ABSTRACT SERVICE

Abstracts taken from the annual EASD meeting held at Barcelona, Spain, on Sep. 8-12, 1998.

EPIDEMIOLOGY

ADA vs WHO diagnostic criteria for diabetes : identification of classes with a different pattern of risk factors.

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The opportunity for European countries to adopt the new ADA diabetes diagnostic criteria should be evaluated on the basis of European population data. Out aim was to compare the different classes of subjects identified by both WHO and ADA criteria in order to highlight possible differences in terms of cardiovascular risk factors. The study is based on the data collected through the Cremona population study. Standardised oral glucose tolerance test results as well as further laboratory and clinical data were available. We confined our evaluation to subjects without known diabetes and aged 40 years or more (n=1935).
These subjects were classified as follows:

WHO (fasting and/or 2nd h glucose) and ADA (fasting glucose only).

	Diabetes	IGT	Normal	Total (WHO)
Diabetes	23	7	6	36
IFG	8	27	68	103
Normal	19	119	1658	1796
Total	50	153	1732	

Diabetic subjects identified by ADA only (n=13) were younger, fatter and with higher fasting insulin levels than those identified by WHO only (n=27) (age: 58 ± 13 vs 67 ± 2, p=0.03; BMI: 29. 4 ± 1. 2 vs 25.8±0.8, p=0.02; insulin: 20±3 vs 16±1, p=0.13). IFG subjects ADA only, n =75) were younger (60±1 vs 64±1, p=0.005), fatter (28.3±06 vs 27.1±04, p=0.04) and higher triglycerides (138±6 vs 120±3, p=0.04) and higher insulin (18±1 vs 15±1. p=0.04) than IGT subjects (WHO only, n=126). Analogously, ADA normal subjects (n=138) were significantly older than the WHO ones (n=74) and with a significantly healthier cardiovascular risk factors pattern. These differences were confirmed even after controlling for age and gender. In conclusion, despite the fact that the ADA criteria are based on lower basal cut-off levels, they identify less abnormal subjects but with higher cardiovascular risk factors levels, with respect to the previous diagnostic criteria.

Impact of the application of new American Diabetes Association diagnostic criteria. Features of the impaired fasting glucose category.

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American Diabates Association 1997 (ADA) diagnostic criteria recommends the use of fasting glucose (126 mg/dl) to diagnose diabetes (DM) and defines the impaired fasting glucose (IFG) CATEGORY (110 - 126 mg/dl). Aim (I) To compare the transcendence of the application of 1997 ADA and the 1985 WHO criteria to diagnose DM. (ii) To analyse clinical characteristics of subjects from a Mediterranean area with IFG. Subjects and methods. A sample of 616 subjects, aged 25-65 years, all employees of a bank, were studied. Their previous oral glucose tolerance was unknown. Body mass index (BMI), blood pressure (BP), lipid profile and the response to an oral glucose tolerance test (OGTT) were recorded. According to WHO criteria, subjects were classified depending on the 2h-glucose (G-2h) into; normal glucose tolerance, imparied glucose tolerance (GT) and DM. Based on the basal glucose (G-o) we divided twice the sample in two groups at the cut point of; G-O' >=140 mg/dl and G-O' >=126 md/dl (WHO-85 and ADA-97). IFG subjects were compared with those subjects with G-0'<110 mg/dl. Results. 81% of the sample were men and 35% of the sample had a BMI >27 kg/m2. According to G-2h, we found a 8.2% of IGT and a 3.2% of DM. Only 25% of the subjects with DM, based on OGTT, and g-0'>=140 mg/dl and 56% of DM subjects, displayed a G-0'>126 mg/dl. IFG subjects had higher proportions of abnormal glucose tolerance (14.8%DM, 33.3%IGT) than in the G-0' <110 mg/dl group (0.9% DM, 7% IGT), p<0.01. In addition, they were more obese (BMI, kg/m2; 29.0 ±4.2 vs. 25.7±3.4, p<0.01) and high blood pressure (BP>=130/85 mmHg) was more frequently detected (SBP; 132.3±13.6 vs. 122.9 ±13.5 and DBP; 85.4 ±9.4 vs. 76.6±9.6, p<0.01). Conclusion. The applications of ADA criteria in our Mediterranean are diminishes the number of people with undiagnosed diabetes compared to WHO criteria. IFG includes subjects with a high rate of IGT, DM and other features of insulin-resistance syndrome.

