422

DETERMINANTS OF FIRST & SECOND PHASE INSULIN SECRETION (FPIS, SPIS) IN HEALTHY ADOLESCENTS. S. Arslanian and A. Austin, Children's Hospital of Pgh., Pgh., PA & Children's Hospital National Medical Center, Washington, D.C., U.S.A.

Diminished FPIS is proposed to be a metabolic marker in the diagnosis and follow up of prediabetes in trials of intervention to prevent IDDM. However, data are scarce regarding the determinants of insulin secretion in normal children. This study aimed to investigate the relationship of physical fitness (FP) and body composition (BC) to in-vivo insulin secretion during a hyperglycemic clamp in 12 (6M/6F) healthy adolescents (Tanner II-IV). Age was 14.0±0.6 yrs and body mass index (BMI) 19.1±0.5 kg/m². BC was assessed by bioelectric impedance plethysmography; PF by maximum oxygen consumption (V_{O2max}) during progressive bicycle ergometry; and FPIS (0-10 min) and SPIS (10-120 min) during a 120 min hyperglycemic clamp (125 mg/dl above fasting plasma glucose). FPIS was 75.1±9.0 µU/ml and SPIS 105.0±9.6 µU/ml. FPIS and SPIS were inversely correlated with V_{O2max} (r=-.60 p=0.02, r=-0.70 p=0.005), with no relationship to BC or % body fat. % body fat showed an inverse relationship (r=-0.53 p=0.04) to insulin sensitivity index. Males had significantly lower % BF, higher V_{O2max} and higher insulin sensitivity compared with females, but no difference in FPIS and SPIS.

These results suggest that the lack of compensatory hyperinsulinemia with increasing body fat, in nonobese healthy adolescents, is due to the strong relationship of insulin secretion to physical fitness which may override the contribution of body composition.

423

INCIPIENT DIABETIC NEPHROPATHY IN IDDM ADOLESCENTS: MICROALBUMINURIA PRECEDES THE RISE IN SYSTEMIC BLOOD PRESSURE. E. Socher, I. Poon, JW Balfe, D. Daneman, Dept of Paediatrics, University of Toronto, Hospital for Sick Children, Toronto, Canada M5G 1X8.

The temporal relationship between the onset of diabetic nephropathy and the development of systemic hypertension remains uncertain. Our aim was to evaluate whether differences in systemic BP in IDDM adolescents with (MA) and without (nMA) microalbuminuria could be detected by ambulatory blood pressure monitoring (aBPM). 20 IDDM adolescents (9 MA, 11 nMA), well matched for sex, age (MA 17.1±1.8 yr, nMA 17.3±1.5 yr), body mass index (23.3±2.2 and 24.3±3.0 kg/m²) and IDDM duration (8.8±4.2 and 8.2±3.6 yr). HbA_{1c} (9.4±2.0 and 8.6±1.3%), and creatinine clearance (1.46±0.77 and 1.63±0.42 ml/s/1.73 m²) were similar in the 2 groups; they differed only in albumin excretion rate: MA group 111±171, nMA group 6.2±3.7 µg/min (p<0.01). 24 hr aBPMs were obtained using the Takeda tm2422 machine (every 15 min from 1000-2200 h, and hourly from 2200-1000 h). We compared the two groups in terms of 24 h mean arterial (MAP), systolic (s) and diastolic (d) BPs, mean s and d daytime and nighttime BPs, percentage of s and d readings >95th percentile for age; there were no significant differences in any of the BP measurements. The % sBP >95th percentile tended to be higher in those with MA (28±25%) than those in the nMA (15±15) group, but this difference was not statistically significant. Other studies have shown significant BP differences in aBPM in IDDM subjects with and without MA; however, these subjects were older and had longer duration disease. Our data suggest, however, that systemic hypertension may be a consequence of the earliest changes of diabetic nephropathy and not a prerequisite for its development. A longitudinal study is warranted to assess changes in aBPM profiles in these individuals as they progress towards overt nephropathy.

* 424

BETA-CELL DESTRUCTION IN INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)- A STEPWISE SERIES OF EVENTS

B.G. Cuartero^{1,3}, D. Hougaard², F. Pociot¹, J. Argente³, L.I. Larsson², J. Nerup¹, Steno Diabetes Center¹, State Serum Institute², Denmark and The Hospital of Niño Jesús, Madrid, Spain.

Interleukin-18 (IL-18) is cytotoxic to beta-cells. IL-18 induces a "race" between protective, (e.g., oxidative stress proteins, manganese superoxide dismutase (MnSOD) and deleterious (free oxygen and nitric oxide radicals) events in all cell types. By means of non-radioactive *in situ* hybridization, Northern and dot blot analysis and functional studies, IL-18 (150 pg/ml) induction of heme oxygenase (HO) 1 and 2, MnSOD and nitric oxide synthases (NOS) was studied in isolated rat islets *in vitro* during 0-48 h of exposure to IL-18. HO1, HO2 and MnSOD mRNAs were maximally induced after 1, 6 and 24 h, respectively and the inducible form of NOS (NOS2-release) after 6-12 h and the constitutive, calcium-dependent NOS after 24-48 h. Beta-cell function (insulin release) deteriorated after 6 h, maximally at 24 h. This suggests that in beta-cells the deleterious events prevail. Thus, beta-cell destruction in the initial phases of IDDM pathogenesis may be a stepwise, well-defined series of molecular events.

