# Insulin Infusion During Normoglycemia Modulates Insulin Secretion According to Whole-Body Insulin Sensitivity

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**OBJECTIVE**—Glucose is the major stimulus for insulin release. Time course and amount of insulin secreted after glycemic stimulus are different between type 2 diabetes mellitus (T2DM) patients and healthy subjects. In rodents, it was demonstrated that insulin can modulate its own release. Previous studies in humans yielded contrasting results: Insulin was shown to have an enhancing effect, no effect, or a suppressive effect on its own secretion. Thus, we aimed to evaluate short-term effects of human insulin infusion on insulin secretion during normoglycemia in healthy humans and T2DM subjects of both sex.

**RESEARCH DESIGN AND METHODS**—Hyperinsulinemic-isoglycemic clamps with whole-body insulin-sensitivity ($M$) and C-peptide measurements for insulin secretion modeling were performed in 65 insulin-sensitive (IS) subjects (45 ± 1 year, BMI: 24.8 ± 0.5 kg/m$^2$), 17 insulin-resistant (IR) subjects (46 ± 2 years, 28.1 ± 1.3 kg/m$^2$), and 20 T2DM patients (56 ± 2 years, 28.0 ± 0.8 kg/m$^2$; HbA$_{1c}$ = 6.7 ± 0.1%).

**RESULTS**—IS subjects ($M$ = 8.8 ± 0.3 mg · min$^{-1}$ · kg$^{-1}$) had higher ($P < 0.00001$) whole-body insulin sensitivity than IR subjects ($M$ = 4.0 ± 0.2) and T2DM patients ($M$ = 4.3 ± 0.5). Insulin secretion profiles during clamp were different ($P < 0.00001$) among the groups, increasing in IS subjects (slope: 0.56 ± 0.11 pmol/min$^2$) but declining in IR (−0.41 ± 0.14) and T2DM (−0.87 ± 0.12, $P < 0.00002$ IR and T2DM vs. IS) subjects. Insulin secretion changes during clamp directly correlated with $M$ ($r$ = 0.6, $P < 0.00001$).

**CONCLUSIONS**—Insulin release during normoglycemia can be modulated by exogenous insulin infusion and directly depends on whole-body insulin sensitivity. Thus, in highly sensitive subjects, insulin increases its own secretion. On the other hand, a suppressive effect of insulin on its own secretion occurs in IR and T2DM subjects.

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Impaired insulin secretion, as seen in type 2 diabetes mellitus (T2DM) or prediabetic states, results in prolonged hyperglycemic episodes (1). Both the time course and the amount of secreted insulin are different in T2DM patients compared with healthy subjects (1).

Because the β-cell not only secretes insulin but also expresses insulin receptors to activate the insulin signal transduction cascade (2), it might follow that insulin has the potential to modulate its own release, depending on the intactness of the insulin signaling cascade, which is impaired in insulin resistance and T2DM (3).

Previous contrasting results have shown that, in both healthy and T2DM subjects, insulin infusion during maintained normoglycemia had no effect (4–6) or had a suppressive (7–10) effect on C-peptide release. Such contrasting results may be partially due to the fact that, in those previous studies (4–10), insulin sensitivity was not assessed. However, a most recent study described insulin to enhance its own secretion in insulin-sensitive (IS) humans (11). Thus, we aimed to study the short-term effects of an infusion of human insulin on insulin secretion during normoglycemia in IS, insulin-resistant (IR), and T2DM subjects.

## RESEARCH DESIGN AND METHODS

—Subjects, recruited by means of local advertising from January 2002 to March 2005, gave informed consent to the protocols, approved by the ethics board of the Vienna Medical University. All participants were recruited by means of local advertising, as previously explained in detail (12,13). An oral glucose tolerance test was performed in nondiabetic subjects (NDS) to confirm their nondiabetic metabolism (13). A total of 102 humans were included (Table 1), 20 of whom had T2DM. NDS were in excellent health and in absence of any regular drug intake (12–15). Among the NDS, 24 reported to be first-degree offspring of patients with T2DM. T2DM subjects had known diabetes for at least 3 years and no clinical existence of renal, hepatic, and cardiovascular diseases (12); their treatment included metformin, sulfonylureas/glinides, and/or α-glucosidase inhibitors.

