HHS Public Access

Author manuscript

Diabet Med. Author manuscript; available in PMC 2015 May 07.

Published in final edited form as:

Diabet Med. 2012 November ; 29(11): 1399–1406. doi:10.1111/j.1464-5491.2012.03625.x.

Biomarker models as surrogates for the disposition index in the Insulin Resistance Atherosclerosis Study

S. M. Watkins[1], **M. W. Rowe**[1], **J. A. Kolberg**[1], **L. E. Wagenknecht**[2], and **R. N. Bergman**[3]

[1]Tethys Bioscience Inc., Emeryville, CA

[2]Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC

[3]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Abstract

Aims—Insulin sensitivity and acute insulin response measure key components of Type 2 diabetes aetiology that contribute independently to risk in the Insulin Resistance Atherosclerosis Study. As insulin sensitivity and acute insulin response are not routinely measured in a clinical setting, we evaluated three fasting biomarker models, homeostasis model assessment of insulin sensitivity (HOMA-%S), β-cell function (HOMA-%B) and a Diabetes Risk Score, as potential surrogates for risk associated with insulin sensitivity, acute insulin response and the interaction of these two measures, the disposition index.

Methods—Models were calculated from baseline plasma biomarker concentrations for 664 participants who underwent a frequently sampled intravenous glucose tolerance test. To assess relationships among biomarker models and test measures, we calculated improvement in risk estimation gained by combining each fasting measure with each frequently sampled intravenous glucose tolerance test measure using logistic regression.

Results—The strongest correlates of acute insulin response, insulin sensitivity and disposition index were HOMA-%B (r_s^2 = 0.23), HOMA-%S (r_s^2 = 0.48) and Diabetes Risk Score (r_s^2 = 0.34), respectively. Individual areas under the curves for prediction of diabetes were 0.549 (HOMA-%B), 0.694 (HOMA-%S), 0.700 (insulin sensitivity), 0.714 (acute insulin response), 0.756 (Diabetes Risk Score) and 0.817 (disposition index). Models combining acute insulin response with Diabetes Risk Score (area under the curve 0.798) or HOMA-%S (area under the curve 0.805) nearly equalled disposition index, outperforming other individual measures ($P < 0.05$). Insulin sensitivity plus Diabetes Risk Score (area under the curve 0.760) was better than insulin sensitivity ($P = 0.03$), but not better than Diabetes Risk Score alone. HOMA-%S plus insulin sensitivity (area under the curve 0.704) was not significantly better than either alone.

Correspondence to: Steven Watkins. smwatkins@tethysbio.com.

Competing interests

SMW, MWR and JAK are employees and shareholders of Tethys Bioscience Inc., which developed and markets the Diabetes Risk Score. RNB is Chair of the Scientific Advisory Board of Tethys Bioscience and has a financial interest in the Company. LEW is a consultant to Tethys Bioscience.

Conclusions—The Diabetes Risk Score and HOMA-%S were excellent surrogates for insulin sensitivity, capturing the predictive power of insulin sensitivity. Diabetes Risk Score captured some of the additional predictive power of acute insulin response, but the HOMA models did not. No fasting model was as predictive as disposition index, but the Diabetes Risk Score was the best surrogate.

Introduction

Type 2 diabetes results when pancreatic β-cells lose the ability to secrete sufficient insulin to compensate for increasing insulin resistance. While many discrete factors, including inflammation [1,2], adipose function [3] and diet [4,5], may contribute to the complex mechanisms underlying disease progression, this straightforward biology—insulin resistance and a compensatory insulin secretion—is the fundamental basis of glucose homeostasis [6]. Impairment of insulin sensitivity and secretion commonly take many years to develop and we have only imperfect measures of these physiologies available in the clinic prior to the emergence of overt disease. Thus, while it is possible to measure glucose status directly, it is difficult to predict the rate of progression towards disease. Clinically convenient tools that measure a broader scope of diabetes physiology will improve the assessment of insulin resistance and β-cell function and thus enable improved strategies for diabetes prevention and management.

Measures of insulin sensitivity and insulin secretion (acute insulin response) can be determined from a minimal model (MINMOD) analysis of a frequently sampled intravenous glucose tolerance test (FSIGT) [7]. A decrease in insulin sensitivity occurs during the years or decades that precede a diagnosis of Type 2 diabetes and reduced insulin sensitivity has been shown to be associated with increased risk of diabetes [8,9]. Decreased acute insulin response is present in participants with impaired glucose tolerance or diabetes and a reduced acute insulin response is associated with an increased risk for Type 2 diabetes [9-13]. The interaction (product) of insulin sensitivity and acute insulin response, termed the disposition index, was previously reported as the best predictor of future diabetes in the Insulin Resistance Atherosclerosis Study [8]. The disposition index is a measure of the ability of β-cells to compensate for insulin resistance and can be thought of as a measure of β-cell functionality [6,7,9-14].

While FSIGT measurements provide useful biological and prognostic information in a research setting, the MINMOD approach is not utilized in clinical practice, presumably attributable to cost and practicality concerns. We hypothesized that biomarker-based models requiring only a fasting blood draw might capture the same biological information provided by the MINMOD. If so, such models could be more amenable to routine clinical practice. The present study tests the extent to which each of the three MINMOD measures provides diabetes prediction that is independent of the three biomarker models. Further, we test whether combinations of MINMOD components and biomarker models can rival the disposition index in the prediction of diabetes. This approach is not intended to imply that combinations of biomarker models and MINMOD measures are clinically relevant prediction tools. Rather, this method is used to test the extent to which the predictiveness of

biomarker models can be specifically linked to the underlying physiology of insulin sensitivity and acute insulin response and the disposition index.

One biomarker model, the homeostasis model assessment (HOMA) generates β-cell function (HOMA-%B) and insulin sensitivity (HOMA-%S) or insulin resistance (HOMA-IR) estimates that have been widely cited in the literature [15]. HOMA attempts to model the complex dynamics between insulin and glucose concentrations as regulated by the β-cells and liver. Another biomarker model is the PreDx® Diabetes Risk Score (DRS). The Diabetes Risk Score is a tool for assessing the 5-year risk of Type 2 diabetes that utilizes the concentrations of adiponectin, C-reactive protein, ferritin, glucose, HbA_{1c}, insulin and interleukin-2 receptor α. The Diabetes Risk Score has been shown to provide a more accurate assessment of diabetes risk than fasting plasma glucose or insulin alone [16-19] and is available to physicians in the USA as a laboratory-developed test (Tethys Bioscience, Emeryville, CA, USA).

Previous cross-sectional studies have assessed the association between HOMA measures and the outputs of the MINMOD [15,20-22], but the moderate correlations that were observed do not necessarily imply that the same underlying physiology is being measured. We reason that, because insulin sensitivity and acute insulin response are strong independent predictors of diabetes, the link between biomarker models and the dynamic physiological response to glucose measured by the MINMOD analysis could be assessed more accurately by exploring the degree to which the biomarker models substitute for the MINMOD components as prognostic indicators for development of diabetes.

The Insulin Resistance Atherosclerosis Study is a multi-centre observational study of a large multi-ethnic US cohort. It was originally designed to explore the relationships between insulin resistance and other biochemical and physiological variables in the development of cardiovascular disease in individuals with different levels of glucose tolerance [23]. The Insulin Resistance Atherosclerosis Study is the largest longitudinal study to date that included a baseline FSIGT and is thus a unique cohort for evaluation of these measures in assessing diabetes risk. Five-year follow-up data from the study cohort documented the progression of some individuals to Type 2 diabetes [24]. We evaluated how well baseline measures of HOMA-%S, HOMA-%B and the Diabetes Risk Score correlated with each of the MINMOD outputs and the extent to which they coincided in their ability to predict incident Type 2 diabetes.

Patients and methods

Participants

The selection of participants and the study design for the Insulin Resistance Atherosclerosis Study cohort have been previously described [23]. For the current study, Type 2 diabetes was diagnosed according to current World Health Organization diagnostic criteria [25]. Baseline plasma specimens were available from 664 individuals without diabetes at baseline who had complete HOMA and MINMOD measures and who participated in the 5-year follow-up examination, including specimens from 114 individuals who developed diabetes during the study.

Laboratory and clinical measurements

The clinical procedures have been previously described [23]. Briefly, baseline evaluations of subjects included a FSIGT, administered with two modifications: an injection of regular insulin rather than tolbutamide, and a reduced sampling protocol with 12 rather than 30 samples [26]. Insulin sensitivity, expressed as the insulin sensitivity, was calculated using mathematical modelling methods [MINMOD version 3.0 (1994)] [7,27]. First-phase insulin secretion, expressed as the acute insulin response, was calculated from the mean increment in the plasma insulin concentration above basal at 2, 4 and 8 min after the administration of glucose. Plasma glucose was measured on an auto-analyser (Yellow Springs Instruments, Yellow Springs, OH, USA) and insulin was measured using a dextran–charcoal radioimmunoassay at the time of the baseline examination. The remaining biomarkers were assayed at Tethys Bioscience from the baseline samples that had been stored at −80 °C, as described previously [19].

Statistical analysis

All analyses were performed using the R statistical computing environment (version 2.12) [28]. HOMA-%S and HOMA-%B were calculated using the 2004 HOMA2 computer model [29]. Variables were transformed so that their distributions were more normal. HOMA-%S and HOMA-%B were log transformed. Because zero is a valid value for insulin sensitivity [30], but its logarithm is undefined, insulin sensitivity + 1 was (natural) log transformed. Both acute insulin response and disposition index may have negative values, so a signed square root transform was applied [31]; for example, the square root of the absolute value of acute insulin response was multiplied by its sign. Because the Diabetes Risk Score is estimated from a logistic regression model, it was logit transformed after dividing by 10.

