CLINICAL STUDY

Insulin sensitivity in women: a comparison among values derived from intravenous glucose tolerance tests with different sampling frequency, oral glucose tolerance test or fasting

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Abstract

Objective: To determine the correlation between insulin sensitivity (SI) obtained by the minimal model method applied to a frequently sampled (n = 33) intravenous glucose tolerance test (FSIGT33), and values obtained by reduced FSIGTs, oral glucose tolerance test (OGTT), or fasting.

Methods: A total of 78 FSIGT33, and 59 OGTT were performed in non-diabetic women of which 10 were young cyclic females in the early follicular menstrual phase, 10 were young non-obese subjects with polycystic ovary syndrome (PCOS) and 30 were in post-menopause. Some of these individuals were investigated both prior to and during specified treatments. FSIGT33 was transformed into FSIGT22 and FSIGT12 by removing samples from the analysis. Values of SI derived from reduced FSIGTs or calculations performed on glucose and insulin values observed in fasting conditions and/or during OGTT were related to those of FSIGT33.

Results: SI values derived from FSIGT33 were highly correlated with those derived from FSIGT22 (r = 0.965) or FSIGT12 (r = 0.955), but were only weakly correlated with those derived from fasting or OGTT calculations (r below 0.5). Between-group (PCOS vs normal) or within-group (prior to and during treatment) comparisons showed that reduced FSIGTs were only slightly less powerful than FSIGT33 in detecting differences in SI.

Conclusions: In non-diabetic women, reduced FSIGTs but not calculations based on fasting or OGTT values may be used in place of FSIGT33 to document SI and its variation.

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Introduction

Determination of insulin resistance is becoming critical in clinical practice. Insulin resistance represents a pathogenic mechanism for the polycystic ovary syndrome (PCOS) (1), and an important risk factor for cardiovascular diseases (2, 3). In 1997, the Consensus Development Conference on Insulin Resistance of the American Diabetes Association (4) established that only two methods can accurately estimate peripheral resistance to insulin, i.e. the euglycemic insulin clamp and the minimal model method applied to a frequently sampled intravenous glucose tolerance test (FSIGT). Both methods are cumbersome and not applicable either to large clinical trials or to the daily clinical investigation. Accordingly, several authors have proposed analyses of insulin sensitivity (SI) based on reduced FSIGT procedures (5–7), or on mathematical calculations applied to fasting glucose and insulin values including the fasting glucose/insulin ratio (8–10), the fasting insulin resistance index (FIRI) (11–13), the homeostasis model assessment of insulin resistance (HOMA-IR) (14–16), the sensitivity index (Sib) (17) and the quantitative insulin sensitivity check index (QUICKI) (18). Other indices based on oral glucose tolerance test (OGTT) values have also been proposed, i.e. the sensitivity index at 2 h of OGTT (Si2h) (17), the Sim (Sib+Si2h/2) (17), the ratio of the areas under the curves of glucose/insulin during the OGTT (19), or the product of the two areas (19). Furthermore, Cederholm and Wibell (20), Belfiore et al. (21) and Matsuda and DeFronzo (22) have recently proposed more complex calculations on fasting and OGTT-derived insulin and glucose values. The aim of the present study was twofold: (i) to evaluate the relationship among values of SI obtained with the original FSIGT procedure, modified with the i.v. administration of insulin (23, 24) and those obtained either with...
reduced FSIGTs or with calculations performed on fasting and/or OGTT values; (ii) in the case of strict relationship, to compare both in cross-sectional and longitudinal studies the capability of the alternative method vs the original FSIGT in detecting differences in $S_I$.

