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The Possible Role of Insulin Release in Cardiovascular Morbidity and Mortality in NIDDM Patients

In his commentary, Lebovitz (1) underlines the roles of hyperglycemia and insulin resistance as risk factors for macrovascular disease in non-insulin-dependent diabetes mellitus (NIDDM), but he does not emphasize the roles of obesity and insulin release. NIDDM is a different disease in obese (mainly insulin resistant) and nonobese (mainly insulinopenic) patients. Body weight also seems important in the clinical picture of secondary failure (SF) of oral hypoglycemic agents, as SF is usually irreversible in nonobese patients, but reversible after weight loss in the obese (2).

In SF patients, we have evaluated risk factors for major complications and mortality. In 1989, 76 SF patients, 51 obese (body mass index [BMI] 32.8 ± 0.8 kg/m^2), and 25 nonobese (BMI 23.6 ± 0.3, $P < 0.01$), were hospitalized to ameliorate metabolic control, including body-weight reduction and adjustment of insulin treatment (patients with serum creatinine levels >1.5 mg/dl were excluded), and to evaluate C-peptide release and diabetic complications. Obese patients differed from nonobese in hypertension (systolic blood pressure [BP] 157 ± 2.9 vs. 147 ± 4.5 mmHg, $P < 0.05$; diastolic BP 91 ± 1.8 vs. 85 ± 1.9 mmHg, $P < 0.05$); use of hypotensive drugs 31/51 vs. 7/25, $P < 0.05$) and C-peptide levels (2.2 ± 0.3 vs. 1.2 ± 0.2 ng/ml, $P < 0.05$). On univariate analysis in 76 patients, ischemic heart disease (IHD) was associated with C-peptide (2.2 ± 0.3 vs. 1.0 ± 0.2 ng/ml, $P < 0.01$ at 0 min; 3.7 ± 0.5 vs. 1.7 ± 0.4 ng/ml 6 min after intravenous glucagon, $P < 0.05$), serum creatinine levels (CREA, 1.0 ± 0.0 vs. 0.9 ± 0.0 mg/dl, $P < 0.01$), and diastolic BP (92 ± 1.7 vs. 86 ± 2.1 mmHg, $P < 0.05$). CREA correlated with age ($r = 0.29$, $P < 0.05$). At stepwise regression analysis (Statview II, Macintosh), C-peptide and CREA were significant risk factors for IHD, age and sex for CREA.

Status was ascertained 48 months later in 39 patients. Six patients (five obese) had died. At baseline they differed from live patients for age (65 ± 1.4 vs. 58 ± 1.5 y, $P < 0.05$), BMI (31.6 ± 2.1 vs. 27.1 ± 0.9, $P < 0.05$), insulin dose (51 ± 12.5 vs. 29.4 ± 3.6 U/day, $P < 0.05$), C-peptide (1.1 ± 0.2 vs. 0.6 ± 0.1 ng/ml at 0 min, $P < 0.01$; 1.6 ± 0.3 vs. 1.0 ± 0.1 ng/ml at 6 min, $P < 0.05$), serum triglycerides (298 ± 75 vs. 156 ± 13 mg/dl, $P < 0.01$), CREA (1.2 ± 0.1 vs. 0.9 ± 0.0 mg/dl, $P < 0.01$), and IHD (5/6 vs. 10/33, $P < 0.05$). At stepwise regression analysis, C-peptide was the only significant risk factor for mortality.

In our view, these data underline the primary role of insulin resistance, linked inter alia to BMI, in cardiovascular morbidity and mortality and suggest that insulin or drugs stimulating insulin release should be avoided in the presence of well preserved insulin release (1–3), as is in obese NIDDM patients.

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Intrauterine Devices Are Safe and Effective Contraceptives for Type I Diabetic Women

Further evidence

Two prospective controlled trials (1,2) with state-of-the-art copper intrauterine devices (IUDs) in type I diabetic women have shown that IUDs are as safe and effective as in nondiabetic women. However, there is still a widespread belief among physicians that diabetic women have a higher risk of IUD-associated pelvic inflammatory disease (PID) (3). The skepticism is probably due to the fact that in one of the above studies, 103 women were followed for only 1 year (1) and in the other study, only 58 women were evaluated, albeit for 3 years

(2). In a study about contraception and other reproductive issues in consecutively chosen women with type I diabetes (age 16–46 years) on intensified insulin therapy, we had the opportunity to evaluate the use of IUDs among a large group of young diabetic women (n = 808; age 31 ± 7 years; duration of diabetes 14 ± 5 years; mean ± SD [4]).

Through a multiple-choice questionnaire, the women were asked about current and previous contraception, satisfaction with their contraceptive method, and duration of use. If they were using or had previously used an IUD, the women were asked if they had pain, increased menstrual or additional bleeding, accidental pregnancies, or a PID. There were 94 current users (age 32 [20–45] years, 70% nullipara, HbA_{1c} 8.0 ± 1.7%) who had used the IUD for 5 (0.1–20) years, a cumulated use of 466 person-years. Of those, there were nine who indicated less than full satisfaction because of pain and/or bleeding. There were 33 ex-users who had used the IUD for 6 (0.5–16) years, a cumulated use of 146 person-years. Among those, there were two accidental pregnancies, three cases of PID, and twelve cases of bleeding and/or pain. If we combine users and ex-users, one can evaluate 612 person-years in 127 type I diabetic women. The rate of accidental pregnancies per 100 person-years is 0.3 (Pearl index), the rate of PID per 100 person-years is 0.5, and the rate of pain and/or bleeding per 100 person-years is 3.4. These results are well within the corresponding rates seen in large prospective studies of the use of modern copper IUDs in nondiabetic women (5).

We are aware of the problems with self-reported and retrospective data; however, in our questionnaire, the answers were rather complete. We do not think that the diabetic women had any reason not to report or to have forgotten accidental pregnancies and PIDs associated with the use of an IUD. Thus, we believe that our data support the results of previous prospective studies showing that modern copper IUDs are as safe, effective, and well-tolerated in well-controlled diabetic women as in nondiabetic women.

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Insulin and Proinsulin Secretion in Subjects With Abnormal Glucose Tolerance and a Mitochondrial $tRNA^{Leu(UUR)}$ Mutation

Recent work has linked the mitochondrial $tRNA^{Leu(UUR)}$ mutation at position 3243 with the development of maternally inherited diabetes and a cluster of neurological abnormalities (1,2). The mechanisms leading to the development of diabetes remain unclear, although decreased insulin secretion has been reported by several groups (2,3). We examined, therefore, the relationship between proinsulin and insulin secretory profiles in subjects with the $tRNA^{Leu(UUR)}$ mutation and abnormal glucose tolerance.

Five subjects with $tRNA^{Leu(UUR)}$ mutation and abnormal glucose tolerance (four with impaired glucose tolerance and one with islet cell antibody–negative/C-peptide–positive diabetes) were studied. All had sensorineural deafness, and two had encephalopathy but were otherwise fully mobile. For each affected subject, two control subjects with no family history of diabetes or neurological deficit were pair-matched for age, sex, and body mass index (BMI).

Glucose tolerance was assessed by standard oral glucose tolerance test (OGTT). First-phase insulin secretion (FPIS) and proinsulin secretion (FPPS) (determined as Δ0–10 min hormone area/Δ0–10 min glucose area) were assessed after an intravenous glucose tolerance test (IVGTT) (0.3 g/kg). Whole-body insulin sensitivity was calculated as K_g (index of glucose tolerance) divided by Δ0–40 min insulin area (4), which has been validated against the euglycemic-