

Research Article

Integrative Diabetes and Cardiovascular Diseases

Insulin Sensitivity Measured with the Oral Minimal Model is lower in Obese Subjects Who Report omitting their Breakfast

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Abstract

Introduction: Omitting the breakfast has been reported to promote weight gain and to impair insulin sensitivity. However this latter effect was only assessed with simple surrogates. We thus aimed at verifying if insulin sensitivity is lowered in individuals who omit their breakfast with a more quantitative assessment, using the “Oral Minimal Model” (OMM) i.e., an extension of Bergman’s minimal model to oral glucose tolerance-tests, in a cross-sectional study of a population exhibiting the full range of body mass indices.

Materials and methods: We selected on our database of patients, explored for weight and/or eating disorders, 27 individuals omitting their breakfast (defined on the basis of an alimentary standardized questionnaire) and compared them to 103 matched subjects taking a hyperglucidic breakfast. The breakfast was analyzed with the OMM for the assessment of insulin sensitivity. Insulin secretion was assessed with a previously reported procedure, allowing the calculation of the parameters of phase 1 and 2 of insulin secretion of Cobelli and Mari’s models. In addition, it is already known that Mari’s model provides an index of post stimulatory potentiation of insulin secretion. Disposition indices (product of SI and insulin secretion parameters) were also determined.

Results: In the 27 subjects omitting their breakfast compared to the 103 matched subjects the difference in insulin sensitivity was not found. No difference in insulin secretion parameters is detected. Homeostasis between insulin secretion and insulin sensitivity appears to be functional. However when splitting the sample in categories of BMI the expected difference appears in the range 30-40. In this subgroup (Omitting (n=9) BMI: 35.4±0.99 vs. non-omitting (n=47) BMI: 34.1±0.37 kg/m²) insulin sensitivity was lower in individuals omitting their breakfast (4.32 10⁻⁴ min⁻¹(μU/ml)± 0.94 vs. 9.33±1.84, p=0.03). Despite a slight increase in insulin levels and in the overall insulin secretion rate, a decrease in potentiation and in disposition index was evidenced in individuals omitting their breakfast. The lowering effect of omitting the breakfast on insulin sensitivity is thus evidenced in obese subjects in this sample (but not in those with a BMI below 30). This impairment in insulin sensitivity resulted in a decrease of glucose tolerance by 34%. This finding, based on a cross-sectional study but using a sophisticated measurement, is in agreement with the previous report that omission of the breakfast may induce resistance to insulin. It suggests that the worsening effect on SI that was experimentally found in an interventional study in healthy women becomes important enough in obese subjects to be detected in a cross-sectional study, and that this effect associates a decrease in SI and an

incomplete adaptation of insulin release to this reduction in SI, and thus a decrease in glucose tolerance.

Keywords: Breakfast, Insulin secretion, Insulin resistance, Oral minimal model, Hyperglucidic

Introduction

It becomes more and more usual in westernized societies to skip the breakfast. Although one could think it is a good idea, since it can decrease the total daily caloric intake, there is a host of epidemiological reports suggesting that this habit is rather associated with a higher prevalence of obesity [1-4]. In a longitudinal cohort study it can be evidenced that skipping breakfast is associated with weight gain [5]. In addition recent studies in Europe indicate that skipping breakfast is also associated with impaired cardiovascular fitness [6-7], a factor that is well known to be a strong determinant of metabolic health [8].

Kobayashi and coworkers [9] evaluated in a randomized repeated-measure design with or without breakfast, the effect of breakfast skipping on diurnal variation of energy metabolism and blood glucose. They observed that skipping breakfast increased overall 24 h average of blood glucose and concluded that after breakfast skipping, changes in glucose homeostasis appeared very early and preceded that of energy balance and body composition. In another randomized controlled crossover trial, Nas [10] evidenced that breakfast skipping resulted in higher postprandial insulin concentrations and increased fat oxidation. Moreover, it increased the inflammatory potential of peripheral blood cells after lunch. This study adds some mechanistic explanations to the preceding one that breakfast skipping, due to prolonged fasting, induces metabolic inflexibility that may in the long term lead to low-grade inflammation and impaired glucose homeostasis.

An impressive additional finding supporting the importance of the breakfast recently came from a study, showing that breakfast taking/skipping regulates the expression of the clock gene [11]. A genetic study on a large population in UK observed causal links between genetically determined breakfast skipping and higher body mass index, more depressive symptoms, and smoking. Thus, linking clock regulation with food timing and further suggesting a possible beneficial role of regular breakfast intake as part of a healthy lifestyle [12].

The recent literature sparks renewed interest in an older study that had showed that experimentally omitting the breakfast increases the area under the curve of post-

meal insulin response in healthy women, suggesting that insulin sensitivity was decreased [13]. This study showed that omitting breakfast induced insulin resistance, i.e., a very important concept for the diabetologists. Unfortunately, the demonstration of a decrease in insulin sensitivity was weak, because it was based on surrogates (area under the curve (AUC) of postprandial peripheral insulin) rather than a direct measurement. The concern is that AUC is primarily a measurement of insulin secretion rather than insulin sensitivity and may reflect changes in insulin secretion (or insulin clearance). AUC can also mirror changes in insulin sensitivity since insulin release increases when insulin sensitivity decreases [14].

Actually from insulin and glucose data it is possible to perform a more precise measurement of insulin sensitivity with the oral minimal model (OMM) [15,16], which is the application of the well-known technique developed by RN Bergman on the intravenous glucose tolerance test [17] to an oral glucose challenge [18]. The minimal model is a model of glucose disposal selected among many others to be the best compromise between accuracy and simplicity. It was not easy to transfer from the intravenous glucose tolerance test in which it was initially developed to the glucose tolerance test but it was successfully done by Caumo and coworkers [18] from the team of C. Cobelli, and later extensively validated.

We thus investigated this issue on a large personal database of breakfast tests, performed for measuring insulin sensitivity in obese or lean subjects, with the OMM model. The study objective was to ascertain whether individuals having reported omitting their breakfast on a regular basis, had lower values of insulin sensitivity, as measured through the OMM.

Materials and Methods

Subjects

We selected on our database of patients explored for weight and/or eating disorders 27 individuals omitting their breakfast (defined based on an alimentary standardized questionnaire) and compared them to 103 matched subjects consuming a hyperglucidic breakfast. The test was called hyperglucidic because it contained 76 g of carbohydrate i.e., almost the same content as the standard OGTT. The rationale for designing such a breakfast test was to propose a physiological alternative

to OGTT avoiding the fall of blood glucose which occurs in more than 20% of subjects when oral glucose is used as the stimulus and that has no clinical relevance. Therefore this test is proposed for detecting both hyperglycemia and hypoglycemia [18-20]. In addition, mathematical analysis using various published models can be applied to this test to calculate insulin sensitivity and insulin secretion [19,20]. Characteristics of subjects are shown on table 1.

Breakfast test

The method of the breakfast test has been previously published [18-20]. Subjects had been asked to fast for 12 h before commencement of the standardized breakfast

that was composed of bread (80 g), butter (10 g), jam (20 g), skimmed concentrated milk (80 ml) (Gloria SA, Paris, France), sugar (10 g), and powder coffee (2.5 g). The breakfast thus comprised 2,070 kilojoules with 9.1% proteins, 27.5% lipids, and 63.4% carbohydrates. The average time for consuming the meal was 6 min. Blood samples were taken twice before the meal and at 15, 30, 60, 90, 120, 150, 180, 210, 240 min following the start of the meal. This test, which has been designed to detect postprandial reactive hypoglycemia [18], elicits the same glycemic response as the conventional OGTT. All samples in this study were analyzed for plasma insulin with the kit Bi Insulin IRMA (Schering CIS bio international, Gif-sur Yvette, France) and for plasma glucose content with an Olympus 2700 automate.

Table 1: Characteristics of subjects.

	Weight (kg)	Height (m)	Body mass index (kg/m ²)
Subjects omitting their breakfast (n=27)	90.11±5.2	1.65±0.02	32.99±1.69
Subjects regularly ingesting a breakfast (n=103)	82.24±2.24	1.64±0.01	30.85±0.75

Mean ± SEM. No significant difference.

Insulin sensitivity was calculated with Caumo's "oral minimal model" [15] which is the application to OGTT or meal tests of the equations previously developed by R.N. Bergman for IVGTT [17]. It is based on the analysis of changes in plasma glucose and insulin concentrations and measured after the standardized breakfast. SI is given by a modified set of equations called "oral minimal model". This model is essentially the same as the model initially developed for IVGTT by Bergman, but the concern with an oral glucose challenge was that glucose does not suddenly fill all its diffusion space like during IVGTT and rather appears gradually. Therefore it was necessary to add to Bergman's equations another term called Ra OGTT added to the first equation and representing glucose coming from the digestive tract.

Parameters quantifying the β -cell response were calculated according to the two most widely accepted models available in the literature [21,22]. Since in the database C peptide data were not available we calculated insulin secretion rates (ISR) with a simplified model based on insulin concentration as previously reported [20].

The most simplistic expression were maximal insulin secretion (pMol/min/m²) i.e., the highest value of Insulin secretion rate (ISR) during the test, and total insulin release over 210 min (pMol/m²) which is calculated as the area under the curve. Another measurement of total insulin

secretion global index of β -cell sensitivity to glucose, Φ (10⁹ min⁻¹), was calculated as follows, according to Breda [21] as the ratio between the AUC of total insulin secretion and the AUC of blood glucose concentration. β -cell sensitivity to glucose which is approximately equivalent to the static sensitivity index Φ_s (10⁹ min⁻¹) measures the effect of glucose on β -cell secretion at steady state. It is calculated as the slope (pMol/min/mmol/m²) of the relationship between ISR and glucose concentration. In a recent study we reported that these two indexes of second phase insulin response (Breda's Φ and Mari's β -cell sensitivity to glucose) are closely related to the magnitude of functional pancreatic islets mass [23]. Two indexes of first phase insulin secretion were measured. The derivative component, also called "rate sensitivity" or k_1 (pMol.m².mmol⁻¹) according to Mari [22] is the dynamic dependence of insulin secretion on the rate of change of glucose concentration. The dynamic sensitivity index Φ_D (10⁹) is a measure of the stimulatory effect of the rate at which glucose increases upon insulin secretion. It is the additional component of ISR induced by a rapid increase of glucose. It is defined as the amount of insulin (per unit of C-peptide distribution volume) released in response to the maximum glucose concentration (G_{max}) achieved during the experiment, normalized by the glucose increase $G_{max} - G_b$. This parameter Φ_D is calculated according to Breda [21]. Basal insulin secretion (pMol/min/m²) was also calculated, and also expressed as an index of basal

β -cell sensitivity Φ_b (10^9 min^{-1}). The potentiation factor ratio was also calculated according to Mari [22] as a time-varying factor, which is set to be a positive function of time and to average one during the experiment, encompassing all factors that may modulate insulin secretion (glucose and non-glucose substrates, gastro intestinal hormones, neuromodulation). It expresses a relative potentiation of insulin secretory response to glucose.

A disposition index expressing the magnitude of insulin secretion parameters as a function of the level of insulin sensitivity was calculated in analogy with Bergman et al. [14,17]. Since insulin release is physiologically increased when insulin sensitivity decreases the disposition index is a more precise assessment of insulin secretion. Actually, three different disposition indexes can be calculated after mixed-meal ingestion, by multiplying k_1 , β -cell sensitivity to glucose, and total insulin secretion Φ by SI.

Results

Overall comparisons between the 27 subjects omitting their breakfast versus the 103 matched subjects who do not omit it did not exhibit any significant difference in glucose homeostasis parameters. Figure 1 shows blood glucose response to the test. It shows that there was no significant difference in glucose response to the breakfast between the two groups. Figure 2 shows that there was no significant difference in insulin concentrations after the standardized breakfast between the two groups. Figure 3 shows that there was no significant difference in insulin secretion rate predicted by the insulin model [20] in response to the breakfast test between the two groups. Figure 4 shows that there is no significant difference in insulin secretion model parameters between subjects omitting vs. not omitting their breakfast on the whole sample. Figure 5 shows the disposition index, i.e., the homeostasis loop between insulin sensitivity and insulin release (maximal insulin secretion rate predicted with the insulin model) in subjects omitting vs. not omitting their breakfast on the whole sample. Here again, no significant difference can be detected.

Actually things became different if we focus on the subgroup of obese subjects. When splitting the whole sample in categories of BMI the expected difference appears in the range 30-40 kg/m^2 . Since the subgroups $\text{BMI}<30$ and $\text{BMI}>40$ are too small for analysis we focused on this range 30-40. Subjects omitting their breakfast ($n=9$, $\text{BMI}: 35.4 \pm 0.99 \text{ kg/m}^2$) appear to be matched with subjects non-omitting their breakfast ($n=47$; $\text{BMI}: 34.1 \pm 0.37 \text{ kg/m}^2$). Figure 6 shows the comparison of blood glucose and insulin responses in subjects whose

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BMI ranges between 30 and 40 and who omit vs. do not omit their breakfast. It can be seen that omitting the breakfast is associated with a significantly higher insulin response ($p<0.001$) which is significant at 60 and 150 min ($p<0.02$) and a lower post load blood glucose value. Figure 7 shows the comparison of insulin secretion rate over time reconstructed with the model in the two groups and a difference appeared between subjects who omit their breakfast and the others. Insulin secretion rate is slightly higher in subjects omitting their breakfast. Figure 8 shows the comparison of insulin sensitivity and insulin secretory response. Omitting breakfast is associated with a significantly lower insulin sensitivity (4.32 ± 0.94 vs. 9.33 ± 1.84 ; $p = 0.03$). Parameters of insulin response presented on this figure exhibit a nonsignificant tendency to be higher in the group of subjects who omit the breakfast. On figure 8, more sophisticated parameters, provided by Breda and Cobelli's model are shown. As indicated above in the section 'materials and methods', these parameters provide a description of insulin secretion in terms of, overall insulin secretion (F_{oral}), basal insulin secretion (F_{basal}), first phase ("dynamic") response (F_{D}), and second phase ("static") response (F_{S}). On figure 8 it can be seen that there was a significantly higher value of basal insulin secretion (F_{basal}), and a significantly higher value of overall insulin secretion (F_{oral}) in subjects who omit their breakfast compared to those who take it. By contrast, the first phase response (F_{D}) was not significantly different between the two groups. Figure 9 shows the comparison of the homeostasis loop between insulin sensitivity and insulin release (maximal insulin secretion rate predicted with the insulin model). In the two groups the classical hyperbolic shape was evidenced, indicating the homeostasis loop is still functional. However, as shown on figure 10, omitting breakfast is associated with a significantly lower disposition index ($p<0.001$), i.e., a disturbance of this homeostasis loop resulting in a defect in glucose tolerance. In addition, the index of potentiation provided by Mari's model (which expresses the ability to increase the level of insulin response of the beta-cell when the stimulus glucose persists) is also lower ($p<0.001$) in subjects omitting their breakfast. This finding means that insulin response to glucose is not amplified enough when the stimulus glucose remains high, compared to subjects who regularly eat a breakfast.

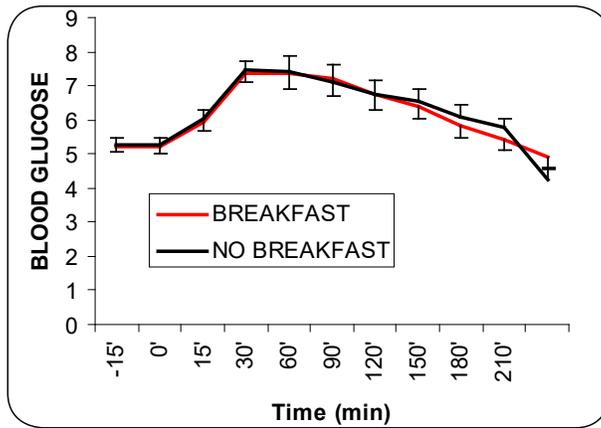


Figure 1: Comparison of blood glucose response to the breakfast test in subjects omitting vs. not omitting their breakfast on the whole sample. No significant difference.

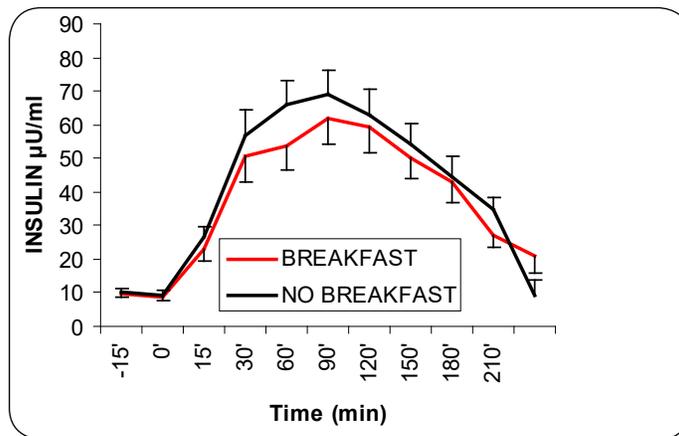


Figure 2: Comparison of insulin response to the breakfast test in subjects omitting vs. not omitting their breakfast on the whole sample. No significant difference. Figure 4: Comparison of insulin secretion model parameters in subjects omitting vs. not omitting their breakfast on the whole sample. No significant difference.