After a 10-h overnight fast, two catheters (Vasofix; Braun, Melsungen, Germany) were inserted into the left and right antecubital veins for blood sampling and infusions, respectively. For glucose measurement, venous blood was drawn in an arterializing manner (16,17). The mean of three fasting plasma glucose measurements was assigned as the isoglycemic clamp goal. Whenever the goal was <4.44 or >5.55 mmol/L, 4.44 or 5.55 mmol/L was chosen, respectively (13–17). The hyperinsulinemic-isoglycemic clamp was performed for 120 min in NDS and 150 min in T2DM subjects, with a primed continuous (40 mU min$^{-1}$ · m$^{-2}$ body surface area) infusion of regular

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**Table 1—*Baseline anthropometric and clinical characteristics (at fasting), and basal and end-clamp results in IS, IR, and T2DM subjects***

| | IS | IR | T2DM | *P* (ANOVA) |
|---|---|---|---|---|
| Baseline anthropometric and clinical characteristics | | | | |
| *N* | 65 | 17 | 20 | — |
| Sex (% female/% male) | 65/35 | 65/35 | 40/60 | 0.134 |
| Body weight (kg) | 72.7 ± 1.5 | 81.6 ± 4.5 | 82.5 ± 2.6# | **0.004** |
| BMI (kg/m$^2$) | 24.8 ± 0.5 | 28.1 ± 1.3* | 28.0 ± 0.8# | **0.001** |
| Age (years) | 45 ± 1 | 46 ± 2 | 56 ± 2#§ | **<0.001** |
| Serum creatinine (mg/dL) | 0.82 ± 0.02 | 0.83 ± 0.04 | 0.94 ± 0.04# | **0.009** |
| Serum uric acid (mg/dL) | 4.8 ± 0.2 | 4.8 ± 0.3 | 5.8 ± 0.3#§ | **0.033** |
| $HbA_{1c}$ (%) | 5.4 ± 0.0 | 5.6 ± 0.1 | 6.7 ± 0.1#§ | **<0.001** |
| Serum triglycerides (mg/dL) | 91 ± 5 | 96 ± 16 | 166 ± 12#§ | **<0.001** |
| Serum total cholesterol (mg/dL) | 207 ± 5 | 207 ± 10 | 273 ± 16#§ | **<0.001** |
| Serum HDL cholesterol (mg/dL) | 60 ± 2 | 54 ± 3 | 54 ± 2 | 0.106 |
| Serum LDL cholesterol (mg/dL) | 129 ± 4 | 134 ± 10 | 186 ± 15#§ | **<0.001** |
| Serum ASAT (GOT) (units/L) | 24 ± 1 | 25 ± 2 | 23 ± 1 | 0.673 |
| Serum ALAT (GPT) (units/L) | 22 ± 1 | 28 ± 5 | 30 ± 2# | **0.012** |
| Plasma glucose (mmol/L) | 4.9 ± 0.1 | 5.0 ± 0.1 | 7.5 ± 0.3#§ | **<0.001** |
| Hyperinsulinemic-isoglycemic clamp | | | | |
| Plasma glucose slope (mg · dL$^{-1}$ · min$^{-1}$) | −0.01 ± 0.01 | −0.05 ± 0.01 | −0.22 ± 0.04#§ | **<0.001** |
| Plasma insulin (nmol/L) | | | | |
| Basal | 0.05 ± 0.00 | 0.10 ± 0.03* | 0.10 ± 0.02# | **0.001** |
| Clamp-end | 0.50 ± 0.02 | 0.55 ± 0.04 | 0.54 ± 0.02 | 0.204 |
| Plasma C-peptide (nmol/L) | | | | |
| Basal | 0.49 ± 0.03 | 0.75 ± 0.09* | 1.04 ± 0.07#§ | **<0.001** |
| Clamp-end | 0.68 ± 0.05 | 0.65 ± 0.07 | 0.59 ± 0.04 | 0.594 |
| *M* (mg glucose · min$^{-1}$ · kg$^{-1}$) | | | | |
| final 20-min interval | 8.8 ± 0.3 | 4.0 ± 0.2* | 4.3 ± 0.5# | **<0.001** |

Data are means ± SE. Significant *P* values from ANOVA are presented in boldface type. ALAT, alanine aminotransaminase; ASAT, aspartate aminotransaminase; *M*, clamp *M*-value. ANOVA after a Bonferroni post hoc test: *$P < 0.05$ IR vs. IS. #$P < 0.05$ T2DM vs. IS. §$P < 0.05$ T2DM vs. IR.

