.2]</td>
<td>6.1 [29.6–165.2]</td>
</tr>
<tr>
<td>GLP-1 at 120 min, pg/ml</td>
<td>7.8 [3.6–14.4]</td>
<td>9.0 [7.1–25.5]</td>
</tr>
<tr>
<td>Baseline C-peptide, ng/ml</td>
<td>3.7 [1.9–7.1]</td>
<td>6.0 [3.6–9.6]</td>
</tr>
<tr>
<td>C-peptide at 30 min, ng/ml</td>
<td>5.1 [2.5–14.6]</td>
<td>13.1 [7.2–16.0]</td>
</tr>
<tr>
<td>C-peptide at 120 min, ng/ml</td>
<td>3.0 [1.4–5.7]</td>
<td>7.3 [4.5–16.0]</td>
</tr>
<tr>
<td>Baseline insulin/C-peptide ratio, nmol/l</td>
<td>0.2 [0.1–0.3]</td>
<td>0.5 [0.2–0.7]</td>
</tr>
<tr>
<td>Insulin/C-peptide ratio at 30 min, nmol/l</td>
<td>0.3 [0.2–0.8]</td>
<td>0.5 [0.2–0.7]</td>
</tr>
<tr>
<td>Insulin/C-peptide ratio at 120 min, nmol/l</td>
<td>0.2 [0.1–0.5]</td>
<td>0.4 [0.2–0.9]</td>
</tr>
<tr>
<td>Baseline HOMA-IR</td>
<td>0.8 [0.5–1.7]</td>
<td>3.4 [1.6–6.6]</td>
</tr>
</tbody>
</table>

Independence of occasions was assumed and each “individual + glucose dose occasion” was considered as one study individual. Data are presented as median [minimum-maximum] or number of studied individuals (%). GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; HOMA-IR, index for homeostasis model assessment of insulin resistance; NA, not available. *Gastric emptying for lean healthy adults receiving 75 g of glucose has been replaced by the median gastric emptying profile from two previous trials performed in the same conditions (12, 42).
baseline glucose concentrations were estimated. Endogenous glucose production rate was evaluated in various models to account for time varying gluconeogenesis. However, available data did not support precise estimation of this parameter and thus glucose production rate was expressed as a function of glucose clearance and baseline glucose in the final model.

The dynamic individual glucose absorption profiles were described using a power function depending on the dynamic individual gastric emptying rates as described in Eq. 1:

$$K_s(t) = TVK_s \times \left( \frac{\text{Gast}(t)}{\text{median(Gast)}} \right)^{\text{EXPO}_{\text{Gast}}}$$

Eq. 1

$K_s(t)$ represents the total glucose absorption rate after accounting for interactions between gastric emptying and glucose absorption process. TVK$_s$ is the typical glucose absorption rate of an individual with a gastric emptying rate equal to the median in the population. The parameter Gast represents the observed dynamic gastric emptying rates. Gast is centered on the median value in the population, set at 13% dose/h for lean and obese individuals. The exponent EXPO$_{\text{Gast}}$ quantifies the effect of gastric emptying rate on $K_s$. The bioavailability was fixed to 100% for unity in evaluated models.

An effect compartment was added to describe the delayed insulin response on glucose clearance. The insulin-related effect on glucose clearance was described with a sigmoidal function plateauing at a maximum insulin-dependent effect on glucose clearance was described with a sigmoidal function plateauing at maximum insulin-dependent effect on glucose clearance was described with a sigmoidal function plateauing at 100% for unity in evaluated models. Available data did not support estimation of insulin or glucose effect on glucose absorption and thus only the effect of the insulin on glucose absorption was modeled. The parameter $\text{Ins}_{50}$ was determined to be more informative than C-peptide alone or insulin over C-peptide ratio.

The following equations represent the three compartments of developed model (see Glossary for parameter interpretations):

$$\frac{d}{dt}A(t) = -K_s(t) \times A(t)$$

Eq. 2

$$\frac{d}{dt}\text{Gluc}(t) = \text{K}_\text{prod} + K_s(t) \times A(t) - \left[ \frac{\text{Gluc}(t)}{\frac{\text{CL}}{V} + \frac{\text{CL}_{\text{Ins}}}{V} \times \frac{\text{Ins}_{\text{E}}(t)^H}{\text{Ins}_{50}^H + \text{Ins}_{\text{E}}(t)^H}} \right]$$

Eq. 3

$$\frac{d}{dt}\text{Ins}_{\text{E}}(t) = \text{Ins}(t) \times K_1E - K_1E \times \text{Ins}_{\text{E}}(t)$$

