Quantitative Estimation of Insulin Sensitivity in Type 1 Diabetic Subjects Wearing a Sensor-Augmented Insulin Pump

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OBJECTIVE

The goal was to develop a new index of insulin sensitivity in patients with type 1 diabetes estimated from continuous glucose monitoring (CGM) and subcutaneous insulin delivery data under carefully controlled conditions.

RESEARCH DESIGN AND METHODS

The database consists of 12 subjects with type 1 diabetes, studied during breakfast, lunch, and dinner, in a clinical research unit, wearing both subcutaneous insulin pump and CGM device. Frequent blood samples were drawn for measurements of plasma glucose and insulin concentrations in order to estimate insulin sensitivity with the oral minimal model (S_I^{MM}). The new index of insulin sensitivity (S_I^{SP}) was calculated with a simple algebraic formula for each meal, using only CGM and insulin pump data and compared with S_I^{MM}.

RESULTS

S_I^{SP} was well correlated with S_I^{MM} ($r = 0.825$; $P < 10^{-8}$), and diurnal pattern was also similar to S_I^{MM}.

CONCLUSIONS

A novel method for estimating insulin sensitivity in subjects with type 1 diabetes on sensor-augmented insulin pump therapy has been presented. This new index correlates well with the reference oral minimal model estimate of insulin sensitivity. The knowledge of patient-specific insulin sensitivity and its diurnal variation can help in optimizing insulin therapy in type 1 diabetes and could also inform next-generation closed-loop control systems.

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The standard therapy for type 1 diabetes consists of exogenous insulin administration, either by multiple daily injections or with continuous subcutaneous insulin infusion (CSII) through the insulin pump, adjusted according to self-monitored blood glucose (SMBG) levels 3–4 times per day. However, in the past 10–15 years, new possibilities in diabetes therapy have emerged thanks to continuous glucose monitoring (CGM) and CSII, which substitute SMBG and multiple daily injection therapy, respectively. Minimally invasive CGM devices can measure, in real time, interstitial glucose (IG) concentrations in continuous time for up to several

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days. CSII uses the subcutaneous route and administers insulin with a basal/bolus strategy, i.e., continuously deliver insulin over 24 h and inject boluses.

In order to determine the appropriate meal insulin bolus, it would be important to know the subject-specific insulin sensitivity, i.e., the ability of insulin to stimulate glucose utilization and inhibit glucose production. Indices of insulin sensitivity include those based on hyperinsulinemic-euglycemic clamp (1), intravenous glucose tolerance test (2), and, more recently, meal and oral glucose tolerance test. These indices include the oral glucose minimal model (3,4), a minimal model based integral formula (5), and surrogate measures (6–8). However, all the above require the measurement of both plasma glucose and insulin concentrations and therefore cannot be used in everyday life. In the outpatient setting, the only usable approach is the risk method proposed by Breton and Kovatchev (9), which uses SMBG data collected over a period of 2–6 weeks and some patient parameters. This index measures the average insulin sensitivity in the preceding 2 weeks and thus cannot be used to assess the intraday variability of insulin sensitivity.

Here we propose a method to estimate insulin sensitivity from CGM sensor and insulin pump data and validate it against the oral minimal model, which uses plasma glucose and insulin concentrations. The method is usable in everyday life in patients wearing the two devices.

RESEARCH DESIGN AND METHODS

Database and Protocol

Twelve type 1 diabetic subjects (5 females, aged 39.5 ± 14.2 years, BMI 25.7 ± 3.8 kg/m^2, HbA_{1c} ≤8.5% or 69 mmol/mol) were studied for 3 days in the clinical research unit of the Mayo Clinic Center for Translational Science Activities as part of a separate study to determine diurnal patterns of insulin sensitivity (10). Briefly, once per day, a triple-tracer mixed-meal study protocol was performed during breakfast, lunch, or dinner in Latin square design. Blood samples were collected at −180, −30, 0, 5, 10, 20, 30, 60, 90, 120, 150, 180, 240, 300, and 360, with t = 0 corresponding to meal time, for measurement of plasma glucose and insulin concentrations in order to estimate S_I with the oral minimal model (3), here considered as reference. More details can be found in Hinshaw et al. (10). Subjects also wore both subcutaneous insulin pump (Medtronic or Insulet OmniPod) and CGM (Dexcom Seven Plus). Within-subject mean absolute relative difference between CGM readings and reference was equal to 12.1 ± 3.3%, and no systematic variation over time was found (mean [SD] within subjects was 5.3 ± 3.7%). This is perfectly in line with published reports (11). Figure 1 shows CGM and insulin infusion rate in a representative subject. The 12 subjects have been chosen among the 19 reported by Hinshaw et al. (10) since they had the complete CGM and CSII data required for the calculation described below. Of note, one CGM trace was missing in one subject during one meal.

