OBES SURG
DOI 10.1007/s11695-012-0683-3

CLINICAL RESEARCH

Correlations of HOMA2-IR and HbA1c with Algorithms Derived from Bioimpedance and Spectrophotometric Devices

Chaim Elinton Adami · Renata Cristina Gobato · Martinho Antonio Gestic · Everton Cazzo · Murilo Utrini Pimentel · Marcelo de Carvalho Ramos

© Springer Science+Business Media, LLC 2012

Abstract
Background Homeostasis model assessment of insulin resistance (HOMA2-IR) and HbA1c, markers of metabolic syndrome and glycemic control, were compared with Electro Sensor (ES) Complex software algorithms. ES complex software integrates data from Electro Sensor Oxi (ESO; spectrophotometry) and Electro Sensor-Body Composition (ES-BC; bioimpedance).
Methods One hundred forty-eight Brazilian obese candidates for bariatric surgery underwent complete physical examinations, laboratory tests (fasting plasma glucose, fasting plasma insulin, and HbA1c) and ES complex assessments. HOMA2-IR was calculated from fasting plasma glucose and fasting plasma insulin using free software provided by The University of Oxford Diabetes Trial Unit. ES complex–insulin resistance (ESC-IR) and ES complex–blood glucose control (ESC-BCG) were calculated from ESO and ES-BC data using ES complex software. Correlations between HOMA2-IR and ESC-IR and between ESC-BGC and HbA1c were determined.
Results ESC-BGC was correlated with HbA1c (r=0.85). ESC-BCG values >3 were predictive of HbA1c>6.5 % (φ=0.94; unweighted κ=0.9383). ESC-IR was correlated with HOMA2-IR (r=0.84). Patients with ESC-IR score >2.5 or >3 were more likely to have metabolic syndrome or insulin resistance, respectively, compared with HOMA2-IR value >1.4 and >1.8, respectively. ESC-IR performance was evaluated by receiver operating characteristic curves. The areas under the curve for metabolic syndrome and insulin resistance were 0.9413 and 0.9022, respectively.
Conclusion The results of this study in Brazilian subjects with obesity suggest that ES complex algorithms will be useful in large-scale screening studies to predict insulin resistance, metabolic syndrome, and HbA1c >6.5 %. Additional studies are needed to confirm these correlations in non-obese subjects and in other ethnic groups.

Keywords Obesity · Insulin resistance · Metabolic syndrome · Electro Sensor Complex software · HOMA2-IR · HbA1c

Introduction

Homeostatic model assessment (HOMA) is widely used in clinical and investigational settings [1, 2]. This model was derived from animal and human studies and predicts insulin resistance (IR) based on fasting glucose and plasma insulin levels [3]. The accuracy of HOMA for assessing IR has been compared with that of the gold standard method, the hyperinsulinemic-euglycemic clamp, and with other procedures, such as the minimal-model analysis intravenous glucose tolerance test and the oral glucose tolerance test. These comparisons have confirmed that HOMA is a robust clinical and epidemiological tool [4]. Recently, Caumo et al., proposed a new algorithm, termed HOMA2-IR, and reported that it was more reliable than the original HOMA-IR algorithm [5].

C. E. Adami (✉) · R. C. Gobato · M. A. Gestic · E. Cazzo · M. U. Pimentel · M. de Carvalho Ramos
Department of Surgery,
Faculty of Medical Sciences (FCM/UNICAMP),
Campinas University, Cidade Universitária Zeferino Vaz,
Barão Geraldo,
13083970, Campinas, SP, Brazil
e-mail: chaim@hc.unicamp.br

Published online: 08 September 2012

Fig. 1 Integration of the ES complex software with the ES-BC and ESO devices

In Brazilian subjects [6], metabolic syndrome (MetS) can be assessed using HOMA2-IR, as a cutoff value of 1.4 shows equivalent diagnostic utility to a body mass index (BMI) >30 kg/m^2. The American Diabetes Association Standards of Medical Care in Diabetes, 2010, added HbA1c≥48 mmol/mol (≥6.5 %) as another criterion for the diagnosis of diabetes and for the risk of complications of diabetes [7].

