

## ● 428

TIME COURSE OF INCREASED LIPID AND GLUCOSE OXIDATION DURING THE EARLY PHASE OF CHILDHOOD OBESITY. C. Le Stunff and P.F. Bougnères, Pediatric Endocrinology, INSERM U342, St Vincent de Paul, Paris, FR.

To determine the time-course of metabolic dysfunctions in recent active obesity, we used indirect calorimetry in basal overnight conditions in 31 children (16M/15F) aged 11.9±0.4y with obesity duration 1-11y compared with 14 controls. Obese children produce 15% more energy than controls (p<0.005), oxidize twice as much lipids (56±4 mg/min) than controls (25±5 mg/min, p<0.0005), so that lipid oxidation provided 61±6% of overall energy production in the obese (33±3% in controls, p<0.0005). Glucose oxidation was only 93±6 mg/min in the obese vs 136±6 mg/min in the controls (p<0.0005). The results were similar when normalized to body surface or lean body mass. While increased lipid oxidation was already present in the earlier stages of obesity, decreased glucose oxidation appeared only after ≥4y of obesity, and worsened with obesity duration (r=0.72, p<0.0005). We hypothesize that increased lipid oxidation being one of the earlier abnormalities observed in recent obesity, it may induce a progressive decrease of glucose oxidation through the mechanisms described by P. Randle and lead to insulin resistance and increased fasting insulin secretion.

## ● 429

THE EFFECTS OF rhIGF-1 ON GH, IGF-BP3 AND IGF-BP1 CONCENTRATIONS AND INSULIN SENSITIVITY IN ADOLESCENTS WITH INSULIN DEPENDENT DIABETES MELLITUS (IDDM). ID Cheetham(1), J.M. Holly(2), A.M. Taylor(3), S.C. Wyfan-Jones(2), J. Jones(3), D. Harris(1), D.B. Dunger(1). Dept. Paediatrics, University of Oxford(1), Dept. Chemical Endocrinology, St. Bartholomews Hospital(2), Institute of Child Health, London(3).

Insulin resistance and poor growth during adolescence in IDDM have been linked with reduced IGF bioactivity and elevated GH levels. In a double blind placebo controlled study we have examined the effects of a single sc injection of rhIGF-1 (40ug/kg) on total IGF-1, IGF-BP1, IGF-BP3 and GH concentrations in 9 adolescents with IDDM (aged 14-18y, Tanner Stage 4 or 5, HbA1c range 7.1-17%). rhIGF-1 or placebo were given at 18.00h, blood glucose was clamped around 5.0mmol/L between 02.00-08.00h to assess insulin sensitivity, and sampling was continued for a total of 22 h. Peak IGF-1 levels were achieved at 5.5h and declined with a T/2 of 17.3h. Mean levels were 350±26 ng/ml after rhIGF-1 vs 204±21 ng/ml on control night (p<0.001). Both IGF-BP1 and IGF-BP3 tended to be higher after rhIGF-1. IGF bioactivity was increased by 56%. Overall mean GH concentrations were reduced after rhIGF-1 (16.9±3.2 vs 27.7±4.6 μU/L, p<0.001) and there was no evidence of rebound GH secretion over 22h. During the stable clamp period, insulin requirements following rhIGF-1 were reduced (0.25±0.12 vs 0.31±0.07 μU/kg/min, p<0.03) as were levels of free insulin (31.9±2.7 vs 67.9±16 μU/L, p<0.001). B0Hbutyrate and acetoacetate tended to be lower during rhIGF-1 administration whereas lactate levels were unchanged. rhIGF-1 administration in adolescents with IDDM results in a significant reduction in GH concentrations and insulin requirements either as a result of increased free IGF-1 or reduced GH concentrations.

## 430

THE RELATIONSHIP BETWEEN GH, IGF-1, IGFBP-3 AND GH BINDING PROTEIN (GHBP) IN NORMAL AND ADOLESCENTS WITH INSULIN-DEPENDENT DIABETES MELLITUS (IDDM).

