Published in final edited form as:

Clin Endocrinol (Oxf). 2012 February ; 76(2): 212–219. doi:10.1111/j.1365-2265.2011.04159.x.

A Concerted Decline in Insulin Secretion and Action occurs across the Spectrum of Fasting and Post-Challenge Glucose Concentrations

Airani Sathananthan^{1,*}, Chiara Dalla Man^{2,*}, Alan R. Zinsmeister³, Michael Camilleri⁴, Richard J. Rodeheffer⁵, Gianna Toffolo², Claudio Cobelli², Robert A. Rizza¹, and Adrian Vella¹

¹Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, MN

²Department of Information Engineering, University of Padua, Padua, Italy

³Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

⁴Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

⁵Division of Cardiovascular Disease, Mayo Clinic, Rochester, MN

Abstract

Aims/hypothesis: Individuals with impaired fasting glucose (IFG) are at increased risk of developing diabetes over the subsequent decade. However, there is uncertainty as to the mechanisms contributing to the development of diabetes. We sought to quantitate insulin secretion and action across the pre-diabetic range of fasting glucose.

Methods: We studied a cohort of 173 individuals with a fasting glucose concentration < 7.0mmol/L after an overnight fast using a 75g oral glucose tolerance test (OGTT). Insulin action (S_i) was estimated using the oral glucose minimal model and β -cell responsivity indices (ϕ) were estimated by using the oral C-peptide minimal model. The Disposition Index (DI) for each individual was calculated. The relationship of DI, ϕ and S_i with fasting and post-challenge glucose, as well as other covariates, were explored using a generalized linear regression model.

Results: In this cross-sectional study, S_i and DI were inversely related to fasting glucose concentrations. On the other hand, ϕ was unrelated to fasting glucose concentrations. S_i , ϕ and DI were all inversely related to area-above-basal glucose concentrations after glucose challenge. Multiple parameters including body composition and gender contributed to the variability of S_i and DI at a given fasting or post-challenge glucose concentration.

Conclusions/Interpretation: Defects in insulin secretion and action interact with body composition and gender to influence post-challenge glucose concentrations. There is considerable heterogeneity of insulin secretion and action for a given fasting glucose likely because of patient subsets with isolated IFG and normal glucose tolerance.

Address for Correspondence: Adrian Vella MD Endocrine Research Unit, 5 Jo -194 Mayo Clinic College of Medicine 200 First ST SW Rochester, MN55905 (T) 507-255-6515 (F) 507-255-4828 vella.adrian@mayo.edu.

*Both Authors contributed equally to this work.

DUALITY OF INTEREST

The authors have no relevant conflict of interest to disclose.

Keywords

Insulin Secretion; Insulin Action; Impaired Fasting Glucose; Disposition Index; Hepatic Extraction; Pre-diabetes

INTRODUCTION

The states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) place affected individuals at higher risk of progression to overt type 2 diabetes^{1, 2} and are associated with an increased incidence of cardiovascular disease³. Understanding the defects that lead to these pre-diabetic states may help better predict individual risk of diabetes as well as increase understanding of diabetes pathogenesis thereby leading to targeted strategies for prevention and treatment. For example, in Olmsted County, MN ~ 40% of people with a fasting glucose in the 6.9 – 7.0 mmol/l range progress to overt diabetes within a 10 year period⁴. While this is higher than the rate of progression (5%) in those with a fasting glucose < 5.3 mmol/l (over a 10 year period), the reasons underlying the heterogeneity of progression to diabetes in people with IFG remain uncertain.

The presence of IGT may be a better predictor of future diabetes risk than IFG, either because the response to an oral glucose challenge is more representative of carbohydrate homeostasis in a given individual, or IFG and IGT represents two distinct phenotypes⁵. Indeed prior studies have suggested the existence of subjects with isolated IFG who have normal glucose tolerance and β -cell function^{6, 7}. In healthy individuals, glucose concentrations are closely regulated by insulin in a feedback-control system whereby insulin is secreted in response to rising glucose concentrations and inhibited when glucose concentrations fall. The integrity of this system depends on the ability of insulin to suppress glucose production and stimulate glucose uptake (insulin action) and the ability of the beta cell to secrete insulin in response to glucose (β -cell responsivity). Both of these processes are impaired in type 2 diabetes⁸, and in IFG⁹⁻¹². However, the relative importance of these processes to the development of diabetes has been uncertain. Cross-sectional data has suggested that defects in insulin action ultimately lead to the development of diabetes - insulin secretion increases to adapt to progressively impaired insulin action up to a point beyond which this compensatory response fails and diabetes develops – the so-called ‘Starling Curve of the pancreas’¹³.

Measurements of insulin secretion that utilize peripheral insulin concentrations correlate weakly with acute insulin response¹⁴ in part because insulin appearing in the systemic circulation has already undergone hepatic extraction¹⁵. Moreover, hepatic insulin extraction may be altered by factors such as obesity^{16, 17}, ethnicity¹⁸, or β -cell function¹⁹ which confound interpretation of such measures in cross-sectional studies. In an attempt to relate insulin secretion to the prevailing insulin action, Bergman et al. developed the concept of Disposition Index (DI) to embody the (hyperbolic) relationship between the 2 parameters²⁰. However, the assumptions that underlie the calculation of DI have been challenged by some authors suggesting that the relationship between insulin secretion and action differs across differing states of glucose tolerance²¹. However, this contention is based on the measurement of insulin secretion and of insulin action on different days under differing conditions which may not be relevant to physiologic stimuli such as meal ingestion^{22, 23}.

Previously, we had combined the oral c-peptide and insulin minimal models to compare insulin secretion and action in people with normal fasting glucose/glucose tolerance and IFG, in response to a labeled mixed meal. In subjects with IFG and IGT, postprandial hyperglycemia was associated with decreases in both insulin secretion and action. These

data implied that hyperglycemia resulted when defects in insulin action could not be adequately compensated by increases in insulin secretion⁷. However, those studies involved a relatively small number of subjects and hepatic insulin extraction was not directly measured. The present experiments sought to clarify the relative contributions of alterations in insulin secretion and action to postprandial hyperglycemia and to specifically determine if there was a threshold wherein insulin secretion follows the 'pancreatic Starling Curve' i.e. it ceases to increase and then decreases, leading to hyperglycemia. In order to do so, we measured insulin secretion, hepatic extraction and insulin action in response to a 75 gram glucose challenge in a large number of subjects across the spectrum of fasting glucose and glucose tolerance^{24, 25}. Multivariate analyses were undertaken to identify covariates that might affect these parameters in non-diabetic individuals.

METHODS

Subjects

After approval by the Mayo Institutional Review Board, subjects who previously participated in a population-based, cross-sectional study²⁶ were contacted by means of a letter and invited to participate. Subjects with a prior diagnosis of diabetes or a fasting glucose 126mg/dL (>7mmol/l) at the time of screening were excluded, as were those taking medications that could affect glucose metabolism. A total of 173 subjects (92 women, 81 men) gave informed written consent to participate in the study. All subjects were in good health and were at a stable weight and did not engage in regular vigorous exercise. All subjects were instructed to follow a weight-maintenance diet containing 55% carbohydrate, 30% fat and 15% protein for at least three days prior to the study. Despite a fasting glucose < 7mmol/l at the time of screening, one subject presented with a fasting glucose of 7.4mmol/l on the day of study.

Experimental Design

Body composition was measured using dual-energy X-ray absorptiometry (DPX scanner; Lunar, Madison, WI) at the time of screening. Participating subjects were admitted to the Mayo Clinic Clinical Research Unit at 0630 after an overnight fast. An 18-gauge cannula was inserted in a retrograde fashion into a dorsal hand vein of the non-dominant arm. The hand was placed in a heated box (55°C) to enable sampling of arterialized venous blood. At 0700 (time 0), subjects ingested 75g of glucose over a period of five minutes. Blood was drawn for glucose and hormone measurements at 0, 10, 20, 30, 60, 90 and 120 minutes.

Analytical techniques

Arterialized plasma samples were placed in ice, centrifuged at 4°C, separated, and stored at -20°C until assay. Plasma glucose concentrations were measured using a glucose oxidase method (Analox Instruments Inc., Lunenburg, MA). Plasma insulin concentrations were measured using a chemiluminescence assay with reagents obtained from Beckman (Access Assay, Beckman, Chaska, MN). Plasma C-peptide concentrations were measured by radioimmunoassay (Linco Research, St. Louis, MO).