Electro sensor (ES) complex software (LD Technology, Miami, FL, USA) manages and integrates data from two medical devices, the Electro sensor Oxi (ESO) and the Electro sensor-body composition (ES-BC) analyzers (LD Technology). ESO is a spectrophotometric pulse oximeter, while ES-BC uses bioimpedance to measure body composition. Figure 1 shows both medical devices

Table 1 Subject characteristics

General demographic data	Means
Men/women	31/117
Age (years)±SD	38.7±20
BMI(kg.m2)±SD	46.5±14
Systolic Pressure(mmHg)	Mean 134 (min: 88, max:214)
Diastolic Pressure(mmHg)	Mean 81.7 (min:59, max: 147)
Treatments	Number of patients
Oral anti-diabetic agent	10
Oral anti-diabetic agent and antihypertensive agent	14
Antihypertensive agent	28
Thyroid hormones	1
Oral anti-diabetic agent and Thyroid hormones	2
Thyroid hormones and antihypertensive agent	2
Insulin	32

BMI body mass index, *min* minimum, *max* maximum

operating under ES complex software. The combined ESO and ES-BC test is rapid (~5 min), cost effective, easy to conduct, non-invasive, and can be performed by medical assistants. Both devices have been cleared for clinical use by the US Food and Drug Administration and comply with ISO 13485-2003.

The ES-BC device transmits a weak current at a frequency of 50 kHz in the tetrapolar mode to measure the electrical resistance of one pathway of the human body. The device can estimate several parameters of body composition, including fat mass. Bioimpedance analysis is only predictive when integrated with variables such as weight, age, sex, and ethnicity. A clinical study conducted at the University of Miami showed adequate relative and absolute agreement between ES-BC and DEXA for fat mass (r=0.97, P< 0.001), overestimating fat mass by just 0.2 lb (90 g) [8]. The device also showed good agreement for body

Table 2 BMI percentiles

Percentiles		95 % Confidence Interval
2.5	34.6525	32.8109–35.4536
5	35.37	34.5164–38.0624
10	38.32	35.4988–39.8672
25	41.125	40.4000–42.1000
75	51.1	50.1739–52.9332
90	55.72	54.3328–57.2518
95	57.505	56.0594–64.4891
97.5	61.7	57.3196–78.1662

fat percentage (r=0.92, P<0.001), overestimating fat percentage by 0.4 % [8].

The ESO device displays the arterial waveform and heart rate. From the arterial waveform, the photoelectrical plethysmography analysis estimates stiffness index (SI_{DVP}) corresponding to arterial stiffness. In one study, arterial stiffness calculated from SI_{DVP} showed good correlation with carotid–femoral pulse wave velocity obtained by applanation tonometry (r=0.65, P<0.0001) [9].

The device also assesses heart rate variability, by determining parameters in the time domain [e.g., standard deviation normal to normal (SDNN)] and in the frequency domain [e.g., low frequency of the Fast Fourier transform (LF)], which represent autonomic nervous system activity [10].

In 1996, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology proposed clinical standards for the measurement, physiological interpretation, clinical use and description, and intended use of SDNN and LF [10].

The objective of the present study was to determine correlations of algorithms embedded in ES complex software for data from the ESO and ES-BC devices with HOMA2-IR and HbA1c for the prediction of IR, diabetes, and diabetic complications.

Subjects and Methods

The study was approved by the regional ethics committee, and was conducted according to the ethical principles of the Declaration of Helsinki. All of the subjects provided written informed consent, and confidentiality was maintained for all subjects.

Sample Size

The sample size (n≥100 and α=5 %) was determined using MedCalc software (http://www.medcalc.org/publications/journals.php).