Should fasting plasma glucose levels be lowered further in the diagnosis of diabetes?

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The recent ADA Expert Committee report on classification and diagnosis of diabetes suggests a lowering of fasting plasma glucose (FPG) levels from 7.8 mmol/L (140 mg/dl) to 7.0 mmol/L (126 mg/dl). The new cut off value was proposed so that it would be comparable to the 2 hour post glucose (2hr PG) level of 11.1 mmol/L (200mg/dl). Few studies however have directly tried to correlate the FPG and 2hr PG values during an oral glucose tolerance test (OGTT). We took up a retrospective study based on 5936 GTT's done at our centre and found that an FPG level of 6.4 - 6.7 mmol/L (116 mg/dl to 120 mg/dl) corresponds to a 2hr PG of 11.1 mmol/L (200 mg/dl). Using different logistic regression models correlation between the FPG and 2hr PG values were done. The regression equation obtained using log-log model which produced the best fit was

log(log FPG mg/dl)=1.4522+0.00054815 (2hr PG mg/dl). Using this model 2hr PG value of 11.1 mmol/L (200mg/dl) corresponds ot an FPG value of 6.5 mmol/L (118 mg/dl). Our data suggests that an FPG value of 6.5 mmol/L(118 mg/dl) corresponds better to a 2hr value of 11.1 mmol/L(200mg/dl) than the 7.0 mmol/L (126 mg/dl) proposed by the ADA expert committee report.

Follow-up of women with gestational diabetes. Incidence and factors associated with later development of abnormal glucose tolerance.

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Women with gestational diabetes (GD) have an increased risk for later development of diabetes mellitus. The aim of the study was to determine the 6 year cumulative incidence of abnormal glucose tolerance (AGT) (diabetes mellitus and glucose intolerance), to identify factors which may predict future development of AGT and to evaluate the relationship of AGT to other components of the metabolic syndrome. METHODS: 276 women diagnosed as having GD between 1991-95 were prospectively followed with annual oral glucose (75 g.) tolerance tests (OGTT) and assessment of variables related to the metabolic syndrome. The actuarial method was used to determine the cumulative incidence of AGT. Differences in survival experience for predictive factors were determined by log-rank test. The relation of the area under the curve for OGTT at the end of the study with components of the metabolic syndrome was analysed using correlation coefficients. RESULTS: The 6-year cumulative incidence of AGT was 59.1% (39.6% for diabetes mellitus). Predictive factors for AGT were: prepregnancy body mass index, fasting glucose during pregnancy and insulin treatment during pregnancy *p <0.001); gestational age at diagnosis of GD, postprandial glucose and HbA1c during pregnancy and waist-to-hip ratio after pregnancy ($p<0.01$); and number of abnormal values in the 3-hour OGTT (100 g.) during pregnancy ($p<0.05$). The degree of glucose tolerance (area under the curve for IGTT) at the end of the study was significantly related to: waist circumference ($r = 0.441$), waist-to-hip ratio ($r=0.378$), body mass index ($r = 0.353$), systolic ($r=0.270$) and diastolic blood pressure ($r=0.258$) ($p<0.001$); and triglyceride levels ($r=0.201$; $p<0.01$). CONCLUSIONS: GD is associated with a considerably increased risk of developing AGT later in life. The severity of glucose intolerance during pregnancy, prepregnancy obesity and abdominal fat distribution predict the occurrence of AGT. AGT in women with previous GD is related to other components of the metabolic syndrome, therefore GD should be considered as an early indicator of the metabolic syndrome.

Diabetes Complications in Asia.