Calculations

Net insulin sensitivity (S_i), which measures the overall effect of insulin to stimulate glucose disposal and suppress endogenous glucose production was estimated from plasma insulin and glucose concentrations using the unlabeled oral minimal model²⁴. Beta Cell responsivity indexes were estimated from the plasma glucose and C-peptide concentrations observed during the experiment by using the oral C-peptide minimal model, incorporating age-associated changes in C-peptide kinetics as measured by Van Cauter et al.²⁷. The model

assumes that insulin secretion is comprised of a static and dynamic component. The parameter ϕ_{dynamic} defines the dynamic responsivity index and is proportional to the rate of increase of glucose concentrations. ϕ_{static} represents the provision of new insulin to the releasable pool. An index of total beta-cell responsivity to glucose (ϕ) is derived from both indices. Disposition indices (DI) were subsequently calculated from ϕ and S_i as reviewed previously²³.

Statistical analysis

The aim of the analyses was to examine the relationship between glucose and DI_{Total} . This was achieved by evaluating various generalized linear regression models for predicting DI_{Total} using plasma glucose concentrations and other relevant covariates. Locally Weighted Robust Scatterplot Smoothing (LOWESS) splines were fitted to scatter plot data to provide guidance on the terms to include in the regression models (See Appendix). The distribution of DI was positively skewed and the generalized linear regression models for predicting DI assumed a gamma distribution for DI. The models employed an identity link function incorporating gender (1=Males, 0=Females) and baseline plasma glucose ($Glucose_0$) in all models.

Several models which included BMI or percent body fat, plasma glucose at 120 minutes ($Glucose_{120}$), post-challenge glucose excursion expressed as area above baseline (AAB) – calculated using the trapezoidal rule – were also examined ($Glucose_{\text{AAB}}$). The overall fit of the model for predicting DI was assessed by computing the (Pearson linear) correlation (r) between the observed DI and the model-predicted disposition index – $DI_{\text{Predicted}}$. A similar correlation was computed between the (observed) measured S_i and a predicted measure of insulin action – $S_{i-\text{Predicted}}$ – calculated by dividing $DI_{\text{Predicted}}$ by ϕ . The associations between several covariates and insulin secretion (ϕ), insulin action (S_i), and DI were also summarized via Spearman correlation coefficients (R_s).

We subsequently used repeated cross validation to evaluate the models. To do so, a “development” subset (66% of the total cohort) was randomly selected stratified by gender and the distribution of DI (categorized using quartiles) with the remaining 34% kept as a “validation” subset. The generalized linear regression model parameters were estimated using the development subset and then applied to the data in the validation subset. This was repeated 100 times. The distribution of correlation coefficients (e.g. between observed DI values and $DI_{\text{Predicted}}$ values in the validation subset) was then summarized (median [range]). All other data are presented as means $\pm$ SEM unless otherwise noted.

RESULTS

Subjects were initially categorized by fasting and 120 minute glucose values (NFG = normal fasting glucose i.e. < 5.56 mmol/l, NGT = normal glucose tolerance < 7.78 mmol/l, IFG = impaired fasting glucose > 5.56 mmol/l < 7.0 mmol/l, IGT = impaired glucose tolerance > 7.78 mmol/l < 11.1 mmol/l, DM = > 11.1 mmol/l). The mean fasting glucose for NFG/NGT, IFG/NGT, NFG/IGT, IFG/IGT and IFG/DM was 5.24 ± 0.04 , 5.92 ± 0.06 , 5.28 ± 0.04 , 5.94 ± 0.04 and 6.29 ± 0.13 mmol/l respectively. Similarly, the mean 120minute glucose value for NFG/NGT, IFG/NGT, NFG/IGT, IFG/IGT and IFG/DM was 6.87 ± 0.10 , 6.45 ± 0.18 , 9.45 ± 0.20 , 8.94 ± 0.13 and 13.16 ± 0.31 mmol/l respectively.

Insulin action (S_i), insulin secretion (ϕ) and Disposition Indices (DI) across a categorical classification of pre-diabetes (Figure 1 and Table 1)

Although insulin action (S_i) was associated overall with subgroup status, subjects with isolated IFG did not differ significantly from NFG / NGT subjects. However, S_i was

significantly impaired in subjects with IGT. (figure 1, upper panel). Insulin secretion (ϕ) differed from NFG / NGT subjects in NFG / IGT and IFG / DM subjects (figure 1, middle panel). However, when ϕ was expressed as function of S_i as a Disposition Index (DI) this differed from that observed in NFG / NGT subjects in all subjects with IGT (figure 1, lower panel).

