Associations of Glucose Control with Insulin Sensitivity and Pancreatic β-Cell Responsiveness in Newly Presenting Type 2 Diabetes

Journal of Clinical Endocrinology and Metabolism - Volume 87, Issue 1 (January 2002) - Copyright © 2002 the Endocrine Society - About This Journal 198

AHMED I. **ALBARRAK** 1
STEPHEN D. LUZIO 2
LUDOVIC J. CHASSIN 1
REBECCA A. PLAYLE 2
DAVID R. OWENS 2
ROMANHOVORKA1

1 Metabolic Modelling Group (A.I.A., L.J.C., R.H.), Centre for Measurement and Information in Medicine, City University, London, EC1V OHB, United Kingdom; 2 and Diabetes Research Unit (S.D.L., R.A.P., D.R.O.), University of Wales College of Medicine, Academic Centre, Llandough Hospital and Community NHS Trust, Penarth CF64 2XX, South Glamorgan, United Kingdom

Received April 16, 2001.
Accepted October 1, 2001.

Address all correspondence and requests for reprints to: Dr. Roman Hovorka, Metabolic Modeling Group, Centre for Measurement and Information in Medicine, City University, and Northampton Square, London, EC1V OHB, United Kingdom. E-mail: r.hovorka@soi.city.ac.uk.

Abbreviations:

AIRG
First-phase insulin secretion
AUCGlucose

Incremental area under the curve of plasma glucose during MTT

AUCInsulin

Incremental area under the curve of insulin during MTT

BMI: Body mass index

Cmax, Glucose

Maximum incremental plasma glucose concentration during the MTT

Cmax, Insulin

Maximum incremental plasma insulin concentration during the **MTT**

DI disposition index

FPG fasting plasma glucose

FPI fasting plasma insulin

HbA1C glycated hemoglobin

IVGTT iv glucose tolerance test

M0 fasting pancreatic β-cell responsiveness

MI postprandial pancreatic β-cell responsiveness

MTT meal tolerance test

SG glucose effectiveness

SI insulin sensitivity

We examined the ability of indices of insulin sensitivity and pancreatic β-cell responsiveness to explain interindividual variability of clinical measures of glucose control in newly presenting type 2 diabetes. Subjects with newly presenting type 2 diabetes (n = 65; 53 males and 12 females; age, 54 ± 1 yr; body mass index, 30.5 ± 0.7 kg/m2 ; mean ± SE) underwent an insulin-modified iv glucose tolerance test to determine minimal model-derived insulin sensitivity (SI), glucose effectiveness, first-phase insulin secretion, and disposition index. Subjects also underwent a standard meal tolerance test (MTT) to measure fasting/basal (M0) and postprandial (MI) pancreatic β-cell responsiveness. Stepwise linear regression used these indices to explain interindividual variability of fasting and postprandial plasma glucose and insulin concentrations and glycated hemoglobin (HbA1 C). All measures of pancreatic β-cell responsiveness (M0 , MI , and first-phase insulin secretion) were negatively correlated with fasting plasma glucose ($P < 0.01$) and positively correlated with fasting plasma insulin (FPI) and insulin responses to MTT ($P < 0.05$). SI demonstrated negative

correlation with FPI (P < 0.001) but failed to correlate with any glucose variable. MI followed by disposition index (composite index of insulin sensitivity and pancreatic β-cell responsiveness) were most informative in explaining interindividual variability. It was possible to explain 70–80% interindividual variability of fasting plasma glucose, FPI, HbA1C , and insulin responses to MTT, and only 25–40% interindividual variability of postprandial glucose. In conclusion, postprandial insulin deficiency is the most powerful explanatory factor of deteriorating glucose control in newly presenting type 2 diabetes. Indices of insulin sensitivity and pancreatic β-cell responsiveness explain fasting glucose and HbA1 C well but fail to explain postprandial glucose. (J Clin Endocrinol Metab 87: 198–203, 2002)

THE PATHOGENESIS OF type 2 diabetes is complex and has yet to be fully understood [1] [2] , however, it has been established that both insulin resistance and deficient insulin secretion play decisive roles in the development of type 2 diabetes [3] [4] .

