

Visfatin Response to Glucose Is Reduced in Women With Gestational Diabetes Mellitus

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The insulin-mimetic adipocytokine visfatin has been associated with insulin resistance in some studies and is regulated by glucose. We hypothesized that glucose-induced changes in plasma visfatin are different in women with gestational diabetes mellitus (GDM). Plasma visfatin concentrations were studied in 10 women with GDM and 10 age-matched healthy women, in pregnancy weeks 24–28, during a standard oral glucose tolerance test (OGTT). Women with GDM had lower systemic visfatin concentrations than control subjects (1.9 ± 0.8 vs. 5.2 ± 4.4 ng/ml, respectively, $P < 0.05$), which were associated with fasting glucose ($P < 0.05$). The glucose-induced increase in visfatin over baseline was smaller in women with GDM, with an area under the curve of 409 ± 106 vs. 780 ± 345 ng · ml⁻¹ · min⁻¹ in control subjects ($P < 0.05$). Reduced glucose-induced increases in circulating visfatin may be associated with impaired glucose tolerance in women with GDM.

Women with GDM are at increased risk for developing type 2 diabetes; however, the pathophysiology is still poorly understood. Nonetheless, a variety of abnormalities that are also found in patients with type 2 diabetes are seen early in women in GDM (1). Among the factors that might contribute to altered glucose handling are changes in adipocytokines. For example, plasma adiponectin concentrations are lowered (2), and leptin and

resistin persistently increased after delivery in women with GDM and are associated with hyperglycemia and insulin resistance (3,4).

The adipocytokine visfatin has been reported to mimic actions of insulin by activating the insulin signal transduction pathway through binding to the same receptor (5). Systemic visfatin concentrations are acutely regulated by glucose and insulin (6) and elevated in patients with insulin resistance, obesity, and diabetes, as well as by rosiglitazone treatment (7–11).

In an effort to address the question whether plasma visfatin regulation is altered in women with GDM, we have studied its concentration during pregnancy weeks 24–28 and compared it with that of matched healthy pregnant women during a standard OGTT.

RESEARCH DESIGN AND METHODS

Ten women with GDM (aged 33 ± 2 years) diagnosed during pregnancy weeks 24–28 were invited to participate in the study. GDM was defined as two or more of the following criteria: fasting morning plasma glucose after a minimum of 3 days of unrestricted diet and unlimited physical activity ≥ 5.3 mmol/l, 1-h postload 75-g glucose value ≥ 10.0 mmol/l, or 2-h postload glucose value ≥ 8.6 mmol/l. As control subjects, age-matched (34 ± 1 years) pregnant women with normal OGTT were included.

Inclusion criteria were signed informed consent, absence of a clinically relevant illness, normal findings in the medical history and physical examination except for GDM, and normal laboratory values. Subjects were excluded if any clinically relevant abnormality was found as part of the screening or in any of the laboratory tests including circulating anti-insulin antibodies and anti-islet cell antibodies. No subject was on a special diet or reported intake of any medication, including “over-the-counter” drugs, at the time of blood sampling.

Study protocol

Venous blood samples for measurement of lipid status, glucose, insulin, and visfatin concentrations were taken 1 h before a standard 75-g OGTT and was carried out after overnight fasting. Venous blood sampling was repeated 30, 60, and 120 min after an oral glucose load. Insulin sensitivity during an OGTT was assessed by the oral glucose insulin sensitivity index, which describes glucose clearance (12). Standard laboratory parameters were quantified according to certified routine methods at the Clinical Institute for Medical and Chemical Laboratory Diagnostics, Allgemeines Krankenhaus Wien.

Measurement of visfatin

Plasma samples were stored at -70°C until analysis. Visfatin was analyzed using a commercially available enzyme-linked immunosorbent assay kit (Phoenix Peptides, Karlsruhe, Germany), with an inter- and intra-assay coefficient of variation $< 6\%$.

Statistical analysis

All datasets were tested for normal distribution using the Kolmogorov-Smirnov test. Changes over baseline were assessed from the areas under the concentration versus time curves. Differences between groups were compared using the Mann-Whitney *U* test. Effects of OGTT were assessed by repeated-measures ANOVA. All calculations were performed using the Statistica software package (release 4.5; StatSoft, Tulsa, OK). $P < 0.05$ was considered significant. Data are expressed as means \pm SD, unless otherwise indicated.

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Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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RESULTS— Groups of pregnant women were comparable regarding age, BMI, and anthropometric and metabolic parameters, except for higher fasting plasma glucose concentrations (5.4 ± 0.6 vs. 4.2 ± 0.7 mmol/l, $P < 0.05$) and lower oral glucose insulin sensitivity index values (376.5 ± 21.1 vs. 493.4 ± 37.1 ml/min per m^2 , $P < 0.05$) in women with GDM. Fasting plasma visfatin concentrations were lower in women with GDM (Fig. 1) and increased between 0.6–3.8 and 0.6–7.1 ng/ml in women with GDM and control subjects, respectively.

The glucose-induced change in visfatin over baseline as calculated by the area under the curve was 409 ± 106 ng \cdot ml $^{-1}$ \cdot min $^{-1}$ in GDM and 780 ± 345 ng \cdot ml $^{-1}$ \cdot min $^{-1}$ in control subjects ($P < 0.05$ between groups, Mann-Whitney U test). A significant correlation was detectable between fasting glucose and visfatin concentrations in both groups ($r = 0.46$, $P < 0.05$ in GDM and $r = 0.45$, $P < 0.05$ in control subjects) but not among other parameters.