Eq. 4

with $K_\text{prod} = \text{GL0} \times \text{CL}$

Eq. 5

The initial conditions at time $t = 0$ are the following:

$$A(0) = 0$$

Eq. 6

$$\text{Gluc}(0) = \text{GL0} \times V$$

Eq. 7

$$\text{Ins}_{\text{E}}(0) = \text{INS0}$$

Eq. 8

Interindividual variability components in the final model. Interindividual variability (IIV) was estimated on the key model parameters: $K_s$, CL, CL$_{\text{Ins}}$, and GL0. Available data did not support estimation of IIV on bioavailability, $\text{Ins}_{50}$, $H$, and $K_1E$, and thus IIV of these model parameters was set to 0. For similar reasons, IIV on volume of distribution $V$ was fixed to 10%. Log-normal parameter distributions were assumed. A proportional error model was applied within each of the two study populations to account for residual variability, including measurement errors, in observed glucose values.

Population and covariate effects on the final model. Study population, lean healthy vs. nondiabetic obese subjects, was found to have an effect on baseline glucose (GL0) and insulin-dependent glucose clearance (CL$_{\text{Ins}}$). The parameter $\text{Ins}_{50}$ was determined to be more informative than C-peptide alone or insulin over C-peptide ratio. Gender effects on baseline glucose, glucose absorption, and elimination parameters were not statistically significant. Age was not tested in the covariate analysis due to its narrow range. Effects of incretin hormones (GIP and GLP-1) were tested on glucose absorption rates in place of and in addition to gastric emptying rates, but their effect remain minor compared with gastric emptying.

Interpretation of the final model parameters. The typical glucose absorption rate (TVK$_s$) was estimated to be 0.013 min$^{-1}$ in an individual with gastric emptying rate equal to the median. After the interactions between individual gastric emptying and glucose absorption profiles were accounted, the typical glucose absorption rate was estimated to be the same in lean healthy and nondiabetic obese patients. Figure 2A shows the kinetics of individual predicted glucose absorption rates ($K_s$). Figure 2B illustrates the relationship between individual $K_s$ and gastric emptying rates in both lean healthy and nondiabetic obese patients for the different glucose doses.

The typical glucose insulin-independent clearance (CL) and baseline glucose (GL0) were found to be 0.12 l/min and 4.9 mmol/l, respectively, in a lean healthy adult. This leads to an endogenous glucose production rate ($K_{\text{prod}}$) of 0.58 mmol/min for a typical lean control subject. The volume of distribution ($V$) was estimated at 3.2 liters. The typical equilibration rate constant of the insulin effect compartments ($K_{\text{E}}$) was estimated to be 0.014 min$^{-1}$. Estimates of parameters and their IIV from the final model are provided in Table 2.

Final Model Evaluation

Table 2 shows estimations of model parameters. RSEs of all parameters were less than 30%. According to goodness-of-fit plots, glucose kinetics were adequately fitted by the final model in both lean healthy and nondiabetic obese adults (Fig. 3A). Generated pcVPCs demonstrate that observed glucose values are in agreement with model-simulated glucose values, consistent with good predictive performance of the final model (Fig. 3B).

Parameter estimates of the analyses using data from all glucose dose occasions pooled at the individual level (12 lean healthy subjects, 12 nondiabetic obese subjects) were comparable to those assuming independence of occasions (results not shown).

Lean vs. Obese Comparison

The typical baseline glucose concentration (GL0) was estimated to be ~5% higher in nondiabetic obese subjects as compared with lean controls (GL0$_{\text{Lean}} = 4.9$ mmol/l vs. GL0$_{\text{Obese}} = 5.2$ mmol/l). The insulin-dependent component of
glucose clearance (CL\textsubscript{Ins}) was found to be \textasciitilde44\% lower in nondiabetic obese subjects as compared with lean controls (CL\textsubscript{Ins\textsubscript{Lean}} = 0.052 l/min vs. CL\textsubscript{Ins\textsubscript{Obese}} = 0.029 l/min). The insulin concentration in the effect compartment associated with 50\% of insulin-dependent glucose elimination rate (Ins\textsubscript{50}) was approximately twofold higher in nondiabetic obese subjects compared with lean controls (Ins\textsubscript{50\textsubscript{Lean}} = 7.1 \textmu U/ml vs. Ins\textsubscript{50\textsubscript{Obese}} = 15.3 \textmu U/ml). These findings suggest that: 1) insulin-dependent glucose clearance is cut in half in nondiabetic obese subjects as compared with lean controls; and 2) higher insulin levels are required in nondiabetic obese subjects to maintain insulin effects on glucose clearance similar to those observed in lean controls.

