Early-Onset Insulin-Resistant Diabetes in Obese Caucasians Has Features of Typical Type 2 Diabetes, but 3 Decades Earlier

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Obesity has dramatically increased in Irish adolescents and young adults and is related to changes in physical activity and diet (1,2). Severe obesity is associated with a much earlier presentation of type 2 diabetes (3–6), as noted in Irish Caucasian patients (7). Most studies of early-onset type 2 diabetes have been in minority populations with higher risk of type 2 diabetes than Caucasians (4–6). The potential for diabetes complications in these young individuals has immediate implications for diagnosis and treatment and longer-term implications for public health. We measured insulin resistance, insulin secretion, and a range of cardiovascular risk markers in an obese group of young Irish subjects with type 2 diabetes and compared them with a matched group of obese nondiabetic subjects and a representative group of older subjects with type 2 diabetes. All of the subjects were from the same clinic, and all were matched for obesity and duration of diabetes.

RESEARCH DESIGN AND METHODS

— Eleven subjects with early-onset (age <25 years) and 14 subjects with typical-onset (age >40 years) type 2 diabetes were recruited, as well as 13 nondiabetic control subjects who were age and obesity matched to the young type 2 diabetic group. The protocol had ethical approval, and written informed consent was obtained. An oral glucose tolerance test was used to confirm glucose tolerance.

Intravenous glucose tolerance test

An insulin-modified frequently sampled intravenous glucose tolerance test was performed (8,9). Oral hypoglycemic agents were withheld for 7 days before the test. Subjects regularly treated with insulin were given short-acting insulin the night before the study, omitted on the morning of the study. At 8:00 A.M. after an overnight fast, blood samples were taken for glucose, insulin, lipid profile, and soluble cell adhesion markers. Subsequently, a 0.3-g/kg glucose bolus was administered intravenously over 1 min. At 20 min, a 0.05-units/kg insulin bolus (Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was administered intravenously and samples collected until 180 min. Minimal model analysis (8,10) was used to assess first-phase insulin secretion, insulin sensitivity (S_I), glucose effectiveness (S_G), and the disposition index (9).

Laboratory analysis

Serum insulin and C-peptide were measured by fluoroimmunoassays (AutoDelfia). Cholesterol and triglycerides were measured using enzymatic methods (Human liquicolor kits; Hitachi Modular). HDL and LDL cholesterol were measured directly with enzymatic methods (Randox direct kits; Hitachi Modular). Plasma glucose was measured using a glucose oxidase method and HbA_{1c} with a Hi-Auto A1c analyzer (Menarini HA 8140). GAD antibodies were measured using a direct radioligand assay (Centrak anti-GAD65; Medipan Diagnostica). Intercellular adhesion molecule, vascular cell adhesion molecule, E-selectin, and P-selectin were measured using monoclonal antibody enzyme-linked immunosorbent assays (R & D Systems). High-sensitivity C-reactive protein was measured using a nephelometric immunoassay (BNII nephelometer; Dade Behring).

RESULTS

Clinical characteristics

The clinical characteristics and metabolic parameters are shown in Table 1. All groups were similarly obese, although the young type 2 diabetic group was taller ($P = 0.002$) and weighed ~20 kg more ($P = 0.005$) than the older type 2 diabetic group. Both diabetic groups had a similar duration of disease of ~3 years. All subjects were negative for GAD antibodies. All but one (adopted) subject in the young type 2 diabetic group had a history of type 2 diabetes in two generations and at least one first-degree relative. Fifty-four percent of the obese control group and 50% of the older type 2 diabetic group had a history of type 2 diabetes in a first-degree relative. The young type 2 diabetic group was receiving oral hypoglycemic agents; one subject was treated with a combination of metformin and insulin. Three members of the young type 2 diabetic group and three of the control group had acanthosis nigricans, which was not present in the older subjects.

Metabolic variables

Glycemic control was similar between the young type 2 diabetic and older diabetic groups (HbA_{1c} 8.9 and 8.4%, NS). The

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

Table 1—*Clinical and metabolic characteristics of young obese, young type 2 diabetic, and older type 2 diabetic patients*

	Young obese	Young type 2 diabetes	Older type 2 diabetes
n (male/female)	13 (3/10)	11 (8/3)	14 (8/6)
Age (years)	19.0 ± 1.2	22.5 ± 1.2	53.7 ± 1.5*
Age at diagnosis (years)		19.5 ± 1.2	50.5 ± 1.5
Weight (kg)	104.7 ± 4.8	110.3 ± 5.9	91.1 ± 2.9*†
Height (m)	1.72 ± 0.02	1.79 ± 0.03	1.66 ± 0.02†
BMI (kg/m^2)	35.1 ± 1.3	34.2 ± 1.5	33.2 ± 1.0
Systolic blood pressure (mmHg)	121 ± 4	125 ± 4	130 ± 4
Diastolic blood pressure (mmHg)	77 ± 2	78 ± 2	77 ± 2
Waist-to-hip ratio			
Male	0.95 ± 0.01	1.03 ± 0.02	1.01 ± 0.01
Female	0.94 ± 0.03	0.97 ± 0.01	0.93 ± 0.03
Plasma glucose (mmol/l)	4.8 ± 0.2	11.2 ± 1.1*	11.2 ± 0.6*
Serum insulin (pmol/l)	146 ± 19	160 ± 39	79 ± 8*†
Total cholesterol (mmol/l)	4.1 ± 0.2	4.5 ± 0.2	5.3 ± 0.3
HDL cholesterol (mmol/l)	1.06 ± 0.06	0.96 ± 0.04	1.09 ± 0.04†
LDL cholesterol (mmol/l)	2.5 ± 0.2	3.2 ± 0.3	3.4 ± 0.3
Triglycerides (mmol/l)	1.26 ± 0.09	1.9 ± 0.2*	2.4 ± 0.5*
S_I [10^{-4} min^{-1}(μU/ml)]	1.47 ± 0.27	0.59 ± 0.11*	0.44 ± 0.07*
S_G (min^{-1})	0.022 ± 0.001	0.017 ± 0.002*	0.016 ± 0.001*
First-phase insulin secretion (μU/ml)	182.4 ± 34.0	32.9 ± 8.1*	18.0 ± 2.0*†
Disposition index (10^{-4} min^{-1})	242.0 ± 47.4	18.2 ± 4.9*	8.0 ± 1.7*†
hs-CRP (mg/l)	5.3 ± 1.5	6.8 ± 2.2	5.5 ± 1.0
ICAM (ng/ml)	354 ± 29	363 ± 28	403 ± 34
VCAM (ng/ml)	504 ± 73	689 ± 131	716 ± 49†
E-selectin (ng/ml)	76 ± 10	93 ± 8	100 ± 11
P-selectin (ng/ml)	118 ± 7	122 ± 8	83 ± 5*†

Data presented are means ± SE. *Significantly different from young obese. †Significantly different from young type 2 diabetes. hs-CRP, high-sensitivity C-reactive protein; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule.

young type 2 diabetic and young obese groups had fasting hyperinsulinemia, but despite a similar duration of diabetes, the older type 2 diabetic group had significantly lower fasting insulin ($P = 0.02$).

Fasting lipid profiles were similar in the two diabetic groups with elevated triglycerides and LDL cholesterol in comparison to the young obese control subjects. HDL cholesterol was significantly lower in the young type 2 diabetic group than either the obese control subjects or the older type 2 diabetic group.

All groups were insulin resistant [S_I for lean control subjects, age 28 ± 3 years, BMI 23.4 ± 1.2 kg/m^2, at this center 7.0 ± 1.3 10^{-4} min^{-1}/(μU/ml)]. Both diabetic groups were significantly more insulin resistant than the obese nondiabetic group. S_G was similar between both diabetic groups and significantly lower than the young obese group. Though severely blunted, first-phase insulin secretion and the disposition index were significantly greater in the young type 2 diabetic than in the older type 2 diabetic group, reflecting a less-advanced loss of β-cell function in the young type 2 diabetic subjects.

Inflammatory and soluble cell adhesion markers

Soluble cell adhesion molecules and high-sensitivity C-reactive protein were elevated in all groups. In the young type 2 diabetic group, intercellular adhesion molecules, vascular cell adhesion molecules, and E-selectin were positively associated with fasting serum insulin ($r = 0.84$, $P = 0.002$; $r = 0.79$, $P = 0.007$; and $r = 0.85$, $P = 0.002$, respectively) and the first-phase insulin secretory response ($r = 0.84$, $P = 0.002$; $r = 0.77$, $P = 0.01$; and $r = 0.86$, $P = 0.001$, respectively). P-selectin was associated with fasting plasma glucose ($r = 0.65$, $P = 0.04$).

CONCLUSIONS — Early-onset type 2 diabetes increases the lifelong duration of diabetes and the risk of diabetes-related complications, particularly cardiovascular disease (11,12). Rare monogenic forms of early-onset non–type 1 diabetes, such as maturity-onset diabetes of the young and mitochondrial diabetes, vary in their potential to cause cardiovascular complications but are less aggressive than typical type 2 diabetes. Our young diabetic subjects have classical features of type 2 diabetes and are dyslipidemic in comparison to age-matched obese control subjects, with a reduction in HDL cholesterol and an elevation of LDL cholesterol and triglycerides. Our subjects are more dyslipidemic than a previously reported group of obese 12-year-old children who were shown to have arterial wall stiffness and endothelial dysfunction (13). Soluble cell adhesion markers were similar to, or greater than, other published studies of type 2 diabetic subjects (14–16). High-sensitivity C-reactive protein >5 mg/l (in all groups) is consistent with a markedly increased risk of cardiovascular events (17,18). In conclusion, young Caucasian subjects present with type 2 diabetes exactly the same as typical type 2 diabetes of later onset, characterized by severe obesity, insulin resistance, and loss of first-phase insulin secretion. This cohort has, in addition to these metabolic features, a marked dyslipidemia and evidence of high risk for accelerated cardiovascular complications.

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