Relationship of insulin action (S_i), insulin secretion (ϕ) and Disposition Indices (DI) with fasting and postprandial glucose concentrations (Figure 2)

Insulin action (S_i) was inversely related ($R_s = -0.37, p < 0.001$) to fasting glucose concentrations and (figure 2, left upper panel). Similarly, S_i was inversely related ($R_s = -0.58, p < 0.001$) to area above basal glucose concentrations (right upper panel).

Insulin secretion (ϕ) did not exhibit a relationship ($R_s = 0.10, p = 0.20$) with fasting glucose (left middle panel). In contrast, Insulin secretion (ϕ) was inversely related ($R_s = -0.36, p < 0.001$) to area above basal glucose concentrations (right, middle panel).

However, when ϕ was expressed as function of S_i as the Disposition Index (DI) an inverse relationship with both fasting glucose ($R_s = -0.32, p < 0.001$) and glucose area above basal ($R_s = -0.73, p < 0.001$) were observed (left and right lower panel respectively).

Relationship of Insulin action (S_i) with % Body Fat and gender (Figure 3)

Insulin action (S_i) was inversely related to % body fat in both females ($R_s = -0.48$) and males ($R_s = -0.18$). However, for a given % Body Fat, females exhibit a decreased S_i compared to males.

Relationship of Disposition Index adjusted for covariates with fasting and postprandial glucose concentrations (Figure 4)

The (independent) relationship of DI with fasting glucose ($r = -0.06, p = 0.45$), adjusted for gender, %body fat and $\text{Glucose}_{\text{AAB}}$ - is shown in Figure 4 (upper panel), and the corresponding (independent) relationship of DI with $\text{Glucose}_{\text{AAB}}$ ($r = -0.73, p < 0.001$), again adjusted for gender, %body fat and Glucose_0 , is shown in Figure 4 (lower panel).

Relationship of Disposition Index to Hepatic Extraction of insulin (Figure 5)

Hepatic Extraction (HE) was calculated as previously described²⁵ and exhibited a direct relationship with DI ($R_s = 0.39, p < 0.001$). Higher hepatic extraction of secreted insulin was observed at higher values of DI. Incorporating hepatic extraction in the generalized linear regression model (See Appendix) indicated hepatic extraction was a significant predictor ($p < 0.001$), but the overall correlation of observed DI vs. $\text{DI}_{\text{Predicted}}$ only increased to 0.87 (from 0.86) and thus did not appreciably improve the prediction of DI shown in Appendix Figure 2.

DISCUSSION

In this cross-sectional sample of non-diabetic individuals, when insulin secretion (ϕ) is expressed as a function of insulin action (S_i), the resulting disposition index (DI) is inversely related to both fasting and post-challenge glucose concentrations. This supports the prior observation that both defects in insulin secretion and action contribute to the development of diabetes⁷. In this study population, there does not appear to be a specific threshold of fasting and post-challenge glucose concentration associated with decreased insulin secretion and action, whether this is expressed as DI or the constituent indices (ϕ, S_i) are examined separately. Of note, for a given % Body Fat, females exhibit a decreased S_i compared to

males, illustrating the importance of gender as a covariate in determining insulin secretion and action.

Despite adjusting for covariates, there is considerable inter-individual variation in Disposition Index especially at the lower end of fasting blood glucose concentrations. An obvious explanation is that individuals with NFG may have normal or impaired glucose tolerance and individuals with IFG may have normal, impaired glucose tolerance or 2-hour glucose concentrations in the diabetic range. This variation cannot be wholly accounted for by age, gender, weight and body composition and it remains to be ascertained whether other unmeasured covariates can contribute to the observed variability of DI. Genetic association studies have implicated multiple genes in the pathogenesis of type 2 diabetes²⁸ as well as loci that affect fasting glucose concentrations independently of glucose tolerance or diabetes risk^{28,29}. Taken together with the current and prior observations^{7,10} that people with isolated IFG have normal β -cell function this reinforces the notion that IFG and IGT may have distinct pathophysiology⁵, with isolated IFG explained by altered set-point regulation of fasting glucose.