The DCDCP (Diabcare - Asia) Study Group

Diabetes complications such as retinopathy, blindness, nephropathy, neuropathy, amputation, cerebrovascular disease and coronary heart disease are resulting in increasing diasability and mortality. While several reports for studies of diabetes complications were documented in western countries, relatively few studies examining diabetes complications in Asia have been carried out. In the first phase of the Diabetes Care Data Collection Project (DCDCP, 1997), we aimed to provide an overview of the complication status in the Asian diabetes population. A total of about 26, 500 patients, with mean age of 58.3 $\pm$ 12.0 years were recruited from 154 participating diabetes centres in 6 participating countries (China, Indonesia, Malaysia, Philippines, Thailand and Vietnam). They were assessed for known risk factors associated with occurrence of diabetes complications, eye, feet and severe late complications using well documented medical criteria and tests. Satisfactory compliance was achieved in majority of the patients in terms of body weight, blood pressure, smoking and alcohol intake. However, control of serum lipids levels was poor in about 20-30% of the patients - 30% had serum triglycerides >2.2 mmol/1, 20% had total cholesterol >6.5 mmol/l and 18% had HDL<0.9mmol/l. Screening for micro-or macroalbuminuria was very rare (7%) compared to proteinuria monitoring (45%). Similarly, screening for eye (photocoagulation, cataract, retinopathy and advanced eye diseases) and feet (foot pulse, healed ulcer, acute ulcer, neuropathy, amputation and angioplasty) complications were relatively infrequent (about 30%). The average prevalence of cataract, retinopathy, neuropathy, myocardial infraction and cerebral stroke was 44,33,39, 5 and 6 percent respectively. Hence the incidence of patients with cataract and neuropathy was relatively high in the six countries studied. In conclusion, our data show that regular screening for microalbuminuria, eye and feet complications was not performed or at least not recorded. As early detection of eye and feet complications, as well as renal impairment can provide direction for preventive strategies, the DCDCP study calls for vigorous efforts aimed at improving awareness among health professionals of the potential of reducing major long term diabetes complications in Asia.

Mortality in insulin treated diabetes mellitus 1993-1996.

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Estimating diabetes associated mortality is complicated by the inadequacy of official published data; diabetes is not always the underlying cause of death, and may not feature on the death certificate at all. The aim of this study was to determine excess mortality in the populations aged 15 years and older with insulin treated diabetes and to register of people with diabetes and office of National Statistics (ONS) mortality data, record linkage using Auto Match software was undertaken to determine mortality observed during the years 1993 to 1996 inclusive. After computerised matching records were reviewed to maximise the accuracy of linkage. Standardised mortality ratios

(SMR) and 95% confidence intervals (95% ci) were estimated using confidence interval analysis software. The England and Wales population and death rates for 1995 were used as the standard. The population with insulin treated diabetes numbered 5358 aged 15 years and older in mid 1995. A total of 706 deaths were identified distributed evenly over the 4 years, 167 in 1993, 173 in 1994, 190 in 1995 and 176 in 1996. There were 321 (46%) females and 385(55%) males. The median age at death was 71 years, range 19 to 95 years. The overall SMRs (95% ci) for the 4 years were significantly raised for females, 173(155 to 194) and for males, 158 (142 to 174). Ischaemic heart disease, (ICD codes 4100414) accounted for 281 (40%) deaths, and the SMRs for females 340 (284 to 403) and males 223 (188 to 261) were significantly raised. 43 (6%) deaths were due to cerebrovascular disease, (ICD codes 430-438) with SMRs 116 (76 to 170) for females and 83(48 to 133) for males. The males SMR for all neoplasms was significantly lowered 74 (55 to 99). Despite ongoing improvements in the mangement of diabetes, significant excess mortality in both males and females with insulin treated diabetes was observed in this study.

ETIOPATHOLOGY

Impaired postprandial release glucagon like peptide-1 in patients with type 2 diabetes.