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The relationship between GH, IGF-1, GHBP and IGFBP-3 level in normals and adolescents with IDDM have not been adequately defined. We have measured IGF-1 and IGFBP-3 (RIA), GHBP (LIFA) in samples from 89 normal (40F, 49M) and 94 IDDM (54F, 40M) subjects matched for puberty stage (G1-S, B1-S). Coincident mean overnight GH data (15 minute sampling, 20.00h-08.00h, IRMA) were available from 33 normal and 30 IDDM subjects. Maximal IGF-1 levels were noted at G4, B3 in normals and G5, B3 in IDDM. Levels were significantly lower in diabetics at G5 (p<0.05) and B4 (p<0.002). In normals and diabetics maximal IGFBP-3 were noted at B3 (6.7±1.2 ng/ml and 5.3±1.0 ng/ml respectively) and G4 (6.4±0.7 ng/ml and 4.6±1.0 ng/ml) with reduced levels in the diabetics at B2, B4 and G2-S. GHBP did not change significantly during puberty in normals or IDDM but the latter had lower levels at B3-4, G1-3. GH concentrations were greatest at B2-3 and G4-5 in normals and were greater in diabetics at all stages. In normals there was a correlation after log transformation between GH and GHBP (r=0.59, p<0.001) and IGF-1 and IGFBP-3 (r=0.51, p<0.001). In IDDM the relationship between IGF-1 and IGFBP-3 (r=0.55, p<0.001) was retained, there was no correlation between GH and GHBP, however a weak correlation between GH and IGF-1 (r=0.36, p<0.04) was evident. During puberty GH is increased, yet IGF-1, IGFBP-3 and GHBP are reduced in IDDM. The normal negative correlation between GH and GHBP is lost. The relationship between IGF-1 and IGFBP-3 is similar in both groups of subjects.

## \* 431

ANTI-RETROVIRUS ANTIBODIES IN INSULIN-DEPENDENT DIABETIC CHILDREN AT DIAGNOSIS AND DURING 1-2.6 YRS FOLLOW-UP.

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Viruses have long been implicated in the pathogenesis of insulin-dependent diabetes (IDDM). Recently it has been observed that β-cell specific expression of endogenous retrovirus is associated with the development of insulinitis and diabetes in non-obese diabetic (NOD) mice. The aim of our study was to evaluate the presence of retroviral markers in 27 newly diagnosed IDDM children, aged 9.6±3.8 yrs (range 3-15.9 yrs). In all patients anti-islet cell (ICA), anti-insulin (IAA), anti-thyroid (TgA and MSA) antibodies were evaluated and HLA typing was performed. Virological studies included the search for anti-retrovirus (HTLVs) antibodies using the western immunoblotting (WIB) and the HTLV-I DNA amplification by polymerase chain reaction (PCR) for tax/rex pol, and gag (P15) regions. At onset of IDDM ICA were present in 19 patients (70%) and IAA in 2 of them, while all patients were negative for TgA and MSA. HTLVs antibodies were detected in 10 out of the 27 patients (37%) while no HTLV-I DNA sequences were detected using our PCR assay. Interestingly, we have observed a frequent association between the presence of HTLVs antibodies and the presence of HLA-DR3 and DQ2 antigens. Until now, during 1-2.6 yrs follow-up we could reevaluate 13 children, four with HTLVs antibodies and 9 without antibodies. In 2/4 patients the HTLVs antibodies disappeared and in another boy, with five antibodies at onset of IDDM (directed against p 19, rgp21, p24, p26, p36) only one antibody (directed against rgp 21) was constantly present.

## 432

AUTOANTIBODIES IN NEW ONSET CHILDHOOD IDDM. C.F. Verge, N.J. Howard, \*T. Tuomi, M. Egan, H. Hulinska, T. Arundel, I. Hulinsky, \*P. Z. Zimmet and M. Simik. Ray Williams Institute of Endocrinology, Royal Alexandra Hospital for Children, Sydney, & \*The Centre for Molecular Biology, Monash University, Melbourne, Australia.