As a group, individuals characterized solely by the presence of IFG have defects in insulin secretion and insulin action⁹⁻¹². However, more recently, in a cohort of 3,450 individuals with NGT, glucose concentrations one hour after glucose challenge were a better predictor of diabetes risk than fasting concentrations, underlining the heterogeneity of glucose tolerance, β -cell function and diabetes risk in people with IFG³⁰. Indeed in the present data, when DI was adjusted for covariates such as age, weight, post-challenge glucose and gender, there was no relationship with fasting glucose concentrations. The indices of insulin secretion, unlike those of insulin action, were unrelated to fasting glucose concentrations, although inappropriate for the prevailing insulin action.

In contrast, Abdul-Ghani³¹ and Utzschneider³² reported that disposition indices (insulin secretion expressed as a function of insulin action) measured respectively with an oral glucose tolerance test (OGTT) and an intravenous glucose tolerance test (IVGTT) were decreased in individuals with IFG. Defects in insulin secretion, rather than action were the primary cause of decrease in DI. In support of these findings, Ritzel et al. reported a curvilinear relationship between β -cell volume (measured from autopsy specimen) and fasting blood glucose concentration, suggesting that small decreases in β -cell numbers may have large adverse effects on glucose concentrations³³. There are, however, limitations to be taken into account when interpreting these studies. Abdul-Ghani et al. utilized a measure of insulin secretion that is weakly correlated with acute insulin response and did not comment on the relationship of insulin action to fasting glucose concentrations¹⁴. Utzschneider et al. measured insulin secretion following an intravenous bolus of glucose; the studies could not determine whether individuals with IFG also had impaired glucose tolerance (IGT)³². The autopsy data discussed above was obtained from obese subjects (Body Mass Index (BMI) > 27 kg/m²) in whom no data on individual glucose tolerance was available³³. It is also important to appreciate that insulin secretion as measured by the oral C-peptide minimal model is dependent on the nature of the stimulus. The response to an intravenous glucose tolerance test (IVGTT) likely tests different compartments of the insulin secretory process as compared to more physiologic oral challenges, hence the relatively poor correlation of ϕ_{dynamic} with 1st phase insulin secretion (ϕ_1) and that of ϕ_{static} with the 2nd phase of insulin secretion (ϕ_2) measured by IVGTT^{22,23}. This distinction needs to be borne in mind when comparing DI across studies²³.

Of note, hepatic extraction of insulin increased as disposition indices rose. Although this was not an important covariate in DI (see appendix), it underscores the unreliability of peripheral measures of insulin secretion (i.e. based on insulin concentrations) since

peripheral insulin concentrations variably reflect portal insulin concentrations (as derived from peripheral C-peptide concentrations). Reliance on peripheral insulin concentrations as a surrogate of insulin secretion in individuals with widely differing degrees of glucose tolerance (and therefore hepatic extraction) likely introduces a systematic error in such a comparison. This phenomenon has been observed previously where hepatic extraction in the basal state as well as during glucose infusion rises in proportion to insulin secretory-burst mass¹⁹, likely due to insulin-receptor binding kinetics³⁴. This would be in keeping with the suggestion that insulin secretory pulses are necessary for the maintenance of hepatocyte insulin receptors³⁵ and the observation that insulin pulsatility³⁶ and hepatic insulin extraction³⁷ are decreased in type 2 diabetes.

In conclusion, our study of insulin secretion and action and their relationship to impaired fasting glucose and impaired glucose tolerance demonstrates that the relationship is not characterized by a defined threshold but is continuous across the entire spectrum. Moreover, fasting glucose concentrations may be a poor marker for the presence or absence of β -cell dysfunction in individuals with IFG. The observation of a parallel decline in insulin secretion and action across the spectrum of pre-diabetes in our study suggests the inter-relatedness of these processes. The failure of insulin secretion to compensate for defective insulin action seems to be apparent even in patients with mild hyperglycemia and declines in concert with decreasing insulin action. Future interventional studies using an acute intervention that alters one parameter e.g. insulin action will be necessary to dissect the relationship between insulin secretion and insulin action across the spectrum of prediabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support: The authors acknowledge the support of the Mayo Clinic CTSA grant (RR24150), Minnesota Obesity Center grant (DK50456), the Mayo Clinic CR20 program (grant to Dr Vella); Dr. Vella is supported by DK78646, Dr. Rizza by DK29953, and Dr Camilleri DK 67071. The original cohort development for the Olmsted County Heart Function Study was funded by HL-55502.

Abbreviations

AAB	Area Above Basal
BMI	Body Mass Index
DI	Disposition Index
DM	Diabetes Mellitus
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IVGTT	Intravenous Glucose Tolerance Test
LOWESS	Locally Weighted Robust Scatterplot Smoothing
OGTT	Oral Glucose Tolerance Test

REFERENCES

1. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346:393–403. [PubMed: 11832527]

2. Tirosch A, Shai I, Tekes-Manova D, et al. Normal fasting plasma glucose levels and type 2 diabetes in young men. *N Engl J Med*. 2005; 353:1454–1462. [PubMed: 16207847]
3. Meigs JB, Nathan DM, D'Agostino RB Sr. et al. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. *Diabetes Care*. 2002; 25:1845–1850. [PubMed: 12351489]
4. Dinneen SF, Maldonado D 3rd, Leibson CL, et al. Effects of changing diagnostic criteria on the risk of developing diabetes. *Diabetes Care*. 1998; 21:1408–1413. [PubMed: 9727885]
5. Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. *Diabetes*. 2003; 52:1475–1484. [PubMed: 12765960]
6. Kim SH, Reaven GM. Isolated impaired fasting glucose and peripheral insulin sensitivity: not a simple relationship. *Diabetes Care*. 2008; 31:347–352. [PubMed: 18000184]
7. Bock G, Dalla Man C, Campioni M, et al. Pathogenesis of pre-diabetes: mechanisms of fasting and postprandial hyperglycemia in people with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes*. 2006; 55:3536–3549. [PubMed: 17130502]
8. Basu A, Alzaid A, Dinneen S, et al. Effects of a change in the pattern of insulin delivery on carbohydrate tolerance in diabetic and nondiabetic humans in the presence of differing degrees of insulin resistance. *J Clin Invest*. 1996; 97:2351–2361. [PubMed: 8636416]
9. Laakso M, Zilinskaite J, Hansen T, et al. Insulin sensitivity, insulin release and glucagonlike peptide-1 levels in persons with impaired fasting glucose and/or impaired glucose tolerance in the EUGENE2 study. *Diabetologia*. 2008; 51:502–511. [PubMed: 18080106]
10. Meyer C, Pimenta W, Woerle HJ, et al. Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. *Diabetes Care*. 2006; 29:1909–1914. [PubMed: 16873801]
11. Abdul-Ghani MA, Jenkinson CP, Richardson DK, et al. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes*. 2006; 55:1430–1435. [PubMed: 16644701]
12. Ferrannini E, Gastaldelli A, Miyazaki Y, et al. beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab*. 2005; 90:493–500. [PubMed: 15483086]
13. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes*. 1988; 37:667–687.
14. Tripathy D, Almgren P, Tuomi T, et al. Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. *Diabetes Care*. 2004; 27:2204–2210. [PubMed: 15333485]
15. Caumo A, Luzi L. First-phase insulin secretion: does it exist in real life? Considerations on shape and function. *Am J Physiol Endocrinol Metab*. 2004; 287:E371–385. [PubMed: 15308473]
16. Polonsky KS, Given BD, Hirsch L, et al. Quantitative study of insulin secretion and clearance in normal and obese subjects. *Journal of Clinical Investigation*. 1988; 81:435–441. [PubMed: 3276729]
17. Rossell R, Gomis R, Casamitjana R, et al. Reduced hepatic insulin extraction in obesity: relationship with plasma insulin levels. *Journal of Clinical Endocrinology & Metabolism*. 1983; 56:608–611. [PubMed: 6337182]
18. Osei K, Schuster DP, Owusu SK, et al. Race and ethnicity determine serum insulin and C-peptide concentrations and hepatic insulin extraction and insulin clearance: comparative studies of three populations of West African ancestry and white Americans. *Metabolism: Clinical & Experimental*. 1997; 46:53–58. [PubMed: 9005969]
19. Meier JJ, Veldhuis JD, Butler PC. Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans. *Diabetes*. 2005; 54:1649–1656. [PubMed: 15919785]
20. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest*. 1981; 68:1456–1467. [PubMed: 7033284]