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GLP-1 is released from intestinal endocrine L-cells in response to orally administered nutrients, especially carbohydrates and fat. The aim of the present study was to characterise the effect of a standardised 621 kcal mixed meal on the released of glucose, insulin, C-peptide, glucagon, glucose dependent insulin releasing polypeptide (GIP) and GLP-1 in terms of total area under curve (AUC) during 3h after the meal. In the study participated 20 well matched normal weight (MBI 20-26) subjects; 7 healthy control subjects, and 13 patients with type 2 diabetes of whom 6 patients had an acceptable metabolic control on diet treatment alone and 7 patients experienced secondary failure on oral sulphonylurea (SU). Highly specific radioimmunoassays, determining only biologically active hormone, were used for the investigation. Logarithmically transformed data were compared using Dunnett's test for multiple comparison of means. As expected, postprandial glucose levels were significantly elevated in both diabetes groups during the entire investigation. Insulin levels proved lower in the SU failure group as compared to controls only during the first 90 minutes of the investigation (13,993 vs. 32,001, $p<0.01$), as did C-peptide levels in both diabetes groups (102 and 127 vs. 202, $p<0.01$ and $p<0.05$, respectively). Glucagon, however was slightly elevated in the diabetes groups (total area 7,390 and 6,184 vs. 4,699), and GIP (total area 9,284 and 9,873 vs. 10,392) were insignificantly different from controls. The GLP-1 response during the last 90 minutes and the total 180 minutes was markedly decreased and delayed in the SU failure group (area 90-180 minutes 960 vs. 1,511, total area 1,856 vs, 2,826, $p<0.05$), while the diet-treated group displayed an intermediary release of GLP-1. This alteration in GLP-1 response may play a role in the pathogenesis of glucose intolerance, and specifically the decreased insulin and enhanced glucagon secretion characterising this disease.

Birthweight and analytic data in blood of umbilical cord: A possible association with NIDDM in adult life.

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According to the hypothesis of "thirty phenotype" a low birthweight and a reduced growth in fetal life is associated to the appearance of non-insulin-dependent diabetes (NIDDM), as well as of other clinical correlates of the insulin resistance syndrome (IRS) in adult life. The aim of this study was to investigate the association between anthropometric parameters of the mothers and their newborn children and analytic data in blood of umbilical cord. We performed a cross-sectional study of 96 non-diabetic mothers, aged 28.2 $\pm$ 4.4 years (range 16-40), and their 96 newborn children. Birthweight (BW) was 3151.9 $\pm$ 370.8 g (range 2054-3840). We analyzed in mothers: gestational age (GA) and prepregnancy body mass index (BMI); in newborn babies: weight, height, BMI, cephalic (CP) and thoracic (TP) perimeters, and in blood of umbilical cord: glucose, total cholesterol (TC), HDL-cholesterol and triglycerides (TG) levels. We did not find significant differences between parameters studied in 9/96 babies with low BW (<=2500) and those of normal BW (>2500). However, GA was correlated (Pearson's correlation coefficient) with BW ($r=0.28$, $p=0.005$) and with TG ($r=0.23$, $p=0.02$) and with TP ($r=0.21$, $p=0.04$); and TG was correlated with CP ($r=0.23$, $p=0.02$) and with TP ($r=0.21$, $p=0.04$). In conclusion, the association between anthropometric parameters and some analytic correlates of the IRS in blood of umbilical cord suggests that not only the BW but also the gestational age could have some influence on the IRS in adult life.

An association between UCP2 and body mass index in a South Indian population

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The uncoupling proteins (UCP) play an important role in energy expenditure and therefore are candidate genes for the aetiology of both obesity and Type 2 diabetes. Recently, linkage has been found between markers close to uncoupling protein 2 (UCP2) and resting metabolic rate. The purpose of our studies was to study a newly described UCP2 variant in exon 8 in obesity and Type 2 diabetes.