CONCLUSIONS— This study demonstrates that a glucose-induced visfatin increase is blunted in women with GDM, who also have lower fasting plasma concentrations compared with age-matched pregnant women. This finding extends previous studies from different populations with GDM, where increased (13) or decreased (14) circulating visfatin concentrations have been reported. The discrepancy of these finding is unclear but may be related to differences regarding sampling time during pregnancy. The present data nevertheless confirm the regulatory role of glucose on circulating visfatin levels, which is consistent with results obtained during hyperglycemic clamp studies in healthy young men (6).

The cause of reduced fasting visfatin and mitigated response to glucose challenge in women with GDM is not directly accessible from this study. It has been demonstrated that plasma visfatin concentrations are inversely correlated to progressive β -cell deterioration in patients with type 1 or type 2 diabetes (15). The present data argue against an assumption that altered pancreatic insulin secretion has contributed to reduced plasma visfatin in GDM because insulin plasma concentrations were comparable in fasting conditions. This is important, as insulin is known to suppress glucose-induced visfatin release in vitro and in vivo (6). Further, glucose-induced insu-

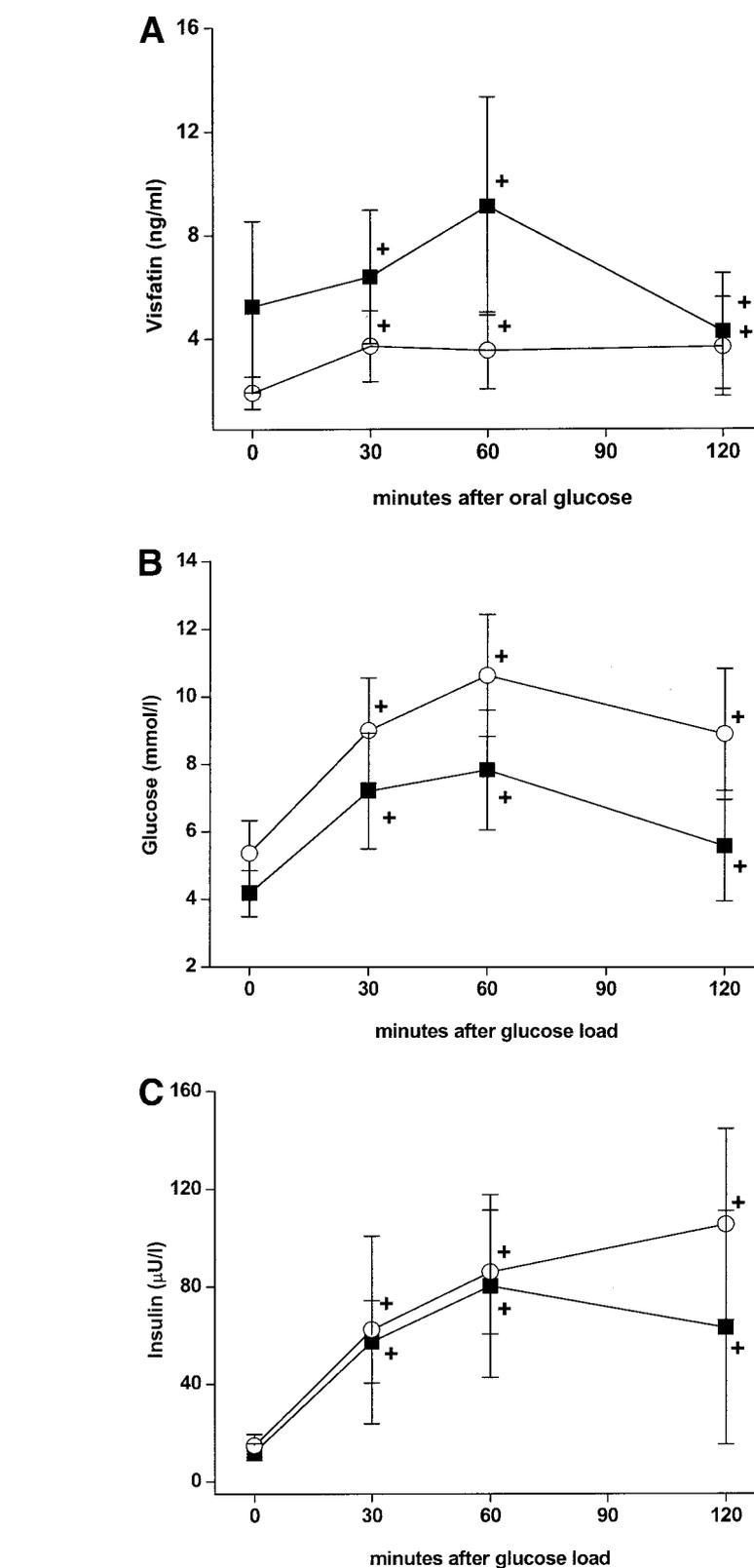


Figure 1— Plasma concentrations of visfatin (A), glucose (B), and insulin (C) during an OGTT in women with GDM (○) and age-matched healthy pregnant control subjects (■). Data are means \pm SE. + $P < 0.05$ vs. baseline (repeated-measures ANOVA).

lin release was similar in women with GDM as in healthy control subjects 60 min after an oral glucose load.

On the contrary, as it is known that glucose induces visfatin release, which is also a consistent finding in this study, one

might have expected higher visfatin concentrations in women with GDM. Thus, factors other than glucose and insulin alone seem to influence the regulation of visfatin in pregnancy, such as proinflammatory cytokines (2). Indeed, an association between plasma tumor necrosis factor- α and visfatin mRNA in subcutaneous adipose tissue has recently been reported (16). It is unclear if differences in fasting or glucose-stimulated plasma visfatin can be regarded as compensatory mechanisms to maintain glucose homeostasis in GDM.

In summary, GDM is associated with lower visfatin concentrations than that found in healthy women during pregnancy. Visfatin is transiently increased after an oral glucose load, but this response is mitigated in GDM.

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