Basis

The starting point is the derivation of insulin sensitivity by integrating the oral minimal model equations (3), as described by Caumo et al. (5). Then, the calculation is adapted to allow the use of CGM and CSII data, instead of plasma glucose and insulin concentrations. The oral minimal model (3) is

$$\begin{cases} \dot{G}(t) = -[p_1 + X(t)] \cdot G(t) + p_1 \cdot G_b + \dfrac{Ra_G(t)}{V_G} & G(0) = G_b \\ \dot{X}(t) = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] & X(0) = 0, \end{cases} \quad (1)$$

where G is plasma glucose concentration (milligrams per deciliter), with G_b denoting its basal value; X is insulin action (min^{-1}); I is plasma insulin concentration (microunits per milliliter), with I_b denoting its basal value; Ra_G is

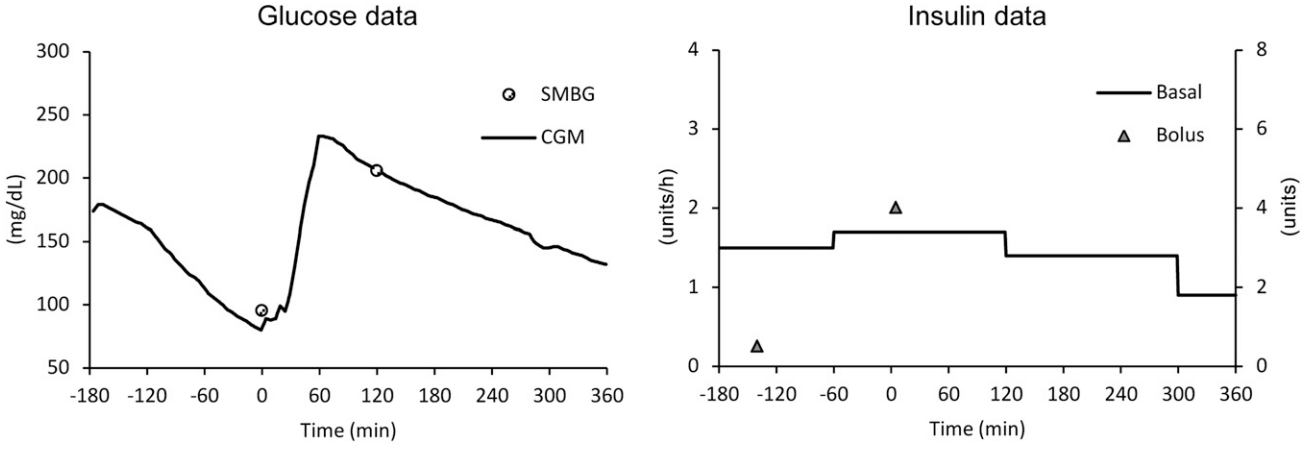

Figure 1—Data needed for the estimation of insulin sensitivity. Glucose data are measured by CGM (*left-hand* panel, black line), with some SMBG data available for sensor recalibration (*left-hand* panel, gray dots). Insulin data are the basal infusion and boluses administered by insulin pump (*right-hand* panel, black line and gray triangles, respectively).

posthepatic appearance of meal glucose (milligrams per kilograms per minute); V_G is glucose distribution volume (deciliters per kilogram); p_2 is speed of rise and decay of insulin action (min^{-1}); and p_3 is its size (min^{-2} per microunit per milliliter). Insulin sensitivity is defined as

$$S_I = \frac{p_3}{p_2} \cdot V_G. \tag{2}$$

By substituting $X(t) = \frac{p_3}{p_2} \cdot X'(t)$ and $p_1 = \frac{GEZI}{V_G} + \frac{S_I}{V_G} \cdot I_b$ into Eq. 1, we obtain

$$\begin{cases} \dot{G}(t) = -\left[\frac{GEZI}{V_G} + \frac{S_I}{V_G} \cdot I_b + \frac{S_I}{V_G} \cdot X'(t)\right] \cdot G(t) + \left(\frac{GEZI}{V_G} + \frac{S_I}{V_G} \cdot I_b\right) \cdot G_b + \frac{Ra_G(t)}{V_G} & G(0) = G_b \\ \dot{X}'(t) = -p_2 \cdot X'(t) + p_2 \cdot [I(t) - I_b] & X(0) = 0. \end{cases} \tag{3}$$