Exon 8 of UCP 2 was sequenced and a 45 base pair insertion was identified which is a duplication of the preceding 45 base pairs. DNA was prepared from 449 South Indian subjects from a cross-sectional survey and 71 South Indian families consisting of parents and a child with Type 2 diabetes. DNA was separated by agarose gel electrophoresis after amplification of exon 8. Three genotypes were identified II (homozygous for insertion), ID and DD (homozygous wild). No association or linkage was found between Type 2 diabetes and UCP2 variant in the South Indian families using the transmission disequilibrium test. In the parents of the families a positive association was found between BMI and the UCP2 variant ($p<0.001$), mean BMI 32.7 for II (n=5), 25.2 for ID (n=47) and 24.9 for DD (n=91). To verify this positive observation we then screened the 449 South Indian samples. The positive association with BMI was replicated in females only, ($p=0.019$), mean BMI 26.4 for II (n=9), 22.1 for ID (n=62), 23.2 for DD (n=147); furthermore, no association was found with Type 2 diabetes ($p=0.83$). In conclusion, the UCP2 exon 8 variant appears to be associated with increased BMI but not with Type 2 diabetes in a South Indian ethnic population.

Increased frequency of the PPAR-Gamma polymorphism (P12A) in patients with NIDDM.

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Peroxisome proliferator activating receptors (PPAR) are important regulators of several genes involved in glucose and lipid metabolism. Activation of PPAR gamma by thiazolidinediones results in amelioration of glucose homeostasis by increasing insulin sensitivity. Thus PPAR gamma may play a role in the manifestation of NIDDM. Recently a polymorphism in the PPAR gamma gene has been described (Pro 12 Ala). We investigated the frequency of this polymorphism in patients with NIDDM (n=40), with and without accompanying hypertiriglyceridemia (HTG). For comparison patients (n=92) without NIDDM with or without HTG were analysed. The following table shows the number of patients analysed until now, body mass index (MBI) in kg/m2, plasma triglycerides (TG) in mg/dl, and the frequency of the P12A polymorphism and A-carriers (in %).

AB	N	BMI	TG	PP	PA	AA	A-car
+NIDDM + HTG	20	30	874	11	7	2	45
+NIDDM - HTG	20	26	176	14	6	0	30
-NIDDM + HTG	30	28	476	23	7	0	23
-NIDDM - HTG	62	24	152	49	12	1	21

Thus the frequency of the A allele was higher in patients with NIDDM than in patients without NIDDM ($p = 0.04$) Though the highest A allelle frequency was observed in patients with NIDDM and HTG the frequency of the A allele did not differ in non diabetics with or without HTG. Our results suggest a role for variation in the PPAR-gamma gene in the pathogenesis of NIDDM.

The impact of genetic and environmental factors on the insulin resistance syndrome among male and female twins.

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An strong association has been demonstrated between glucose intolerance (2h OGTT plasma glucose>=7.8 mM), hyperinsulinaemia (fasting plasma insulin>60 mM), abdominal obesity (WHR male>0.95, female>0.85), hypertension (blood pressure (BP) > 160/9+5 mmHg) and dyslipidaemia (triglycerides>1.7 mM, HDL-cholesterol male<0.9 mM; female<1.1mM), which often is referred to as the "insulin resistance syndrome (IRS)". In order to study the relative importance of genetic and environmental factors responsible for these components we examined 303 twin pairs (125 monozygotic (MZ), 178 dizygotic (DZ); 125 male, 178 female) between 55 and 74 years of age. Seventeen twins (1.7%) fulfilled the criteria of IRS. The concordance rate was higher, though not significantly higher, among MZ twins compared to DZ twins (MZ: 0.29; DZ : 0). The heritability for WHR (0.06), however, was low, indicating a major influence of environmental factors on the distribution of obesity. Glucose tolerance (0.34), insulin resistance (0.28) and plasma triglycerides (0.40) seem to have a major environmental etiological factor. However, a genetic influence on the level of systolic (0.78) and diastolic (0.66) blood pressure and HDL cholesterol (0.70) is indicated due to the relatively high heritability estimates. We observed differences in heritability among male and female twins for BMI (male: 0.54, female: 1.00), fasting glucose (male: -0.16, female: 0.88), systolic BP (male: 1.00, female: 0.56), diastolic BP (male: 0.06, female: 0.82) and triglycerides (male: 0.72, female: 0.06). In conclusion the present study confirms the notion of an multifactorial etiology of the insulin resistance syndrome and its components including both genetic and non-genetic factors. Furthermore, the differences in heritability between male and female twins propose an influence of gender on several of the components of the insulin resistance syndrome.

