

# New approach to beta cell function screening by nitric oxide assessment of obese individuals at the population level

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**Background:** Approximately 27% of Americans today are obese, and this condition increases the prevalence of metabolic syndrome and diabetes. The UK Prospective Diabetes Study suggests that loss of beta cell function can begin at least 10 years before diagnosis, and mean beta cell function is already less than 50% at diagnosis. The aim of this research was to assess the possibility of detecting loss of beta cell function in obese patients by a novel approach involving nitric oxide assessment using a combination of technologies.

**Materials and methods:** One hundred and fifteen obese patients (93 women, 22 men) of mean age 39 (range 17–62) years, who were candidates for bariatric surgery were included in the study, and underwent laboratory tests, including fasting blood glucose, fasting insulin plasma, and examination with the Electro Sensor complex. The Electro Sensor complex offers a new way to assess nitric oxide production using five technologies managed by software, ie, the galvanic skin response, photoelectrical plethysmography, heart rate variability analysis, bioimpedance analysis, and blood pressure oscillometric measurements. The homeostasis model assessment 2% beta cell function (HOMA2%  $\beta$ ) algorithm was calculated from fasting blood glucose and fasting insulin plasma using free software provided by The University of Oxford Diabetes Trial Unit. The Electro Sensor complex percent beta (ESC%  $\beta$ ) algorithm was calculated from the Electro Sensor complex data and statistical neural network. Statistical analysis was performed to correlate ESC%  $\beta$  and HOMA2%  $\beta$  using the coefficient of correlation and Spearman's coefficient of rank correlation. Receiver-operating characteristic curves were also constructed to determine the specificity and sensitivity of ESC%  $\beta$  in detecting a HOMA2%  $\beta$  value  $< 100$ .

**Results:** The coefficient of correlation between ESC%  $\beta$  and HOMA2%  $\beta$  was 0.72 (using log values) and the Spearman's coefficient of rank correlation ( $\rho$ ) was 0.799 ( $P < 0.0001$ ). ESC%  $\beta$  had a sensitivity of 77.14% and specificity of 78.21% (cutoff  $\leq 157$ , corresponding to 40% after conversion into a 0%–100% scale) to detect a HOMA2%  $\beta$  value  $< 100$  ( $P < 0.0001$ ).

**Conclusion:** The ESC%  $\beta$  algorithm has a high predictive correlation with HOMA2%  $\beta$ , and good specificity and sensitivity to detect a HOMA2%  $\beta$  value  $< 100$ . Therefore, the Electro Sensor complex enabling nitric oxide assessment represents a novel method of screening for beta cell function in the obese population on a large scale. Such a tool, which is easy to administer, noninvasive, and cost-effective, would be of great benefit for widespread screening of beta cell function in obese patients.

**Keywords:** beta cell function, Electro Sensor complex, nitric oxide assessment, ESC%  $\beta$  algorithm, HOMA2%  $\beta$  algorithm, obese population, screening

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## Introduction

During the past 20 years, the US has succumbed to a pervasive obesity epidemic.<sup>1,2</sup> In 1980, less than 47% of Americans were overweight (body mass index  $> 25$  kg/m<sup>2</sup>)

and less than 15% were obese (body mass index  $> 30 \text{ kg/m}^2$ ). Today, approximately 67% of Americans are overweight and over 27% are obese.<sup>2,3</sup> Obesity increases the prevalence of the metabolic syndrome and diabetes.<sup>4,5</sup> The pathogenesis of type 2 diabetes is hypothesized to be related to two principal factors, ie, insulin resistance and impaired glucose tolerance cell function.<sup>6</sup> How do insulin resistance and beta cell dysfunction combine to cause type 2 diabetes?<sup>7</sup> Over time, changes in insulin resistance and secretion lead to the onset of type 2 diabetes. In the early stages, as insulin resistance rises, there is a compensatory increase in insulin secretion and glucose levels remain normal (normoglycemia). However, in the long term, as beta cell function begins to fail, insulin secretion decreases, impaired glucose tolerance and hyperglycemia become apparent, and frank type 2 diabetes develops.

