

OBSERVATIONS

Anti-Pituitary Antibodies and Hypogonadotropic Hypogonadism in Type 2 Diabetes: In Search of a Role

Subnormal testosterone concentrations have been found in 25% of men with type 2 diabetes in association with inappropriately low luteinizing hormone and follicle-stimulating hormone concentrations (1), which suggests that the primary defect may be at the hypothalamic-hypophyseal level. Circulating anti-pituitary antibodies (APAs) were first detected by Kobayashi et al. (2) in sera from 91 patients with type 2 diabetes at a relatively high frequency (24.2%). Thus far, a possible role of pituitary autoimmunity in diabetic patients with hypogonadotropic hypogonadism (HH) has never been investigated.

Ninety-five consecutive male patients with type 2 diabetes and aged >35 years were recruited among those attending the Unit of Endocrinology and Metabolic Diseases at the Second University of Naples from September 2010 to September 2012. Patients with severe obesity (BMI >35 kg/m²) were excluded. The diagnosis of isolated HH included a serum testosterone level <12.0 nmol/L, normal or low gonadotropin concentrations, and symptoms and signs of androgen deficiency. Erectile dysfunction was diagnosed in the presence of an International Index of Erectile Dysfunction-5 score <21. APAs were assessed by an indirect immunofluorescence method on cryostat sections of young baboon pituitary gland (3). Immunostaining patterns were classified as type 1 (cytoplasmic fluorescence of few pituitary cells) and type 2 (diffuse fluorescence in almost all cells in the pituitary section) (4).

Thirty-seven diabetic patients had HH (group 1), and none showed alteration of resonance magnetic imaging at the hypothalamic-pituitary region. Compared with 100 age-matched control subjects (Table 1), all diabetic patients showed an increased prevalence of APAs

(26/95, 27.3%, *P* < 0.001), which was highest in group 1 (15/37, 40%, *P* = 0.002 vs. group 2). High titers (≥1/16) of APAs were detected in all patients of group 1, with a type 1 immunostaining pattern; in group 2 (no HH), 10 of 11 patients presented APAs at low titer (<1/8), with most presenting a type 2 immunofluorescence pattern. In both groups 1 and 2, APAs were detected the most (70–80%) in newly diagnosed patients. APAs selectively immunostained gonadotrophs and only rarely some prolactin-secreting cells in group 1, whereas in group 2 none immunostained gonadotropin-secreting cells.

Our results confirm the high prevalence of HH in patients with type 2 diabetes and suggest a possible autoimmune pathogenesis of HH in some of them, as indicated by the presence of APAs at high titers with an immunostaining pattern predictive of hypopituitarism (4) and supported by the identification of these

antibodies as targeting gonadotropin-secreting cells. We also found the highest APA prevalence in HH patients with newly diagnosed diabetes; this suggests that some APAs may be harmless and tend to disappear over time, whereas others, which persist over time, can exert biological function. This may also explain the results of Takeda et al. (5), who found APAs in only 2.2% of type 2 diabetic patients with long duration of disease (>10 years on the average). Prospective studies are needed in order to clarify the natural history of HH in type 2 diabetes and whether APAs may play a significant role.

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Table 1—Characteristics of type 2 diabetic patients and control subjects

Parameter	Diabetes with HH: group 1	Diabetes without HH: group 2	Control subjects	<i>P</i>
<i>n</i>	37	58	100	
Age (years)	54.2 ± 10.7	52.1 ± 10.5	53.4 ± 10.9	0.841
Newly diagnosed, <i>n/n</i>	18/37	21/58		0.323
Duration of disease (years)	5.8 ± 5.3	5.5 ± 5.1		0.567
BMI (kg/m ²)	32.1 ± 3.4	30.6 ± 4.1	26.7 ± 4.3	<0.01
Waist (cm)	107.7 ± 10.6	104.5 ± 11.4	98.3 ± 12.1	<0.01
Hypertension, <i>n/n</i>	15/37	26/58	19/100	<0.001
Fasting glucose (mg/dL)	140.2 ± 32.3	145.6 ± 30.9	94.3 ± 12.7	<0.001
A1C (%)	7.5 ± 1.4	7.4 ± 2.3	5.7 ± 1.9	<0.001
A1C (mmol/mol)	58	57	39	<0.001
HOMA index	4.2 ± 1.5	4.5 ± 1.7	2.1 ± 0.8	0.005
HDL cholesterol	44.6 ± 7.2	48.9 ± 11.6	49.5 ± 9.2	0.02
LDL cholesterol	112 ± 30.5	110 ± 24.9	91.2 ± 47.4	0.01
Triglyceride	159.7 ± 69.7	144.7 ± 53.3	141.5 ± 51.9	0.04
Diabetes therapy				
Insulin/OAD/diet/none, <i>n/n/n/n</i>	5/11/3/18	7/26/9/16		
FSH (UI/L)	2.2 ± 1.7	3.4 ± 1.5	3.2 ± 1.8	0.432
LH (UI/L)	1.7 ± 1.2	3.8 ± 1.6	3.8 ± 1.7	0.05
Testosterone (nmol/L)	8.9 ± 2.2*	17.1 ± 4.5	17.4 ± 3.9	<0.001
SHBG (nmol/L)	33.9 ± 4.6	35.8 ± 4.5	50.3 ± 8.3	<0.001
Free testosterone (pmol/L)	217.4 ± 12.1*	491.8 ± 168.5	535.3 ± 162.4	<0.001
ED, <i>n/n</i> (%)	25/37 (67)	33/58 (56)	26/100 (26)	<0.001
APAs, <i>n/n</i> (%)	15/37 (40)**	11/58 (18)	5/100 (5)	<0.001
Titer ≥1/16	15	1	0	
Titer <1/16	0	10	5	
APAs: newly diagnosed, <i>n/n</i> (%)	11/15 (73.3)	9/11 (81.8)		
APAs: chronic disease, <i>n/n</i> (%)	4/15 (26.6)†	2/11 (18.1)‡		
Type 1 fluorescence pattern	15	3	0	
Type 2 fluorescence pattern	0	8	5	

Data are means ± SD or percentages unless otherwise indicated. ANOVA with Bonferroni correction and χ^2 or Fisher exact test. ED, erectile dysfunction; FSH, follicle-stimulating hormone; HOMA, homeostasis model assessment; LH, luteinizing hormone; OAD, oral antidiabetes drugs. **P* < 0.001 vs. group 2. ***P* = 0.002 vs. group 2. †*P* = 0.028 vs. newly diagnosed. ‡*P* = 0.01 vs. newly diagnosed.

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revised the manuscript for important intellectual content, gave final approval of the article, provided study materials, provided statistical expertise, and collected and assembled data. L.O. analyzed and interpreted data, critically revised the article for important intellectual content, gave final approval of the article, provided study materials, and collected and assembled data. A.D.B. analyzed and interpreted data, critically revised the article for important intellectual content, gave final approval of the article, and provided study materials. D.G. analyzed and interpreted data, critically revised the article for important intellectual content, gave final approval of the article, obtained funding, and provided administrative, technical, or logistic support. K.E. analyzed and interpreted data, drafted the article, critically revised the article for important intellectual content, gave final approval of the article, obtained funding, and provided administrative, technical, or logistic support. D.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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