Evidence for a physiological role or leptin in human pregnancy

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There is increasing evidence suggesting that leptin is not only a major regulator of adipose tissue metabolism and energy homeostasis, but might also be involved in the regulation of the neuroendocrine and the reproductive system. Recently, it has been shown that leptin is

synthesized in and secreted from the human placenta. The aim of our study was to elucidate the role of leptin in human pregnancy by measuring serum leptin levels in a large number of consecutive pregnant women with normal (n-173) and impaired (n=67) glucose tolerance in relation to BMI and various metabolic variables, including specific insulin and proinsulin levels during a 2h OGTT (20-31 weeks of pregnancy). In 53 women, serum leptin was measured during pregnancy and post partum (mean : 10.7 months). Results - During pregnancy serum leptin was significantly related to body weight (r=0.39), BMI (r=0.44), fasting immunoreactive insulin (r=0.31), specific insulin (r=0.40) and proinsulin (r=0.28) (all p=values =0.0001), but not to age, blood glucose levels and the increment of insulin relative to the increment of glucose at 60min, as a measure of insulin secretory capacity. Leptin was significantly higher during pregnancy compared to post partum (mean$\pm$SE: 24.2$\pm$1.4 vs. 20.0$\pm$1.6 ng/ml, p=0.001). The difference remained significant after adjustment for change in BMI and change in fasting insulin (p=0.042). In multiple regression analysis BMI and fasting insulin predicted 20% of the variability in leptin levels during pregnancy, whereas in the same women the same variables explained more than twice of leptin-variability post partum (44%). In women with gestational diabetes leptin levels were lower compared to women with normal glucose tolerance after adjusting for BMI and fasting insulin (26.37 vs 16.06 ng/ml, p<0.006). Out data add to the evidence that leptin might be added to the catalogue of placenta derived hormones playing a physiological role during human pregnancy.

PED/PEA- 15 gene controls glucose transport and is overexpressed in type 2 diabetes mellitus.

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Type 2 diabetes mellitus is determined by both environmental and genetic factors. We have used differential display to identify genes whose expression is altered in type 2 diabetes thus contributing to its pathogenesis. One mRNA is overexpressed in fibroblasts from 12 type 2 diabetics compared to 13 non-diabetic individuals (p<0.01 by t-test analysis), as well as in skeletal muscle (p<0.05) and adipose tissues (p<0.01), the two major sites of insulin-resistance in type 2 diabetes. The levels of the protein encoded by this mRNA are also 2-fold elevated in type 2 diabetic skeletal muscle (p<0.01); thus, we named it PED for Phosphoprotein Enriched in Diabetes. PED cloning shows that it encodes a 15 Kda phosphoprotein identical to the PKC substrate PEA-15. PED gene maps on human chromosome 1q21-22. Transfection of PED/PEA-15 in differentiating L6 skeletal muscle cells increases the content of Glut1 transporters on the plasma membrane by 4-fold. However, insulin-stimulated 2-deozy-D-glucose uptake and cell-surface recruitment of Glut 4, the major insulin-sensitive glucose transporter, were reduced by > 80%. These effects of PED overexpression are reverted by blocking PKC activity with Staurosporine. Overexpression of PED/PEA-15 gene may contribute to insulin-resistance in glucose uptake in type 2 diabetes.

Novel polymorphisms in the coding region of the receptor for advanced glycation end products (RAGE) gene.

