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# Elevated 1-Hour Postload Plasma Glucose Levels Identify Subjects With Normal Glucose Tolerance but Impaired β-Cell Function, Insulin Resistance, and Worse Cardiovascular Risk Profile: The GENFIEV Study

Cristina Bianchi, Roberto Miccoli, Maddalena Trombetta, Francesco Giorgino, Simona Frontoni, Emanuela Faloia, Giulio Marchesini, Maria A. Dolci, Franco Cavalot, Gisella Cavallo, Frida Leonetti, Riccardo C. Bonadonna, and Stefano Del Prato, on behalf of the GENFIEV Investigators*†

**Context:** In subjects with normal glucose tolerance (NGT) 1-hour postload plasma glucose (1-h oral glucose tolerance test [OGTT]) of >155 mg/dL predicts type 2 diabetes (T2DM) and is associated with subclinical atherosclerosis.

**Objective:** The purpose of this study was to evaluate β-cell function, insulin resistance, and cardiovascular risk profile in subjects with NGT with a 1-h OGTT glucose of >155 mg/dL.

**Patients and Methods:** The GENFIEV (Genetics, PHYsiopathology, and Evolution of Type 2 diabetes) study is a multicenter study recruiting individuals at high risk of T2DM. A total of 926 subjects underwent a 75-g OGTT for assessment of plasma glucose and C-peptide for mathematical modeling of β-cell function (derivative and proportional control). Fasting insulin, lipid profile, and clinical parameters were determined as well.

**Results:** A 1-hour OGTT glucose of >155 mg/dL was found in 39% of subjects with NGT, 76% with impaired fasting glucose (IFG), 90% with impaired glucose tolerance (IGT), and 99% and 98% with IFG + IGT or newly diagnosed T2DM, respectively. Among subjects with NGT (n = 474), those with 1-hour OGTT glucose of >155 mg/dL were more insulin-resistant and had worse β-cell function than those with 1-hour OGTT glucose of ≤155 mg/dL. Moreover, glycosylated hemoglobin, blood pressure, low-density lipoprotein cholesterol, and triglycerides were higher in subjects with NGT with 1-hour OGTT glucose of >155 mg/dL, whereas high-density lipoprotein cholesterol was lower compared with that in subjects with NGT with 1-hour OGTT glucose of ≤155 mg/dL. Compared with subjects with IGT, those with NGT with 1-hour OGTT glucose of >155 mg/dL had comparable cardiovascular risk profile and insulin resistance but slightly better β-cell function.

**Conclusions:** Among subjects with NGT, those with 1-hour OGTT glucose of >155 mg/dL showed lower insulin sensitivity, impaired β-cell function, and worse cardiovascular risk profile and therefore are at greater risk of developing T2DM and cardiovascular disease. **(*J Clin Endocrinol Metab* 98: 0000–0000, 2013)**

Reliable models for identification of individuals at high risk of type 2 diabetes (T2DM) are essential to improve strategies for the prevention of the disease. The oral glucose tolerance test (OGTT) is commonly used to identify high-risk individuals (1) who may benefit from lifestyle or pharmacological intervention (2, 3). However, longitudinal studies have shown that 30% to 40% of subjects developing T2DM may not proceed through the intermediate condition of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) (1). More re-

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† Author affiliations are shown at the bottom of the next page

Abbreviations: B-IS, basal insulin secretion rate; BMI, body mass index; BSA, body surface area; $HbA_{1c}$, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; RISC, Relationship between Insulin Sensitivity and Cardiovascular Risk; S-DC, sensitivity derivative control; T2DM, type 2 diabetes.

cently, glycosylated hemoglobin ($HbA_{1c}$) has been proposed as a diagnostic tool for identification of high-risk individuals, although the real predictive power of this parameter is still under scrutiny (4). Data obtained in population studies have suggested that plasma glucose concentration determined 1 hour after the ingestion of a 75-g oral glucose load (1-hour OGTT) can provide a better predictor for development of T2DM than fasting or 2-hour OGTT plasma glucose (5). In particular, 1-hour OGTT plasma glucose levels of >155 mg/dL have been shown to identify subjects with normal glucose tolerance (NGT) with high risk of T2DM (6, 7). In a relatively small sample, they were found to be more insulin-resistant, to have worse β-cell function (8), and to have an atherogenic profile and carotid intima-media thickness similar to those of subjects with IGT (9). In the attempt to gain further information, we have determined, in a larger population of subjects at risk of T2DM, the ability of the proposed diagnostic value of a 1-hour OGTT glucose of >155 mg/dL to identify individuals with impaired glucose regulation (ie, subjects with IFG and/or IGT) and/or newly diagnosed T2DM. In these individuals, we have determined insulin secretion and action as well as cardiovascular risk profile to be compared with individuals with NGT, NGT with 1-hour OGTT glucose of >155 mg/dL, and IGT in an attempt to discern whether and to what extent pathophysiological mechanisms and cardiovascular risk may differ with respect to glucose tolerance criteria.

## Patients and Methods

All subjects participated in the GENFIEV (Genetics, PHYsiopathology, and Evolution of Type 2 diabetes) study, a multicenter nationwide Italian study designed to improve phenotypic and genotypic description of subjects at high risk of T2DM (http://clinicaltrials.gov/ct2/show/NCT00879801?term=GENFIEV&rank=1). To recruit high-risk individuals, nondiabetic subjects deemed at risk of diabetes (known family history, first-degree relatives with T2DM, phenotype, dyslipidemia, prior recognition of impaired fasting plasma glucose, and other risk factors) by primary care physicians and willing to participate were referred to the local diabetes clinic for further evaluation. A total of 929 subjects were recruited through such an opportunistic screening among individuals referred by their primary care physicians to nine diabetes clinics because of risk of T2DM. Local institutional review boards approved the study protocol, and all subjects gave written informed consent before entering the study.

Medical history, physical examination, electrocardiogram recordings, and blood tests were obtained for all subjects before administration of a 75-g OGTT as described previously (10). All OGTTs were performed after an overnight fast with all subjects refraining from smoking for no less than 12 hours before the test. In all subjects, an antecubital vein was cannulated to collect blood samples for determination of plasma glucose, insulin, and C-peptide levels and a lipid profile before ingestion of the 75-g glucose load. Blood sample were then drawn at 15, 30, 60, 90, and 120 minutes for plasma glucose and C-peptide determinations.

All biochemical parameters were determined by standard methods on a Roche Modular Autoanalyzer (Roche, Milan, Italy). Insulin and C-peptide levels were determined centrally by immunoassay (Immulite; DPC, Los Angeles, California). Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Based on the OGTT results, subjects were divided into four categories: NGT, IFG, IGT, and T2DM according to the 1997 American Diabetes Association criteria (11). The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated (fasting insulin [milliunits per liter] × fasting plasma glucose [millimoles per liter)/22.5] as described by Matthews et al (12). The insulinogenic index was calculated as $CP_{30} - CP_0/18 \times (G_{30} - G_0)$, where $CP_0$ and $G_0$ are the fasting plasma levels of plasma C-peptide and glucose, respectively, and $CP_{30}$ and $G_{30}$ are their levels at 30 minutes during an OGTT. β-Cell function was also estimated by minimal model analysis of plasma glucose and C-peptide response to OGTT (13). This analysis allows quantification of the basal (prehepatic) insulin secretion rate (B-IS) and β-cell sensitivity at glucose concentration, ie, both the derivative control (S-DC) ([picomoles per square meter body surface area (BSA)] · [millimoles per liter per minute][1]) and the proportional control of β-cell response to glucose, the latter presented as the stimulus-response curve of insulin secretion rate at graded glucose concentrations ([picomoles per minute per square meter BSA] at 4.0, 5.5, 8.0, and 11.0 mM glucose). Modeling analyses have also been reported in a previous article (14). The disposition index was calculated as the insulinogenic index-to-HOMA-IR ratio.

All statistical analyses were performed using StatView software (SAS Institute, Cary, North Carolina) on a Power Mac G5 computer (Apple, Cupertino, California). Data are expressed as means ± SD. A nonparametric statistic was used to compare categorical variables among groups. ANOVA was used to test mean differences among groups. Values of $P < .05$ were considered statistically significant.