The minimal model analysis [5] using the standard or insulin-modified iv glucose tolerance test (IVGTT) measures insulin sensitivity (SI) and glucose effectiveness (SG). IVGTT also provides a measure of the first-phase insulin secretion (AIR G). The minimal model has been widely used to assess insulin resistance in various pathophysiological states [5] and has become invaluable especially in population studies due to its simpler experimental design compared with the glucose clamp technique [6] .

The insulin secretion model is an approach that was developed recently to measure fasting (M0) and postprandial (MI) pancreatic β-cell responsiveness during a meal tolerance test (MTT) [7] . The MTT is a standardized physiological test and has the benefit of a typical postprandial exposure of the pancreas to glucose, other nutrients (fat, protein), gut and vagal hormones. The insulin secretion model has been shown to discriminate across a wide spectrum of pancreatic β-cell responsiveness [7] .

The generally accepted but as yet not confirmed hypothesis is that the IVGTT and/or MTT facilitate the estimation of essential indices of the whole-body carbohydrate metabolism. The aim of this study was to investigate whether these indices are able to explain interindividual variability of clinical measures of glucose control such as fasting plasma glucose (FPG) and insulin, glycated hemoglobin (HbA1 C), and the glucose and insulin responses to a meal. In

this study, subjects with newly diagnosed type 2 diabetes were studied because they present the end-point of the natural development of the disease before therapeutic intervention.

Subjects and Methods

Subjects

Subjects with newly presenting type 2 diabetes according to WHO criteria participated in the study [n = 65; 53 males and 12 females; age 54 ± 1 yr; body mass index (BMI), 30.5 ± 0.7 kg/m2 ; mean ± SE]. The study was approved by Bro Taf Local Research Ethics Committee (Cardiff, UK).

Experimental design

The subjects were admitted on two consecutive study days to the Diabetes Research Unit, Llandough Hospital (Penarth, UK), after an overnight 12-h fast. Each subject underwent two procedures in random order.

The insulin-modified IVGTT consisted of a 0.3 g/kg glucose bolus per body weight given at 0 min over 2 min, followed by 0.05 mU/kg insulin (Actrapid; Novo Nordisk, Bagsvaerd, Denmark) at 20 min [8] . Blood samples were taken at −30, −15, 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 min for measurement of plasma glucose, insulin, and C-peptide.

A standard 500-kcal meal was consumed at 0 min (75 g carbohydrates; calorie contribution, 58% carbohydrate, 23% fat, and 19% protein) [8] . Subjects were required to consume the whole meal within 10 min. Blood samples were taken at −30, 0, 10, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, and 240 min to measure plasma glucose, insulin, and C-peptide.

In both tests, blood was taken via an indwelling iv cannula that was inserted into the antecubital fossa vein and connected via a three-way tap to a slow-running saline infusion to maintain the patency of the vein.

Assay method

Glucose was assayed using the glucose oxidase method (model 2300 Yellow Springs Analyzer, YSI, Inc., Yellow Springs, OH) (intra-assay coefficient of variation <2%). Insulin and C-peptide were assayed using immunoassays using monoclonal antibodies (DAKO

Corp., Ely, Cambridgeshire, UK) (intra-assay coefficient of variation <5% and <6%, respectively).

Data analysis

Glucose and insulin levels.

FPG and fasting plasma insulin (FPI) were obtained as mean values of pretest IVGTT and MTT measurements. Cmax,Glucose and Cmax,Insulin were the maximum incremental plasma glucose and insulin concentrations during the MTT. AUCGlucose and AUCInsulin were the incremental area under the curve of plasma glucose and insulin during MTT from 0–240 min.

Minimal model analysis.

The minimal model analysis of IVGTT data gave insulin sensitivity (S I , ability of insulin to enhance the net glucose disappearance from plasma) and SG (ability of glucose to promote its own disposal) [9] [10] . Both SI and SG are measures of insulin sensitivity; the former measures insulin sensitivity at an incremental insulin concentration, the latter at the basal insulin concentration.

The AIRG (measure of pancreatic β-cell responsiveness) was calculated as the incremental area under the curve from 2–8 min during the IVGTT [11] . The disposition index (DI ; composite measure of insulin sensitivity and pancreatic β-cell responsiveness) was calculated as DI = SI × AIR G [11] .

Insulin secretion model.

Insulin secretion model was used to quantify pancreatic β-cell responsiveness from MTT data, providing M0 (ability of fasting glucose to stimulate C-peptide secretion) and MI (ability of postprandial glucose to stimulate C-peptide secretion) [7] .