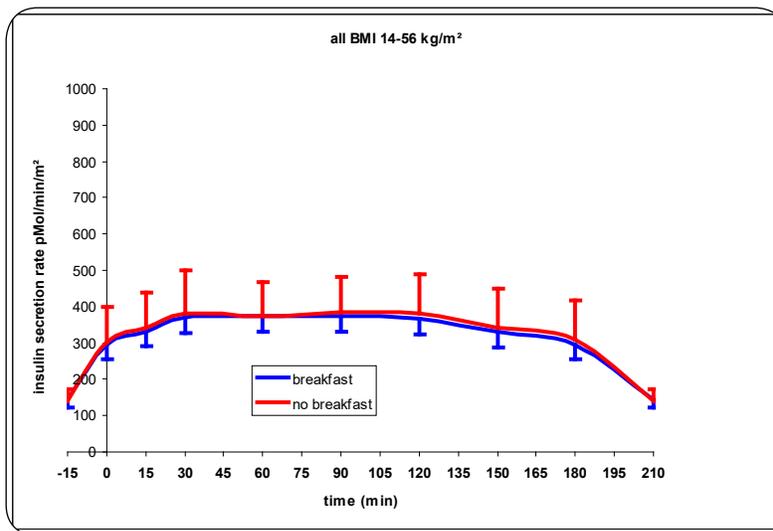


Figure 3: Comparison of insulin secretion rate predicted by the insulin model [20] in response to the breakfast test in subjects omitting vs. not omitting their breakfast on the whole sample. No significant difference.

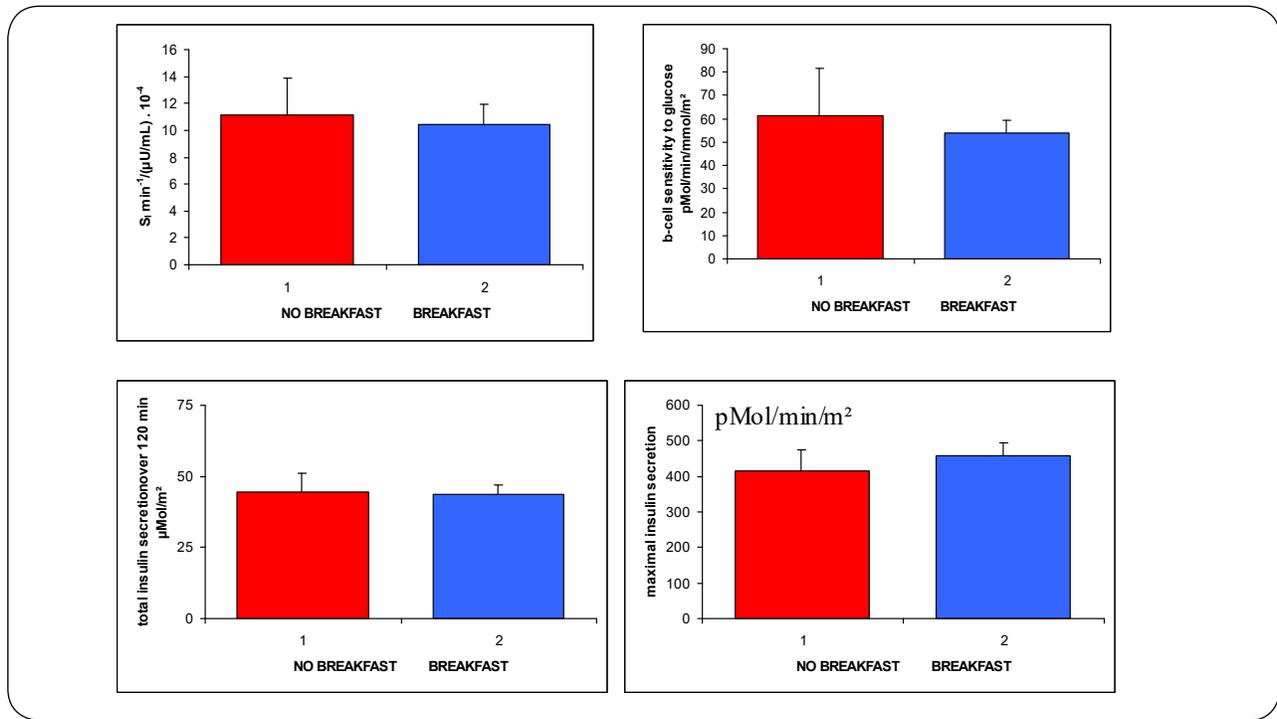


Figure 4: Comparison of insulin secretion model parameters in subjects omitting vs. not omitting their breakfast on the whole sample. No significant difference.