By integrating the differential equation (Eq. 3) from the time of the meal ingestion (t_{meal}) to the end of the experiment (t_{end}) and rearranging, one has

$$S_I = \frac{\int_{t_{meal}}^{t_{end}} Ra_G(t)dt - GEZI \int_{t_{meal}}^{t_{end}} \Delta G(t)dt - V_G \int_{t_{meal}}^{t_{end}} \dot{G}(t)dt}{\int_{t_{meal}}^{t_{end}} X'(t) \cdot G(t)dt + I_b \int_{t_{meal}}^{t_{end}} \Delta G(t)dt}. \tag{4}$$

The first integral in the numerator can be rewritten as

$$\int_{t_{meal}}^{t_{end}} Ra_G(t)dt = \frac{D \cdot f(t_{end})}{BW}, \tag{5}$$

where D (milligrams) is the amount of glucose ingested during the meal and $f(t_{end})$ is the fraction of the ingested dose, which at $t = t_{end}$ has reached plasma. X' in Eq. 4 is usually not available because model parameters are unknown, thus the denominator of Eq. 4 is substituted with the average of glucose excursion times the overall insulin stimulus:

$$\frac{1}{(t_{end} - t_{meal})} \cdot \int_{t_{meal}}^{t_{end}} I(t)dt \cdot \int_{t_{meal}}^{t_{end}} |\Delta G(t)|dt, \tag{6}$$

where $|\Delta G|$ is above basal plasma glucose concentration.

Thus S_I is given by

$$S_I = \frac{\frac{D \cdot f(t_{end})}{BW} - GEZI \cdot AUC(\Delta G) - V_G \cdot [G(t_{end}) - G(t_{meal})]}{AUC(I) \cdot \left[\frac{AUC(|\Delta G|)}{t_{end} - t_{meal}}\right]}, \tag{7}$$

where AUC is the area under the curve calculated from the start of the meal (t_{meal}) to the end of the experiment (t_{end}). Subject-specific parameters used by the formula are the body weight (BW) (kilograms), height (meters), and age (years). BW is explicitly used in Eq. 7 and, together with height and age, used for the calculation of plasma insulin clearance (CL), as discussed below. Parameter fixed to population values are glucose effectiveness at zero insulin GEZI [deciliters per kilogram per minute; fixed to 0.01 dL/kg/min for diabetic subjects (10,12)] and volume of glucose distribution V_G [deciliters per kilogram; fixed to 1.45 dL/kg, according to Dalla Man et al. (3)].

G, ΔG, and I are not directly available but can be derived from CGM and subcutaneous insulin delivery as detailed below.

Glucose Signal From CGM

CGM measures the IG concentration, which is related to plasma glucose by a first-order differential equation, i.e., IG is a delayed version of plasma glucose:

$$\begin{cases} \dot{IG}(t) = -k \cdot IG(t) + k \cdot G(t) & \mathrm{IG}(0) = G_b \\ CGM(t) = IG(t) \end{cases}. \tag{8}$$

Thus, with a well-calibrated device, assuming $IG(t_{end}) = IG(t_{meal})$, one has

$$\int_{t_{meal}}^{t_{end}} \dot{IG}(t)dt = 0 = -k \cdot \int_{t_{meal}}^{t_{end}} IG(t)dt + k \cdot \int_{t_{meal}}^{t_{end}} G(t)dt, \tag{9}$$

i.e.,

$$AUC(G) = AUC(IG) = AUC(CGM). \tag{10}$$

Similarly, for the above basal glucose signal, one has

$$AUC(\Delta G) = AUC(\Delta CGM). \tag{11}$$

Thus one can safely assume that, in the presence of a well-calibrated device, AUC(ΔCGM) and AUC(|ΔCGM|) are good approximations of AUC(ΔG) and AUC(|ΔG|), respectively.

In presence of a noncalibrated device, if at least two SMBG samples are available, it is possible to offline recalibrate the CGM profile (13,14).

Insulin Signal From CSII

For the calculation of AUC(I), we assume that insulin is not degraded locally in the

site of infusion. In this case, the integral of plasma insulin can be obtained from subcutaneous insulin infusion divided by the plasma insulin clearance CL. In fact, plasma insulin kinetics can be described with a single compartment model (15):

$$\dot{I}(t) = -n \cdot I(t) + \frac{Ra_I(t)}{V_I}, \quad (12)$$

where $I(t)$ is the plasma insulin concentration, $Ra_I(t)$ is the insulin rate of appearance in plasma, V_I is the insulin volume of distribution, and n the fractional insulin clearance rate ($n = CL/V_I$).