Table 3 r coefficient for the correlation between ESC-BGC and HbA1c

Variable Y	ESC-BGC E
Variable X	HbA1c
Sample size	148
Correlation coefficient r	0.8470
Significance level	P<0.0001
95 % Confidence internal for r	0.7942–0.8871

Table 4 Spearman's ρ coefficient for the correlation between ESC-BGC and HbA1c

Variable Y	ESC-BGC E
Variable X	HbA1c
Sample size	148
Spearman´s coefficient of rank correlate(rho)	0.786
Significance level	P<0.0001
95 % Confidence internal for rho	0.715–0.841

Subjects

A total of 148 obese subjects, candidates for bariatric surgery, were enrolled. The subjects included non-diabetic, insulin-resistant, and diabetic patients undergoing different treatments. Their characteristics are summarized in Tables 1 and 2. Patients were excluded from the study if they had any contraindication to tests with the ES-BC or ESO devices, including: (1) inability to consent to the study; (2) use of an automatic external defibrillator device; (3) presence of erratic, accelerated, or mechanically controlled irregular heart rhythms; (4) presence of arterial fibrillation/flutter; (5) presence of atrioventricular block; (6) presence of excessive hair that prevent effective placement of the electrodes; (7) use of an implanted electronic device; (8) during or within 2 days of menstruation; (9) fever >37 °C during the assessment; (10) use of diuretics; (11) history of renal or heart failure; (12) excessive consumption of alcohol or stimulants (e.g., amphetamines) 12 h before examination; (13) diarrhea during the assessment; (14) had engaged in intense physical activity or had used a sauna 8 h before examination.

Laboratory Tests

Fasting plasma glucose (FPG; mg/dL) was measured using a colorimetric enzymatic method. Fasting plasma insulin (FPI; μUI/mL) was measured by a chemiluminescent immunoassay. Subjects fasted for at least 8 h before blood sampling for these tests.

HOMA2-IR

HOMA2-IR was calculated from FPG and FPI after converting the concentrations to mmol/L, and pmol/L, respectively. Calculations were performed using free software provided by the University of Oxford Diabetes Trial Unit (http://www.dtu.ox.ac.uk/homacalculator). As HOMA is a steady state model, only clinically realistic values in fasting subjects were included in the analysis (FPG: 3.5–25 mmol/L; FPI: 20–350 pmol/L).