insulin (Actrapid; NovoNordisk, Bagsvaerd, Denmark) (12–15,17). Clamp goal was maintained by infusing variable amounts of a 20% D-glucose solution. The difference between fasting plasma glucose and clamp glucose goal was on average 0.04 mmol/L in NDS but 0.82 mmol/L in T2DM subjects. The plasma glucose coefficient of variation during the final clamp hour was 7 ± 0% for NDS, 6 ± 1% for T2DM subjects, 8 ± 0% for IS subjects, and 5 ± 0% for IR subjects. For measurement of insulin, C-peptide, and FFA, blood was collected in EDTA-containing tubes at baseline, at −60 min, at −30 min, and immediately before the end of the clamp to be centrifuged and stored at −70° C. As previously shown (14,15), the threshold for insulin resistance is insulin-stimulated glucose utilization (*M*) <5 mg · min$^{-1}$ · kg$^{-1}$; NDS were defined as IR ($M \leq 5.0$) or IS ($M > 5.0$).

All of the variables characterizing the groups (Table 1) were assessed using routine laboratory methods (13–17). Glucose was measured by glucose oxidase (Glucose Analyzer II; Beckman, Fullerton, CA) (13); plasma insulin and C-peptide were measured by radioimmunoassays (Linco, St. Charles, MO) (13). FFA was measured with a microfluorometric assay (Wako Chemicals, Richmond, VA). Insulin sensitivity was calculated as the mean *M* during 20-min intervals of the clamp (14,15,17). Total insulin secretion was calculated from plasma C-peptide concentrations by deconvolution (18). Sensitivity of the β-cell to glucose was determined by dividing insulin secretion by corresponding plasma glucose concentrations. The gradients of insulin secretion in relation to and of plasma glucose during clamp were calculated as the slope of the linear fit of its values over time.

Normal distribution was tested by applying the Kolmogorov–Smirnov test. Differences between groups were analyzed by ANOVA after a two-sided Bonferroni post hoc test. Pearson's product moment correlation was used to estimate linear relationships between variables. A stepwise backward regression was performed. Data are presented as means ± SE; $P < 0.05$ was considered statistically significant (SPSS 13.0; SPSS Inc., Chicago, IL).

**RESULTS**—Body mass was similar in IR and T2DM subjects but smaller in IS subjects (Table 1). T2DM subjects were older with higher creatinine, uric acid, triglycerides, total/LDL cholesterol, and alanine aminotransaminase. Baseline plasma insulin was similar in IR and T2DM subjects but lower in IS subjects. Plasma insulin in the three groups was similar at the end of the clamp (Fig. 1*F*). C-peptide was different at baseline in all three groups but similar at the end of the test (Fig. 1*G*). Insulin sensitivity (*M*) was approximately twofold higher in the IS group than in both IR and T2DM groups (Table 1).

Basal insulin secretion from C-peptide was the highest in T2DM subjects (+112% vs. IS: $P < 0.00001$; +34% vs. IR: $P < 0.02$; IR vs. IS +58%, $P < 0.002$; Fig. 1*A*). During the final 60 min, insulin secretion (C-peptide secretion [CPS]) became comparable in all groups. The slope of CPS was positive in IS subjects but negative in IR and T2DM subjects (Fig. 1*A inset*). Because of the more pronounced glucose decline in T2DM subjects, we adjusted insulin secretion for plasma glucose by dividing CPS by the corresponding plasma