Impaired glucose tolerance may be defined as higher than normal blood glucose levels, but not high enough to be called diabetes. People with impaired glucose tolerance may or may not go on to develop diabetes. Glucose levels before (fasting) and after (post-prandial) meals increase steadily as the individual progresses from normoglycemia to impaired glucose tolerance and, finally, to type 2 diabetes.

Extrapolation of the observed rate of decline in beta cell function in diet-treated subjects in the UK Prospective Diabetes Study suggests that loss of beta cell function can start at least 10 years before diagnosis of diabetes, and that mean beta cell function may already be less than 50% at diagnosis.<sup>8,9</sup> None of the therapies used in the UK Prospective Diabetes Study (sulfonylureas, metformin, and insulin) were able to prevent or delay the progressive deterioration of beta cell function.<sup>10</sup> On average, beta cell function declines by 1% per year with normal aging, compared with 4% per year in diabetes.<sup>10,11</sup> In view of these facts and the studies that have already established the correlation between obesity and insulin resistance, we undertook this study of screening for beta cell function in the obese population.

Beta cell function diagnostics are already available. The gold standard test includes the hyperinsulinemic-euglycemic clamp,<sup>11</sup> and another accepted method is the minimal-model analysis frequently sampled intravenous glucose tolerance test.<sup>12</sup> The oral glucose tolerance test is also accepted as a noninvasive minimal model for analysis.<sup>12</sup> However, these tests are invasive, labor-intensive, and/or expensive, which discourages their use in large population-based epidemiologic studies. Sometimes used as a marker for beta cell dysfunction, the ratio of proinsulin (the precursor of insulin that is converted to insulin) to total insulin provides a measure of the efficiency of proinsulin processing.<sup>13</sup> C-peptide is also used to

assess beta cell function in type 1 diabetes when the insulin level is not interpretable due to insulin medication.<sup>14</sup>

The homeostasis model assessment percent beta (HOMA%  $\beta$ ) algorithm is appropriate for large-scale screening,<sup>15</sup> and the new HOMA2%  $\beta$  algorithm improves the ability to assess beta cell function compared with the HOMA1%  $\beta$  algorithm.<sup>16</sup> The HOMA2%  $\beta$  is an algorithm calculated from fasting blood glucose and plasma insulin, and correlates well with estimates using the euglycemic clamp method. It has been tested extensively against minimal-model analysis, and has been accepted for large-scale screening of beta cell function,<sup>17</sup> with some restrictions, ie, in older patients.<sup>18</sup>

The Electro Sensor complex (LD Technology, Miami, FL) is a combination of five technologies managed by software, and the accuracy of some features, such as fat mass and cardiac output measurements, has been compared with recognized standardized assessment.<sup>19</sup> The Electro Sensor complex features include the galvanic skin response, heart rate variability analysis, photoelectrical plethysmography analysis, and blood pressure measurements. We consider that the Electro Sensor complex data are related to production of nitric oxide.

## Electro Sensor complex data and nitric oxide

With regard to the galvanic skin response, electrical skin stimulation seems to be a mechanical shear stress which causes a phosphorylation cascade that removes phosphate groups from proteins and kinases, activating endothelial nitric oxide synthase to synthesize nitric oxide. Nitric oxide is produced, facilitating the release of cyclic guanosine monophosphate and a change in potassium permeability. Relaxation of smooth muscle and vasodilatation of vessels allows an exchange between the vessels and sweat glands, which facilitates the production of sweat.<sup>20,21</sup>

Photoelectrical plethysmography analysis provides a stiffness index, and blood pressure measurements are related to endothelial cell function which is related to nitric oxide production.<sup>22</sup> Fat mass is also related to nitric oxide.<sup>23</sup> Finally, a study by Sartori et al found a significant relationship between nitric oxide production and heart rate variability analysis.<sup>24</sup> Zeng and Quon have performed a study showing the relationship between insulin production and nitric oxide using administration of wortmannin.<sup>25</sup> The ESC%  $\beta$  algorithm can be calculated from Electro Sensor complex data. The aim of this research was to assess the possibility of detecting loss of beta cell function in obese patients using a novel approach of nitric oxide assessment using a combination of technologies comparing ESC%  $\beta$  and HOMA2%  $\beta$ .