**Materials and methods**

**Subjects**

Seventy-eight FSIGTs were performed in 50 non-diabetic women aged between 17 and 63 years (mean age $43.9\pm 2.7$ years), with a body mass index (BMI) between 20 and 29 ($23.3\pm 0.7$) (Table 1). Most of these FSIGTs were performed during specific protocols and part of these results have already been published ($25$, $26$). In 59 cases, an analogue of gonadotropin-releasing hormone (GnRH) analogs (3.6 mg Zoladex; Zeneca, Milan, Italy) was administered for 3 months to women in post-menopause (Organon Italia, SpA, Rome, Italy; 2.5 mg/day; n$^\hat{8}$). FSIGTs were repeated twice, prior to and during a particular treatment. Gonadotropin-releasing hormone (GnRH) analogs were administered to patients suffering from non insulin-dependent diabetes mellitus (NIDDM) or IDDM, nor was on medications known to influence glucose metabolism. As part of ongoing clinical trials in our laboratory, in most of the subjects FSIGTs were repeated twice, prior to and during a particular treatment. Gonadotropin-releasing hormone (GnRH) analogs (3.6 mg Zoladex; Zeneca, Milan, Italy) were administered for 3 months to young individuals with (n$=8$) and without (n$=7$) PCOS, while tibolone (Organon Italia, SpA, Rome, Italy; 2.5 mg/day; n$=13$) was administered for 3 months to women in post-menopause. Results of these trials and their rationale have already been published ($25$, $26$). In 59 cases, an OGTT had also been performed in the 7 days preceding FSIGT.

**Table 1** Subjects characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>PCOS</th>
<th>Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.5±1.5</td>
<td>22.8±1.3</td>
<td>52.9±0.9*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.1±0.6</td>
<td>20.5±0.8</td>
<td>23.4±0.4*</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>3.9±0.2</td>
<td>3.7±0.1</td>
<td>4.8±0.1*</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>66.7±13.0</td>
<td>108.6±20.1†</td>
<td>62.7±4.4</td>
</tr>
</tbody>
</table>

*P < 0.01 vs. Young and PCOS; †P < 0.01 vs Young and Menopause.

**Methods**

**Frequently sampled intravenous glucose tolerance test** Two polyethylene catheters placed in two ante-cubital veins were kept patent by a slow infusion of saline solution. One catheter was used for intravenous glucose or insulin administration and the other for blood collection. Glucose (0.3 g/kg) was injected over 1 min intravenously and was followed 20 min later by an i.v. insulin bolus (0.03 U/kg). As reported by Welch et al. ($24$), arterialized blood was collected at time $-15$, $-10$, $-5$, $-1$, $1$, $2$, $3$, $4$, $5$, $6$, $7$, $8$, $10$, $12$, $14$, $16$, $20$, $22$, $23$, $24$, $25$, $27$, $30$, $40$, $50$, $60$, $70$, $80$, $90$, $100$, $120$, $160$ and $180$ min after glucose load (FSIGT$^{13}$).

**Oral glucose tolerance test** A polyethylene catheter was inserted in an ante-cubital vein, and was kept patent by a slow infusion of saline solution. Samples of arterialized blood, obtained by forearm warming, were collected at $-15$, $0$, $15$, $30$, $60$, $90$, $120$ and $180$ min following an oral glucose load of 75 g over 5 min.

**Processing of samples** Blood samples were collected into heparinized glass tubes, placed on ice, and immediately centrifuged in a refrigerated centrifuge.

Glucose and insulin were measured in all samples. Serum glucose was immediately assayed by an autoanalyzer using the glucose oxidase method. Another aliquot of serum was immediately frozen at $-25$ °C until assayed. Insulin levels were assayed in duplicate by a radioimmunometric method using a commercially available kit (Biodata, Guidonia Montecelio, Rome, Italy) ($25$), with intra- and interassay coefficients of variation of 6.2% and 7% respectively, and a sensitivity of 14.35 pmol/l.

All the results are expressed as the mean±standard error.

**Calculations**

**Comparisons of different FSIGT tests** Glucose and insulin values obtained during the FSIGTs were used to calculate $S_I$, which is inversely related to insulin resistance, and fractional glucose utilization independent on insulin ($S_e$) ($23$, $24$). Analyses were performed by the minimal model method, using a computerized algorithm (MINMOD) ($23$, $24$). $S_I$ was expressed in units×10$^{-4}$/min×mU/ml, and $S_e$ in units×10$^{-4}$/min. Furthermore, $AIRg$ (incremental insulin above baseline at the different time points between 2 and 10 min of FSIGT/number of time points considered), the disposition index ($AIRg/\times S_e$), basal insulin effectiveness (BIE; $S_e$×fasting insulin), and glucose effectiveness at zero insulin (GEZI; $S_e$−BIE) were also calculated ($28$).