In the present study, the Diabetes Risk Score was calculated in the Insulin Resistance Atherosclerosis Study cohort using the same Diabetes Risk Score algorithm that was developed using the Inter99 cohort [19], without refit. The Diabetes Risk Score is a logistic regression model, where the log odds of conversion are estimated from the linear sum of transformed glucose, HbA_{1c}, insulin, adiponectin, C-reactive protein, ferritin and interleukin-2 receptor a concentrations, age and sex. Because HbA_{1c} values at baseline were not available for the Insulin Resistance Atherosclerosis Study cohort, data from the 2001–2008 National Health and Nutrition Examination Survey (NHANES) surveys [32] were used to estimate an appropriate mean HbA_{1c} of 36 mmol/mol (5.4%) for use in the model, taking into account the higher diabetes conversion rate in the Insulin Resistance Atherosclerosis Study. As the same HbA_{1c} value was used for all individuals, it has no effect on discrimination between converters and non-converters in this analysis.

To summarize the characteristics of the population at baseline, proportions, or medians and interquartile ranges of continuous measures, were calculated for all participants by diabetes status at the baseline visit. The statistical significance of differences was assessed by χ^2-tests (factors) or Wilcoxon rank sum tests (continuous measures). Spearman rank correlation coefficients (r_s) were calculated for each biomarker model with each MINMOD output. *P*-values were calculated assuming that r_s follows an approximate asymptotic *t*-distribution.

To further explore how these risk prediction tools complement each other, logistic regression models of conversion status were fitted, using each measure alone, and all pairwise combinations of the three transformed MINMOD outputs with each of the three biomarker models as predictors. Note that the individual terms of the Diabetes Risk Score were not refitted; the coefficients were fixed. Each regression model's ability to discriminate between converters and non-converters was assessed by calculating the area under the receiver operating characteristic curve. To correct for possible over-fit, a bootstrap cross-validation approach was used to compare performance between pairs of regression models [33].

Results

The characteristics of the study population are presented in Table 1. There were significant differences between participants with and without diabetes at follow-up in all of the characteristics presented, except sex, race/ethnicity, diastolic blood pressure and HOMA-%B.

Biomarker models were correlated with the dynamic MINMOD measures among study participants at baseline. In Fig. 1, HOMA-%B, HOMA-%S and Diabetes Risk Score values are each plotted against acute insulin response, insulin sensitivity and disposition index. All pairs of measures showed statistically significant correlation ($P < 0.0001$), except HOMA-%B with the disposition index. HOMA-%B and Diabetes Risk Score were strongly inversely correlated to insulin sensitivity and thus correlated with insulin resistance. HOMA-%B is meant to act as a surrogate measure of β-cell function or insulin secretion and 23% of its rank variance may be explained by correlation with the more direct measure acute insulin response, greater than either HOMA-%S or Diabetes Risk Score. The r_s^2 value of HOMA-%S with insulin sensitivity was 48%, consistent with its objective as a surrogate measure of insulin sensitivity, but 30% of the rank variance in Diabetes Risk Score, and 28% in HOMA-%B, were also shared with insulin sensitivity. Of the three biomarker models, Diabetes Risk Score was the most strongly related to disposition index, with an r_s^2 of 34%, compared with 14% for HOMA-%S and less than 1% for HOMA-%B.

As a way of understanding how each biomarker model related to the underlying biology of acute insulin response and insulin sensitivity, we explored whether combining each of the biomarker models with acute insulin response or insulin sensitivity in logistic regression models could match the predictive power of the disposition index. The bootstrap cross-validated area under the curve of each combination is presented Table 2. When comparing a composite model to its MINMOD constituent, a significant improvement in the area under the curve of the combination indicated that the biomarker model was independent and complementary to the MINMOD output, while a lack of significant improvement implied redundancy in terms of the physiology being measured. For example, the combination of insulin sensitivity and acute insulin response had an area under the curve of 0.814 (data not shown), which was significantly greater than either insulin sensitivity or acute insulin response alone, demonstrating that the two measures were complementary in capturing the aspects of physiology that put people at risk for diabetes. As expected, the area under the curve of the model combining the two was equivalent to the area under the curve of the

disposition index, the product of insulin sensitivity and acute insulin response. The area under the curves of the individual measures and combinations from Table 2 are presented graphically in Fig. 2 to highlight the key comparisons. None of the combinations were significantly superior to the disposition index alone.

The relationship between HOMA-%B and the MINMOD outputs is illustrated in Fig. 2a. HOMA-%B alone was a poor predictor of future diabetes in the Insulin Resistance Atherosclerosis Study, with an area under the curve of 0.549. Although meant to be a surrogate of β-cell function, the combination of HOMA-%B with insulin sensitivity was not more predictive than insulin sensitivity alone, while combining HOMA-%B with acute insulin response increased the area under the curve by 0.052 over acute insulin response alone.