## Materials and methods

### Subjects

Obesity is associated with the metabolic syndrome and diabetes, and this study included obese patients who were candidates for bariatric surgery. Patients were excluded if they were on insulin or secretagogue treatment, had a neurological disorder precluding the ability to sign a consent form, were clinically unsuitable candidates for the trial in the opinion of the investigators, and/or had any contraindications to use of the Electro Sensor complex system. Use of the Electro Sensor complex system is contraindicated in the presence of an external defibrillator, skin lesions likely to come into contact with the electrodes, excessive perspiration, a cardiac pacemaker, electronic life support, any implanted electronic device, inability to remain still for three minutes, metallic pins or prostheses in digits or joints, and absence of a limb.

One hundred and fifteen obese patients (93 women, 22 men) of mean age 39 (range 17–62) years were sent to the laboratory for fasting blood glucose and fasting insulin plasma tests. The patients underwent an Electro Sensor complex measurement before these laboratory tests. The study was approved by the regional ethics committee, and adhered to the ethical principles of the Declaration of Helsinki. Each patient signed an informed consent form, and confidentiality was observed for all participants.

### Laboratory tests

Fasting plasma glucose levels (mg/dL) were measured using the colorimetric enzymatic method. Fasting plasma insulin levels ( $\mu\text{UI/mL}$ ) were determined using the chemoluminescent immunoassay. Fasting for 8 hours was required for both tests. The HOMA2%  $\beta$  algorithm was calculated from fasting blood glucose and fasting insulin plasma. Glucose and insulin concentrations were converted to mmol/L and pmol/L, respectively. Calculations were performed using the free software provided by The University of Oxford Diabetes Trial Unit (<http://www.dtu.ox.ac.uk/homacalculator>). Because HOMA is a steady-state model, only clinical realistic values seen in a fasting subject were accepted for analysis (plasma glucose level 3.5–25 mmol/L and plasma insulin level 20–350 pmol/L).

### Electro Sensor complex system and ESC% $\beta$ algorithm

The Electro Sensor complex system is a novel method for assessing nitric oxide production using five technologies managed by software, ie, the galvanic skin response, photoelectrical plethysmography, heart rate variability analysis,

bioimpedance analysis, and blood pressure oscillometric measurements.

Nitric oxide assessment is expressed in the ESC%  $\beta$  algorithm, and calculated from the following data:

- Conductance of the foot-foot pathway, expressed in  $\mu\text{Si}$  (microSiemens), with a normal range of 8.33–14.71  $\mu\text{Si}$ , from galvanic skin response technology
- Stiffness index, calculated from the height of the patient (in meters) divided by the time (seconds) between the two systolic peaks of the wave provided by the oximeter (photoelectrical plethysmography), expressed in m/sec, with a normal range of 7–9
- Standard deviation normal-to-normal represents the standard deviation of the entire recording of time between each heartbeat, expressed in msec, normal range 40–80, from heart rate variability domain analysis technology
- Fat mass percentage, expressed in kg, with a normal range according to age and gender, from bioimpedance analysis technology
- Systolic pressure, normal range < 140 mmHg, from the blood pressure device using oscillometric technology.

The ESC%  $\beta$  algorithm was performed using statistical neural network analysis software Statistica Version 7.<sup>26</sup> Like the HOMA2%  $\beta$  algorithm, the ESC%  $\beta$  algorithm uses a calculator which is integrated into the Electro Sensor complex software, and the results are expressed in percentage form. The scale of results is 0–100, and the normal range is 40%–60%.