The same calculations performed on the FSIGT$^{13}$ were repeated by progressively removing some time points, and thus obtaining the FSIGT$^{22}$ ($-15$, $-10$, $-5$, $-1$, $2$, $3$, $4$, $5$, $6$, $8$, $10$, $14$, $20$, $22$, $25$, $30$, $40$, $50$, $52$, $60$, $70$, $80$, $90$, $100$, $120$, $160$ and $180$ min after glucose load (FSIGT$^{11}$).
70, 100, 160 and 180), and the FSIGT12 (-5, 2, 4, 8, 20, 22, 30, 40, 50, 70, 100 and 180), the latter two were similar to those used by Saad et al. (5). Values of the different indices calculated with FSIGT22 and FSIGT12 were regressed on the corresponding values of FSIGT33 by linear regression analysis.

Furthermore, the capability of FSIGT22 and FSIGT12 to detect differences in S_{i} and S_{G} among different groups of subjects (by Student’s t-test) or in the same group of subjects prior to and during a treatment (by t-test for paired data) was also tested. Analysis of variance (ANOVA) was also used as specified, and when significant was followed by the post-hoc test of Scheffe.

**Comparison of FSIGT with fasting calculations**
Calculations of S_{i} obtained by considering fasting levels of glucose and insulin, as obtained during the FSIGT33 procedure, were regressed on S_{i} values obtained with FSIGT33. The following calculations were tested: fasting glucose/fasting insulin (G/I) (8–10); FIRI: fasting values of glucose×insulin/25 (11–13); HOMA-IR: fasting values of glucose×insulin/22.5 (14–16); Sib: 10^{8}/fasting glucose×fasting insulin×150×kg (17); QUICKI: 1/(log fasting glucose+log fasting insulin) (18).

**Comparison of FSIGT with OGTT-derived calculations**
Calculations of S_{i} obtained by considering calculations on levels of glucose and insulin during OGTT were regressed on S_{i} values obtained with FSIGT33. The following calculations were tested: area under the curve of glucose/area under the curve of insulin during OGTT (G/I OGTT) (8); area under the curve of glucose/area under the curve of insulin during OGTT (G×I OGTT) (19); S_{2h}: 10^{8}/glucose at 2 h of OGTT×insulin at 2 h of OGTT×150×kg (17); Sim: Sib+Si2h/2 (17); Cederholm equation: M/MPG/log MSI; where M is oral glucose load in mg/120 + (0 h – 2 h glucose levels in mmol/l) × 180 × 0.19×body weight/120; MPG is mean glucose at 0 h and 2 h of OGTT and MSI is mean insulin at 0 h and 2 h of OGTT (20, 29); Belfiore equation: 2/mean OGTT glucose×mean OGTT insulin/constant+1 (21); Composite evaluation: 10 000/square root of (mean glucose of OGTT×mean insulin of OGTT)×(fasting glucose×fasting insulin) (22).

**Results**
The clinical data of the three subsets of subjects in which investigations were performed are shown in Table 1.

**FSIGT33 vs FSIGT22 and FSIGT12**
Modeling of the results was not possible with both FSIGT22 and FSIGT12 in 3 out of the 78 investigations (3.8%) in which modeling was possible with FSIGT33. Linear regression analysis furnished a strong relationship between S_{i} obtained from FSIGT33 and that from FSIGT22 \( r_{0}^{0} : 0.965; \ P_{0}^{0} : 0.0001 \)† or FSIGT12 \( r_{0}^{0} : 0.955; \ P_{0}^{0} : 0.0001 \)†. A lower relationship was observed for S_{G} values obtained from FSIGT33 and those from FSIGT22 \( r_{0}^{0} : 0.754; \ P_{0}^{0} : 0.0001 \)† or FSIGT12 \( r_{0}^{0} : 0.726; \ P_{0}^{0} : 0.0001 \)†.

