the drug's effect, which in turn may enhance drug efficacy and patient compliance.

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Gestational Diabetes Mellitus Is Associated With an Increase in the Total Concentration of Amylin Molecules

Fasting concentrations of amylin, a 37 amino acid polypeptide secreted by the pancreatic β-cells, have been shown to be elevated in a number of conditions associated with insulin resistance (1), but have not been systematically studied in gestational diabetes mellitus (GDM). Previous studies in GDM have been small and may not have been appropriately matched for other factors that could have an influence on amylin concentrations (2,3). A recent paper showed an elevation in pregnancy but no significant difference between women with GDM and pregnant control subjects (4). To describe the association between GDM and fasting and post-glucose amylin concentrations, we therefore undertook a matched case-control study, using stored plasma samples from a previously conducted study of glucose tolerance in pregnancy (5).

Patients and control subjects were identified from a cohort study of all pregnant women in Cambridgeshire, U.K., who attended the antenatal clinic between August 1992 and July 1993. A total of 63 women were diagnosed as having GDM on the basis of a 3rd-trimester 75-g oral glucose tolerance test (OGTT). Of these, 52 women had complete biochemical data and were selected as patients for this study. Those 52 women who had a normal 3rd-trimester OGTT were selected as control subjects and were individually matched with patients by age and BMI. There was no significant difference in the gestational age at the time of the OGTT between patients (mean 31.8 ± 2.6 weeks) and control subjects (32.7 ± 1.8 weeks). Amylin was measured at all time points during the OGTT using two different assays (6). The first measures unmodified amylin, and the other measures the total of all amylin molecules. The difference between the total and unmodified amylin is mainly due to the presence of amylin molecules that have been modified by the attachment of O-linked oligosaccharide groups at threonine residues near the NH_2-terminus (7).

There was no significant difference in the concentration of unmodified amylin in women with GDM compared with control subjects at fasting or 30 or 90 min after the glucose load. At 120 min, there was a significant elevation in women with GDM (geometric mean 4.38 pmol/l, 95% CI 3.3–5.9) compared with control subjects (geometric mean 2.42 pmol/l, 95% CI 1.8–3.2, $P = 0.03$). In contrast, the concentration of total amylin was significantly higher in women with GDM compared with control subjects at each time point during the OGTT. The fasting concentration in women with GDM was 5.13 pmol/l (95% CI 3.7–7.1) compared with 2.58 pmol/l (95% CI 2.1–3.2) in control subjects ($P < 0.001$).

Patients and control subjects were allocated to quartiles on the basis of their fasting total amylin concentration. The relationship between the concentrations of total amylin and GDM was then determined using conditional logistic regression analysis. A strong linear association was demonstrated with an odds ratio for GDM per quartile of fasting total amylin of 2.31 (95% CI 1.5–3.5, $P < 0.001$). The odds ratio for the top quartile compared with the bottom quartile was 10.0, demonstrating the strength of this association. In contrast, when a similar analysis was undertaken using quartiles for fasting intact proinsulin, which we have previously demonstrated to be elevated in GDM, the odds per quartile was 1.48 (1.02–2.14), suggesting that the association of elevated fasting total amylin with GDM was much stronger. Because amylin has been shown to be co-secreted with insulin (8), we also examined the extent to which this association was independent of insulin by introducing this as a covariate in the logistic model. The overall association between quartile of fasting total amylin and GDM was unaffected (odds ratio 2.28, 95% CI 1.49–3.51), suggesting that this association cannot be explained by confounding by insulin concentrations.

We conclude from this study that concentrations of total amylin are increased in women with GDM compared with age- and BMI-matched pregnant control subjects of a similar gestational age. This association is stronger than that between intact proinsulin and GDM and cannot simply be explained by confounding by insulin. There was no elevation of fasting unmodified amylin in women with GDM. Although this could be explained by the fact that the concentrations of unmodified amylin are lower than that of total amylin and the power to detect a true difference was therefore greatest for total amylin, it is also possible that it is the glycosylated forms of amylin that are elevated in GDM. Further research should be directed toward the development of assays to measure these amylin species directly and to understand their pathophysiological role and usefulness as markers of diabetes risk.