21. Ferrannini E, Mari A. Beta cell function and its relation to insulin action in humans: a critical appraisal. *Diabetologia*. 2004; 47:943–956. [PubMed: 15105990]
22. Cobelli C, Toffolo GM, Dalla Man C, et al. Assessment of beta-cell function in humans, simultaneously with insulin sensitivity and hepatic extraction, from intravenous and oral glucose tests. *Am J Physiol Endocrinol Metab*. 2007; 293:E1–E15. [PubMed: 17341552]
23. Cobelli C, Dalla Man C, Sparacino G, et al. Diabetes: Models, Signals, and Control. *IEEE Reviews in Biomedical Engineering*. 2009; 2:54–96. [PubMed: 20936056]
24. Dalla Man C, Campioni M, Polonsky KS, et al. Two-hour seven-sample oral glucose tolerance test and meal protocol: minimal model assessment of beta-cell responsivity and insulin sensitivity in nondiabetic individuals. *Diabetes*. 2005; 54:3265–3273. [PubMed: 16249454]
25. Campioni M, Toffolo G, Basu R, et al. Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. *Am J Physiol Endocrinol Metab*. 2009; 297:E941–948. [PubMed: 19671837]
26. Redfield MM, Jacobsen SJ, Burnett JC Jr. et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama*. 2003; 289:194–202. [PubMed: 12517230]
27. Van Cauter E, Mestrez F, Sturis J, et al. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes*. 1992; 41:368–377.
28. Smushkin G, Vella A. Genetics of type 2 diabetes. *Curr Opin Clin Nutr Metab Care*. 2010; 13:471–477. [PubMed: 20473152]
29. Saxena R, Hivert MF, Langenberg C, et al. Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet*. 2010; 42:142–148. [PubMed: 20081857]
30. Abdul-Ghani MA, Stern MP, Lyssenko V, et al. Minimal contribution of fasting hyperglycemia to the incidence of type 2 diabetes in subjects with normal 2-h plasma glucose. *Diabetes Care*. 2010; 33:557–561. [PubMed: 20007945]
31. Abdul-Ghani MA, Matsuda M, Jani R, et al. The relationship between fasting hyperglycemia and insulin secretion in subjects with normal or impaired glucose tolerance. *Am J Physiol Endocrinol Metab*. 2008; 295:E401–406. [PubMed: 18492770]
32. Utzschneider KM, Prigeon RL, Carr DB, et al. Impact of differences in fasting glucose and glucose tolerance on the hyperbolic relationship between insulin sensitivity and insulin responses. *Diabetes Care*. 2006; 29:356–362. [PubMed: 16443887]
33. Ritzel RA, Butler AE, Rizza RA, et al. Relationship between beta-cell mass and fasting blood glucose concentration in humans. *Diabetes Care*. 2006; 29:717–718. [PubMed: 16505537]
34. Levy JR, Olefsky JM. The trafficking and processing of insulin and insulin receptors in cultured rat hepatocytes. *Endocrinology*. 1987; 121:2075–2086. [PubMed: 3315635]
35. Matthews DR. Physiological implications of pulsatile hormone secretion. *Ann N Y Acad Sci*. 1991; 618:28–37. [PubMed: 2006790]
36. Porksen N, Hollingdal M, Juhl C, et al. Pulsatile insulin secretion: detection, regulation, and role in diabetes. *Diabetes*. 2002; 51(Suppl 1):S245–254. [PubMed: 11815487]
37. Sando H, Lee YS, Iwamoto Y, et al. Isoproterenol-stimulated C-peptide and insulin secretion in diabetic and nonobese normal subjects: decreased hepatic extraction of endogenous insulin in diabetes. *J Clin Endocrinol Metab*. 1980; 51:1143–1149. [PubMed: 6999008]

Figure 1.

Insulin action (top panel), insulin secretion (middle panel) and disposition index (lower panel) across groups classified by fasting glucose and glucose tolerance status. NFG = Normal Fasting Glucose i.e. < 5.56 mmol/l, IFG = Impaired Fasting Glucose i.e. > 5.56 and < 7.0 mmol/l. NGT = Normal Glucose Tolerance i.e. 2-hour post OGTT glucose < 7.78 mmol/l, IGT = Impaired Glucose Tolerance > 7.78 and < 11.1 mmol/l, DM = Diabetes Mellitus > 11.1 mmol/l.

Figure 2.