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**Figure 1** Regression analysis between insulin sensitivity (S_{i}; on the left) or glucose utilization independent of insulin (S_{G}; on the right) obtained with FSIGT33 and those obtained with FSIGT22 (top) and FSIGT12 (bottom).
Application to cross-sectional studies Overall $S_I$ and $S_G$ values obtained from FSIGT$_{33}$ were similar to those obtained from FSIGT$_{22}$ or FSIGT$_{12}$ (Fig. 2).

When $S_I$ or $S_G$ values obtained with the three different procedures were compared in the different subgroups of subjects, FSIGT$_{12}$ tended to furnish similar $S_I$ values in young (6.029 ± 2.06 vs 5.27 ± 1.24; -2.3%) and postmenopausal (4.25 ± 0.39 vs 4.16 ± 0.44; -2.6%) women, and higher $S_I$ values in young non-obese women with PCOS (2.9 ± 0.32 vs 3.34 ± 0.43; +13.8%; $P < 0.025$) (Fig. 2). The difference in $S_I$ between young non-obese women with and without PCOS detected with FSIGT$_{33}$ ($P < 0.026$) was reduced but still significant when the same data were analyzed with FSIGT$_{22}$ ($P = 0.039$) and FSIGT$_{12}$ ($P = 0.048$).

$S_G$ obtained with FSIGT$_{12}$ was similar to that obtained with FSIGT$_{33}$ in both young normal (0.26 ± 0.004 vs 0.03 ± 0.003; +7.9%) and postmenopausal (0.031 ± 0.004 vs 0.03 ± 0.003; +9.2%) women, but was significantly higher in women with PCOS (0.026 ± 0.003 vs 0.029 ± 0.004; +32.3%; $P < 0.05$) (Fig. 2).

Application to prospective studies By using FSIGT$_{13}$, we documented, as previously reported (26), that in postmenopausal women ($n = 13$) the administration of tibolone for 2 months enhances $S_I$ (5.34 ± 0.485 vs 8.44 ± 1.4; $P = 0.04$). This conclusion was confirmed also with FSIGT$_{22}$ (5.64 ± 0.45 vs 7.35 ± 0.9; $P = 0.046$) and FSIGT$_{12}$ (5.84 ± 0.6 vs 8.64 ± 1.1; $P = 0.039$). The same was true for non-obese women with PCOS, in which the administration for 3 months of a GnRH analog ($n = 8$) increased $S_I$ as evaluated by FSIGT$_{33}$ (3.1 ± 0.38 vs 4.0 ± 0.20; $P = 0.004$). The statistical significance remained although reduced with FSIGT$_{22}$ (3.46 ± 0.43 vs 4.23 ± 0.17; $P = 0.036$) and FSIGT$_{12}$ (3.57 ± 0.44 vs 4.5 ± 0.16; $P = 0.040$). In young non-PCOS women the administration for 3 months of the GnRH analog did not modify $S_I$ as evaluated by FSIGT$_{33}$ (4.1 ± 0.4 vs 4.6 ± 1.5). Similarly, no difference was observed with FSIGT$_{22}$ (4.2 ± 0.5 vs 4.5 ± 1.1) or FSIGT$_{12}$ (4.2 ± 0.5 vs 5.0 ± 1.3).

Comparison of FSIGT with fasting calculations

$S_I$ values obtained with FSIGT$_{33}$ were weakly related to $S_I$ values obtained by fasting values of glucose or insulin and the derived calculations. Among all, the best correlation was found with Sib. However, the coefficient of correlation between Sib and $S_I$ derived from FSIGT$_{33}$ was only 0.324 (Table 2).
Table 3 Coefficients of Correlation among Insulin Sensitivity Derived from FSIGT33 (F33) and Insulin Sensitivity Derived from Calculations Performed on Glucose and Insulin Values Observed During OGTT (n = 59).