## Results

Based on the OGTT results, 51% of the study population had NGT, 4% had IFG, 24% had IGT, 7% had both IFG

Department of Clinical and Experimental Medicine (C.B., R.M., S.D.P.), Section of Diabetes and Metabolic Diseases, University of Pisa, 56124 Pisa, Italy; Department of Biomedical and Surgical Sciences (M.T., R.C.B.), Section of Endocrinology and Metabolic Diseases, University of Verona, 37134 Verona, Italy; Department of Emergency and Organ Transplantation (F.G.), Section on Internal Medicine, Endocrinology and Metabolic Diseases, University of Bari, 70124 Bari, Italy; Diabetes Center (S.F.), Department of Internal Medicine, University of Rome Tor Vergata, 00133 Rome, Italy; Division of Endocrinology (E.F.), Polytechnic University of Marche, 60121 Ancona, Italy; Clinical Dietetics (G.M.), Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy; Section of Diabetes and Metabolic Diseases (M.A.D.), Ss Giacomo e Cristoforo Hospital, 54100 Massa, Italy; Diabetes Unit (F.C.), Department of Clinical Biological Sciences, University of Turin, 10043 Turin, Italy; Department of Clinic and Medical Therapy (G.C.) and Department of Clinical Sciences (F.L.), University of Rome "La Sapienza," 00161 Rome, Italy