Relationship of Insulin action (top panel), insulin secretion (middle panel) and disposition index (lower panel) with fasting glucose concentrations - Glucose_0 = Plasma glucose at 0 minutes (left) and area-above-basal after oral glucose challenge - $\text{Glucose}_{\text{AAB}}$ (right). The inset panels represent the rank transformed values of S_i , ϕ and DI plotted against fasting and area above basal glucose values.

Figure 3. Relationship of measured S_i with $\% \text{ Body Fat}$ in males (●) and females (○). The regression line for males (dashed) and females (solid) are included.

Figure 4. Relationship of Disposition index, adjusted for gender, %body fat and $\text{Glucose}_{\text{AAB}}$, with fasting glucose concentrations (top panel), and relationship of Disposition index, adjusted for gender, %body fat and Glucose_0 , and area-above-basal after oral glucose challenge (bottom panel).

Figure 5.
Relationship of Hepatic Extraction of secreted insulin (HE) with Disposition Index.

Table 1

Subject characteristics and indices of insulin secretion and action according to fasting and 120 minute glucose values (NFG = normal fasting glucose i.e. < 5.56 mmol/l, NGT = normal glucose tolerance < 7.78 mmol/l, IFG = impaired fasting glucose > 5.56 mmol/l < 7.0 mmol/l, IGT = impaired glucose tolerance > 7.78 mmol/l < 11.1 mmol/l, DM = > 11.1 mmol/l). Data represent Mean $\pm$ SEM. **P*** = p-value calculated by ANOVA. **P[#]** = p-value calculated by t-test in comparison to NFG / NGT.

	NFG / NGT	IFG / NGT	NFG / IGT	IFG / IGT	IFG / DM	P*
n	41	17	46	53	16	
Gender (M / F)	19 / 22	10 / 7	14 / 32	30 / 23	8 / 8	
Age (years)	64.1 $\pm$ 1.0	62.1 $\pm$ 2.0	68.2 $\pm$ 1.1	67.3 $\pm$ 1.0	68.4 $\pm$ 1.7	< 0.01
P[#]		0.31	0.008	0.03	0.03	
BMI (kg/m²)	26.0 $\pm$ 0.7	28.4 $\pm$ 0.8	25.9 $\pm$ 0.6	29.0 $\pm$ 0.7	28.0 $\pm$ 0.9	< 0.01
P[#]		0.04	0.94	0.003	0.10	
Body Fat (%)	38.4 $\pm$ 1.6	40.3 $\pm$ 2.4	41.0 $\pm$ 1.3	41.9 $\pm$ 1.2	43.3 $\pm$ 2.4	0.33
$\phi_d(10^{-9})$	670 $\pm$ 73	559 $\pm$ 77	502 $\pm$ 37	605 $\pm$ 37	377 $\pm$ 61	0.02
P[#]		0.38	0.04	0.41	0.02	
$\phi_s(10^{-9} \text{ min}^{-1})$	48 $\pm$ 2	57 $\pm$ 7	42 $\pm$ 3	51 $\pm$ 3	38 $\pm$ 3	0.02
P[#]		0.12	0.13	0.52	0.01	
$\phi(10^{-9} \text{ min}^{-1})$	55.6 $\pm$ 2.8	63.8 $\pm$ 7.5	46.5 $\pm$ 3.4	56.6 $\pm$ 3.1	40.8 $\pm$ 2.7	< 0.01
P[#]		0.21	0.05	0.82	0.003	
$S_i(10^{-4} \text{ dl/kg/min}/\mu\text{U/ml})$	20.6 $\pm$ 2.3	18.4 $\pm$ 2.2	10.8 $\pm$ 1.0	8.7 $\pm$ 1.0	3.1 $\pm$ 0.8	< 0.01
P[#]		0.57	1.3×10^{-4}	1.9×10^{-6}	2.3×10^{-5}	
DI($10^{-14} \text{ dl/kg/min}^{-2}$ per pmol/l)	1709 $\pm$ 172	1920 $\pm$ 321	804 $\pm$ 98	682 $\pm$ 63	211 $\pm$ 50	< 0.01
P[#]		0.53	1.0×10^{-5}	2.2×10^{-8}	1.7×10^{-6}	
Hepatic Extraction (%)	42.5 $\pm$ 2	47.0 $\pm$ 4	48.7 $\pm$ 2	38.3 $\pm$ 3	40.0 $\pm$ 4	0.02
P[#]		0.24	0.03	0.25	0.52	