<table>
<thead>
<tr>
<th></th>
<th>F33</th>
<th>G/I OGTT</th>
<th>G×1 OGTT</th>
<th>Si2h</th>
<th>Sim</th>
<th>Cederholm</th>
<th>Belfiore</th>
<th>Composite</th>
</tr>
</thead>
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<tr>
<td>F33</td>
<td>1</td>
<td>0.199</td>
<td>0.194</td>
<td>0.079</td>
<td>0.449</td>
<td>0.411</td>
<td>0.208</td>
<td>0.192</td>
</tr>
<tr>
<td>G/I OGTT</td>
<td>1</td>
<td>0.155</td>
<td>0.434</td>
<td>0.500</td>
<td>0.261</td>
<td>0.743</td>
<td>0.292</td>
<td></td>
</tr>
<tr>
<td>G×1 OGTT</td>
<td>1</td>
<td>0.311</td>
<td>0.652</td>
<td>0.317</td>
<td>0.698</td>
<td>0.0168</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Si2h</td>
<td>1</td>
<td>0.169</td>
<td>0.612</td>
<td>0.619</td>
<td>0.941</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sim</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cederholm</td>
<td>1</td>
<td>0.639</td>
<td>0.682</td>
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<tr>
<td>Belfiore</td>
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</table>

Comparison of FSIGT with OGTT-Derived Calculations

Among the indices derived from OGTT calculations, two were more related than others to SI derived from FSIGT33; i.e., Sim and the SI from the Cederholm calculation. Values of SI derived from the Belfiore calculation or the Composite evaluation were only weakly related to SI values derived from FSIGT33 (Table 3).

Comparisons of FSIGT with Fasting or OGTT-Derived Calculations in More Insulin Resistant Subjects

Correlations of SI derived from FSIGT33 with those derived from FSIGT22 or FSIGT12 were virtually unchanged in individuals whose SI was below 4 (n = 42). On the other hand, a better but still low correlation was observed with SI derived from HOMA/FIRI (r = 0.363), Sib (r = 0.367) or QUICKI (r = 0.34). In this subset of more insulin resistant individuals, SI derived from FSIGT33 was also better correlated with calculations performed on OGTT as G/I OGTT (r = 0.41), Si2h (r = 0.25), Sim (r = 0.59), the Cederholm’s index (r = 0.59), the Belfiore’s index (r = 0.43), or the Composite evaluation (r = 0.25). Also, in this subset Sim and the Cederholm’s calculations were the two which were more closely related to values of SI derived from FSIGT33.

Discussion

In this study, we considered SI obtained by the minimal model method associated with FSIGT33 as the reference value towards which to compare SI obtained by other methods or calculations. All the methods used to evaluate SI are based on assumptions that may reduce their accuracy. Some clinicians consider that the ‘gold standard’ to evaluate SI is the clamp. This method is highly reproducible and capable of furnishing accurate data on glucose metabolism by the liver when associated with isotopes. On the other hand, it is very cumbersome, and requires multiple investigations at different insulin levels in order to assess the full spectrum of SI (4). In spite of its reputation, the clamp does not distinguish between insulin-dependent and -independent glucose utilization, and investigates the effect of insulin in a steady state, which is reached very slowly. This is different from the physiological dynamic of insulin which is secreted in acute bursts, followed by quick declines dependent upon insulin clearance. How well the steady state insulin predicts the effect of insulin in a dynamic situation is presently unknown. The minimal model method evaluates the effect of insulin in a dynamic situation. It is easier to perform and, in contrast to the clamp, allows the separate determination of insulin-dependent and insulin-independent glucose utilization (30). The drawbacks of this method are that it does not distinguish between hepatic and peripheral glucose utilization, and that it is based on the assumption that liver extraction of insulin is constant throughout the test. Furthermore, it has been suggested that physiological oversimplification by the model leads to errors in estimation of SG (31, 32), although very likely not of SI (33, 34). In spite of the differences between the minimal model method and the clamp, values of SI obtained by the two methods are strongly related (correlation coefficient of r = 0.89) (23), and are likely predictive of true SI (4).