M0 represents fasting prehepatic insulin secretion divided by the FPG. MI represents the increase in prehepatic insulin secretion given an increment in postprandial glucose.

Statistical analysis.

A Spearman correlation analysis with a Bonferroni correction was carried out to assess relationships between indices classified as independent variables for the purposes of the study (measures of insulin sensitivity and pancreatic β-cell responsiveness: SI , SG , AIRG , DI , M0 , and MI), and dependent variables (clinical measures of glucose control: FPG, FPI, AUCGlucose , Cmax,Glucose , AUCInsulin , and Cmax,Insulin). The stepwise multilinear regression analysis was used to relate the measures of insulin sensitivity and pancreatic β-cell

responsiveness to the clinical measures of glucose control. The probability of F for entry and removal of a variable to/from regression formulae were 0.05 and 0.1, respectively. The amount of explained interindividual variability was calculated by the ANOVA. The dependent and independent variables were tested for normal distribution and, where appropriate, were logarithmically transformed. The results are expressed as mean ± SE unless stated otherwise. SPSS for Windows V9.0 (SPSS, Inc., Chicago, IL) was used to perform statistical calculations.

Results

Plasma glucose, insulin, and C-peptide

Elevated FPG and HbA1C , shown in Table 1 , document the lack of control in the newly diagnosed subjects who also presented elevated BMI (see Subjects and Methods). However, FPI was comparable to that measured in healthy subjects, indicating a gross reduction in insulin secretion when corrected to the glucose stimulus.

The profiles of plasma glucose, insulin, and C-peptide during IVGTT and MTT are shown in Fig. 1 . During IVGTT, the effect of exogenous insulin at 20 min on glucose lowering is clearly visible. At the start of the experiment, the glucose bolus failed to stimulate an immediate insulin response, as documented by an early drop in C-peptide, and resulted in a paradoxical temporary suppression of insulin secretion. During MTT, the glucose and insulin levels remained elevated for longer than in nondiabetic subjects, with peak values reached at 60–90 min. The paradoxical suppression of endogenous insulin secretion was not present.

Minimal model and insulin secretion model

Results of model analyses are given in Table 1 . All parameters were estimated with acceptable accuracy (data not shown). As expected, insulin sensitivity SI was markedly reduced by about 70% and SG by about 20%, compared with healthy subjects [12] . M0 and MI were low, compared with those measured in healthy subjects [13] (reduction by about 50 and 80%, respectively; n = 16; age, 50 ± 10 yr; BMI, 29.2 ± 3.6 kg/m2 ; FPG, 5.1 ± 0.5 mmol/liter).

Correlation analysis

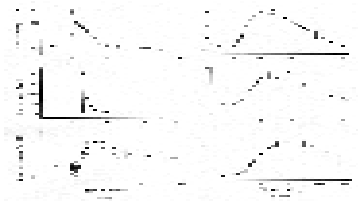
The results of the Spearman correlation analysis are given in Table 2 . FPG was negatively correlated with all measures of pancreatic β-cell responsiveness (most strongly with MI) and

the composite index DI . HbA1C followed a similar pattern with an even stronger correlation with MI but correlation with DI failing to reach significance after the Bonferroni

TABLE 1 -- Summary statistics of variables representing glucose control FPG, FPI, AUCGlucose , AUCInsulin , Cmax,Glucose , Cmax,Insulin , and HbA1C and characteristics of glucose metabolism SI , S G , AIRG , DI , M0 and MI

Variable	Mean	SE (interquartile range)
FPG (mmol/liter)	11.0	0.4
FPI (pmol/liter)	60	(31–81)
AUC Glucose (mmol/liter per 180 min)	607	41
Cmax,Glucose (mmol/liter)	5.2	0.2
AUCinsulin (mmol/liter per 180 min)	28.7	(13.6–36.6)
Cmax,Insulin (pmol/liter)	233	(115–320)
HbA1C (%)	7.9	(6.1–9.3)
SI × 10 −5 (1/min per pmol/liter)	1.07	(0.40–1.51)
SG × 10−2 (1/min)	1.5	0.1
AIRG (pmol/liter per 6 min)	313	(143–393)
DI (1/min per 6 min)	488	(202–732)
M I × 10−9 (1/min)	20.1	(11.3–27.4)
M0 × 10−9 (1/min)	5.7	(3.4–7.8)

Figure 1. Plasma glucose, insulin and C-peptide profiles (mean ± SE; n = 65) during IVGTT and MTT.



(Conservative) correction. The two MTT-related glucose variables, Cmax, Glucose and AUC Glucose , were also negatively correlated with MI .

All insulin variables (FPI, Cmax, Insulin, and AUCinsulin) were positively correlated with measures of pancreatic β-cell responsiveness. In addition, FPI was strongly negatively and AUC Insulin was weakly negatively correlated with SI. These were the only correlations demonstrated by the two insulin sensitivity indices S I and SG.

Regression analysis and explained interindividual variability

The results of the step-wise multilinear regression analysis are shown in Table 3 . The table lists normalized regression coefficients (z-scores; a higher absolute z-score indicates a stronger explanatory ability; this is achieved by transforming the independent variables to standardized form, which makes the coefficients more comparable because they are all in the same units of measure).

The MI entered all formulae with the exception of that associated with FPI and was the strongest predictor in these regressions. The D I was the second strongest predictor. SI was a strong predictor of FPI and also entered the formula associated with Cmax, Insulin. AIRG predicted AUC Insulin, and M0 predicted FPI. SG did not enter any regression.

The linear regression analysis was powerful in explaining interindividual variability of all variables with the exception of glucose responses to MTT (Fig. 2). Linear regression explained

TABLE 2 -- Spearman correlation between measures of glucose control (FPG, FPI, AUC Glucose , Cmax, Glucose , AUC Insulin , and Cmax, Insulin) and indices of insulin sensitivity and pancreatic β-cell responsiveness (SI , SG , AIRG , DI , M 0 , and MI)

	SI	SG	AIRG	DI	MI	M0
FPG	−0.16	0.10	−0.49 b	−0.58 a	−0.73 a	−0.61 a
FPI	−0.70 a	0.23	0.74 a	−0.06	0.40 c	0.76 a
HbA1C	−0.12	−0.03	−0.37	−0.43	−0.81 a	−0.52 b
Cmax,Glucose	0.16	−0.01	−0.26	−0.08	−0.49 b	−0.36
Cmax,Insulin	−0.38	0.15	0.64 a	0.21	0.78 a	0.77 a
AUCGlucose	0.01	−0.01	−0.26	−0.20	−0.65 a	−0.42 c
AUCInsulin	−0.43 c	0.15	0.64 a	0.19	0.75 a	0.76 a

b $P < 0.01$.

a $P < 0.001$.

c $P < 0.05$.

TABLE 3 -- Results of step-wise linear regression in the form of z-scores (regression coefficients when all variables are expressed in standardized form)

	SI a	SG	AIRG	DI a	M0 a	MI a	P
FPG	—	—	—	−0.41	—	−0.66	<0.001
FPI a	−0.83	—	—	0.44	0.35	—	<0.001
HbA1C a	—	—	—	−0.21	—	−0.73	<0.001
Cmax,Glucose	—	—	—	—	—	−0.50	<0.001
Cmax,Insulin a	−0.47	—	—	0.26	—	0.69	<0.001
AUCGlucose	—	—	—	—	—	−0.65	<0.001

TABLE 3 -- Results of step-wise linear regression in the form of z-scores (regression coefficients when all variables are expressed in standardized form)

	SI a	SG	AIRG	DI a	M0 a	MI a	P
AUC Insulin a	—	—	0.28	—	—	0.65	<0.001

Dash (0) indicates that the independent variables (SI , SG , AIRG , DI , M0 , and MI) did not enter the regression formula for the dependent variables (FPG, FPI, AUC Glucose , Cmax, Glucose , AUC Insulin and Cmax, Insulin).

a Variable log transformed to assure normality.

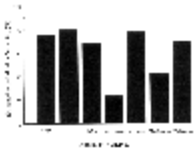


Figure 2. Explained interindividual variability of clinical measures of glucose control using indices of insulin resistance and pancreatic β-cell responsiveness.

70–80% interindividual variability of FPI, FPG, HbA1C, and insulin responses to MTT, and only 25–40% interindividual variability of glucose responses to MTT.

Discussion

The present study confirms that at the time of presentation of type 2 diabetes, pancreatic β-cell deficiency plays the key role in explaining fasting glucose levels. This finding is consistently supported by MTT and IVGTT data.