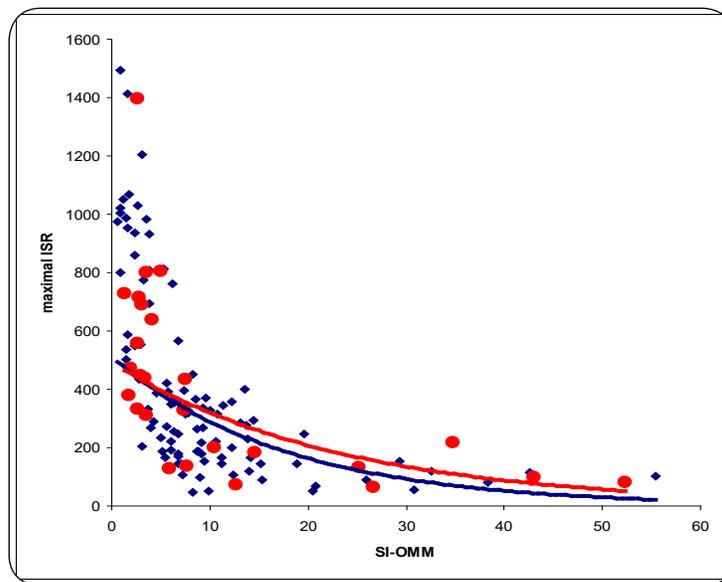


Figure 5: Comparison of the homeostasis loop between insulin sensitivity and insulin release (maximal insulin secretion rate predicted with the insulin model) in subjects omitting vs. not omitting their breakfast on the whole sample. No significant difference.

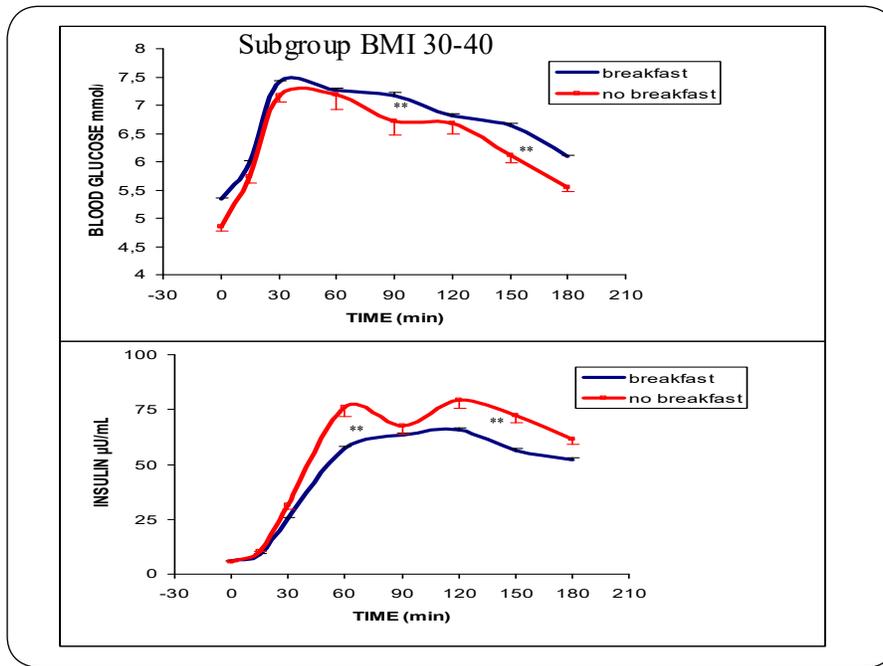


Figure 6: Comparison of blood glucose and insulin response in subjects whose BMI ranges between 30 and 40 and who omit vs. do not omit their breakfast. Omitting breakfast is associated with a significantly higher insulin response. Overall time effect $p < 0.001$, group effect $p < 0.001$, individual comparisons $** p < 0.02$.

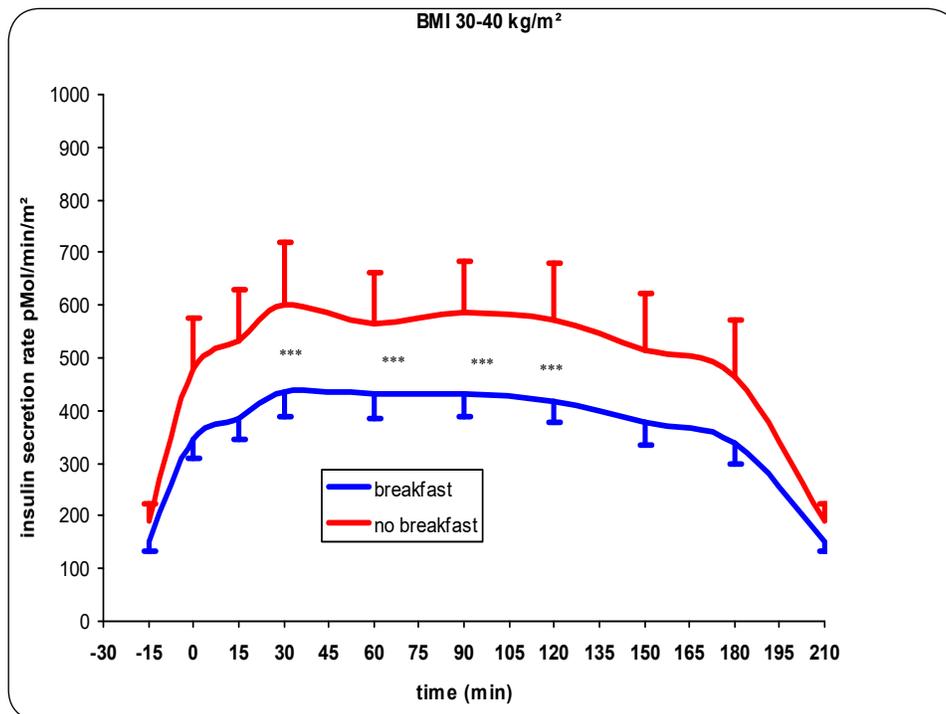


Figure 7: Comparison of insulin secretory rate after the standardized breakfast in subjects whose BMI ranges between 30 and 40 and who omit vs. do not omit their breakfast. Omitting breakfast is associated with a significantly higher insulin response. Overall time effect $p < 0.001$, group effect $p < 0.001$, individual comparisons $*** p < 0.01$.

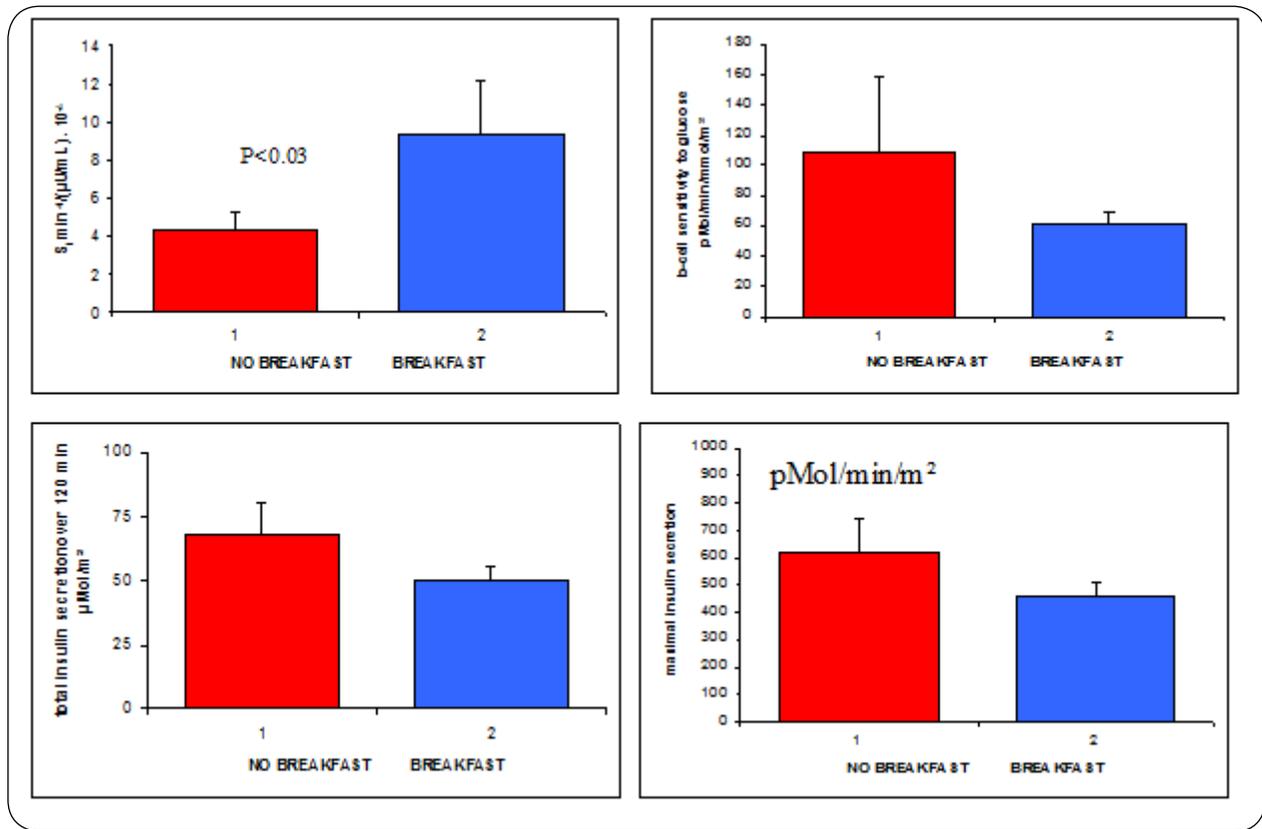


Figure 8: Comparison of insulin sensitivity and insulin secretory response in subjects whose BMI ranges between 30 and 40 and who omit vs. do not omit their breakfast. Omitting breakfast is associated with significantly lower insulin sensitivity. Parameters of insulin response presented on this figure exhibit a nonsignificant tendency to increase.

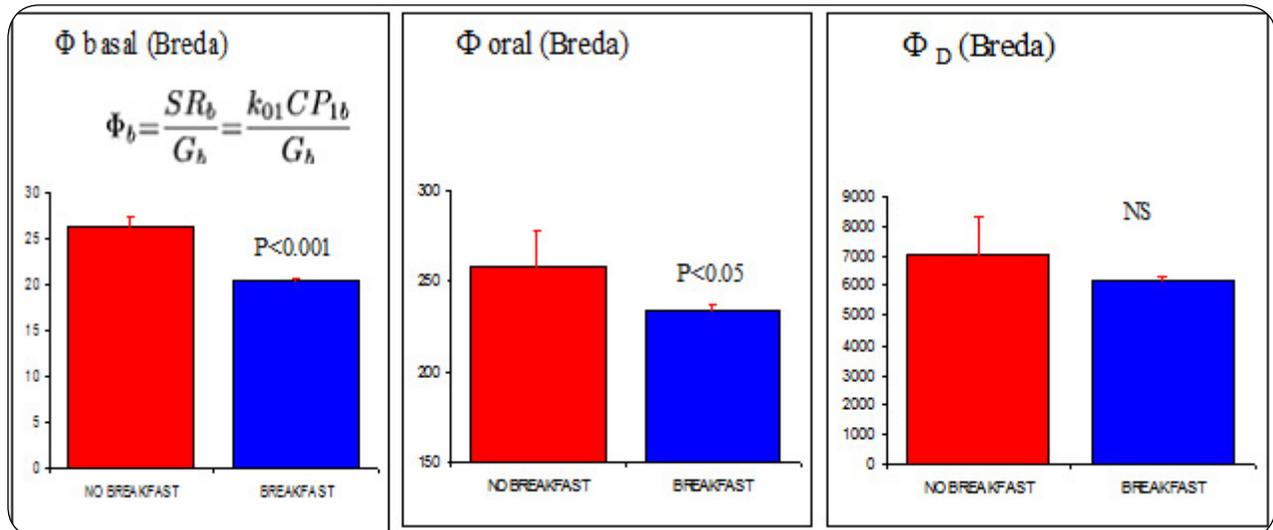


Figure 9: Comparison of insulin sensitivity and insulin secretory response in subjects whose BMI ranges between 30 and 40 and who omit vs. do not omit their breakfast. Omitting breakfast is associated with significantly higher values of basal insulin secretion (F_{basal}), and overall insulin secretion (F_{oral}) while the first phase response (F_D) is not significantly different.