By contrast, HOMA-%S predicted incident diabetes with an area under the curve of 0.694, which was not significantly less than insulin sensitivity alone. As shown in Fig. 2b, combining insulin sensitivity with HOMA-%S did not significantly increase the area under the curve above either insulin sensitivity or HOMA-%S alone. The area under the curve obtained by combining acute insulin response with HOMA-%S was 0.803, not statistically different than the area under the curve of the disposition index. Adding the disposition index to HOMA-%S resulted in an area under the curve of 0.817, significantly increased over HOMA-%S alone ($P = 0.001$), but not significantly over the disposition index alone ($P = 0.4$).

The Diabetes Risk Score was the best predictor of diabetes among the biomarker models with an area under the curve of 0.756, significantly greater than either HOMA-%B or HOMA-%S individually. As shown in Fig. 2c, adding insulin sensitivity to the Diabetes Risk Score did not significantly increase the area under the curve above the Diabetes Risk Score alone, while acute insulin response combined with the Diabetes Risk Score was significantly higher than either the Diabetes Risk Score or acute insulin response alone, and equivalent to the disposition index alone. Although the Diabetes Risk Score was more predictive than insulin sensitivity or acute insulin response individually, it was not as predictive as the disposition index alone. Combining the Diabetes Risk Score with the disposition index did not significantly improve prediction over the disposition index alone.

Discussion

The Insulin Resistance Atherosclerosis Study followed more than 700 participants with baseline FSIGT measurements for a median of 5 years to determine who would develop diabetes. Thus, the study cohort provided a unique opportunity to link the predictiveness of biomarker models obtained from baseline fasting plasma samples to direct measures of insulin sensitivity, acute insulin response and disposition index. The present results are consistent with previous reports from the Insulin Resistance Atherosclerosis Study [8] and other cohorts [12] that the disposition index is a powerful predictor of diabetes. In this study, both acute insulin response and insulin sensitivity were predictive of diabetes, but their product, the disposition index was significantly more predictive than either alone.

Despite the predictive power of the disposition index, the FSIGT is presently only used in a research setting for reasons of practicality. We sought to determine how well HOMA-%B, HOMA-%S and the Diabetes Risk Score could capture the biological information and predictive power that are obtained from dynamic physiological measurements of glucose homeostasis and to relate the fasting measures to physiology. To do this, we assessed the correlation between each biomarker model and each MINMOD output at baseline, as well as the ability of each model to replace insulin sensitivity and acute insulin response in predictive models, using the disposition index as a benchmark.

Among the biomarker models, the Diabetes Risk Score came closest to replicating the ability of the disposition index to predict diabetes status at 5 years (Table 2) and was most strongly correlated to the disposition index (Fig. 1). Additionally, the composite model analysis demonstrated that the Diabetes Risk Score fully captured the predictiveness of insulin sensitivity measured by insulin sensitivity and partially covered the predictiveness of acute insulin response. The Diabetes Risk Score did not, however, possess predictive power beyond the disposition index (Fig. 2c), suggesting that the information inherent in the Diabetes Risk Score may be fully attributed to insulin secretion or sensitivity. One shortcoming of this study is that HbA_{1c} was not available, so the Diabetes Risk Score was approximated using a constant value of HbA_{1c} for all participants. Given the well-established link between HbA_{1c} and diabetes risk, it is possible that the Diabetes Risk Score would have performed differently and perhaps better had measurements of HbA_{1c} been available.

The correlation between HOMA-%S and insulin sensitivity in the present study was significant (Fig. 1), but weaker than some previous reports [15], which presented correlation coefficients as high as 0.88 ($r^2 = 0.77$). These much smaller studies may have overestimated the magnitude of the effect, or the discrepancy may reflect differences between the study populations. Despite the weaker correlation, the composite model containing HOMA-%S and acute insulin response was not significantly less predictive than the disposition index (Table 2, Fig. 2b), suggesting that HOMA-%S did capture the full predictiveness of insulin sensitivity. When insulin sensitivity was combined with HOMA-%S, the area under the curve was not significantly higher than either measure alone, indicating that HOMA-%S is a strong surrogate for insulin sensitivity, and that the biology represented by HOMA-%S is representative of, but not broader than, insulin sensitivity.

The correlation of HOMA-%B with acute insulin response in the present study was also substantially weaker than in previous reports [15], which provided r^2 values in the range of 0.38–0.81. Of particular note is work by Festa and co-workers [20] that reported Spearman correlation coefficients with HOMA-%B of 0.58 (acute insulin response) and −0.27 (insulin sensitivity) in a cross-sectional analysis of 1380 participants in the Insulin Resistance Atherosclerosis Study that included subjects with diabetes at baseline. Because this analysis was more inclusive, there may have been greater variance in the measures, yielding stronger correlations. Although correlation was weaker in the present analysis, HOMA-%B was the biomarker model with the highest correlation to acute insulin response (Fig. 1). Despite this correlation, HOMA-%B was an extremely weak predictor of diabetes in this study and was weaker than all other predictors evaluated. HOMA-%B was actually more strongly

correlated with insulin sensitivity than acute insulin response and, when combined in a composite model with insulin sensitivity instead of acute insulin response, the resulting model was no better than insulin sensitivity alone. Additionally, the composite model of acute insulin response and HOMA-%B significantly improved the area under the curve for diabetes prediction relative to either HOMA-%B or acute insulin response alone, suggesting that HOMA-%B is more closely related to the biology of insulin sensitivity than to insulin secretion.