### Statistical analysis

Statistical analysis of the number of patients needed for the study was calculated using MedCalc software and was 100 on the basis of  $\alpha = 5\%$ , at 80% power = F ( $\Delta$ , N, variability DS), taking into account the judgment criteria  $\Delta$  at approximately 100 DS (5% error).  $P < 0.005$  was accepted as being statistically significant. The statistical analysis was performed to correlate the Electro Sensor complex data and HOMA2%  $\beta$  on the one hand, and to correlate ESC%  $\beta$  and HOMA2%  $\beta$  on the other, using the coefficient of correlation and the Spearman's coefficient of rank correlation. Receiver-operating characteristic curves were also constructed to determine the specificity and sensitivity of ESC%  $\beta$  to detect a HOMA2%  $\beta$  value < 100.

### Results

Demographic data for the 115 patients included in the study are summarized in Table 1. The correlation between HOMA2%  $\beta$  and each parameter are summarized in Table 2.

**Table 1** Demographic data for study participants

General demographic data	
Women/men ratio	4.22
Age	38.7 ± 20
BMI	46.5 ± 14
Treatments	<b>Patients (n)</b>
Metformin treatment	20
Antihypertensive agents	63
Parameters and units	<b>Values</b>
Foot conductance (μSi)	7.8 ± 4.3
SI (m/sec)	8.1 ± 1.16
SDNN (msec)	48.8 ± 12.9
Fat mass % total body weight	45 ± 11
Systolic pressure (mmHg)	134.1 ± 20.6
Algorithms	<b>Values</b>
HOMA2% β	140 ± 73
ESC% β	222 ± 137.7

**Note:** Data are expressed as the mean ± standard deviation.

**Abbreviations:** BMI, body mass index; SI, stress index; SDNN, standard deviation normal-to-normal; HOMA2% β, homeostasis model assessment 2 percent beta cell function; ESC% β, Electro Sensor complex percent beta.

Correlation between the ESC% β and the HOMA2% β algorithms is summarized in Table 3. The coefficient of correlation for ESC% β and HOMA2% β is  $r = 0.72$  using log values ( $P < 0.0001$ ). Spearman's rank coefficient correlation between ESC% β and HOMA2% β is summarized in Table 4 and in Figure 1. Spearman's rank coefficient correlation ( $\rho$ ) was 0.799 ( $P < 0.0001$ ). A receiver-operating characteristic curve was constructed to determine the specificity and sensitivity of ESC% β to detect a HOMA2% β value  $< 100$  (Figure 2 and Table 5). ESC% β had a sensitivity of 77.14% and specificity of 78.21% (cutoff  $\leq 157$  corresponding to 40% after conversion using a scale of 0%–100%) to detect a HOMA2% β value  $< 100$  ( $P < 0.0001$ ).

## Discussion

Mayaudon et al<sup>27</sup> performed a study using a device which measured foot conductance to detect diabetes. In their study, foot conductance was reduced in diabetic patients compared with control subjects. However, this study compared a group of 92 type 2 diabetic patients of mean age  $58.9 \pm 12.1$  years, body

**Table 2** Correlation between HOMA2% β and each parameter

Parameters	r	rho	P
Foot conductance	0.56	0.65	0.01
SI	0.55	0.63	0.01
SDNN	0.64	0.70	0.001
Fat mass	0.44	0.49	0.03
Systolic pressure	0.53	0.62	0.01

**Abbreviations:** SI, stiffness index; SDNN, standard deviation normal-to-normal; r, coefficient of correlation; rho, Spearman's coefficient of rank correlation; HOMA2% β, homeostasis model assessment 2 percent beta cell function.

**Table 3** Correlation between ESC% β algorithm and HOMA2% β algorithm

Correlation	
Variable Y	ESC
Variable X	HOMA
Sample size	115
Correlation coefficient r	0.7216
Significance level	$P < 0.0001$
95% confidence interval for r	0.6204–0.7991

**Abbreviations:** HOMA2% β, homeostasis model assessment 2 percent beta cell function; ESC% β, Electro Sensor complex percent beta.