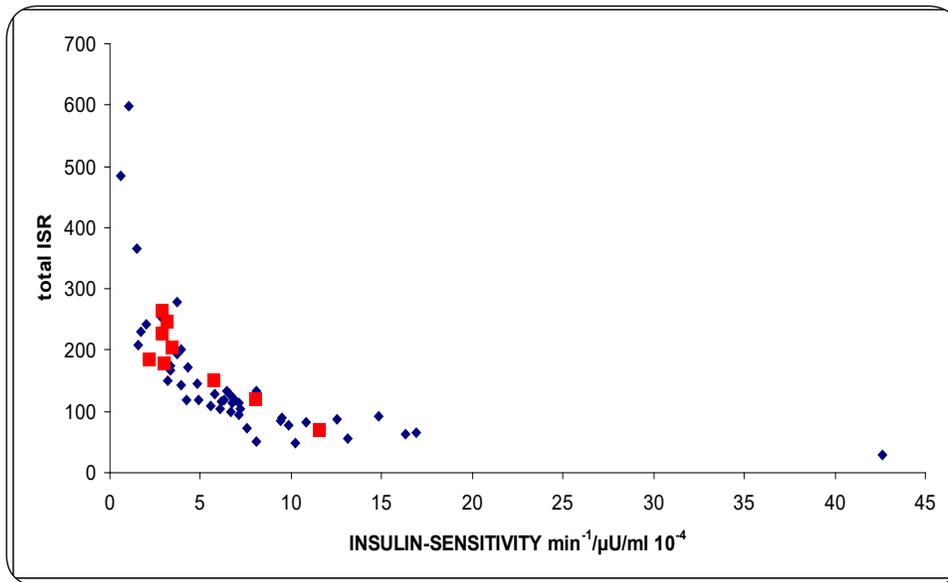


Figure 10: comparison of the homeostasis loop between insulin sensitivity and insulin release (maximal insulin secretion rate predicted with the insulin model) in subjects whose BMI ranges between 30 and 40 and who omit vs. do not omit their breakfast. This picture shows that the homeostasis loop is not completely broken.

