In conclusion, in this prospective 2-year study, cholesterol-lowering therapy was associated with significant reductions in the progressive rise in serum creatinine and urinary protein excretion in 16 NIDDM patients with nephropathy. In addition to the results previously presented [1], these observations provide further support for the potential beneficial effect of cholesterol-lowering therapy on the progression of nephropathy in patients with NIDDM.

Yours sincerely,
K. S. L. Lam, I. J. Lauder

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Normal values of first-phase insulin response to intravenous glucose in healthy Italian children and adolescents

Dear Sir,
Loss of first-phase insulin response (FPIR) to an intravenous glucose tolerance test (IVGTT) in first-degree relatives of diabetic patients with high levels of islet cell antibodies (ICA) and/or insulin autoantibodies, is highly predictive for insulin-dependent diabetes mellitus (IDDM) [1, 2]. Normal values of FPIR for adult subjects have been established [1] but very few papers have been published on the paediatric population [3, 4]. The present study reports normal values of FPIR to IVGTT in a large paediatric population.

Working in close collaboration 21 Italian paediatric diabetes units tested 138 healthy subjects (47 females and 91 males) aged 3–20 years (mean: 10 ± 3.7 (SB) years), without endocrinopathy, short stature, obesity, family history of IDDM, history of drugs, history of hypoglycaemia or fasting plasma glucose more than 5.5 mmol/l. In all subjects sex, age, weight, height, BMI and pubertal stage (according to Tanner) were recorded along with fasting plasma glucose, HbA_{1c}, ICA and antibodies against glutamic acid decarboxylase (GAD_{65}). Subjects were divided into three groups on the basis of pubertal stage: Group 1 at stage I ($n = 70$), Group 2 at stages II–III ($n = 41$) and Group 3 at stages IV–V ($n = 27$). Before the study, the protocol was approved by the local institutional review board for human experimentation in each centre, and parents gave their written informed consent.

The procedure for the IVGTT followed the guidelines of the National Diabetes Data Group [5]. FPIR was expressed as the sum of the insulinaemia values at 1 and 3 min. Fasting insulinaemia/glycaemia (I/G) ratio was also evaluated. Plasma glucose was measured by the glucose oxidase technique (glucose autoanalyzer, Beckman, Brea, California, USA), and HbA_{1c} levels using automatic HPLC (Bio-Rad, Brussels, Belgium). For determination of ICA, each center sent frozen serum from all subjects to Padova University [6]. For GAD_{65} antibodies each center sent frozen serum to Karolinska Institute, Stockholm [7]. In each diabetes center blood samples for insulin assay were centrifuged at 4 °C and then plasma was kept at −20 °C, until analysis. The centers then sent all plasma samples for the measurement of insulinaemia to Parma University, for radioimmunoassay (Radim kit; Rome, Italy). The inter- and intra-assay coefficients of variation were 8.2 % and 6.9 % for low values and 7.7 % and 6.0 % for high values, respectively. Since the FPIRs during IVGTT were not normally distributed, the results are expressed as percentiles. Spearman's rank test was used to correlate fasting I/G ratio with age and pubertal stage (groups 1 to 3).

A significant positive correlation was found between FPIR and chronological age ($p = 0.046$), in spite of the wide range of results observed. An increase in percentile values of FPIR was also found from Group 1 (prepubertal) through to Group 3 (pubertal) without significant differences between boys and girls (Table 1). Moreover, a significant positive relationship was observed between FPIR and pubertal stages ($p = 0.0043$) and BMI ($p = 0.0052$). Also fasting I/G ratio showed a significant correlation with chronological age ($p = 0.0015$) and pubertal stages ($p = 0.0015$) in all subjects.

In our study we demonstrated that FPIR percentile values to an IVGTT increase from the younger children to the oldest group and from prepubertal to pubertal stages. Fasting I/G ratios showed a similar age- and pubertal-related pattern. Similar results have been reported by other authors who evaluated FPIR in ICA-negative first-degree relatives of IDDM patients [8] and in normal subjects [3, 4]. No significant difference was found between our boys and girls in Group 1 to Group 3 in terms of FPIR as Smith et al. [9] and Allen et al. [3] also reported, suggesting that gender does not affect insulinaemia changes during puberty. As children enter puberty at different chronologic ages, and their development is more related to their stage of puberty, we suggest that an accurate clinical staging of puberty rather than chronologic age may make more sense when interpreting IVGTT in young subjects at risk of IDDM followed-up throughout puberty. In fact, children may show rapid growth with pubertal development and thus a changing hormonal milieu that influences insulin sensitivity. Therefore, during the follow-up of children and adolescents at risk of IDDM it is very important to compare FPIR values taking into account pubertal stage instead of chronological age.

Corresponding author: Dr. R. Lorini, Department of Pediatrics, IRCCS Policlinico San Matteo, P.le C. Golgi, 2, I-27100 Pavia, Italy
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Table 1. First-phase insulin response (FPIR) in 138 healthy Italian children and adolescents, divided into three groups according to pubertal development

Group	Subjects *n*	Sex Female/ male	Tanner pubertal stage	FPIR (μU/ml) range	1st	3rd	5th	10th	25th	50th	75th	90th	95th	97th	99th
1	70	20/50	I	53.0–310.0	53.0	61.4	66.6	72.0	93.5	142.1	187.7	223.7	258.0	260.7	310.0
2	41	17/24	II–III	53.6–390.4	53.6	64.5	65.9	91.5	99.1	148.1	202.0	304.0	330.2	358.3	390.4
3	27	10/17	IV–V	76.6–365.1	76.6	76.6	86.0	105.0	126.6	163.5	256.4	324.6	345.2	365.1	365.1

Yours sincerely,
R. Lorini, M. Vanelli on behalf of the Prediabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetology (SIEDP)*

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Age-dependent association of HLA-A24 in Japanese IDDM patients

Dear Sir,
We were interested to read the recent article by Dr. Awata et al. [1]. However, the authors mentioned only HLA class II age-dependent heterogeneity in Japanese insulin-dependent diabetic (IDDM) patients [1]. It has already been reported that HLA-A24 in Japanese IDDM patients shows a significant association with complete beta-cell destruction, suggesting that A24 promoted pancreatic beta-cell destruction in co-operation with other IDDM-susceptible HLA antigens [2]. Adult-onset IDDM has been reported to show a slower progression of pancreatic beta-cell destruction with milder symptoms than juvenile-onset IDDM at the time of diagnosis in both Caucasian and Japanese patients [3, 4]. In Japanese patients, while associations of the HLA class II genes with IDDM have been established, little has been reported regarding the possible age-dependency of HLA class I.

A total of 340 unrelated IDDM patients (200 women and 140 men; mean age of diabetes onset 13.8 ± 6.5 years [range 0–30 years]) were randomly selected from out-patients attending the Diabetes Center, Tokyo Women's Medical College (TWMC) and Hokkaido IDDM Treatment Group (HITG), Japan. All the patients were Japanese and were residents of the Tokyo and Hokkaido areas. There are no regional variations in IDDM risk in Japan [5]. The diagnosis of IDDM was made according to the guidelines of the National Diabetes Data Group [6]. In addition, a daily urinary reactive C-peptide value of less than 6.6 nmol/day [2] or anti-glutamic acid decarboxylase (GAD) antibody value of more than 8 U/ml [7] was used to define IDDM. At the time of this study, all the patients

Corresponding author: Dr. Y. Uchigata, Diabetes Center, Tokyo Women's Medical College, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan