Electronic supplementary material

Methods

Beta cell function modelling The model for the assessment of beta cell function has been described in detail in earlier publications [1, 2]. In the model, insulin secretion $S(t)$ (in pmol/min) is represented as the sum of two components. The first component, $S_g(t)$, expresses a static relationship between insulin secretion and glucose concentration, i.e. it embodies a beta cell dose–response function. The dose–response function $f(G)$ is modulated by a time-varying factor, $P(t)$, representing a potentiation effect upon insulin secretion:

$$S_g(t)=P(t)f(G) \tag{1}$$

$P(t)$ is a positive function of time, represented in discrete form as a piece-wise linear function over 5 min intervals with mean equal to 1 over the experimental time period. A value of $P(t)>1$ indicates insulin secretion above the average predicted by $f(G)$, a value of $P(t)<1$ indicates insulin secretion below this average. In each individual experiment, glucose concentration (G) was smoothed and interpolated as previously described [1].

The beta cell dose–response function $f(G)$, as described in Appendix A of the earlier publication [1], is characterised by the following properties: (1) $f(G)$ is positive for $G>0$; (2) $f(G)$ is quasi-linear for G below or above a given glucose threshold; and (3) the transition between the two quasi-linear portions can be smooth or sharp. The dose–response function $f(G)$ is determined by four variables: (1) the initial and (2) final slopes; (3) the threshold glucose level at which the change in slope occurs; and (4) a variable determining the smoothness of the change.

The second insulin secretion component $S_d(t)$ represents a dynamic dependence of insulin secretion on the rate of change of glucose concentration. $S_d(t)$ is proportional to the derivative of glucose concentration when the derivative is positive; otherwise $S_d(t)$is zero:

$$S_d(t)=\begin{cases} p_d \dfrac{dG(t)}{dt}, \dfrac{dG(t)}{dt} > 0 \\ 0, \dfrac{dG(t)}{dt} = 0 \end{cases} \tag{2}$$

The variable p_d quantifies the early insulin secretory response and is denoted as 'rate sensitivity', dt is time interval. Total insulin secretion is the sum of the two components described above:

$$S(t)=S_g(t)+S_d(t) \quad (3)$$

Total insulin secretion is calculated every 5 min. From insulin secretion, C-peptide is obtained using the two-exponential C-peptide kinetics model proposed by Van Cauter et al. [3], in which the model variables are determined in each participant based on sex, weight, height, age and diabetic status. Plasma C-peptide concentration $C(t)$ is the convolution (denoted by the symbol $\otimes$) of the individualised, two-exponential C-peptide impulse response $h(t)$ and C-peptide (i.e. insulin) secretion, $S(t)$:

$$C(t)=h(t)\otimes S(t) \quad (4)$$

The model resulting from equations 1 to 4 predicts C-peptide concentration once the variables of $f(G)$, p_d and $P(t)$ are known. Conversely, the variables of $f(G)$, p_d and $P(t)$ can be estimated using least-squares techniques from the glucose and C-peptide data. For this purpose, it is necessary to introduce a regularisation constraint on $P(t)$, as done in deconvolution schemes. The regularisation method used adds terms dependent on the smoothness of $P(t)$ to the standard sum of squares, which eliminate the spurious oscillations that $P(t)$ would otherwise exhibit. Details on this procedure are given in the earlier publication [1]. In the estimation method, regularisation variables are tuned so that the residual C-peptide standard deviation is close to that expected from measurement error, as typically done in deconvolution procedures.

Insulin secretion variables were normalised to body surface area. From the estimated model variables, other variables describing beta cell function were determined. From the dose–response function, the insulin secretion value corresponding to a fixed reference glucose concentration close to the basal value (4.5 mmol/l) was calculated. The average slope of the dose–response function in the observed glucose range was also determined. This variable

quantifies beta cell sensitivity to glucose concentration changes and is denoted as ‘beta cell glucose sensitivity’. To quantify the excursion of the potentiation factor, ratios between mean values at different time intervals (e.g. $P(t100–t120)/P(t0–t20)$ and $P(t220–t240)/P(t0–t20)$ were determined. Integrals of insulin secretion over different time intervals were calculated from $S(t)$.

References

1. Mari A, Tura A, Gastaldelli A, Ferrannini E (2002) Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. Diabetes 51(Suppl 1):S221–S226

2. Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E (2002) Meal and oral glucose tests for the assessment of β-cell function: modeling analysis in normal subjects. Am J Physiol Endocrinol Metab 283:E1159–E1166

3. Van Cauter E, Mestrez F, Sturis J, Polonsky KS (1992) Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic variables for C-peptide clearance. Diabetes 41:368–377