425

DECREASED INSULIN RESPONSE TO GLUCOSE IN ISLET CELL ANTIBODY-NEGATIVE SIBLINGS OF TYPE I DIABETIC CHILDREN. J.-C. Carel and P.F. Bougnères, INSERM U342 and Pediatric Endocrinology, Hôpital Saint Vincent de Paul, Paris, FRANCE.

In order to determine immune and possibly non immune factors determining first phase insulin response to glucose (FPIRG) in siblings of type I diabetic patients, we performed a simplified intravenous glucose tolerance test in 170 normal children, 98 ICA negative and 12 ICA positive siblings of type I diabetic children. Normal children (age 3-16, 9.8±0.3 years) were patients hospitalized for reasons not interfering with glucose homeostasis and investigators' and colleagues' children. ICA negative siblings were similar to controls in respect to age (2-16, 9.3±0.4 years) and body mass index. Insulin was measured 1 and 3 minutes after i.v. injection of 0.5 mg/kg b.w. of 50% dextrose in 2.5 minutes. In normal children, FPIRG (1 + 3 minutes insulin measurements) increased with age, giving a linear regression curve of insulin 1+3 = 10.5*age + 11.3 (r=0.45). In comparison ICA negative siblings had a significantly lower FPIRG (86±6 vs 115±6 µU/ml, p<0.005). This difference was distributed evenly throughout the age range giving a linear regression curve of: insulin 1+3 = 4.6*age + 41 (r=0.3). None of the ICA negative siblings developed diabetes after a follow up of 4.5±1.1 years. ICA positive (≥20 JDF units) siblings had a FPIRG at first testing comparable to that of ICA negative siblings (74±13 µU/ml, p<0.02 vs controls). Two of them became diabetic. We conclude that ICA negative siblings of diabetic patients have a decreased FPIRG. Further investigations are needed to elucidate the basis for this difference.

426

PRELIMINARY RESULTS OF A TRIAL OF LOW DOSE CYCLOSPORINE IN PRECLINICAL TYPE I DIABETES. J.-C. Carel and P.F. Bougnères, INSERM U342 and Pediatric Endocrinology, Hôpital Saint Vincent de Paul, Paris, FRANCE.

An open pilot trial of low dose cyclosporine was initiated in first degree relatives of type I diabetic children with the following criteria: age<12 years, HLA haploidentical or identical to the diabetic proband, ICA≥20 JDF units, first phase insulin response to glucose (1+3 minutes) repeatedly <40µU/ml, glucose intolerance according to NDDG criteria.

Initial characteristics									
	age	HLA DR	HLA shared	ICA JDFU	IAA (%)	GAD -Ab	1+3 insulin	FBG mg/dl	OGTT 2h BG
C.W.	6	3/4	twin	160	2.4	++	35	104	150
V.W.	6	4/7	1	20	2	+	31	106	157
D.M.	9	4/8	1	320	9.3	-	37	76	151
A.M.	6	3/4	1	160	1.9	-	19	95	185

Data at last evaluation									
	follow up (mo)	CyA mg/kg/d	ICA JDFU	IAA (%)	GAD -Ab	1+3 insulin	FBG mg/dl	OGTT 2h BG	
C.W.	50	3.5	320	1.9	+++	69	77	72	
V.W.	24	6	5	1.1	-	7	180	440	
D.M.	8	6.5	320	23	-	109	76	97	
A.M.	4	7.5	160	1.6	-	31	61	149	

We conclude that cyclosporine can restore insulin secretion and glucose tolerance in preclinical diabetes. Failure in patient V.W. might be due to a long period of low insulin secretion prior to immunosuppression. The efficacy of this approach should be tested in a larger number of patients.

427

EARLY CHANGES IN INSULIN SECRETION AND SENSITIVITY IN OBESE CHILDREN. C. Le Stunff, J. Lalau-Keraly, P.F. Bougnères, Pediatric Endocrinology U342 INSERM, St Vincent de Paul, Paris, FR.

Hyperinsulinism and insulin resistance characterize obesity in adults. The natural history of these abnormalities was studied in 16 children aged 12.8 ± 1.4 years with obesity of 0.5-8.5 yr duration, compared with 11 age-matched children. Fasting insulin was normal initially, then increased with obesity duration (r=0.68, p<0.005), not with children age (r=0.30, NS). In contrast insulin response to a normal meal was increased by 75% in the first years of obesity without later augmentation (p<0.0005).

Neither fasting nor post-prandial insulin correlated with weight.

Insulin sensitivity was evaluated with a 3 step hyperinsulinemic euglycemic clamp. The maximal rate of glucose uptake was initially normal (19±1 vs 21±1 mmol/m².min), then decreased with obesity duration (r=0.66, p<0.005) and children age (r=0.60, p<0.01), indicating the development of insulin resistance. Fasting insulin and maximal glucose uptake were inversely related (r=0.65, p<0.005). Insulin concentration corresponding to half-maximal uptake was normal (677 vs 654 pM) and did not vary with obesity duration. Abnormal insulin response to meals is an early metabolic alteration in obesity, followed by the co-development of insulin resistance and fasting hyperinsulinemia.