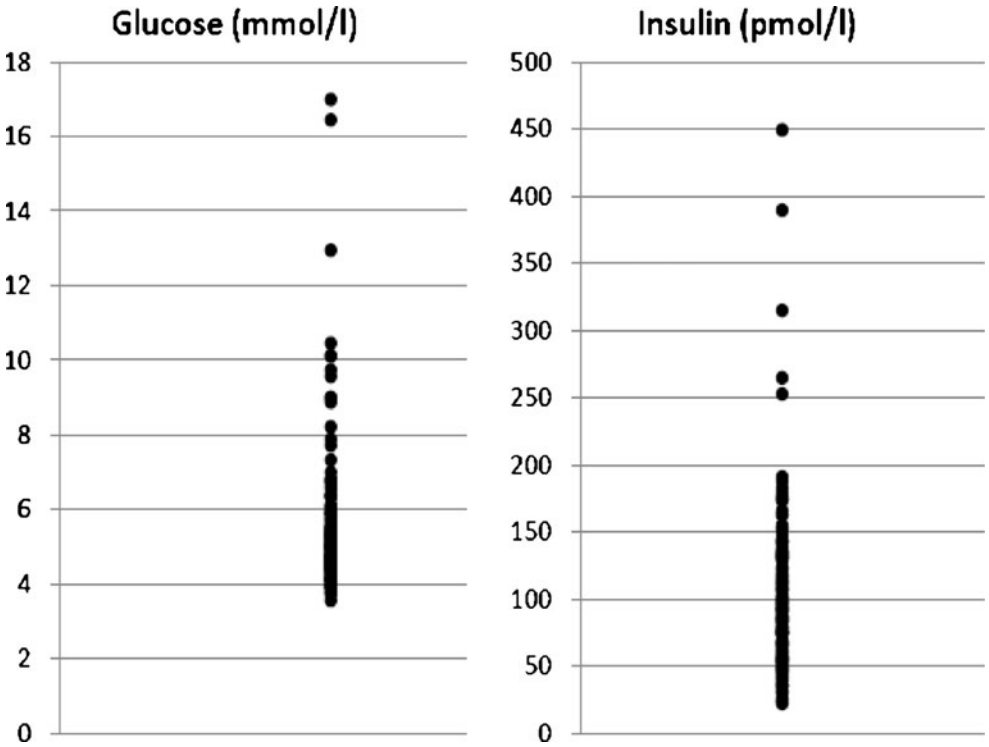

Fig. 2 Scatterplot for ESC-BCG versus HbA1c

ES Complex Algorithms

The ES complex software algorithms were calculated using a neural network (Neural Network Statistica v. 7.0 http://www.statsoft.com/textbook/neural-networks/). The software also determined correlations of ESO and ES-BC data with HOMA2-IR and HbA1c, and then produced algorithms in C++ programming language.

Briefly, ES complex–insulin resistance (ESC-IR) incorporated Log(heart rate), Log(LF), Log(fat mass), and Log (stiffness index) and ES complex–blood glucose control (ESC-BGC) incorporated stiffness index and Log(SDNN).

Statistical Analysis

Spearman's rank correlation coefficients (ρ) and scatter diagrams were used to determine correlations between ESC-IR and HOMA2-IR, and between ES complex–blood glucose control (ESC-BCG) and HbA1c. φ correlation coefficients and unweighted κ values were also determined for the correlations between ESC-BGC and HbA1c, and between ESC-IR and HOMA2-IR. Receiver operating characteristic (ROC) curves were plotted for MetS and IR using HOMA2 cutoff levels of 1.4 and 1.8, respectively. Calculations were performed with MedCalc, Excel 14.0 software (Office 2010; Microsoft, Redmond, VA, USA) and free software from Vassar College (http://faculty.vassar.edu/lowry/).

Table 5 Distribution of subjects according to HbA1c and ESC-BGC cutoff values

HbA1c			
ESC-BGC	≤6.5	>6.5	Total
−3	98	2	100
≥3	2	46	48
Total	100	48	148

Unweighted κ=0.9383; standard error=0.0304; 95 % confidence interval=08787–0.9979

Results

Clinical and demographic data are summarized in Table 1, while BMI percentiles are summarized in Table 2.

Correlations Between HbA1c and ESC-BGC

All 148 subjects were included in this analysis. ESC-BGC was well correlated with HbA1c, as shown in Tables 3 and 4 (r=0.847, ρ=0.786, P<0.0001). The scatterplot for ESC-BCG versus HbA1c is shown in Fig. 2. A contingency analysis was also performed with a cutoff value of 6.5 % for HbA1c, and a cutoff value of 3 for ESC-BGC. The data are shown in Table 5. Using these cutoff values, ESC-BGC >3 was predictive of HbA1c >6.5 % (φ=0.94; κ=0.9383).