Then, integrating Eq. 12 from the time of the premeal bolus (t_{meal}) to the end of the observation period (t_{end}) and assuming that insulin is back to its initial value at the end of the experiment, one has

$$0 = -n \int_{t_{meal}}^{t_{end}} I(t)dt + \int_{t_{meal}}^{t_{end}} \frac{Ra_I(t)}{V_I} dt. \quad (13)$$

Finally, under the assumption that all infused insulin eventually reaches the circulation, one has

$$\int_{t_{meal}}^{t_{end}} I(t)dt = \frac{1}{n \cdot V_I} \int_{t_{meal}}^{t_{end}} Ra_I(t)dt = \frac{1}{CL} \int_{t_{meal}}^{t_{end}} Inf(t)dt. \quad (14)$$

Thus we can compute AUC(I) from the amount of insulin infused subcutaneously and CL:

$$AUC(I) = \frac{1}{CL} \int_{t_{meal}}^{t_{end}} basal(t)dt + \sum_{t_k=t_{meal}}^{t_{end}} \frac{bolus(t_k)}{CL}, \quad (15)$$

where basal(t) is the basal insulin infusion rate during the integration period, bolus(t_k) is the premeal or correction bolus administered at $t = t_k$, and CL (liters per minute) is the plasma insulin clearance, which can be calculated from subject's height, BW, and age by using the population model proposed by Campioni et al. (16). In addition, if correction boluses are administered before the start of the meal, one has to consider that part of that injected insulin could be still active. The residual active insulin can be determined by adopting the same algorithm presented by Patek et al. (17), which uses the insulin on board (IOB) curves adapted from Ellingsen et al. (18). This quantity (IOB[t_{meal}]) must be added to the previously estimated AUC(I). Moreover, if correction boluses are administered before the end of the considered interval, IOB is used to evaluate the active insulin at the end of the study (IOB[t_{end}]), which is subtracted from the previously estimated AUC(I). In summary,

$$AUC(I) = \frac{1}{CL} \int_{t_{meal}}^{t_{end}} basal(t)dt + \sum_{t_k=t_{meal}}^{t_{end}} \frac{bolus(t_k)}{CL} + IOB(t_{meal}) - IOB(t_{end}). \quad (16)$$

Accounting for Carbohydrates on Board

As evident from Eq. 7, an accurate calculation of insulin sensitivity requires the knowledge of the amount of carbohydrates entering the circulation in the integration interval [$D \cdot f(t_{end})$]. In this study, meals were provided at 7:00 A.M., 1:00 P.M.; and 7:00 P.M. each day, thus the time interval between the meals was at least 6 h. However, this may not always be the case. Furthermore, not all the carbohydrates ingested with a meal may be fully absorbed before the ingestion of a second meal. Thus, to account for unabsorbed carbohydrates, e.g., frequent meals close to each other, the concept of carbohydrates on board (COB) is introduced. Similarly to IOB, COB is a function that, at each time t, quantifies the fraction of the ingested carbohydrates that has not yet appeared in the circulation. COB is based on the model of gastrointestinal tract (19): given the amount of carbohydrates ingested at time t_m, COB provides, at each time $t > t_m$, the percentage of carbohydrates not yet absorbed, while for $t–t_m > 360$ min, it is assumed that the carbohydrate absorption is almost completed. The fraction of the ingested dose that has reached plasma at time t, $f(t)$, can be calculated as the ratio between the AUC of the meal rate of appearance and the ingested dose, D (Fig. 2, left panel), assuming that, at the end of the meal, the fraction of the meal appearing in plasma is $f_\infty = 0.9$ (Fig. 2, right panel). The time course of f is shown in Fig. 2, right panel. COB is then calculated as $COB(t) = f_\infty – f(t)$.

To better grasp the use of $f(t)$ and COB(t) for the calculation of insulin sensitivity, let us consider the following example: suppose that a subject eats 50 g of carbohydrates at $t = 0$ min and another 40 g at $t = 180$ min then fasts for more than 360 min. One can calculate two values of S_I, one for each meal ingestion (S_I^{meal1} and S_I^{meal2}). For the calculation of S_I^{meal1}, the amount of ingested glucose to be considered is $50 \cdot f(180)$ g of carbohydrates, while for the calculation of the second, S_I^{meal2}, one should use $50 \cdot COB(180) + 40 \cdot f_\infty$.

Generalizing, the amount of carbohydrates to use in the formula for the ith meal is

$$AoC\left(meal^i\right) = D\left(t_{meal}{}^i\right) \cdot f\left(t_{end}{}^i\right) + COB\left(t_{end}{}^{i-1}\right) \cdot D\left(t_{meal}{}^{i-1}\right), \quad (17)$$

where AoC is the amount of carbohydrates, $D(t_{meal}{}^i)$ is the amount of carbohydrates ingested at the time of the ith meal ($t_{meal}{}^i$), $t_{end}{}^i$ is the time at which the ith meal ends (corresponding to the time of ingestion of the [i+1]th meal), and COB($t_{end}{}^{i-1}$) the COB at the end of the (i–1)th meal, which contained $D(t_{meal}{}^{i-1})$ amount of carbohydrates.