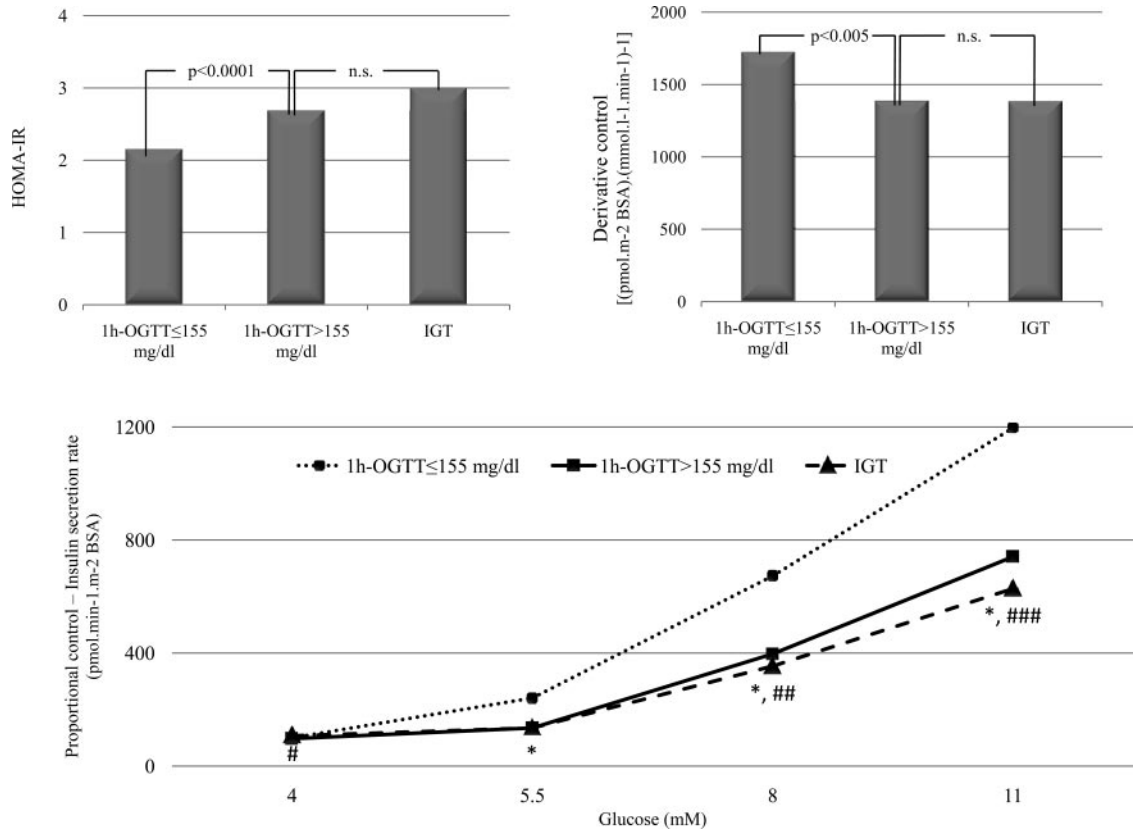


**Figure 1.** Insulin resistance and insulin secretion by minimal model analysis of plasma glucose and C-peptide during an OGTT in subjects with NGT with 1-hour OGTT glucose of >155 mg/dL, subjects with NGT with 1-hour OGTT glucose of ≤ 155 mg/dL, or subjects with IGT. *$P < .0001$, NGT 1-hour OGTT glucose of >155 mg/dL vs NGT 1-hour OGTT glucose of ≤ 155 mg/dL. #$P < .05$, NGT 1-hour OGTT glucose of >155 mg/dL vs IGT; ##$P < .01$, NGT 1-hour OGTT glucose of >155 mg/dL vs IGT; ###$P < .001$, NGT 1-hour OGTT glucose of >155 mg/dL vs IGT.

and IGT, and 14% had newly diagnosed T2DM. A 1-hour OGTT glucose of >155 mg/dL occurred in 39% of those with NGT, 76% of those with IFG, 90% of those with IGT, 99% of those with IFG + IGT, and 98% of those with newly diagnosed T2DM. This 1-hour OGTT cutoff point had high specificity (89%), good sensitivity (69%), and high positive predictive power (92%) for identification of subjects with impaired glucose regulation (IFG and/or IGT) or newly diagnosed T2DM.

Among the 474 subjects with NGT (37% men and 63% women; aged 46 ± 12 years; body mass index [BMI], 28.4 ± 5.3 kg/m$^2$), those with 1-hour OGTT glucose of >155 mg/dL were more insulin-resistant (HOMA-IR, 2.68 ± 1.93 vs 2.14 ± 1.22 mmol/L × μU/mL; $P < .001$) and had worse insulin secretion (insulinogenic index, 0.052 ± 0.030 vs 0.092 ± 0.17; $P < .001$) and β-cell performance (disposition index, 0.026 ± 0.025 vs 0.055 ± 0.097; $P < .0001$) than those with 1-hour OGTT glucose of ≤155 mg/dL. The minimal model analysis confirmed a reduction in first-phase insulin secretion (S-DC, 1381 ± 865 vs 1721 ± 1384 [pmol · m$^{-2}$ BSA] · [mmol · L$^{-1}$ · min$^{-1}$]$^{-1}$; $P < .005$) and lower β-cell sensitivity in subjects with NGT with 1-hour OGTT glucose of >155 mg/dL than in subjects with NGT with 1-hour OGTT glucose of ≤155 mg/dL (Figure 1 and Table 1). No significant differences were detectable in basal insulin secretion (B-IS, 97 ± 45 vs 91 ± 39 pmol · min$^{-1}$ · m$^{-2}$ BSA; $P > .05$).

$HbA_{1c}$ levels were higher in subjects with NGT with 1-hour OGTT glucose of >155 mg/dL (5.6 ± 0.4 vs 5.4 ± 0.4%; $P < .0001$). These individuals also had a worse cardiovascular risk profile (Table 1) as indicated by higher systolic (128 ± 13 vs 122 ± 14 mm Hg; $P < .0001$) and diastolic (81 ± 10 vs 77 ± 11 mm Hg; $P < .0001$) blood pressure, LDL cholesterol (136 ± 41 vs 127 ± 37 mg/dL; $P < .05$), and triglycerides (136 ± 96 vs 117 ± 75 mg/dL; $P < .05$) and lower high-density lipoprotein (HDL) cholesterol (52 ± 14 vs 56 ± 16 mg/dL; $P < .005$).

Compared with subjects with IGT, those with NGT with 1-hour OGTT glucose of >155 mg/dL had a similar cardiovascular risk profile, a comparable degree of insulin resistance, and slightly better β-cell function, as shown in Table 1.