In order to reduce complexity (blood sampling at 1-min intervals) and costs, minimal modeling of intravenous glucose tolerance tests with less frequent sampling have been proposed and used (5–7, 30, 32, 35). In terms of SI, reduction in sampling frequency has already proved satisfactory for the original and the tolbutamide-modified FSIGTs (36, 37). Herein, we show that the same is true for the insulin-modified FSIGT. SI values derived from insulin-modified reduced FSIGTs are not only related among each other, as previously reported (5), but are also strongly related to FSIGT33. The strict correlation is reflected in the capability of reduced FSIGTs to document SI differences in cross-sectional and prospective clinical trials. Indeed, in both between and within groups’ comparisons, reduced FSIGTs were only slightly less powerful than FSIGT33 in detecting SI differences. Accordingly, it can be suggested that reduced FSIGTs, in particular FSIGT12, may replace FSIGT33 in most clinical settings. FSIGT12 is easier to perform because it eliminates samplings at 1-min intervals, requires fewer tubes to handle, and its cost is almost one third that of FSIGT33.
It still requires a time expenditure of 3 h, but this represents the same time required for an OGTT with only 5 more blood samples.

In clinical practice, evaluation of $S_I$ obtained by fasting samples would be preferable. Unfortunately, the present data show that all the indices calculated on fasting values correlate poorly with $S_I$ values obtained by FSIGT$_{33}$. The best correlation with FSIGT$_{33}$ was obtained by Sib, but the correlation coefficient of 0.325 seems too weak to suggest Sib as a valid alternative to FSIGT$_{33}$.

Oral glucose tolerance test is commonly used to evaluate glucose tolerance, and the possibility to obtain a contemporaneous estimate of $S_I$ is appealing. In the present study, $S_I$ estimations derived from mathematical calculations applied to values of OGTT were poorly correlated with those obtained from FSIGT$_{33}$, $S_I$ values derived from Sim (17) or Cederholm (20, 29) calculations were the most related, but the correlation coefficients remained below 0.5 for both of them.

In comparison to the correlation performed among different FSIGTs and fasting, the correlations performed among FSIGT$_{33}$ and OGTT-derived $S_I$ values were performed in a smaller but still significant number of tests ($n = 59$), sufficient to document clear correlations among different $S_I$ values in previously published studies (5, 6, 10–12, 14, 17, 23, 24). In addition, because they necessarily include between-tests and between-days variations, a lower correlation has to be expected. Nevertheless, the very low coefficients of correlation detected may have several additional explanations. All $S_I$ indices derived from OGTT are based on assumptions that although correct bring a mathematical approximation capable of substantially influencing $S_I$ results. Among these assumptions are that in the post-absorptive state, glucose uptake occurs only in insulin-dependent tissues (22), that endogenous glucose production is equal to hepatic glucose production (22), and that hepatic insulin sensitivity is equivalent to peripheral tissue insulin sensitivity (14–16). Most importantly, the route of glucose administration is likely to play a major role. In contrast to the intravenous, the oral administration of glucose activates gastrointestinal factors that may induce marked modifications in insulin secretion and peripheral glucose utilisation (25, 27, 38). Accordingly, OGTT-derived $S_I$ values are frequently not interchangeable with those obtained by intravenous glucose administration, and unfortunately cannot be used in their place to document $S_I$. Reported correlation among $S_I$ values from OGTT or fasting and the clamp are not confirmed by the present data with the minimal model method. Unless it is ascertained that the minimal model method estimation of $S_I$ is completely wrong, we feel that present results do not substantiate the clinical use of OGTT or fasting calculations to assess $S_I$.

In the subset of more insulin resistant individuals, a greater correlation ($r = 0.59$) was observed between values of $S_I$ derived from FSIGT$_{33}$ and those derived from OGTT, particularly for Sim and the Cederholm’s calculation. An alternative index should be related to the method of reference across a wide range of $S_I$ values. However, it is possible that in states of severe insulin resistance a better correlation can be defined between $S_I$ derived from calculations on fasting or OGTT values and those derived from the minimal model method. Indeed, diabetic and frankly obese women were not included in the present study, and our results cannot be applied to this subset of individuals.

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