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Advanced glycation end products (AGEs) have been implicated in the pathogenesis of diabetic vascular complications and their effects may be mediated via the receptor for AGE (RAGE). Evidence indicates a genetic element in the development of these complications and we have therefore screened the coding region of RAGE for allelic variants in 40 Type 2 random diabetes patients and 40 normal volunteers by PCR-SSCP. 9 polymorphisms were confirmed by sequencing, of which 4 were functional amino acid substitutions; Gly82Ser, Thr187Pro, Gly329Arg and Arg389Gln. To evaluate the ethnic prevalence of the common Gly82Ser polymorphism, 195 Caucasian, 156 Asian and 210 Pima Indians were screened. To investigate the prevalence in diabetics and in relation to cardiovascular disease, 258 Type 2 diabetes patients and 280 ischaemic heart disease (IHD) patients were also screened There was no difference in prevalence of Gly82Ser in Caucasian and Asian subjects (87% GG. 12% GS and 1% SS). There was a highly significantly lower prevalence of Gly82Ser in the Pima Indian population (99% GG, 1% GS). [chi]2 of p<0.00001. there was no difference in genotype frequencies between Caucasian controls and either Type 2 diabetics (92% GG and 8% GS) or IHD patients (87% GG and 13% GS), [chi]2 of p>0.05. There was also no association found between genotype and macrovascular disease in the diabetic or IHD patients. In conclusion, the RAGE gene contains common polymorphisms that occur with similar frequencies in Asian and Caucasian populations, but are less common in Prima subjects. The functional nature of this polymorphism is currently being investigated by site-directed mutagenesis and receptor binding studies. Further work is required to investigate these polymorphisms for their role in microvascular complications.

Cytokine mediated nitric oxide production and Fas expression act synergistically on B - cell damage

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Inflammatory cytokines and toxic free radicals have been demonstrated to play a major role early in the pathogenesis of IDDM. However, intracellular signalling pathways of beta cell death are poorly understood. Our investigations focus on cytokine induced molecular mechanisms leading to beta cell damage. Isolated OF1 mouse islets and an established beta cell line (NIT-1) exposed to a combination of pro-inflammatory cytokines (IL-IB, IFN[gamma] and

TNF [alpha]) were assayed for mechanisms leading to impaired insulin secretion. After cytokine exposure, a profound decrease in insulin secretion was observed in both islets (58±3%) and NIT-1 cells (30±5%). This effect was mediated by the production of nitric oxide (NO) synthase (iNOS) was found by RT-PCR in both islets and NIT-1 cells. Furthermore, islets from iNOS deficient mice were resistant to the cytokine induced inhibition of insulin secretion. However, both wild type and iNOS deficient islets showed a significant increase in programmed cell death (30±2%) upon exposure to cytokines. This result suggests and NI-independent signalling pathway leading to apoptosis. Phenotyping of wild type and iNOS deficient islets and NIT-1 cells exposed to cytokines revealed also the upregulation of Fas (CD95/APO-1). Importantly, crosslinking of this surface molecule by soluble Fas ligand (FasL) resulted in enhanced apoptosis (45±7%). In conclusion, these data provide support to the contention that pro-inflammatory cytokines induce beta cell damage via the production of NO radicals and the induction of apoptosis. The latter is also mediated by Fas expression and may be triggered in situ by activated FasL bearing T cells.

COMPLICATIONS

Effect of intense insulin treatment on hyperglycaemia in diabetic patients with acute myocardial infarction.

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Diabetic patients with actue myocardial infarction (AMI) have a dismal prognosis. This may depend on a poor metabolic control. Several studies have shown that admission blood glucose (ABG) is an independent predictor for mortality following an AMI, both among patients with and without diabetes mellitus. Knowledge of the effect of lowering the ABG is, however, lacking.

METHODS: The effect of intensive insulin treatment in 620 diabetic patients with and AMI was tested in DIGAMI, a prospective randomised study. Long term mortality (mean 3.4 years; range 1.6-5.6) decreased from 44% in the control group to 33% in the insulin group (p=0.011). the present study reports on treatment effects in different ABG levels.