## Discussion

The results of the present study are in keeping with previous findings and indicate that a plasma glucose concen-

**Table 1.** Cardiovascular Risk Profile, Insulin Resistance, and β-Cell Function in Subjects With NGT with 1-Hour OGTT Glucose of >155 mg/dL or ≤155 mg/dL and in Individuals With IGT

| | NGT 1-H OGTT Glucose of | | |
|---|---|---|---|
| | ≤155 mg/dL (n = 254) | >155 mg/dL (n = 179) | IGT (n = 214) |
| BMI, kg/m$^2$ | 28.1 ± 5.3 | 28.9 ± 5.2 | 29.9 ± 5.2 |
| Waist circumference, cm | 97 ± 13 | 102 ± 14[a] | 102 ± 12 |
| Systolic blood pressure, mm Hg | 122 ± 14 | 128 ± 13[b] | 133 ± 17[e] |
| Diastolic blood pressure, mm Hg | 77 ± 11 | 81 ± 10[b] | 84 ± 12[f] |
| Total cholesterol, mg/dL | 206 ± 41 | 210 ± 41 | 213 ± 40 |
| LDL cholesterol, mg/dL | 127 ± 37 | 136 ± 4[c] | 136 ± 38 |
| HDL cholesterol, mg/dL | 56 ± 16 | 52 ± 14[d] | 51 ± 14 |
| Triglycerides, mg/dL | 117 ± 75 | 136 ± 96[c] | 155 ± 93[f] |
| $HbA_{1c}$, % | 5.3 ± 0.4 | 5.6 ± 0.4 | 5.7 ± 0.4[e] |
| HOMA-IR, mmol/L × μU/mL | 2.1 ± 1.2 | 2.7 ± 1.9[a] | 3.0 ± 1.7 |
| Insulinogenic index | 0.092 ± 0.17 | 0.052 ± 0.030[d] | 0.048 ± 0.029 |
| β-Cell performance | 0.055 ± 0.097 | 0.026 ± 0.025[b] | 0.021 ± 0.017[e] |
| B-IS, pmol · min$^{-1}$ · m$^{-2}$ BSA | 91 ± 39 | 97 ± 45 | 106 ± 42[f] |
| S-DC, (pmol · m$^{-2}$ BSA) · (mmol · L$^{-1}$ · min$^{-1}$)$^{-1}$ | 1721 ± 1384 | 1381 ± 866[c] | 1377 ± 999 |

NGT 1-hour OGTT glucose <155 mg/dL vs NGT 1-hour OGTT glucose ≤155 mg/dL: [a] $P < .001$; [b] $P < .0001$; [c] $P < .05$; [d] $P < .01$.
NGT 1-hour OGTT glucose <155 mg/dL vs IGT: [e] $P < .01$; [f] $P < .05$.

tration >155 mg/dL at 1 hour during an OGTT may provide a useful tool to identify subjects with NGT who are at high risk of T2DM. This single time point was, indeed, sufficient to discriminate individuals with otherwise NGT. In our study, we found that subjects NGT with 1-hour OGTT glucose of >155 mg/dL were insulin-resistant and had a reduced first phase of insulin secretion compared with subjects with NGT with 1-hour OGTT glucose ≤155 mg/dL. Of interest, the individuals with NGT with 1-hour OGTT glucose of >155 mg/dL had a degree of insulin sensitivity similar to that of individuals with IGT, although the latter had worse insulin secretion. This observation is in keeping with the concept that progressive β-cell failure, rather than insulin resistance, accounts for the progressive deterioration of glucose homeostasis.