DISCUSSION

Obesity is a major health problem related to comorbidities such as T2DM (43). Recent research indicates that dynamics of gastric emptying is altered in obese adults affecting both glucose absorption and glycemic control (16, 18, 24, 27, 28, 32, 40). In addition, differences in gastric emptying rates lead to high variability in postprandial glucose concentrations (17). Despite that, these interactions are still not well understood in nondiabetic obese adults.

We report a physiology-based mathematical model that directly links individual gastric emptying to glucose absorption and compares this dynamic interaction as well as glycemic control in lean healthy and nondiabetic obese adults. The

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>RSE Estimate, %</th>
<th>IIV, %CV</th>
<th>RSE IIV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose absorption rate (TV\textsubscript{K\textsubscript{a}}), \textsubscript{min\textsuperscript{-1}}</td>
<td>0.013</td>
<td>12</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Gastric emptying effect on (EXPO\textsubscript{gast}), dimensionless</td>
<td>1.5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin-independent glucose clearance (CL), l/min</td>
<td>0.12</td>
<td>13</td>
<td>78</td>
<td>13</td>
</tr>
<tr>
<td>Volume of distribution (V), liter</td>
<td>3.2</td>
<td>10</td>
<td>10 FIX</td>
<td></td>
</tr>
<tr>
<td>Baseline glucose in lean individuals (GL\textsubscript{0\textsubscript{Lean}}), mmol/l</td>
<td>4.9</td>
<td>1</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Baseline glucose in obese individuals, (GL\textsubscript{0\textsubscript{Obese}}), mmol/l</td>
<td>5.2</td>
<td>1</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Insulin-dependent clearance in lean individuals (CL\textsubscript{Ins\textsubscript{Lean}}), l/min</td>
<td>0.052</td>
<td>15</td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>Insulin-dependent clearance in obese individuals (CL\textsubscript{Ins\textsubscript{Obese}}), l/min</td>
<td>0.029</td>
<td>18</td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>Insulin efficacy in lean individuals (Ins\textsubscript{50\textsubscript{Lean}}), \textmu U</td>
<td>7.1</td>
<td>14</td>
<td>0 FIX</td>
<td></td>
</tr>
<tr>
<td>Insulin efficacy in obese individuals (Ins\textsubscript{50\textsubscript{Obese}}), \textmu U</td>
<td>15.3</td>
<td>25</td>
<td>0 FIX</td>
<td></td>
</tr>
<tr>
<td>Sigmoidal Hill coefficient (H), dimensionless</td>
<td>3.3</td>
<td>21</td>
<td>0 FIX</td>
<td></td>
</tr>
<tr>
<td>Equilibration rate constant of insulin effect compartment (K1E), \textsubscript{min\textsuperscript{-1}}</td>
<td>0.014</td>
<td>12</td>
<td>0 FIX</td>
<td></td>
</tr>
<tr>
<td>Proportional residual error in lean individuals</td>
<td>10%</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportional residual error in obese individuals</td>
<td>8%</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CV, coefficient of variation; FIX, fixed parameter; IIV, interindividual variability; RSE, relative standard error; Ins\textsubscript{50}, insulin concentration from the effect compartment associated with 50\% of CL\textsubscript{Ins}/V.
glucose absorption rate was modeled as changing with time following the gastric emptying rate kinetics, with decreasing values when OGTT glucose dose increases. We found that incretins (GIP and GLP-1) have a minor effect on glucose absorption compared with gastric emptying rates (39). The insulin effect on glucose clearance was modeled with a saturable mathematical function to account for the fact that this effect reaches a plateau at a certain level.

The main advantage of our proposed model compared with the oral minimal-model of Cobelli et al. (7) is the inclusion of the following physiological components: 1) use of gastric emptying rates data to drive glucose absorption rate profiles by time; 2) distinction between two different clearances, insulin dependent and independent; 3) a saturable insulin effect on glucose clearance; and 4) use of an effect compartment to describe delayed insulin effects on glucose clearance. Previously published models by Silber (19) and Jauslin (36–38) were developed without gastric emptying data. Alskär et al. (1) did use gastric emptying data derived from the acetaminophen absorption test. In contrast, our glucose absorption model is based on gastric emptying data measured with the $^{13}$C sodium acetate breath test, a more reliable method than deriving gastric emptying data from an acetaminophen absorption test. Despite the accuracy of the applied breath test, it should also be noted that variability in intestinal absorption could potentially alter the results.