As the incidence of Type 2 diabetes rises worldwide, there is an increasing need for tools to identify patients at the highest risk for the disease to enable intervention. Both the Diabetes Risk Score and HOMA-%S show promise as convenient surrogates for insulin sensitivity. This study suggests, however, that insulin sensitivity alone is not sufficient to fully assess diabetes risk. This was demonstrated by the predictive power of the disposition index, and the best of its fasting surrogates, the Diabetes Risk Score. All three of the biomarker models use insulin and glucose as inputs, but the Diabetes Risk Score incorporates the concentrations of five additional circulating biomarkers. Thus, it is not surprising that HOMA-%S and HOMA-%B seem to capture similar aspects of the underlying biology, while the Diabetes Risk Score provides a more complete assessment of risk, adding much of the predictive power of acute insulin response to the insulin sensitivity that the HOMA models measure. One shortcoming of the Diabetes Risk Score in light of the results of this study is that it does not report estimates of insulin secretion and insulin resistance separately, a feature that might be useful in guiding preventive therapy. The performance of the Diabetes Risk Score as a surrogate for disposition index, however, makes it a potentially important clinical tool.

Acknowledgements

Parts of this study were presented as an abstract and poster at the 46th Annual Meeting of the European Association for the Study of Diabetes, 20–24 September 2010, Stockholm, Sweden.

The authors gratefully acknowledge the skilful technical work of Amalia Ocampo, Marianne Weinell and Claudia Elkin, Tethys Bioscience. The authors acknowledge the work of Andrea Anderson, Wake Forest University, in assisting in the development of the Insulin Resistance Atherosclerosis Study databases. The authors wish to acknowledge Laura Penny for her help in preparing the manuscript and Bryan Walton for creating the colour figures.

Funding sources

None.

References

1. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes. 2004; 53:693–700. [PubMed: 14988254]
2. Duncan B, Schmidt M, Pankow J, Ballantyne C, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the Atherosclerosis Risk in Communities Study. Diabetes. 2003; 52:1799–1805. [PubMed: 12829649]
3. Li S, Shin JJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. J Am Med Assoc. 2009; 302:179–188.

4. Liese AD, Nichols M, Sun X, D'Agostino RB, Haffner SM. Adherence to the DASH diet is inversely associated with incidence of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. Diabetes Care. 2009; 32:1434–1436. [PubMed: 19487638]
5. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001; 345:790–797. [PubMed: 11556298]
6. Bergman RN. Orchestration of glucose homeostasis: from a small acorn to the California oak. Diabetes. 2007; 56:1489–1501. [PubMed: 17526912]
7. Pacini G, Bergman RN. MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Programs Biomed. 1986; 23:113–122. [PubMed: 3640682]
8. Lorenzo C, Wagenknecht LE, D'Agostino RB, Rewers MJ, Karter AJ, Haffner SM. Insulin resistance, beta-cell dysfunction, and conversion to type 2 diabetes in a multiethnic population: the Insulin Resistance Atherosclerosis Study. Diabetes Care. 2010; 33:67–72. [PubMed: 19808919]
9. Haffner SM, D'Agostino R, Saad MF, Rewers M, Mykkänen L, Selby J, et al. Increased insulin resistance and insulin secretion in non-diabetic African-Americans and Hispanics compared with non-Hispanic whites. The Insulin Resistance Atherosclerosis Study. Diabetes. 1996; 45:742–748. [PubMed: 8635647]
10. Gerich JE. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity. Endocr Rev. 1998; 19:491–503. [PubMed: 9715377]
11. Hanley AJG, D'Agostino R, Wagenknecht LE, Saad MF, Savage PJ, Bergman R, et al. Increased proinsulin levels and decreased acute insulin response independently predict the incidence of type 2 diabetes in the Insulin Resistance Atherosclerosis Study. Diabetes. 2002; 51:1263–1270. [PubMed: 11916954]
12. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999; 104:787–794. [PubMed: 10491414]
13. Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care. 2001; 24:89–94. [PubMed: 11194248]
14. Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. Diabetes. 2002; 51:S212–S220. [PubMed: 11815482]
15. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004; 27:1487–1495. [PubMed: 15161807]
16. Kolberg JA, Jørgensen T, Gerwien RW, Hamren S, McKenna MP, Moler E, et al. Development of a type 2 diabetes risk model from a panel of serum biomarkers from the Inter99 cohort. Diabetes Care. 2009; 32:1207–1212. [PubMed: 19564473]
17. Shafizadeh TB, Moler EJ, Kolberg JA, Nguyen UT, Hansen T, Jørgensen T, et al. Comparison of accuracy of diabetes risk score and components of the metabolic syndrome in assessing risk of incident type 2 diabetes in Inter99 cohort. PLoS ONE. 2011; 6:e22863. [PubMed: 21829540]
18. Lyssenko V, Jørgensen T, Gerwien RW, Hansen T, Rowe MW, McKenna MP, et al. Validation of a multi-marker model for the prediction of incident type 2 diabetes mellitus: combined results of the Inter99 and Botnia studies. Diab Vasc Dis Res. 2011; 9:59–67. [PubMed: 22058089]
19. Urdea M, Kolberg J, Wilber J, Gerwien R, Moler E, Rowe M, et al. Validation of a multimarker model for assessing risk of type 2 diabetes from a five-year prospective study of 6784 Danish people (Inter99). J Diabetes Sci Technol. 2009; 3:748–755. [PubMed: 20144324]
20. Festa A, Williams K, Hanley AJG, Haffner SM. Beta-cell dysfunction in subjects with impaired glucose tolerance and early type 2 diabetes: comparison of surrogate markers with first-phase insulin secretion from an intravenous glucose tolerance test. Diabetes. 2008; 57:1638–1644. [PubMed: 18332099]
21. Hermans MP, Levy JC, Morris RJ, Turner RC. Comparison of insulin sensitivity tests across a range of glucose tolerance from normal to diabetes. Diabetologia. 1999; 42:678–687. [PubMed: 10382587]