Insulin Sensitivity From Sensor and Pump Data

Incorporating the above derivations into Eq. 7, one can estimate insulin sensitivity from sensor and pump data (S_I^{SP}) for the ith meal (20):

$$S_I^{SP}(meal^i) = \frac{\frac{AoC(meal^i)}{BW} - GEZI \cdot AUC(\Delta CGM) - V_G \cdot [CGM(t_{end}{}^i) - CGM(t_{meal}{}^i)]}{\left[\frac{1}{CL}\int_{t_{basal}{}^i}^{t_{end}{}^i} basal(t)dt + \sum_{t_k=t_{meal}{}^i}^{t_{end}{}^i} \frac{bolus(t_k)}{CL} + IOB(t_{meal}{}^i) - IOB(t_{end}{}^i)\right] \cdot \left[\frac{AUC(|\Delta CGM|)}{t_{end}{}^i - t_{meal}{}^i}\right]}. \quad (18)$$

It is important to define the domain of validity of Eq. 18. When CGM is still high 6 h after meal ingestion, S_I^{SP} can become negative. This brings the method working outside its domain of validity. We thus recommend to use the formula only if the recalibrated ΔCGM is lower than 150 mg/dL 6 h after meal ingestion. As a matter of fact, one of our subjects (subject 4) during lunch has recalibrated ΔCGM greater than 150 mg/dL 6 h after meal ingestion, and S_I^{SP} was negative. This subject was thus excluded in the following analysis.

Minimal Model Insulin Sensitivity and Validation of S_I^{SP}

The oral glucose minimal model (3,4) was used to estimate insulin sensitivity, from plasma glucose and insulin concentrations, in 12 subjects studied three times (10). Here we consider these measures as reference values (S_I^{MM}) to which S_I^{SP} is compared for validation.

Assessment in Case of Incompletely Absorbed Meals

In our experimental protocol, meals were well spaced (at least 6 h) and thus completely absorbed before the next meal. However, in daily life, this may not happen consistently. Thus it is important to assess the performance of the method in case of incompletely absorbed meals. We did so by comparing estimates of S_I^{SP} obtained with a 360-min interval to those obtained from shorter intervals (up to 180 min), both with and without using the COB function.

Reproducibility

When proposing a new metric like S_I^{SP}, it is important to assess its reproducibility, i.e., if it provides similar values when repeatedly applied to the same subject under the same experimental conditions. However, due to the large intrasubject variability of insulin sensitivity (10), S_I^{SP} will likely change if the same meal is administered in two occasions to a subject. Thus, to address reproducibility, one can resort to simulation. We evaluated S_I^{SP} reproducibility in simulation using our U.S. Food and Drug Administration-accepted type 1 diabetes simulator (21). We simulated a 7-day scenario for 100 in silico subjects with three meals per day (breakfast from 6:00 to 8:00 A.M., lunch from 11:30 A.M. to 1:30 P.M., and dinner from 6:00 to 8.30 P.M.) with different amounts (breakfast 0.7 – 0.9 g/kg, lunch 0.8 – 1.0 g/kg, and dinner 0.8 – 1.3 g/kg), while subject-specific insulin sensitivity was maintained constant for the whole simulation. A total of 21 S_I^{SP} were thus calculated for each subject (three values per 7 days). To assess the repeatability of the index, we calculated the average (mean), the SD, and the coefficient of variation (CV; SD/mean) of the 21 estimates of S_I^{SP} in each subject.

Statistical Analysis

Data are presented as mean ± SD. Two sample comparisons were done by paired sample *t* test. Pearson's correlation was used to evaluate univariate correlation.