Previous models described glucose absorption and kinetics in patients with T2DM. In contrast, our model characterizes the effects of gastric emptying on glucose absorption and kinetics in the new population of nondiabetic obese adults. Interestingly, baseline glucose was estimated to be only marginally higher in nondiabetic obese subjects as compared with lean controls, whereas insulin-dependent glucose clearance was cut in half in this patient population as compared with clearance in lean controls. The latter finding is in line with previous reports that found differences in glucose clearance between diabetic subjects vs. lean controls (19, 30, 36). In addition, the insulin concentration
associated with 50% of the insulin-dependent glucose elimination rate was twofold higher in nondiabetic obese subjects as compared with that in lean controls. This model-based finding indicates that while baseline glucose concentrations remain controlled in nondiabetic obese subjects, prediabetic obese adults are not able to adapt to increasing plasma glucose levels above a certain threshold with proportionate changes in insulin secretion (4).

The purpose of this work was descriptive and thus the developed model may be used for simulations only if the observed inputs insulin and gastric emptying rates are available or can be predefined. The present model does not include the effect of insulin or glucose on glucose production; additional data would be useful to identify such effect. For our model-based analysis, we assumed independence of occasions and treated each “individual + glucose dose occasion” combination as one study individual. A sensitivity analysis was performed and no difference was observed regarding parameter estimates when considering data from all glucose dose occasions pooled at the individual level. Of course, validation of this model with external data from a larger population of subjects is warranted and direct measure of glucose absorption would be helpful to confirm our results. In addition, the validity of such model has not been yet established in the situation of changed anatomy, and we plan to analyze its applicability in patients after bariatric surgery. Finally, our current model is based on luminal glucose absorption without interactions of other dietary molecules. During digestion and absorption of complex meals, the physiological and digestive functions of the gastrointestinal tract are different from glucose. As a next step we plan to further expand the model to other clinical situations using glucose as a test molecule.

Integrated, mathematical models, such as ours, could be used as a quantitative approach to characterize and understand improvement of glycemic control after bariatric surgery or the effects of oral antidiabetic drugs on glucose absorption. The complex metabolic changes occurring in obese subjects resulting from time-dependent changes from overweight to obesity are recognized as gradual increase in hyperglycemia, caused by a relative insulin deficiency as a result of progressive β-cell degradation and dysfunction in combination with peripheral insulin resistance. Our model permits simulations and predictions of potential mechanisms such as changes in glucose clearance in different disease states.

**Perspectives and Significance**

We developed a physiology-based mathematical model that characterizes and compares dynamic interactions among gastric emptying, the glucose absorption process, and the postprandial glycemic control in healthy lean and nondiabetic obese adults. This paper illustrates how these kinds of advanced models can generate scientific insights and enhance understanding of the dynamic interactions among gastric emptying, glucose absorption, and kinetics in lean healthy subjects, nondiabetic obese subjects and other populations of interest.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

M.W. and M.P. analyzed data; M.W., B.K.W., A.C.M.-G., C.B., and M.P. interpreted results of experiments; M.W. prepared figures; M.W. and B.K.W. drafted manuscript; M.W., B.K.W., A.C.M.-G., C.B., and M.P. edited and revised manuscript; M.W., B.K.W., A.C.M.-G., C.B., and M.P. approved final version of manuscript; B.K.W., A.C.M.-G., and C.B. performed experiments.

**Glossary**

\( A(t) \) Amount of glucose after ingestion
\( CL \) Insulin-independent glucose clearance
\( CL_{\text{Ins}} \) Insulin-dependent glucose clearance
\( EXPo_{\text{Gast}} \) Effect of gastric emptying rate on \( K_a \)
\( Gast(t) \) Observed dynamic gastric emptying rates
\( GL0 \) Baseline glucose concentration
\( Gluc(t) \) Glucose concentration
\( H \) Hill coefficient determining the steepness of the insulin-clearance relationship
\( Ins(t) \) Observed dynamic insulin data
\( INS0 \) Baseline insulin concentration
\( INS_{50} \) Insulin concentration in the effect compartment associated with 50% of insulin-dependent glucose elimination rate (\( CL_{\text{Ins}}/V \))
\( INS_{\text{eff}}(t) \) Insulin concentration in the effect compartment for delayed insulin effects on CL\( \text{Ins} \)
\( K_d(t) \) Total glucose absorption rate after accounting for interactions between gastric emptying and glucose absorption process
\( K_{\text{prod}} \) Glucose endogenous production rate
\( KE \) Equilibration rate constant of the insulin effect compartment
\( TVK_a \) Typical glucose absorption rate of an individual with a gastric emptying rate equal to the median in the population
\( V \) Volume of distribution parameter

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