mass index  $28.3 \pm 5.0$ , and mean diabetes duration  $14 \pm 10$  years, with about 50% having diabetic complications and on antidiabetic agents, including insulin and secretagogues, and a group of 41 healthy volunteers of mean age  $25.5 \pm 6.4$  years, none of whom were on treatment, and body mass index  $23.8 \pm 2.7$ . Therefore, the results are biased in that the study compared two very different populations and it would be impossible to attribute the differences in foot conductance to age, complications, treatment, body mass index, or diabetes detection. Also, an algorithm including foot conductance, age, and body mass index was used, which has a sensitivity of 75% and specificity of 100% to detect diabetes. With regard to the differences in age and body mass index between the two study groups, this algorithm result cannot be considered seriously. Ramachandran et al<sup>28</sup> have also investigated the same device, the same parameters, and the same algorithm in a study from India using an equivalent population, and the specificity for detecting diabetes was more realistic and failed at 54%. Another study<sup>29</sup> using only foot conductance showed this parameter to be useful for evaluating diabetic complications, such as foot neuropathy, but as a sole marker does not have enough specificity and sensitivity to detect diabetes.

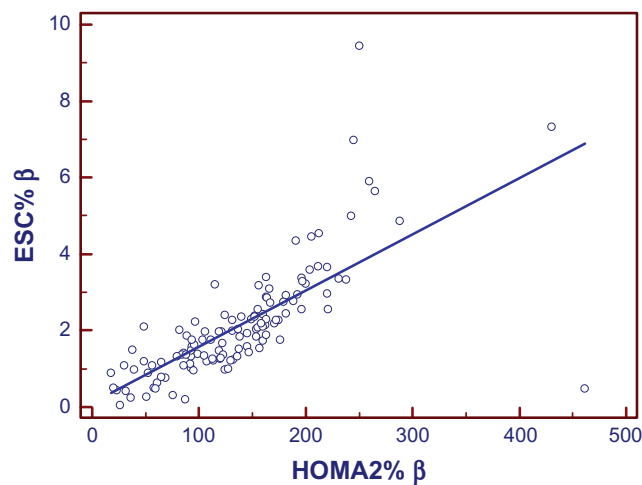
Salomaa et al<sup>30</sup> performed a cross-sectional study to assess the relationship between arterial stiffness, glucose tolerance, and serum insulin levels. All indices of arterial stiffness were higher when fasting glucose was above the normal level.<sup>31</sup>

**Table 4** Spearman's coefficient of rank coefficient between ESC% β and HOMA2% β

Rank correlation	
Variable Y	ESC
Variable X	HOMA
Sample size	115
Spearman's coefficient of rank correlation (rho)	0.799
Significance level	$P < 0.0001$
95% confidence interval for rho	0.721–0.857

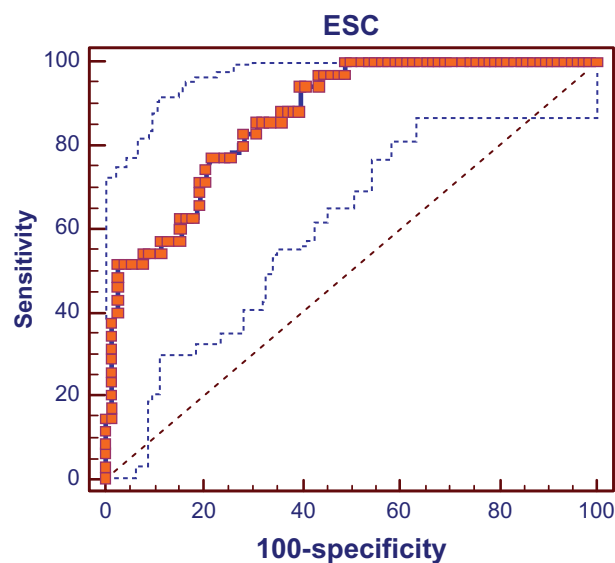
**Abbreviations:** HOMA2% β, homeostasis model assessment 2 percent beta cell function; ESC% β, Electro Sensor complex percent beta.





**Figure 1** Scatter diagram and regression line ESC%  $\beta$  and HOMA2%  $\beta$ .  
**Abbreviations:** HOMA2%  $\beta$ , homeostasis model assessment 2 percent beta cell function; ESC%  $\beta$ , Electro Sensor complex percent beta.