Impaired MI is the most powerful explanatory factor of impaired glucose control. This suggests that the most effective normalization of glucose levels in type 2 diabetes is associated with increased postprandial insulin appearance.

In the present study during MTT, FPG and HbA1C were strongly inversely related to M0 and, to a greater extent, MI . FPG was also inversely correlated with the IVGTT-derived AIRG and more strongly with the DI . This confirms that the DI is useful in characterizing

the overall state of glucose metabolism [11] . However, in newly presenting type 2 diabetes, postprandial insulin secretion is even more useful because it is more closely correlated with FPG.

Glucose meal responses were only correlated with pancreatic β-cell responsiveness but not with insulin resistance. Insulin sensitivity S I failed to demonstrate relationship with FPG and glucose meal responses. Reaven et al. [14] also failed to find a simple relationship between insulin resistance and FPG in nonobese individuals (normal, impaired glucose tolerance, and type 2 diabetes subjects). However, Van Haeften et al. [15] reported the effect of insulin sensitivity as assessed

by hyperglycemic clamp on fasting glucose in subjects with normal and impaired glucose tolerance. Levy et al. [16] documented that the ongoing fall in β-cell function measured by homeostasis model assessment closely followed the rise in FPG in a 10-yr prospective study of newly presenting type 2 diabetes but also failed to find any effect of insulin sensitivity.

The insulin-dependent glucose disposal (production) is the product of two factors, the ambient insulin levels and the ability of insulin to stimulate (suppress) glucose disposal (production). The former factor is influenced by pancreatic β-cell responsiveness, and the latter corresponds to the insulin sensitivity index. It is a paradox that only one factor, the pancreatic deficiency, is related to glucose control (primarily FPG) in the studied subjects. It is unclear why there is a lack of relationship between fasting glucose and insulin resistance. Our interpretation is that when FPG exceeds approximately 7 mmol/liter, insulin sensitivity is greatly reduced with little or no further reduction with increasing fasting hyperglycemia (subjects in the present study had already achieved their maximum insulin resistance). In highly insulin resistant state, insulin-dependent glucose disposal during fasting becomes negligible and FPG is regulated primarily via the insulin-independent pathways such as the mass effect of glucose on its disposal (SG). Thus, at fasting, insulin resistance is so high that insulin fails to exercise any detectable effect on glucose disposal and production, and in turn on glucose concentration.

This interpretation is not, however, fully consistent with another study finding. Insulin sensitivity SI and FPI have been found tightly (negatively) correlated in the present study. This correlation is well documented by others and is normally interpreted by a causal chain

reasoning that includes plasma glucose. The argumentation is that insulin resistance results in elevated plasma glucose, which in turn stimulates insulin secretion. Thus, insulin resistance is the cause of increased FPI. However, this argumentation does not hold in the present study due to the lack of correlation between S I and FPG, and we must seek alternative explanations. Two candidate theories emerge. Either chronic elevation of plasma insulin induces insulin resistance, possibly due to the down-regulation of insulin receptors, or some other metabolic variable acts as the control messenger between insulin resistance and insulin secretion.

Note that tight correlation between SI and FPI in the diabetes group supports methodological validity of SI estimates and suggests that insulin modification of IVGTT enabled insulin sensitivity to be successfully estimated.

Subjects with type 2 diabetes demonstrate both insulin resistance and reduced pancreatic β-cell responsiveness [3] [4] . Our analysis on a subset of the data showed that both insulin sensitivity (SI) and MI are reduced by about 80% compared with BMI-matched healthy subjects, whereas SG and fasting β-cell responsiveness (M0) are reduced by approximately 25 and 50%, respectively [13] .

Subjects were referred directly after diagnosis by their physicians. The subjects had no treatment and did not have any dietary advice. It is possible that they may have made their own dietary adjustments; for example, they may have given up sugar in their tea once they knew they were diabetic, but for all intents and purposes they had had absolutely no treatment for diabetes (treatment naive) before undergoing MTT and IVGTT.

Subjects presented a wide range of FPG and FPI (5.9–18.4 mmol/liter and 20–150 pmol/liter, respectively), probably due to the duration of undetected diabetes and/or individual differences in diet and lifestyle. The mean value of FPI was close to that observed in healthy subjects, whereas the mean value of FPG was considerably elevated. This observation supports the hypothesis that overt diabetes does not appear until the pancreas is not able to meet the body's demand for insulin in the face of increasing insulin resistance [4] [17] [18] . This process is accelerated because glucose is then toxic (glucose toxicity) to the β-cell and peripheral tissues [18] [19] .