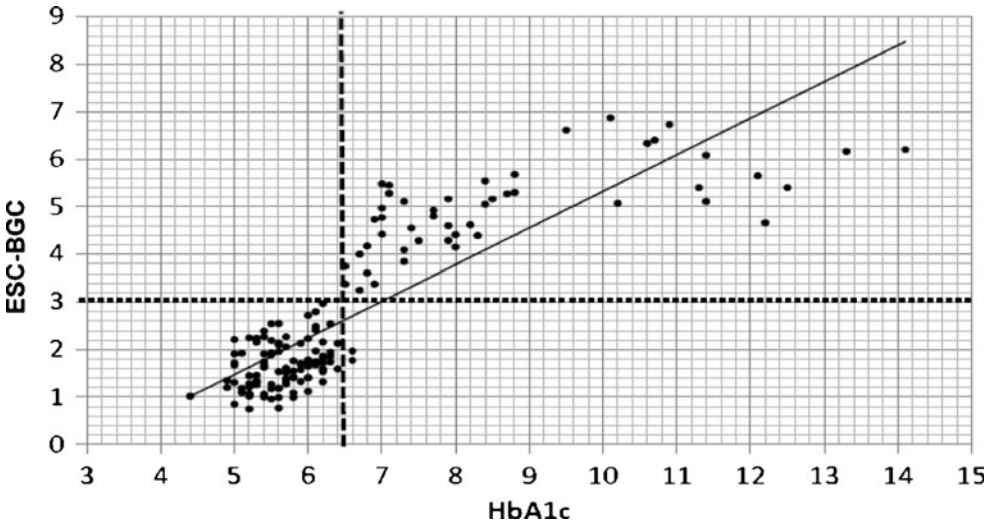

Fig. 3 Distribution of FPG and FPI concentrations in 148 obese subjects

Table 6 *r* coefficient for the correlation between Log(ESC-IR) and Log(HOMA2-R)

Variable Y	(Log)ESC-IR
Variable X	(Log)HOMA2 IR
Sample size	148
Correlation coefficient *r*	0.8605
Significance level	$P<0.0001$
95 % Confidence internal for *r*	0.8119–0.8973

Table 7 Spearman's ρ coefficient for the correlation between ESC-IR and HOMA2-IR

Variable Y	ESC-IR
Variable X	HOMA2_IR
Sample size	148
Spearman´s coefficient of rank correlate(rho)	0.853
Significance level	$P<0.0001$
95 % Confidence internal for rho	0.802–0.892

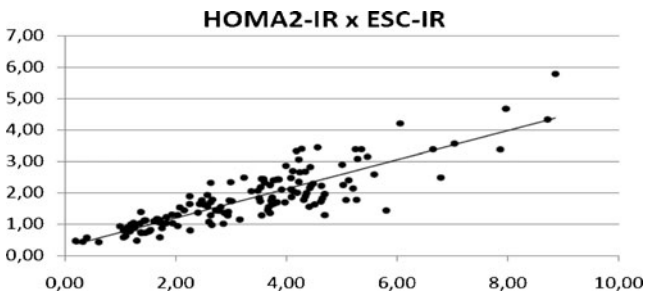

Fig. 4 Scatterplot for ESC-IR versus HOMA2-IR in 141 obese subjects

Correlation Between HOMA2-IR and ESC-IR

The distributions of FPG and FPI concentrations are shown in Fig. 3. FPG ranged from 3.2 to 16 mmol/L. One subject with FPG<3.5 mmol/L was excluded from the analysis of HOMA2-IR. FPI ranged from 13.89 to 449.34 pmol/L. Six additional subjects with FPI >350 pmol/L were excluded from the analysis of HOMA2-IR. Therefore, only 141 patients were included in this analysis. As shown in Tables 6 and 7, ESC-IR, determined from Log values, showed good correlation with HOMA2-IR ($r=0.86$, $\rho=0.853$, $P<0.0001$). The scatterplot for ESC-IR versus HOMA2-IR is shown in Fig. 4.

The Brazilian Metabolic Syndrome Study [6] showed that a HOMA2-IR cutoff value of 1.4 was associated with BMI >30 kg/m^2 and was predictive of MetS. Accordingly, we performed a contingency analysis with a cutoff value of 1.4 for HOMA2-IR and a cutoff value of 2.5 for ESC-IR. The resulting data are shown in Table 8. Using these cutoff values, ESC-IR >2.5 was predictive of HOMA2-IR >1.4 ($\kappa=0.8566$). In a contingency analysis with a cutoff value of 1.8 for HOMA-2-IR, and a cutoff value of 3 for ESC-IR (Table 9), ESC-IR >3 was predictive of HOMA2-IR>1.8 ($\kappa=0.7327$).