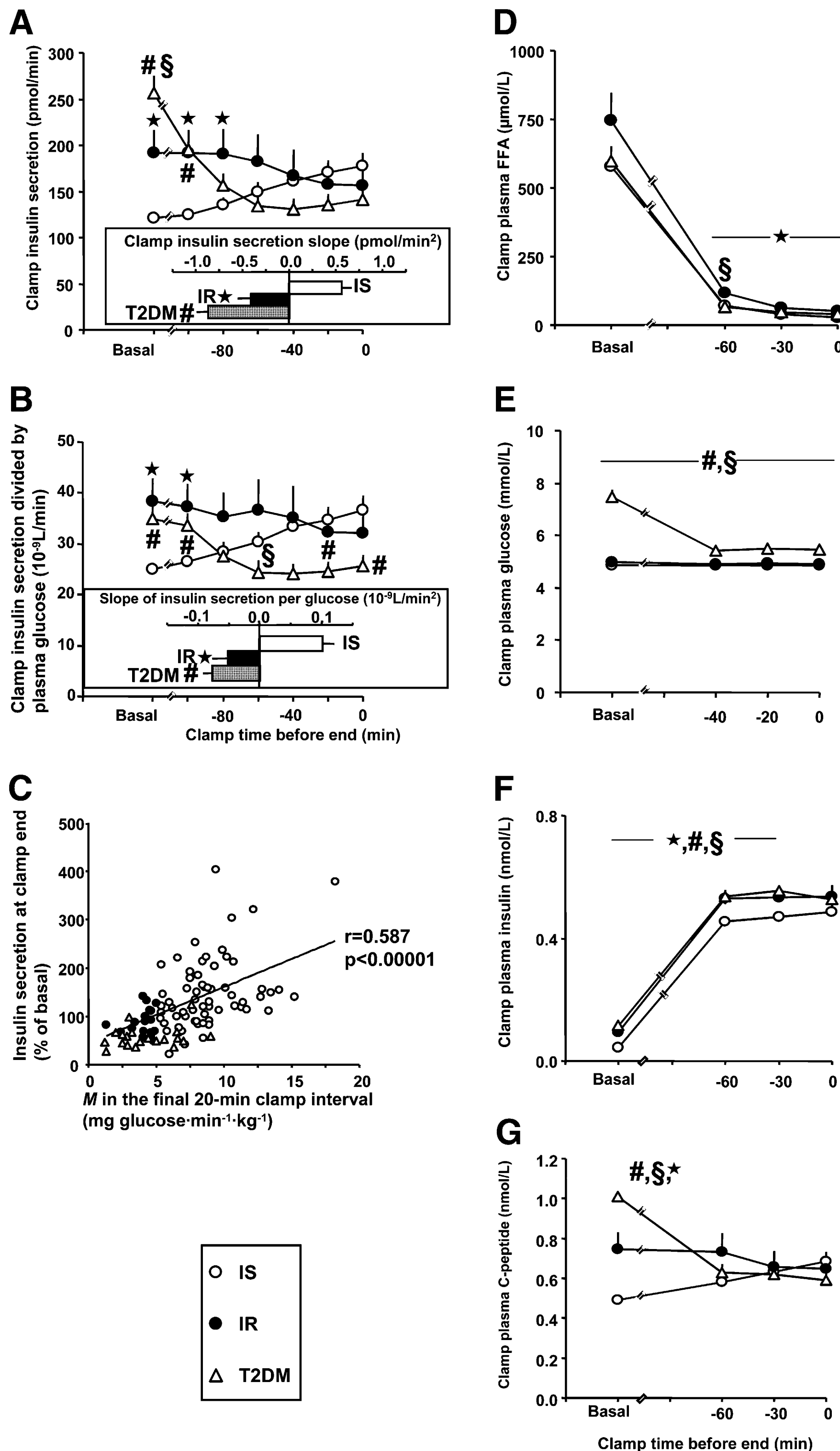


**Figure 1**—*The clamp time course of* (A) *insulin secretion with its slope* (inset) *and of* (B) *insulin secretion adjusted to prevailing plasma glucose concentrations with its slope* (inset). C: *Pearson's product moment correlation. The correlation of insulin secretion change (in %) at the end of the clamp compared with baseline with final 20-min* M. *The clamp time course of FFA* (D), *plasma glucose* (E), *insulin* (F), *and C-peptide* (G) *in IS* (O, n = 65), *IR* (●, n = 17), *and T2DM* (△, n = 20) *subjects. Data are presented as means ± SE. ANOVA after a Bonferroni post hoc test:* *P < 0.05 IR vs. IS; #P < 0.05 T2DM vs. IS; §P < 0.05 T2DM vs. IR.*

glucose concentration (17). This β-cell sensitivity to glucose (Fig. 1*B*) was similar in IR and IS subjects at the end of the test but lower in T2DM subjects. The slopes of β-cell sensitivity to glucose (Fig. 1*B inset*) were also positive in IS subjects but negative in IR and T2DM subjects.

All of the secretion indices correlated directly with *M*: CPS at the end of the clamp (in % of basal; $r = 0.59$, $P < 0.0001$; Fig. 1*C*), the absolute CPS ($r = 0.20$, $P < 0.05$), and the β-cell sensitivity ($r = 0.23$, $P = 0.02$). In contrast, *M* was negatively related to basal CPS ($r = -0.530$, $P < 0.00001$) and when adjusted to glucose ($r = -0.408$, $P < 0.0001$).

FFAs were comparable at fasting, but after insulin-mediated release inhibition, they were higher in IR subjects than in IS and T2DM subjects (Fig. 1*D*). Plasma glucose at fasting was greater by ~2.5 mmol/L in T2DM subjects, which is also reflected by the glucose slope differences (Table 1); thus, the study design imposed a goal in the T2DM subjects greater by ~0.6 mmol/L (Fig. 1*E*).

### Predictors of glucose-adjusted insulin secretion

Age, BMI, whole-body insulin sensitivity (*M*), clamp-end plasma insulin concentration, clamp glucose slope, basal glucose-adjusted insulin secretion, basal plasma concentrations of insulin and glucose, and group affiliation factors (1 = IS, 2 = IR, 3 = T2DM) were included.

The stepwise backward regression ($r^2 = 0.401$) in all participants revealed *M* ($\beta = 0.021 \pm 0.005$, $P < 0.00006$) to be the strongest predictor of β-cell sensitivity, whereas clamp-end insulin concentration ($\beta = 0.266 \pm 0.098$, $P < 0.01$) and group affiliation ($\beta = -0.051 \pm 0.020$, $P < 0.02$) were also predictors, although much weaker.

**CONCLUSIONS**—Insulin secretion was investigated during an infusion of human insulin to increase insulin to postprandial-like concentrations, while maintaining normoglycemia (13,17), in a large cohort ($n = 102$) of IS, IR, and T2DM subjects. The major result of this study is that insulin infusion leads to an increase in insulin secretion in IS humans, whereas a decrease was observed in IR subjects, regardless of the presence of T2DM. To the best of our knowledge, this has never been described before as a whole. In addition, the magnitude of the increase in insulin secretion during insulin infusion directly depends on, and is predominantly predicted by, individual whole-body

insulin sensitivity, which again is a novel finding.

### Insulin release

C-peptide concentration was exploited to estimate insulin secretion (1,18,19), because having infused human insulin, the assay would be unable to discriminate endogenous from exogenous insulin and modeling-based analysis is the only possible way to noninvasively determine CPS. Because glucose levels between fasting and clamp end were different in T2DM, we adjusted insulin release for the prevailing glucose levels to further prove our findings. Basal insulin secretion adjusted to glucose was negatively related to *M*, indicating that the β-cell sensitivity to glucose at fasting aims to compensate for the decline in insulin sensitivity (1). However, during clamp, this association became positive, indicating that exogenous insulin administration has the potential to modulate both insulin secretion and β-cell glucose sensitivity, regardless of glycemia. In contrast, insulin secretion at basal was negatively associated with *M*, which has been shown repeatedly (20). It should be added that if insulin were to exert its effect on β-cell function through the insulin receptor mechanism, then this might be saturatable. In this case, it is possible the IR and T2DM groups are already at the maximum for this pathway, and this could explain the positive association only in the IS group.

Our findings are not in contrast with previous studies reporting enhancement (11), no effect (4–6), or suppression (7–10) by insulin infusion on C-peptide release. In the investigations from the 1970s and 1980s (4–10), insulin sensitivity was not measured; thus, an IR state of those study participants cannot be ruled out.

The most recent study by Bouche et al. (11) did measure both insulin sensitivity and insulin/C-peptide release during insulin infusion using a sophisticated study protocol with B28-Asp insulin analog and stable isotope labeled C-peptide. They found in highly IS humans (*M* of 10–11 $mg \cdot min^{-1} \cdot kg^{-1}$) that insulin increases its own secretion by ~40% (11), which is completely in line with our findings. Despite use of a different but well-established approach, our study furthers this observation because we included IR subjects, in whom insulin-mediated decline on insulin release was clearly demonstrated. Bouche et al. (11) also found a slightly but significantly higher C-peptide clearance by ~7% in the presence of hyperinsulinemia in highly IS subjects, whereas we found no difference in C-peptide degradation in control, obese, and diabetic subjects without renal damage (21). Nevertheless, when assuming a slightly higher C-peptide clearance, measured C-peptide concentrations would be a bit more lowered, so that our calculated insulin secretion pattern (Fig. 1) would be even more pronounced in the IS subjects. Taken together, a slight variation in C-peptide clearance and thus CPS during hyperinsulinemia cannot be completely ruled out, but its effect seems small so that changes of this study's main outcome are unlikely.