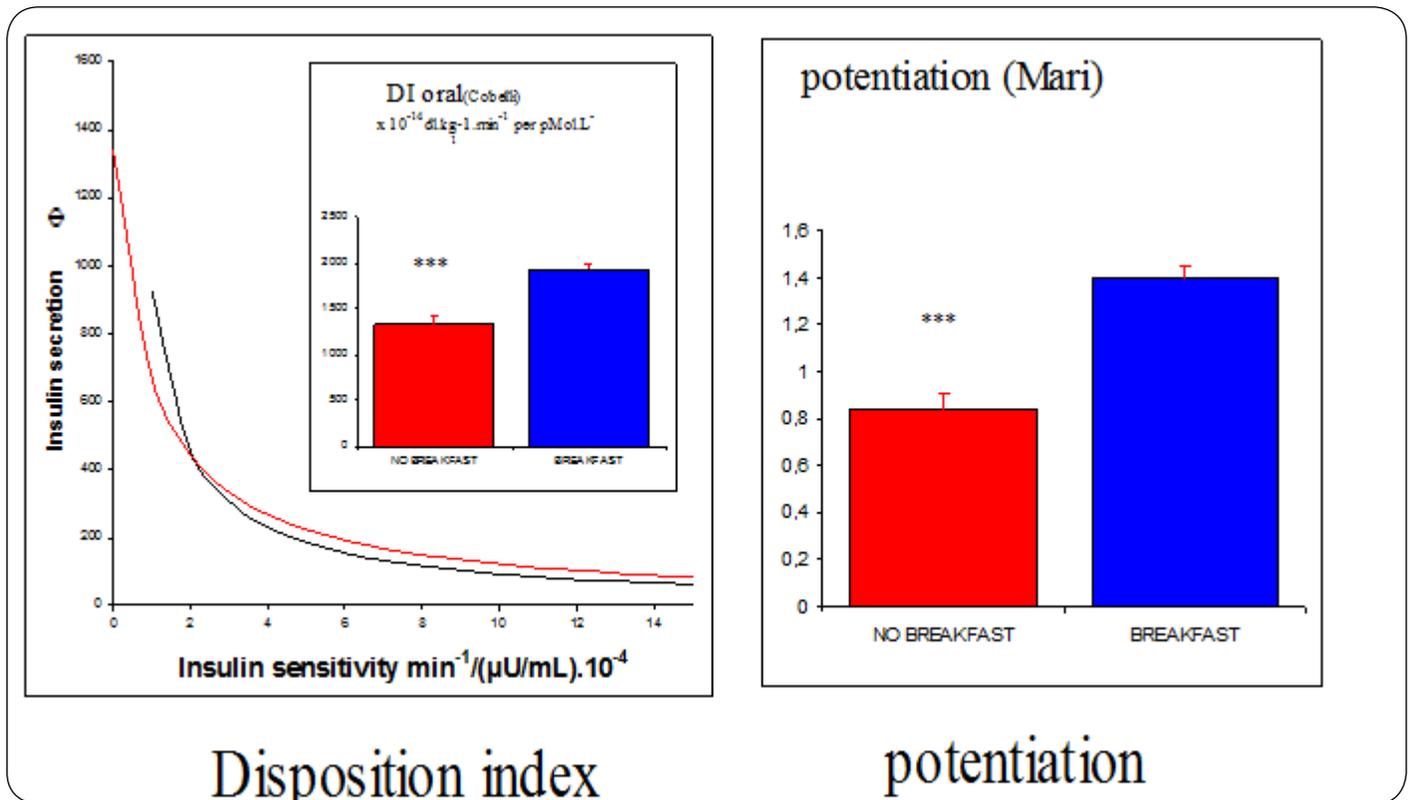


Figure 11: comparison of two model-derived parameters of insulin secretory response in subjects whose BMI ranges between 30 and 40 and who omit vs. do not omit their breakfast. Omitting breakfast is associated with a significantly lower disposition index ($p < 0.001$) and potentiation ($p < 0.001$).

Discussion

The lowering down of insulin sensitivity on breakfast omission was distinctly manifested amongst mild to moderately obese subjects in this sample (but not in

those with a BMI below 30). This impairment in insulin sensitivity resulted in a 34% decreased glucose tolerance.

This finding, based on a cross-sectional study but using a sophisticated measurement, is in agreement

with the previous report that omission of the breakfast may induce a resistance to insulin [1]. It suggests that the impairment in insulin sensitivity experimentally found in an interventional study in healthy women becomes important enough in obese subjects to be detected in a cross-sectional study, and that this effect actually associates a decrease in SI and an incomplete adaptation of insulin release to this reduction in SI, resulting in turn in a decrease in glucose tolerance.

This study has limitations and strengths. Obviously its cross-sectional retrospective design (analysis of a database) is a limitation. By contrast this represents a situation of 'true life' and one can think that a difference which is evidenced in such a cross-sectional study is probably relevant to everyday life. In addition, the study has some strengths, based on the use of a physiological stimulus (standard breakfast [19]) and of highly sophisticated models for the analysis of insulin sensitivity [15,16] and insulin release [21,22]. We recently reported an impressive evidence of the relevance of these models in islet-transplanted diabetic patients with diabetes, in whom we found a fair correlation between the two indices of phase 2 insulin release and the mass of functional pancreatic islets that had been injected [23]. Obviously these models are far more powerful than the more popular surrogates like the insulinogenic index or the homeostasis model assessment [24-26].

Actually in this study we employed a previously published procedure for the calculation of insulin secretion parameters that can be used without C-peptide data. This simplified assessment of insulin secretion provides a fair evaluation of phase 2 insulin secretion parameters and has been shown to be well correlated with functional beta-cell mass [20]. A limitation of this simplified approach is that it is less precise for evaluating phase 1 insulin release. Thus, conclusions on phase 1 in this study should be considered with some caution, and a lack of significant modification of phase 1 in subjects omitting their breakfast may be due to limits of this method.

Therefore, this study shows that obese subjects who chronically skip their breakfast have a lower value of insulin sensitivity which is not completely corrected by a homeostatic amplification of insulin response. All this results in a decrease in the disposition index which is a measurement of glucose tolerance [14]. In addition, the potentiation index provide by Mari's model [22] is decreased in subjects who chronically skip their breakfast.

This potentiation index has recently been interpreted as reflecting two simultaneous mechanisms: glucose-induced potentiation, and incretin-induced potentiation [27]. In the conditions of the current study it is not possible to delineate the incretin effect and the glucose effect, but Tura's paper [27] shows that this incretin effect explains most of the overall potentiation while the glucose effect is more moderate. In addition it is known that lipid infusion, which induces insulin resistance, also decreases incretin-induced potentiation [28]. Since the deleterious effect of breakfast skipping has been shown to result from a prolonged fasting-induced elevation of FFA [10] one can hypothesize that this rise in FFA impairs the incretin-induced potentiation, and that the decrease in the overall potentiation is, to a large extent, due to this effect. This explanation remains speculative since FFA was not measured in this study. Actually on the basis of the data measured in this study we cannot provide a pathophysiological explanation, even if the mathematical analysis focuses on potentiation which is known to be related to incretins and FFA.

Therefore, our findings in obese subjects with BMI ranging between 30 and 40 kg/m² showed that prolonged fasting due to breakfast skipping reduced both, the insulin sensitivity and incretin-induced potentiation of insulin secretion. This resulted in a progressive decline in glucose tolerance that was already obvious in this series of individuals with apparently normal glucose tolerance.

The fact that in this study we were unable to get the breakfast omission effect in non-obese subjects can indicate that this effect is less pronounced in this population. This effect can only be detected in an interventional study, which is in essence more sensitive than a cross-sectional one. One can speculate that a moderate effect as evidenced in Farschi's study [13] was not detectable with a cross-sectional design. This could represent the first step of a progressive impairment in glucose tolerance that will further become obvious in obese subjects. The recent report of a strong link between obesity and timing of food intake [29] is in accordance with this assumption.

Alternatively the fact that we were unable to detect the impairment in insulin sensitivity in subjects with a BMI < 30 kg/m² may indicate that a part of the population is protected against the deleterious effect of omitting the breakfast. They remain lean and with a normal glucose tolerance.

On the whole, this study is the first devoted to this issue and having employed the oral minimal model. It provides an additional evidence of the already reported link between the chronic omission of the breakfast and insulin sensitivity. We also report for the first time that this chronic omission of the breakfast is associated with an impairment in potentiation, which is likely to result from a blunted incretin effect. These two consequences of a lack of breakfast can be assumed to lead to chronic deterioration of glucose tolerance and ultimately, the development of obesity and metabolic syndrome.

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