RESULTS

The correlation between the two indices was very good ($r = 0.825$; $P < 10^{-8}$; Fig. 3, right-hand panel), and diurnal pattern was similar, indicating that, apart from a scale factor, S_I^{SP} closely mirrors S_I^{MM}. S_I^{MM} and S_I^{SP} have been estimated in the 12 subjects at breakfast, lunch, and dinner. S_I^{SP} was significantly higher than S_I^{MM} (13.86 ± 14.56 vs. 6.67 ± 5.63 dL/kg/min per

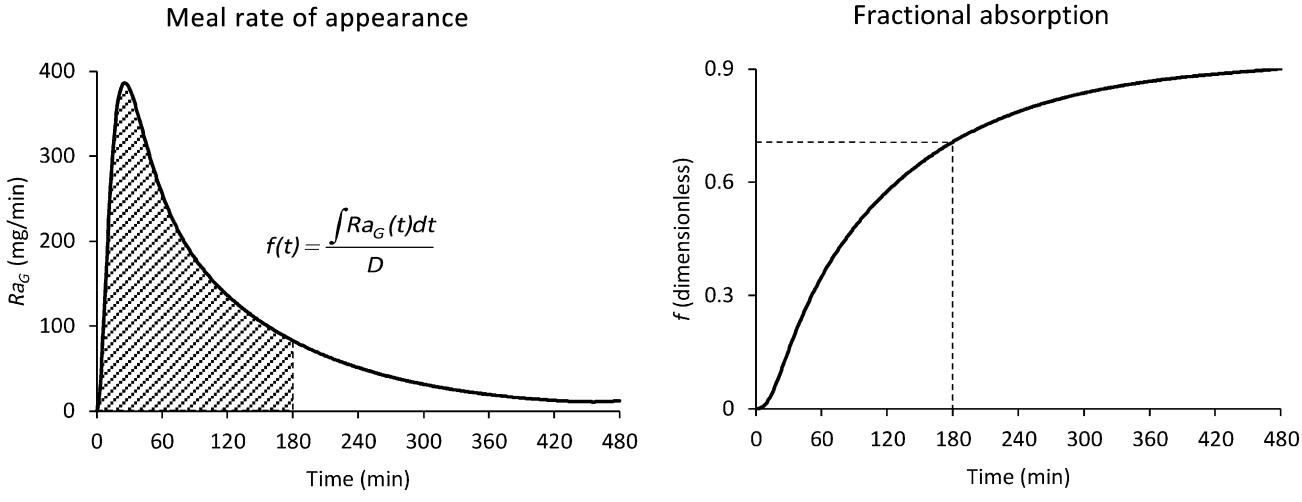

Figure 2—Time course of meal rate of appearance, Ra_G (*left-hand* panel), and fraction of meal that appears in plasma, *f* (*right-hand* panel).

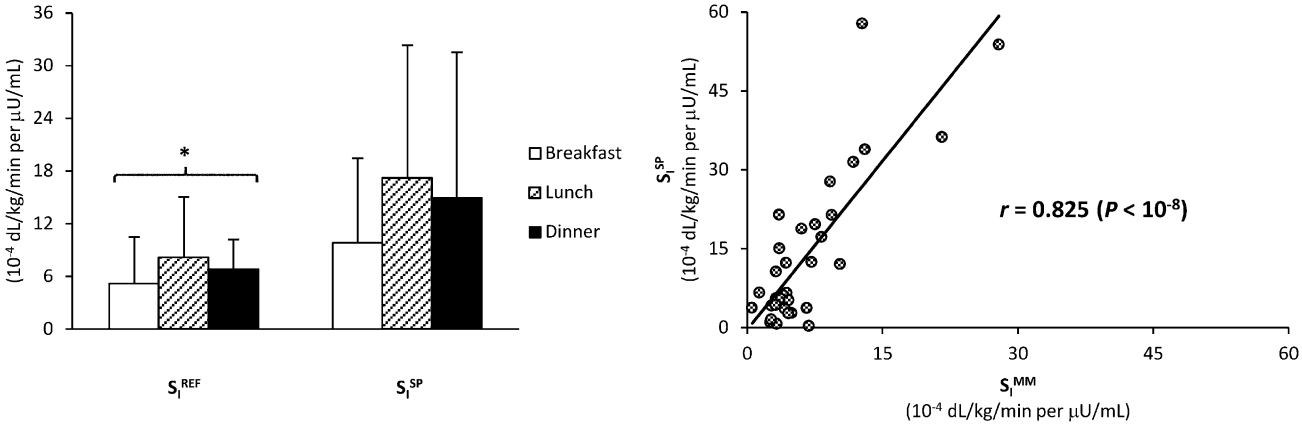

Figure 3—Mean values (*left-hand* panel) and correlation plot (*right-hand* panel) between S_I^{MM} and S_I^{SP} insulin sensitivity indices for breakfast, lunch, and dinner (white, striped, and black bars, respectively). *$P < 10^{-3}$ with paired sample *t* test.

μU/mL; $P < 10^{-3}$; Fig. 3, left-hand panel).