As a clinical implication of our study, it can be affirmed that correcting elevated circulating glucose concentrations by insulin administration in T2DM or critically ill patients seems not to bear any risk, because hyperglycemia per se induces insulin resistance as the result of glucotoxicity (3) and insulin decreases its secretion in insulin resistance. On the other hand, if insulin sensitivity increases during rapid weight loss or recovery from severe illnesses, uncontrolled insulin administration may be risky.

The mechanism for the insulin-stimulated CPS seems difficult to explain: The pancreatic β-cell not only secretes insulin but also expresses insulin receptors to activate the insulin signal transduction cascade (2). By knocking out the β-cell insulin receptor or downstream proteins of the insulin signaling cascade in rodents, Kulkarni et al. (22–24) demonstrated a marked defect in insulin expression and secretion resembling that of T2DM. From this it might follow that insulin has the potential to modulate its own release, possibly through its own signaling cascade. The insulin signaling cascade is impaired in insulin resistance and T2DM (3); thus, the ability of the β-cell to respond to hyperinsulinemia (autocrine or paracrine effect) might be blunted. Circulating FFAs play a crucial role in IR induction (3). Thus, we thought that FFA may affect CPS. However, circulating FFAs were similar in IS and T2DM groups; thus, FFAs seem rather not to be involved in insulin-mediated CPS.

### Study limitations

Serum potassium, which may also affect insulin release, was not measured during the clamp test. In addition, the patients with T2DM were receiving antihyperglycemic agents, which were stopped 1–3 days before the clamp test (12). However, some prolonged effects on CPS, predominantly caused by sulfonylurea metabolites in T2DM, cannot be ruled out, but they would rather increase CPS. Because T2DM subjects had the lowest CPS during insulin infusion compared with NDS, an even more pronounced reduction in T2DM subjects might be possible. The different clamp-test glycemia between T2DM subjects and NDS once again presents the difficulty in comparing humans with and without T2DM during an isoglycemic clamp test, because CPS would be higher when glucose increases over basal in NDS. Thus, we sought to define near-isoglycemia for NDS and took into account the expected glucose decrease in T2DM subjects. Nevertheless, under our study setting, a β-cell rest during the clamp cannot be excluded for the T2DM and IR participants. However, it should be added that, after withdrawal of antidiabetic medication in our subjects with mild T2DM, fasting glucose concentrations with 7.5 mmol/L (Table 1) were still not that increased to induce diminished insulin release (i.e., β-cell rest), which would occur at >9 mmol/L fasting glucose (25).

In addition, age and body mass differences among groups became evident. However, diabetes development is favored by elevated body weight, which in turn downgrades whole-body insulin sensitivity (3,14). Therefore, body mass-matched groups of T2DM subjects and NDS are difficult to recruit. However, the IR group had a BMI comparable to that in the T2DM group to allow for comparison between diabetic subjects and NDS. Of note, regression analysis did not detect any effect from these anthropometric characteristics, so the differences in age and body mass seem not to affect insulin secretion in our population.

Another point may be the differences between NDS and T2DM subjects in fasting glucose concentrations. However, the T2DM subjects were not receiving regular insulin, and antihyperglycemic drugs were withdrawn. Thus, it seems that the study setting bears this disadvantage, but this cannot be easily overcome, because (fasting) hyperglycemia is the given major characteristic of the studied disease.

### Conclusion

Insulin increases its own secretion in IS subjects, whereas in IR subjects, including those with T2DM, insulin exerts suppressive effects on its own release.

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C.A. researched data, analyzed data, wrote the article, and edited the article for revision. A.T., A.G., and J.S. researched data, performed data analysis, contributed to the discussion, and reviewed and edited the article. M.K., M.R., M.G.B., and A.L. reviewed and edited the article. G.P. performed mathematical calculations, wrote the article, and edited the article for revision.

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