This study aimed to measure autoantibody levels in an epidemiologically defined population of new onset diabetic children. All incident cases aged under 15 years in New South Wales were ascertained for a 2 year period. A serum sample was available from 273 of the patients (84%). Islet cell antibodies (ICA) were measured by indirect immunofluorescence on cryostat sections of human pancreas (detection limit: 20 JDFU). Antibodies against Glutamic Acid Decarboxylase (GAD) were measured with a radioimmunoassay on 176 samples collected within 4 days of the start of insulin therapy. Results greater than 3 standard deviations above the mean of a paediatric control group were considered positive for GAD (≥ 25 units) and IAA (≥ 33 nU/ml). Thyroid peroxidase antibodies (TPO) were measured by ELISA. Overall, 71% of the samples were positive for ICA, 65% for GAD, 65% for IAA and 10% for TPO. Only 6.4% of sera were negative for all three of ICA, GAD and IAA. 11.5% of sera were negative for both GAD and IAA. More females (71%) were positive for GAD than males (59%) P = 0.037. There was no significant correlation between GAD or ICA and age. IAA positivity was 91% in the 0-4 yrs age-group, 70% in the 5-9 yrs group and 49% in the 10-14 yrs group (χ<sup>2</sup><sub>adj</sub> = 18.14, P < 0.0001). TPO positivity was 2% in the 0-4 yrs group, 10% in the 5-9 yrs group and 13% in the 10-14 yrs group (χ<sup>2</sup><sub>adj</sub> = 3.84, P = 0.05). ICA correlated with both GAD (r = 0.26, P < 0.0001) and IAA (r = 0.21, P = 0.0055), but there was no significant association between GAD and IAA levels. Conclusions: 93.6% of new onset diabetic children were positive for at least one of ICA, GAD or IAA and 10% were positive for TPO. GAD levels had a significant correlation with ICA. There was no age association for ICA or GAD, but IAA were more prevalent at diagnosis in younger children and TPO were more prevalent in older children.

## 433

FOLLOW-UP OF CHILDREN FROM BACKGROUND POPULATION WITH ISLET CELLS ANTIBODIES (ICA)

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ICA have been tested in 13 390 unselected school-children (age 6-17 yr) as part of a research program on risk factors for Type 1 diabetes in background populations. ICA were detected by the immuno-fluorescence technique using a single human pancreas (limit of detection: 4 JDFu). The overall prevalence of ICA-positivity in these children from background population was 1.5%, and distributed as follows according to ICA titres : 28 sera were found with ICA ≥ 20 JDFu (0.2%) and 170 between 4-20 JDFu (1.3%), the majority of the sera were positive at the detection limit of the assay. The 2 groups of ICA+ and - children did not significantly differ in term of age, distribution of fasting plasma glucose and family history of diabetes. There is a tendency, although not significant, for an increased frequency of HLA-alleles encoding for an amino-acid different from aspartic acid (NA) at the position 57 of the DQB1 chain in the children with high ICA titres in comparison to ICA-negative children :

132 (67%) ICA+ - children have been followed for a median duration of 22 mth. ICA titres were remarkably stable in the group with high ICA titres, among whom one boy has become diabetic; among the remaining ICA+ children, 3 children converted into values > 20 JDFu, and 15% became negative among whom 11 were previously measured at the detection limit. This study emphasizes that, given the low incidence of the disease in France, ICA would probably not be sufficient to predict the subsequent development of Type 1 diabetes in school-children.

NA 57 DQ B1	ICA ≥ 20 JDFu n=14	ICA 4-20 JDFu n=84	ICA- (< 4 JDFu) n=93
2	8 (57%)	39 (46%)	28 (30%)
1	4 (29%)	30 (36%)	41 (44%)
0	2 (14%)	15 (18%)	24 (26%)