The performance of ESC-IR was also evaluated using ROC curves. For MetS and IR, the areas under the curve were 0.9413 and 0.9022, respectively (Fig. 5)

Discussion

In USA, 25.8 million children and adults have diabetes and 1.9 million new cases were reported in 2010 [11, 12]. Hispanics and non-Hispanic blacks have the highest prevalence among the US population [12]. The worldwide

Table 8 Distribution of subjects according to HOMA2-IR and ESC-IR cutoff values for metabolic syndrome

Metabolic Syndrome (HOMA2-IR)			
ESC-IR	<1.4	≥1.4	Total
<2.5	42	5	47
≥2.5	4	90	94
Total	46	95	141

Unweighted κ=0.8566; standard error=0.0446; 95 % confidence interval=0.7643–0.9469

Table 9 Distribution of subjects according to HOMA2-IR and ESC-IR cutoff values for insulin resistance

Insulin Resistance (HOMA2-IR)			
ESC-IR	<1.8	≥1.8	Total
<3	62	3	65
≥3	16	60	76
Total	78	63	141

Unweighted κ=0.7327; standard error=0.0561; 95 % confidence interval=0.6209–0.8445

prevalence of diabetes is expected to double over the next 20 years [13, 14].

Effective interventions focusing on early detection, dietary changes, physical activity, and treatment are needed to address this problem [14]. IR, a preliminary stage in the pathogenesis of type 2 diabetes, is also strongly associated with obesity and increased risk of cardiovascular diseases [14].

In patients with confirmed diabetes, the main assessment of disease status, with the objective of preventing disease complications, is regular measurement of HbA1c, as it is accepted as a reliable method of monitoring treatment success or to predict treatment failure [14].

In this study, 148 Brazilian obese subjects underwent ES complex evaluations, and the results were compared with HOMA2-IR and HbA1c. The prevalence of MetS and IR in this population, based on HOMA2-IR results, was 67.4 and 44.7 %, respectively. We found that HOMA2-IR was strongly correlated with ESC-IR. Contingency analysis and ROC curves revealed that the ESC-IR cutoff values for MetS and IR were 2.5 and 3.0, respectively.

The performance of ESC-BGC was also encouraging when used in the context of preventing diabetes-related complications or treatment failures. HbA1c >6.5 % is indicative of an inadequate control of diabetes in clinical settings. ESC-BGC values >3 were strongly associated with HbA1c values >6.5 %. Based on this threshold, the prevalence of treatment failure in the present study was 27 %. Even in this setting with a moderate prevalence of treatment failure, ESC-BGC showed good performance.

How can the data integrated into the ES complex algorithms detect IR and blood glucose control? Salomaa et al. [15] performed a cross-sectional study to assess the relationship between indices of arterial stiffness and glucose tolerance and serum insulin concentrations. They found that the indices of arterial stiffness were higher in subjects with FPG exceeding the normal level. Schroeder et al. [16] found significant correlations between parameters off heart rate variability (i.e., SDNN and LF) and the