It has been shown that during the natural development of type 2 diabetes, FPI increases and then decreases as insulin resistance develops (the Starling's curve of the pancreas). The increase in FPI is generally regarded as a compensation mechanism aiming to reverse the

effect of insulin resistance and the subsequent decrease as a decompensation mechanism reflecting β-cell exhaustion. However, such analysis fails to take into account the level of the stimuli, i.e. the fasting glucose level. When insulin secretion is normalized to fasting glucose (such as when calculating fasting responsiveness M0), no increase in insulin secretion, i.e. compensation, is observed. There is a consistent pattern of continuously deteriorating fasting pancreatic β-cell responsiveness accompanying elevated fasting glucose. This suggests that no compensation mechanism per se exists and that the apex on the Starling's curve represents a point when the stimuli is not high enough to overcome deteriorating pancreatic β-cell responsiveness. It is also known that the early insulin release (parameter comparable to MI) during an oral load decreases progressively as the 2-hr plasma glucose increases. There is no Starling curve for this parameter of insulin secretion, which is compatible with our data. FPI correlates negatively with insulin sensitivity (-0.70; $P < 0.001$). This correlation can be explained by the effect of insulin resistance on the stimulation of insulin secretion [20] [21] and suggests that elevated FPI is a reliable index of insulin resistance. Bonora et al. [22] also found a negative correlation between insulin sensitivity and FPI in mild glucose intolerance and suggested that overproduction of insulin is due to insulin resistance. Olefsky et al. [20] found a similar correlation in normal subjects, subjects with impaired glucose tolerance and type 2 diabetes, and explained FPI elevation as a result of an attempt to overcome insulin resistance.

The explained interindividual variability of FPG and HbA1C were excellent (>75%) if we consider intra-individual (day-to-day) variability, which could account for 10–20% of unexplained variability [23] . A similarly excellent explanation was found for FPI and insulin responses to meal.

Glucose responses after meal were poorly explained (<45%). It appears that other variables not included in the study such as gut absorption, gut hormones (incretins), and endogenous glucose production are responsible for the residual amount of unexplained variability. Thus, the standard indices of insulin sensitivity and pancreatic β-cell responsiveness do not enable reliable predictions of postprandial glucose to be made.

Other methods exist to measure pancreatic β-cell responsiveness, e.g. hyperglycemic clamp [6] , homeostasis model assessment [24] , and continuous infusion of glucose with model

assessment [25] . The postprandial secretion index MI is basically the ratio (Δ C-peptide secretion)/(Δ plasma glucose concentration) and thus is very similar to that obtained by the continuous infusion of glucose with model assessment method but evaluated during dynamic conditions after meal ingestion. Simple methods have been used in the past to assess postprandial insulin secretion during MTT, such as insulin incremental concentration at 30 min, or insulin incremental concentration at 30 min over glucose incremental concentration at 30 min. However, methodological considerations (the effect of the measurement error and the inter-subject variability in insulin and C-peptide kinetics) suggest superiority of the model-based method over a simple one or two concentration-point assessment. Furthermore, the model-based method has been shown to be reproducible in subjects with type 2 diabetes [26] .

In conclusion, pancreatic β-cell responsiveness indices from IVGTT and MTT are better explanatory factors of FPG, HbA1C , and insulin and glucose responses to meal than insulin resistance indices in newly presenting type 2 diabetes. Postprandial insulin deficiency is the most powerful explanatory factor of elevated FPG, HbA1C , and glucose responses to meal. Indices of insulin sensitivity and pancreatic β-cell responsiveness are able to explain glucose control well, with the exception of glucose response to a meal.