Our study confirms this finding, and we found an acceptable correlation comparing HOMA2%  $\beta$  and stiffness index. Schroeder et al<sup>31</sup> used heart rate variability analysis and the standard deviation normal-to-normal parameter to detect diabetes, and found a good correlation at  $P < 0.01$ . Our study confirms this finding. Ferrannini et al<sup>32</sup> found that fat mass was highly correlated with insulin resistance, but the relationship between fat mass and beta cell function was not clear. Our study included only obese patients with body mass index  $> 40 \text{ kg/m}^2$ , and this parameter has a low correlation with HOMA2%  $\beta$ .



**Figure 2** Receiver operating characteristic curve ESC%  $\beta$  versus HOMA2%  $\beta$  value  $< 100$ .  
**Abbreviations:** HOMA2%  $\beta$ , homeostasis model assessment 2 percent beta cell function; ESC%  $\beta$ , Electro Sensor complex percent beta.

**Table 5** Receiver operating characteristic curve analysis: ESC%  $\beta$  versus HOMA2%  $\beta$  value  $< 100$

Variable	ESC% $\beta$
Classification variable	DIAGNOSIS
Sample size	115
Positive group: diagnosis 0	35
Negative group: diagnosis 1	80
Disease prevalence (%)	31
Area under the ROC curve (AUC)	0.867
Standard error <sup>a</sup>	0.0334
95% confidence interval <sup>b</sup>	0.790–0.924
z statistic	10.978
Significance level $P$ (area = 0.5)	$< 0.0001$

**Notes:** <sup>a</sup>Delong et al 1988 ([http://www.medcalc.org/manual/comparison\\_of\\_roc\\_curves.php](http://www.medcalc.org/manual/comparison_of_roc_curves.php)); <sup>b</sup>binomial exact ([http://www.medcalc.org/manual/comparison\\_of\\_roc\\_curves.php](http://www.medcalc.org/manual/comparison_of_roc_curves.php)).

**Abbreviations:** HOMA2%  $\beta$ , homeostasis model assessment 2 percent beta cell function; ESC%  $\beta$ , Electro Sensor complex percent beta.

Finally, Davies et al<sup>33</sup> compared systolic blood pressure and diabetes screening, and found the same correlation that we obtained in the present study. The ESC%  $\beta$  algorithm has a high predictive correlation with HOMA2%  $\beta$ , and good specificity and sensitivity to detect a HOMA2%  $\beta$  value  $< 100$ . The Electro Sensor complex which provides the ESC%  $\beta$  algorithm could be a new method of estimating beta cell function via nitric oxide assessment using a combination of technologies.

Electro Sensor complex-insulin resistance and Electro Sensor complex-blood glucose control algorithms using different Electro Sensor complex data and formulae have already been investigated and compared, respectively, with HOMA2-IR and glycosylated hemoglobin, with some success (Chaim EA, Gobato RC, Carvalho Ramos M, unpublished data, 2011). Furthermore, the Electro Sensor complex will be useful for early detection of diabetic complications, with regard to the role of nitric oxide in cardiovascular disease<sup>34</sup> and renal oxygenation.<sup>35</sup> New algorithms using Electro Sensor complex data will be investigated to detect cardiovascular risk and kidney risk. Finally, a longitudinal study is underway at the University of Miami using the Electro Sensor complex to detect diabetes not only in obese patients but also in the general population.

## Conclusion

The ESC%  $\beta$  algorithm has a high predictive correlation with the HOMA2%  $\beta$ , and good specificity and sensitivity to detect a HOMA2%  $\beta$  value  $< 100$ , so the Electro Sensor complex system providing nitric oxide assessment would be a new method of screening for beta cell function in the obese population on a large scale. A tool which is easy to administer, noninvasive, and cost-effective would be of advantage and of great benefit for beta cell function screening.

## Disclosure

This study was not sponsored and the authors report no conflicts of interest in this work.

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