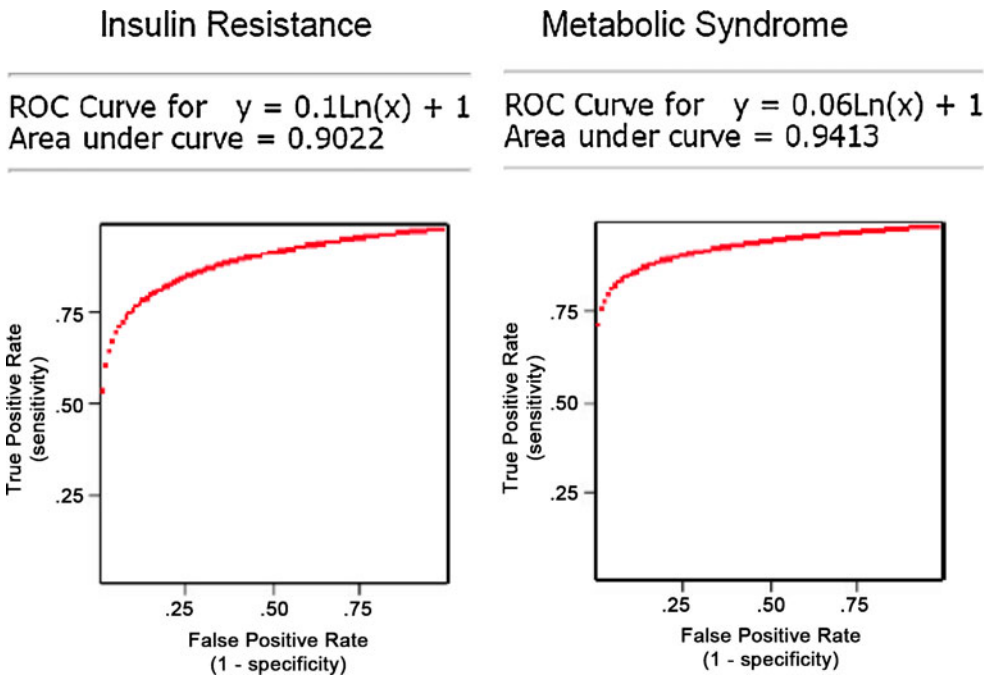

Fig. 5 ROC curves for MetS and IR

presence of diabetes ($P<0.01$). Similarly, Von Känel et al. [17] found good correlations between SDNN and markers of inflammation, which are often associated with insulin resistance. Finally, Ferrannini et al. [18] examined correlations among fat mass and diabetes-related parameters and found that fat mass was highly correlated with insulin resistance.

Conclusion

The results obtained in this study are encouraging. We believe that the ES complex algorithms will be useful for large-scale screening of IR, MetS, and diabetes treatment failure in Brazilian obese populations. Additional studies are needed to confirm these results in non-obese subjects and in other ethnic groups.

Acknowledgments We thank LD Technology for providing the system used in this study.

Conflict of Interest This study was not sponsored. The authors have no conflicts of interest to declare.

References

1. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27:1487–95.
2. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21:2191–2.
3. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetol. 1985;28:412–9.
4. Bergman RN, Prager R, Volund A, et al. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest. 1987;79:790–800.
5. Caumo A, Perseghin G, Lattuada G, et al. Comparing the original (HOMA1) and the updated (HOMA2) method: evidence that HOMA2 is more reliable than HOMA. American Diabetes Association 67th Scientific Sessions 2007, June 22–26, 2007. Chicago, IL. Abstract: 1595-P.
6. Geloneze B. Junqueira Vasques AC, Stabe CFC, et al. HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome. Brazilian Metabolic Syndrome Study (BRAMS). Arq Bras. Endocrinol Metab. 2009;53:281–7.
7. American Diabaetes Association. Executive summary: standards of medical care in diabetes—2010. Diabetes Care. 2010;33 suppl 1:S4–S10.
8. Lewis JE, Melillo AB, Tannenbaum S, et al. Comparing the accuracy of ES-BC, EIS and ES Oxi on body composition, autonomic nervous system activity and cardiac output results versus the recognized standardized assessment. Med Device (Auckl). 2011;4:169–77.
9. Millasseaua SC, Rittera JM, Takazawab K, et al. Contour analysis of the photoplethysmographic pulse measured at the finger. J Hypertens. 2006;24:1449–56.
10. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J. 1996;17:354–81.
11. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. Available at: www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.
12. Sicree R, Shaw J, Zimmet P. Diabetes impaired glucose tolerance—prevalence and projections. In: Gan D, editor. Diabetes atlas. 3rd ed. Brussels: International Diabetes Federation; 2006. p. 15–103.
13. Diabetes Prevention Research Group. Reduction in the evidence of type 2 diabetes with life-style intervention or metformin. N Engl J Med. 2002;346:393–403.
14. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications, in: Report of a WHO Consultation. Part I: Diagnosis and classification of diabetes mellitus. Geneva: WHO; 1999. WHO/NCD/NCS/99.2.
15. Salomaa V, Riley W, Kark JD, et al. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. Circ. 1995;91:1432–43.
16. Schroeder EB, Chambless LE, Liao D, et al. Diabetes, glucose, insulin, and heart rate variability. Diabetes Care. 2005;28:668–74.
17. Von Känel R, Carney RM, Zhao S, et al. Heart rate variability and biomarkers of systemic inflammation in patients with stable coronary heart disease: findings from the heart and soul study. Clin Res Cardiol. 2011;100:241–7.
18. Ferrannini E, Camastra S, Gastaldelli A, et al. Beta-cell function in obesity: effects of weight loss. Diabetes. 2004;53 Suppl 3:S26–33.