References

1. Weyer C, Bogardus C, Mott DM, Pratley RE 1999 The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 104:787–794 Abstract
2. Alzaid AA 1996 Insulin resistance in non-insulin-dependent diabetes mellitus. A review. Acta Diabetol 33:87–99 Citation
3. Zawalich WS, Kelley GG 1995 The pathogenesis of NIDDM: the role of the pancreatic beta cell. Diabetologia 38:986–991 Citation
4. Lebovitz HE 1999 Type 2 diabetes: an overview. Clin Chem 45:1339–1345 Abstract
5. Bergman RN 1989 Toward physiological understanding of glucose tolerance. Minimal model approach. Diabetes 38:1512–1525 Abstract
6. DeFronzo RA, Tobin JD, Andres R 1979 Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237:E214–E223 Abstract

7. Hovorka R, Chassin L, Luzio SD, Playle R, Owens DR 1998 Pancreatic beta-cell responsiveness during meal tolerance test: model assessment in normal subjects and subjects with newly diagnosed noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 83:744–750 Full Text
8. Owens DR, Luzio SD, Coates PA 1996 Insulin secretion and sensitivity in newly diagnosed NIDDM Caucasians in the UK. Diabet Med 13(Suppl 6): S19–S24 Abstract

9. Bergman RN, Finegood DT, Ader M 1985 Assessment of insulin sensitivity in vivo. Endocr Rev 6:45–86 Citation
10. Bergman RN, Steil GM, Bradley DC, Watanabe RM 1992 Modeling of insulin action in vivo. Annu Rev Physiol 54:861–883 Citation
11. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D 1993 Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 42:1663–1672 Abstract
12. Coates PA, Ollerton RL, Luzio SD, Ismail I, Owens DR 1994 A glimpse of the `natural history' of established type 2 (non-insulin dependent) diabetes mellitus from the spectrum of metabolic and hormonal responses to a mixed meal at the time of diagnosis. Diabetes Res Clin Pract 26:177–187 Abstract
13. Chassin L, Luzio SD, Hovorka R, Owens DR 1997 Pancreatic β-cell responsiveness and insulin sensitivity in subjects with newly diagnosed NIDDM. Diabet Med 14(Suppl 1):S29
14. Reaven GM, Hollenbeck CB, Chen YD 1989 Relationship between glucose tolerance, insulin secretion, and insulin action in non-obese individuals with varying degrees of glucose tolerance. Diabetologia 32:52–55 Abstract
15. Van Haeften TW, Pimenta W, Mitrakou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, Gerich JE 2000 Relative contributions of beta-cell function and tissue insulin sensitivity to fasting and postglucose-load glycemia. Metabolism 49:1318–1325 Abstract
16. Levy J, Atkinson AB, Bell PM, McCance DR, Hadden DR 1998 Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. Diabet Med 15:290–296 Abstract

17. O'Rahilly S, Hattersley A, Vaag A, Gray H 1994 Insulin resistance as the major cause of impaired glucose tolerance: a self-fulfilling prophesy? Lancet 344: 585–589 Abstract
18. Reaven GM 1995 The fourth musketeer-from Alexandre Dumas to Claude Bernard. Diabetologia 38:3–13 Abstract
19. Leahy JL, Cooper HE, Deal DA, Weir GC 1986 Chronic hyperglycemia is associated with impaired glucose influence on insulin secretion. A study in normal rats using chronic in vivo glucose infusions. J Clin Invest 77:908–915 Abstract
20. Olefsky J, Farquhar JW, Reaven G 1973 Relationship between fasting plasma insulin level and resistance to insulin-mediated glucose uptake in normal and diabetic subjects. Diabetes 22:507–513 Citation
21. Rudenski AS, Matthews DR, Levy JC, Turner RC 1991 Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. Metabolism 40:908–917 Abstract
22. Bonora E, Manicardi V, Zavaroni I, Coscelli C, Butturini U 1987 Relationships between insulin secretion, insulin metabolism and insulin resistance in mild glucose intolerance. Diabete Metab 13:116–121 Abstract
23. Ollerton RL, Playle R, Ahmed K, Dunstan FD, Luzio SD, Owens DR 1999 Day-to-day variability of fasting plasma glucose in newly diagnosed type 2 diabetic subjects. Diabetes Care 22:394–398 Abstract
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419 Abstract
25. Hosker JP, Matthews DR, Rudenski AS, Burnett MA, Darling P, Bown EG, Turner RC 1985 Continuous infusion of glucose with model assessment: measurement of insulin resistance and β-cell function in man. Diabetologia 28: 401–411 Abstract
26. **Albarrak** AIS, Luzio SD, Playle R, Hovorka R, Owens DR 2001 Pancreatic beta-cell responsiveness is reproducible in type 2 diabetes during MTT. Diabetes 50(Suppl 2):A508