22. Hermans MP, Levy JC, Morris RJ, Turner RC. Comparison of tests of beta-cell function across a range of glucose tolerance from normal to diabetes. Diabetes. 1999; 48:1779–1786. [PubMed: 10480608]

23. Wagenknecht LE, Mayer EJ, Rewers M, Haffner S, Selby J, Borok GM, et al. The insulin resistance atherosclerosis study (IRAS) objectives, design, and recruitment results. Ann Epidemiol. 1995; 5:464–472. [PubMed: 8680609]

24. Mykkanen L, Zaccaro DJ, Hales CN, Festa A, Haffner SM. The relation of proinsulin and insulin to insulin sensitivity and acute insulin response in subjects with newly diagnosed type II diabetes: the Insulin Resistance Atherosclerosis Study. Diabetologia. 1999; 42:1060–1066. [PubMed: 10447516]

25. WHO. Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications: Part 1: Report of a WHO Consultation: Diagnosis and Classification of Diabetes Mellitus. World Health Organiztion; Geneva: 1999.

26. Steil GM, Volund A, Kahn SE, Bergman RN. Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model. Suitability for use in population studies. Diabetes. 1993; 42:250–256. [PubMed: 8425661]

27. Gresl TA, Colman RJ, Havighurst TC, Byerley LO, Allison DB, Schoeller DA, et al. Insulin sensitivity and glucose effectiveness from three minimal models: effects of energy restriction and body fat in adult male rhesus monkeys. Am J Physiol Regul Integr Comp Physiol. 2003; 285:R1340–R1354. [PubMed: 12842866]

28. Team R. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; Vienna: 2010. Available at http://www.R-project.org [Last accessed 10 December 2010]

29. Diabetes Trial Unit, The Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University. [Last accessed 5 December 2010] HOMA Calculator: Home Page. 2004. Available at http://www.dtu.ox.ac.uk/homacalculator/index.php

30. Haffner SM, D'Agostino R, Festa A, Bergman RN, Mykkänen L, Karter A, et al. Low insulin sensitivity (S(i) = 0) in diabetic and non-diabetic subjects in the Insulin Resistance Atherosclerosis Study: is it associated with components of the metabolic syndrome and non-traditional risk factors? Diabetes Care. 2003; 26:2796–2803. [PubMed: 14514582]

31. Wagenknecht LE, Langefeld CD, Scherzinger AL, Norris JM, Haffner SM, Saad MF, et al. Insulin sensitivity, insulin secretion, and abdominal fat: the Insulin Resistance Atherosclerosis Study (IRAS) Family Study. Diabetes. 2003; 52:2490–2496. [PubMed: 14514631]

32. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. US Department of Health and Human Services, Centers for Disease Control and Prevention; Hyattsville, MD: 2001-2008. Available at http://www.cdc.gov/nchs/nhanes/ [Last accessed 2 December 2010]