The potential diagnostic role of 1-hour OGTT plasma glucose levels has been confirmed in other studies. For instance, in the Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study, individuals with NGT with 1-hour postload plasma glucose of >161 mg/dL also had lower insulin sensitivity and β-cell function than individuals with NGT with 1-hour postload plasma glucose of ≤161 mg/dL (15). This observation also suggests that further work may be needed to reach a consensus on the optimal cutoff level of the 1-hour plasma glucose levels to be adopted for identification of people at risk. Nonetheless, the 155 mg/dL plasma glucose level originally proposed by Abdul-Ghani et al (6) seems to be a solid one. In another recent study performed in a smaller Italian cohort, Marini et al (8) also found that subjects with NGT with 1-hour OGTT glucose of >155 mg/dL had a impairment in insulin sensitivity similar to that of individuals with IGT. They also reported that subjects with 1-hour OGTT glucose of >155 mg/dL, compared with subjects with NGT with 1-hour OGTT glucose of ≤155 mg/dL had a lower acute insulin response during an intravenous glucose tolerance test, whereas no difference was apparent in insulin secretion assessed by OGTT-derived indexes. Because of this apparent discrepancy, they proposed that these individuals may retain a substantial incretin effect or, alternatively, a lower sensitivity of the β-cell may already be present. Our results, together with those reported in the RISC study (15), seem to support this second hypothesis. Not only did we find a significant reduction in the insulinogenic and disposition indexes but also, even more importantly, the minimal model analysis confirmed impaired β-cell sensitivity to glucose with no differences in basal insulin secretion. These results lend further support to previous observations that impaired β-cell function is an early defect in people at risk of developing T2DM. In both the San Antonio Metabolism (16) and RISC (15) studies, β-cell function was found to be already dramatically impaired in subjects with NGT with the highest 2-hour OGTT glucose values. However, within this population further risk stratification can be obtained on the basis of the 1-hour OGTT cutoff value of 155 mg/dL.

In this study, the percentage of subjects with NGT with a 1-hour OGTT glucose of >155 mg/dL (36%) was more than 2-fold greater than that reported in the San Antonio Heart Study (16.7%) (6) and in the Botnia (15.9%) study (7) and even greater than that found in another Italian survey (28%) (8). This greater prevalence is most likely

due to the recruiting criteria of the study populations. The GENFIEV study is based on opportunistic screening for recruitment of subjects deemed at risk of T2DM by their primary care physician and referred to a diabetes clinic for further assessment. Although this may be seen as a limitation of our study, it points out the potential of applying the 1-hour OGTT criterion in highly selected risk populations to identify those individuals who may be the target for intensive preventative procedures. A simplified challenge test (1-hour vs 2-hour OGTT) after a prescreening, as could be done with a score system (17), may offer better opportunities for implementing large-scale prevention strategies.

The observational nature of this study does not allow conclusions on the predictive value for future T2DM using a 1-hour OGTT, already demonstrated in previous prospective studies (6, 7), but provides some pathophysiological explanation to justify the use of the 1-hour OGTT plasma glucose value as adjunctive or alternative diagnostic criteria. However, whether the difference in $\beta$-cell function may condition the rate of progression to overt diabetes will require ad hoc prospective studies.

The 1-hour OGTT cutoff of 155 mg/dL has also been shown to discriminate subjects with NGT with respect to their cardiovascular risk profile (9). Individuals with 1-hour OGTT glucose of $>$155 mg/dL were found to have a worse cardiovascular risk profile and signs of early carotid atherosclerosis compared with those with 1-hour OGTT glucose of $\leq$155 mg/dL. Of interest, their carotid intima-media thickness and their metabolic and cardiovascular profiles were similar to those of subjects with IGT (9). Our data largely confirm those results, although we found subjects with NGT with 1-hour OGTT glucose of $>$155 mg/dL to have higher blood pressure values and greater BMI. A major limitation of the present study, as well as of other studies (8, 15), is its cross-sectional nature. Because IGT has already been established as a condition requiring particular attention with respect to cardiovascular risk, assessment of the population with NGT by means of the 1-hour OGTT plasma glucose criterion may help in ensuring early and effective cardiovascular protection. Obviously, a final conclusion and recommendation can only be established after prospective analysis that should also be extended to other ethnicities to determine to what extent this criterion can be used. However, it is encouraging that the proposed cutoff value of 1-hour OGTT glucose of $>$155 mg/dL has provided similar results in Caucasian populations: Finnish from Northern Europe (7); Italian from Southern Europe (8); and Mexican-Americans (6).

In conclusion, 1-hour OGTT glucose of $>$155 mg/dL can discriminate subjects with NGT with lower insulin sensitivity, impaired $\beta$-cell function, and a worse cardiovascular risk profile who are therefore at greater risk of developing T2DM and cardiovascular disease.

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Address all correspondence and requests for reprints to: Stefano Del Prato, MD, Department of Clinical and Experimental Medicine, Section of Metabolic Diseases and Diabetes, Nuovo Ospedale Santa Chiara, Via Paradisa, 2, 56124 Pisa, Italy. E-mail: stefano.delprato@med.unipi.it.

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