When S_I^{SP} was calculated for incompletely absorbed meals, i.e., relying on reduced integration intervals, mean values of S_I^{SP} were virtually the same (Fig. 4, top left) if one uses the COB function. Conversely, S_I^{SP} increased systematically if COB is not used (Fig. 4, top right). Of note, the correlation between S_I^{SP} calculated at the end of the experiment and that obtained from reduced integration intervals decreases only slightly (Fig. 4, middle panels), and the absolute relative error increases (Fig. 4, bottom panels) both with and without using COB. Finally, in silico reproducibility of S_I^{SP} was 23 ± 6%.

CONCLUSIONS

Insulin sensitivity is a key parameter of the metabolic status of an individual, which could be beneficial also for optimizing insulin therapy in type 1 diabetes. In fact, the knowledge of patient-specific S_I and its daily variation can truly help in determining the optimal insulin bolus to be administered to cover the ingested carbohydrates. However, all methods available for the estimation of insulin sensitivity rely on plasma glucose and insulin measurements and thus cannot be used in everyday life of a patient with type 1 diabetes.

In this article, we have proposed an index of insulin sensitivity, S_I^{SP}, which can be estimated in patients with type 1 diabetes wearing a CGM sensor and an insulin pump. We have demonstrated that it is similar to the one obtained with the oral minimal model, which requires plasma glucose and insulin data. The method uses retrospective subcutaneous sensor and insulin delivery data with some anthropometric parameters for each subject and provides, for each meal, the patient's insulin sensitivity by an integral formula.

S_I^{SP} measures how subcutaneously infused insulin affects the CGM profile. Thus S_I^{SP} is not exactly the same index derived with the minimal model (S_I^{MM}), which represents the ability of insulin to suppress endogenous glucose production and stimulate glucose uptake. In other words, S_I^{SP} is a new metric of insulin sensitivity with its own range. In fact, mean values of S_I^{SP} were almost twice S_I^{MM}. However, the correlation between the two indices was excellent ($r = 0.825$; $P < 10^{-8}$).

A robust estimate of insulin sensitivity can be obtained for each meal whenever meals are well spaced (5–6 h). However, we also tested the method in case of incompletely absorbed meals. To deal with this situation, we introduced the concept of COB. Similarly to IOB (18), COB represents, at each time *t*, the amount of ingested glucose that has not yet been absorbed. Thus one can define different COB curves for different types of meal, i.e., fast or slow carbohydrates. We used COB in the S_I^{SP} calculation to evaluate the correct amount of carbohydrates in relation with the observed CGM profiles in a given time interval. We demonstrated the need of using COB; in case of a short time interval between consecutive meals, a robust estimation of S_I^{SP} can only be obtained if carbohydrates absorption is taken into account (Fig. 4, top left-hand versus top right-hand panel).

Possible applications of the new index include its use for assessing intraday and interday variability (e.g., existence of diurnal patterns) of insulin sensitivity in large cohorts of subjects with type 1 diabetes in normal life conditions. For instance, the method is currently being applied to the Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 3 data of type 1 diabetic subjects wearing a sensor-augmented insulin pump (22). This will provide, in each subject, the S_I^{SP} time course during several months and will allow testing for the existence of subject-specific S_I^{SP} daily patterns and correlation of such variation with lifestyle and other factors. Following validation using STAR 3 data, a clinical application would be the use of S_I^{SP} to calculate the optimal insulin-to-carbohydrate ratio (CR) (23,24). Thus optimizing CR based on recent CGM and CSII data collected 1–2 weeks prior to a clinical visit may be useful for physicians to improve patient-specific meal bolus insulin therapy and thus a major component of glucose control. In addition, the knowledge of patient CR daily pattern may help in the design of optimal closed-loop control algorithms relying on patient-specific open-loop insulin therapy at the time of transition from open- to closed-loop therapy. A natural progression of this work would be the development of real-time adaptation of open- or closed-loop therapy based on the presence of well-developed metrics such as the one