33. Harrell, F.; Harrell, F. Regression Modeling Strategies. Springer Verlag; New York: 2001.

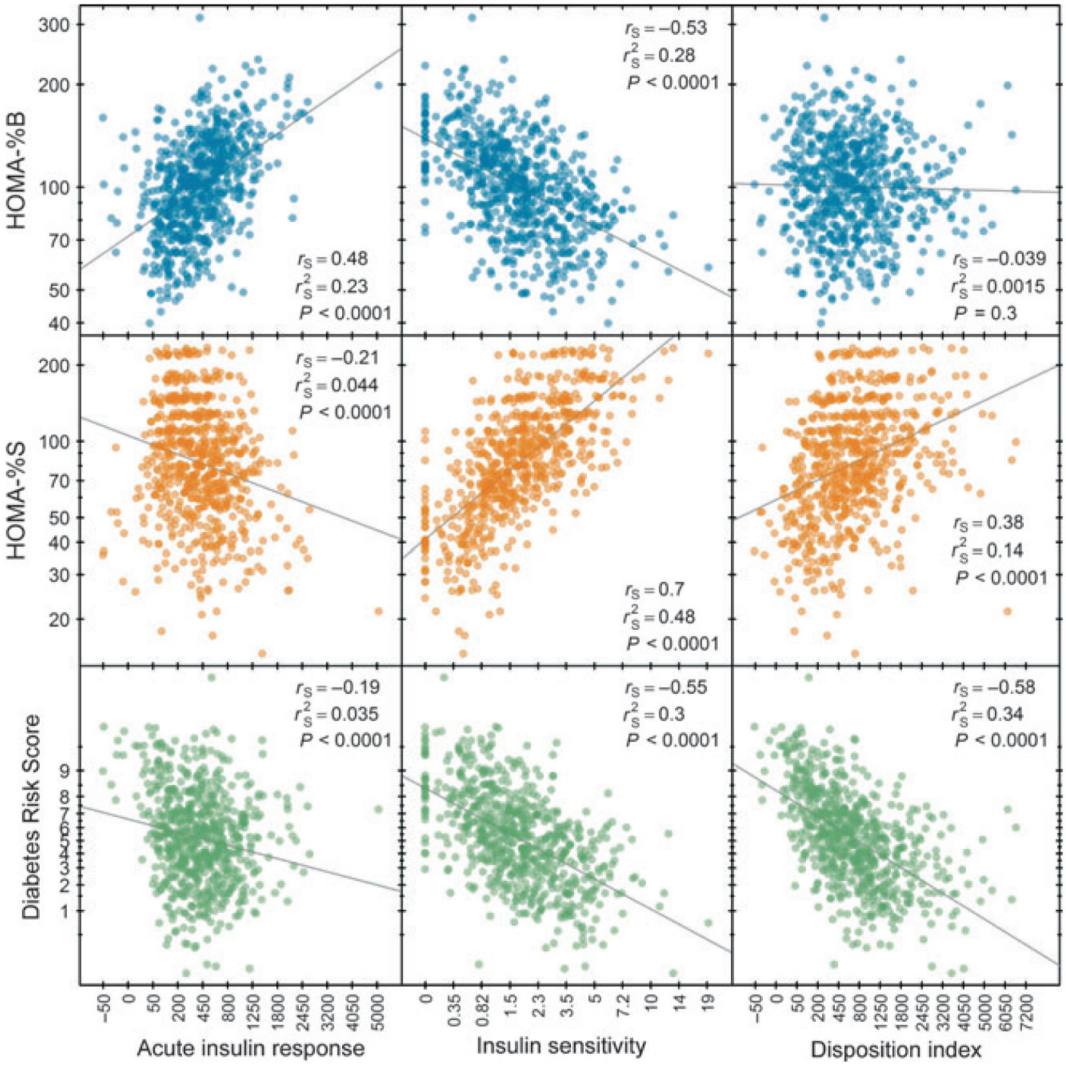

FIGURE 1.

The correlation between biomarker models and minimal model (MINMOD) measures of diabetes risk. In each row, transformed values of the biomarker models are plotted against transformed insulin sensitivity, acute insulin response and disposition index. Spearman rank correlation coefficients (r_S) and their significance (P) are also shown. The regression line of the biomarker model against the MINMOD output is shown in grey. Symbols are semitransparent to give an indication of density where there is overlap.

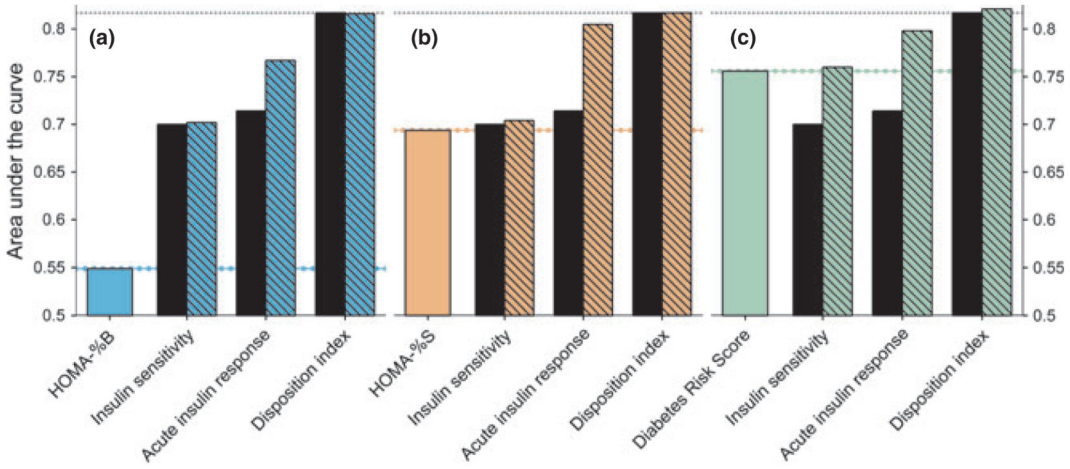

FIGURE 2.