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A Critical Issue

Intensive insulin treatment and macrovascular disease

It is not yet known whether insulin treatment is beneficial, adverse, or neutral for cardiovascular disease in type 2 diabetes (1). The applicability of the Diabetes Control and Complications Trial (DCCT) findings to the prevention of microvascular complications of type 2 diabetes and to its cardiovascular consequences is a matter of controversy (2). Even the authorities who recommend normal glycemic levels as a treatment goal in people with type 2 diabetes (3,4), including the substantial proportion of patients who ultimately need insulin (5), indicate that such goals might have to be moderated in the presence of obesity, severe cardiovascular disease, or advanced age (3,4). The majority of patients with type 2 diabetes in western industrialized countries are obese, have a high prevalence of cardiovascular disease, and are in the later decades of life (6,7). Thus, the optimal degree of intensity of insulin treatment in such patients remains undetermined. Other authorities directly posit that the DCCT findings for type 1 diabetes should not be applied to type 2 diabetes until appropriate trials are conducted (8–10). These uncertainties were anticipated by the Department of Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes (VA CSDM) planning committee when it designed a clinical trial to evaluate the risk-to-benefit ratio of intensive glycemic control on macrovascular disease and other complications in type 2 diabetic patients no longer optimally controlled with diet and oral agents (6,11). The feasibility trial, completed in five medical centers in July 1993, demonstrated that a glycemic separation slightly exceeding that of the DCCT could be maintained for >2 years between study groups receiving standard treatment and intensive treatment without increased risk of severe hypoglycemia (7). Toward the end of the feasibility study, a final protocol for a 7-year trial of 1,400 patients from 18 hospitals was scientifically approved with an outstanding rating by the Department of Veterans Affairs (DVA) Cooperative Studies Program. The approved budget, although modest by National Institutes of Health standards, amply exceeded the usual budget of individual DVA cooperative studies, which often required extramural funding. Preliminary negotiations did not result in firm budgetary commitments, which prompted the DVA Cooperative Studies Program to put the long-term trial on a "waiting for funding" status. Because external funding was not forthcoming, the VA CSDM was removed from the "awaiting for funding" list in 1996. Given the distinguished record of the DVA in cooperative trials and the prevalence of type 2 diabetes in the DVA, it may still address, in the future, a long-term intensive treatment trial on type 2 diabetes.

There has been strong support for such a study. The American Diabetes Association made two presentations to Congress, in 1994 and 1995, and a grassroots campaign was launched among the readers of their journal, *Diabetes Forecast*, on behalf of funding for the VA CSDM (12). The Fifth Regenstrief Conference concluded that this is the single most critical study in type 2 diabetes (13).

On completion of the VA CSDM feasibility trial, an analysis of the high incidence of new cardiovascular endpoints (12%/year) and their correlates indicated a nonsignificant excess of new nonfatal cardiovascular events in the intensive-treatment group and a borderline correlation of new cardiovascular events with lower attained HbA_{1c} (14). Before the publication of the results, one review erroneously reported that there was excess mortality in the intensive-treatment group (9). It could also be erroneously implied that an adverse effect of intensive treatment caused the discontinuation of the long-term trial, otherwise scientifically approved with high priority. In fact, the relative imbalance of new cardiovascular events between groups in the feasibility trial has been considered inconclusive by the VA CSDM group (14), by the external Data Monitoring Board of the VA CSDM in their final report, and also by the 1996 American Diabetes Association consensus statement on the pharmacological treatment of hyperglycemia in NIDDM (5).

The issue of intensive insulin treatment of type 2 diabetes has not gone away. It is often quoted that the large U.K. Diabetes Prospective Study (UKDPS), already in its second decade, might answer whether intensive glycemic control in type 2 diabetes could prevent cardiovascular complications (1,8,15). This large trial compares diet alone with several treatment modalities and will be invaluable in comparing their relative safety and effectiveness. The UKDPS was to be interrupted if a significant difference in cardiovascular mortality occurred in any of the treatment groups (15). This has not happened. A possible reason is that difference in HbA_{1c} has been only 0.7% between the pharmacologically-treated and the control groups (diet alone) (16). This is little more than one-third of that obtained in the DCCT and the VA CSDM. Only individuals