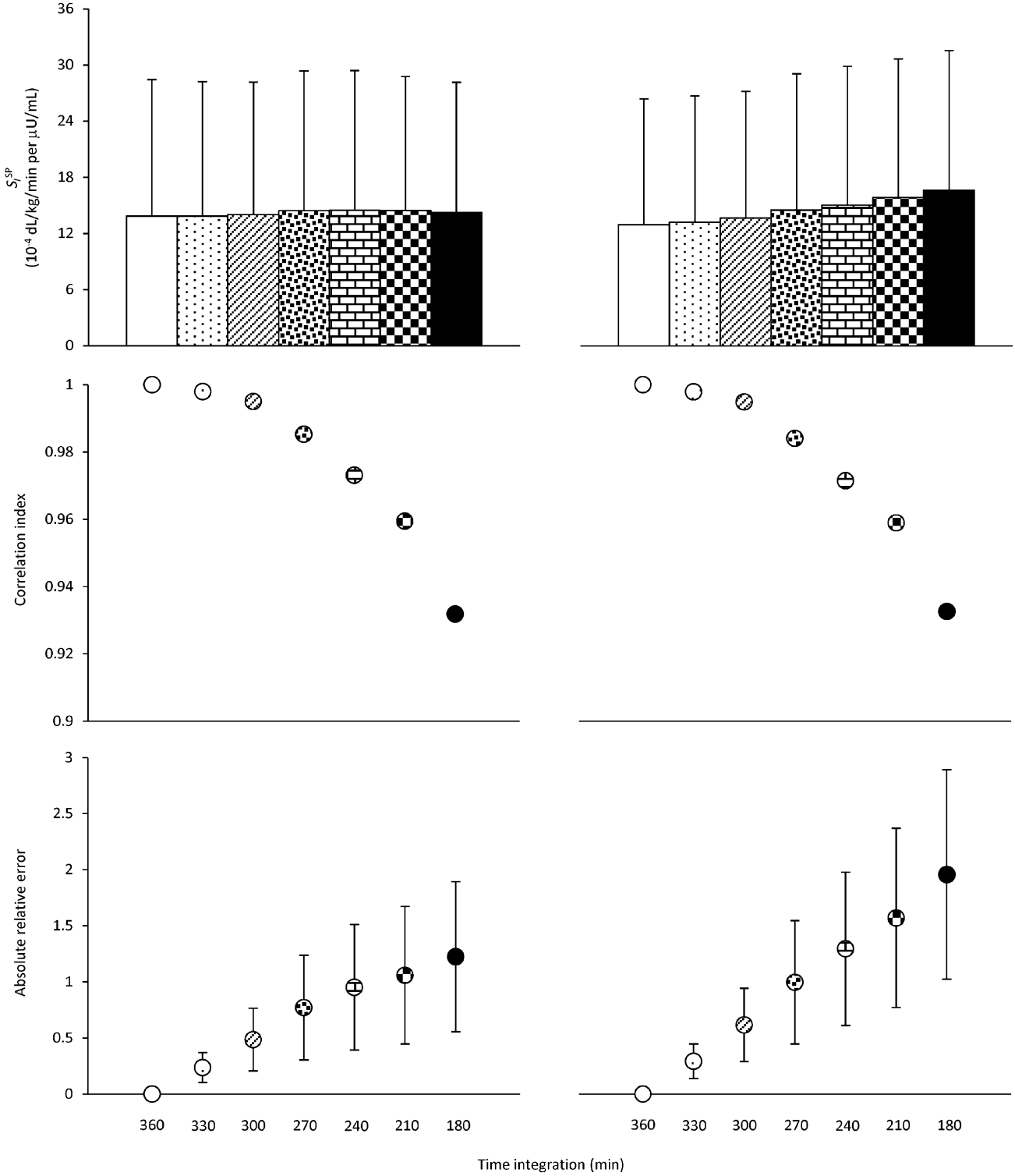

Figure 4—Sensitivity analysis of S_I^{SP} with (*left-hand* panel) and without (*right-hand* panel) accounting for COB for different time integration intervals: mean values of S_I^{SP} (*top*), correlation indices (*middle*), and absolute relative error (*bottom*), calculated with respect to S_I^{SP}, i.e., estimated at t = 360 min.

developed here. Further development of diabetes technology hardware and algorithms should make this a reality over the next several years.

The method relies on data provided by a CGM device that can occasionally suffer from inaccuracies. For instance, the assumption that AUC(CGM) is a good approximation of AUC(*G*) becomes critical if the device is not well calibrated. If this occurs, S_I^{SP} will also reflect sensor inaccuracy. However, to

improve the quality of CGM measurements, some algorithms can be used to recalibrate CGM traces (13,14). Another possible limitation is the need to fix some parameters (GEZI and V_G) to population values (3,10,12) and others calculated from population models (CL) using anthropometric data (16). In order to test the effect of fixing these parameters, we also calculated S_I^{SP} using individualized GEZI, estimated with the oral glucose minimal model (3) and CL, directly estimated from the data in each patient; we obtained values very similar to those obtained with fixed parameters and a slightly higher correlation with S_I^{MM}.

Insulin sensitivity is an important element in the daily life of patients with type 1 diabetes and could be useful to optimize insulin therapy. However, methods to estimate this index by emerging technologies, such as subcutaneous CGM sensor and insulin pump, has never been proposed. We have presented a method that estimates insulin sensitivity from CGM and insulin pump data. Future studies involving a larger databases that include larger cohorts of subjects studied for a longer time are needed to better define the applicability in free-living conditions.

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