Incremental discrimination gained by adding minimal model (MINMOD) measures to fasting biomarker models. In each plot, the discrimination of one of the biomarker models alone (solid colour) is compared with the MINMOD outputs individually (black) and combined as a bivariate logistic regression model (cross-hatched). Incremental improvements beyond homeostasis model assessment of β-cell function (HOMA-%B), homeostasis model assessment of insulin sensitivity (HOMA-%S) and Diabetes Risk Score are shown in (a), (b) and (c), respectively. The area under the curve was calculated using a bootstrap cross-validation method to remove bias attributable to over fit. The coloured dotted lines and black dashed lines indicate the areas under the curves of the biomarker model and the disposition index alone, respectively.

Table 1

Baseline characteristics of the study population by diabetes status at the 5-year follow-up visit*

Baseline characteristic	Diabetes status at 5-year follow-up visit		P†
	No diabetes	Developed diabetes	
n	550 (82.8%)	114 (17.2%)	
Sex			
Female	291 (81.7%)	65 (18.3%)	0.4
Male	259 (84.1%)	49 (15.9%)	
Race or ethnicity			
Non-Hispanic white	225 (82.1%)	49 (17.9%)	0.9
Hispanic	191 (82.7%)	40 (17.3%)	
African-American	134 (84.3%)	25 (15.7%)	
Fasting glucose status			
Normal fasting glucose (< 5.6 mmol/l)	426 (88.9%)	53 (11.1%)	< 0.0001
Impaired fasting glucose (5.6–6.9 mmol/l)	124 (67.0%)	61 (33.0%)	
2-h glucose status			
Normal glucose tolerance (< 7.8 mmol/l)	402 (90.7%)	41 (9.3%)	< 0.0001
Impaired glucose tolerance (7.8–11.0 mmol/l)	148 (67.0%)	73 (33.0%)	
Age (years)	54.5 (47.5–62.3)	56.9 (49.6–63.6)	0.06
BMI (kg/m^2)	21.7 (24.7–29.9)	29.3 (26.5–34.2)	< 0.0001
Waist circumference (cm)	90.0 (81.2–97.3)	94.3 (88.4–102.0)	< 0.0001
Systolic blood pressure (mmHg)	119 (109–131)	126 (114–139)	0.0007
Diastolic blood pressure (mmHg)	78(71–84)	79 (73–85)	0.2
Fasting glucose (mmol/l)	5.1 (4.8–5.5)	5.6 (5.2–6.1)	< 0.0001
2-h glucose (mmol/l)	6.6 (5.3–7.9)	8.3 (7.3–10.0)	< 0.0001
Fasting insulin (pmol/l)	60 (42–84)	84 (60–126)	< 0.0001
Acute insulin response [pmol/(min.ml)]	441 (237–714)	170 (77.6–413)	< 0.0001
Insulin sensitivity [10^{-4}/(min.ìU.ml)]	1.83 (1.02–3.04)	1.00 (0.49–1.68)	< 0.0001
Disposition index	738 (373–1300)	148 (49.2–364)	< 0.0001
HOMA-%B	100 (77.9–127)	106 (86.1–130)	0.1
HOMA-%S	89.0 (63.5–126)	61.8 (41.2–87.2)	< 0.0001
HOMA-IR	1.12 (0.792–1.57)	1.62 (1.15–2.43)	< 0.0001
Diabetes Risk Score	4.7 (2.4–6.9)	7.8 (5.4–9.0)	< 0.0001

HOMA-%B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-%S, homeostasis model assessment of insulin sensitivity.

* Data are n (% of stratum) or median (interquartile range).

† *P*-values were calculated by χ^2-test (factors) or Wilcoxon rank sum test (continuous variables).

Table 2

Discrimination of diabetes outcomes at 5 years by fasting biomarker models, MINMOD measures and composite models using logistic regression

	Insulin sensitivity (0.700*)	**Acute insulin response (0.714*)**	**Disposition index (0.817*)**
HOMA-%B (0.549*)	0.702†§	0.767†‡	0.816†
HOMA-%S (0.694*)	0.704†§	0.805 †‡	0.817†
Diabetes Risk Score (0.756*)	0.760‡	0.798†‡	0.821†

HOMA-%B, homeostasis model assessment of β-cell function; HOMA-%S, homeostasis model assessment of insulin sensitivity; MINMOD, minimal model.

*Area under the curve of biomarker model or MINMOD output alone.

†Significant difference in area under the curve between composite model and the biomarker model alone ($P < 0.05$).

‡Significant difference in area under the curve between composite model and the MINMOD output alone ($P < 0.05$).

§Significant difference in area under the curve between composite model and disposition index alone ($P < 0.05$).