RESULTS: mean ABG was 15.6±4.1 mmol/1 and did not differ between the two groups. In the complete patient cohort both ABG and glycated haemoglobin was independent predictors for long-term mortality. The figure shows mortality (%) by ABG tertiles within the two treatment groups.

CONCLUSION: Insulin-glucose infusion followed by intense SC insulin treatment in diabetics with AMI attenuates the harmful effect of elevated ABG on mortality. This effect seems to be most pronounced in patients with the highest ABG levels.
[See Original for Figure]

Autonomic neuropathy and the cardiovascular risk: the Eurodiab IDDM complications study

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Autonomic neuropathy is associated with poor prognosis. However, [prevalence data are conflicting and potential risk factors has not been definitely identified up to now. The EURODIAB IDDM complications study involved the examination of patients from 31 centres in 16 European countries. Data of 3007 patients were available for the present evaluation. Symptoms and two tests of autonomic function (response of hear rate 30/15 ratio/and blood pressure from lying to standing) were assessed. The prevalence of autonomic neuropathy was 47% with no sex but some geographical differences. Significant correlations were observed between the presence of abnormal 30/15 ratio and age (p<0.01}, duration of diabetes (p<0.0001), quality of metabolic control (p<0.0001), the presence of retinopathy (p<0.0001), micro and macroalbuminuria (p<0.0001), cardiovascular disease (p<0.0001), severe hypoglycaemia (p<0.05) and severe ketoacidosis (p<0.0001). Cardiovascular risk factors such as smoking (p<0.0001), HDL-cholesterol (p<0.01), total cholesterol/HDL cholesterol ratio (p<0.001), fasting triglyceride (p<0.001) and body weight (p<0.001) were also related to abnormal 30/145 ratio. Data were adjusted for age, duration of diabetes and HbA1c. Conclusions: Autonomic neuropathy is one of the most frequent complications in Type 1 diabetes. The study has identified previously known and new potential risk factors which may be important for the development of risk education strategies.

The primary pathology and pathogenesis of human diabetic neuropathy.

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The primary pathology and pathogenesis of human diabetic neuropathy are unclear. We have studied 28 children with Type l diabetes aged 13.0±2.6 yr., duration of diabetes 8.5 ± 3.0 yr., compared to 28 age matched control subjects. Sural nerve biopsy was performed in 8 patients who fulfilled the minimal criteria for neuropathy based on a significant reduction in peroneal nerve motor conduction velocity (ms1) (47.1± 6.1 v 54.1 ± 5.2, p<0.007) and amplitude (uv) (6.2 ± 2.3 v 9.2 ± 3.4, p<0.03), and sural nerve conduction velocity (ms1) 35.1 ± 2.2 v 45.2 ± 3.6m p<0.0001) and amplitude (uv) (ms1) (19.1 ± 11.9 v 31.9 ± 15.6, p<0.04). All morphometric data were compared with 5 age matched control subjects. Myelinated fibre density (no.mm2) did not differ (p=0.14) between diabetic patients (9438 ± 1673) and control subjects (8200 ± 1532). However, teased fibre analysis revealed paranodal abnormalities (16.4 ± 4.1 v 3.5 ± 1.0, p< 0.01) and

segmental demyelination (19.9 ± 10.2 v 1.5 ± 0.3, p<0.01) without axonal degeneration (3.0 ± 1.9 v 1.4 ± 1.2, p<0.6). Myelinated fibre and axonal area did not differ between diabetic patients and control subjects. Diabetic patients demonstrated a reduction in endoneurial capillary luminal area (12.6 ± 3.2 v 24.9 ± 4.7, p<0.09) and an increase in the endothelial cell profile number (4.6 ± 0.2 v 3.9 ± 02., p<0.03) and basement membrane area (92.7 ± 9.7 v 41.1 ± 5.2, p<0.04) without any change in the endothelial cell area(39.0 ± 3.4 v 37.6 ± 7.5, p=0.94), pericyte nuclear no. (0.61 ± 0.1 v 0.6 ± 0.03, p=0.82) or endothelial/pericyte nuclear ratio (2.5 ± 0.4 v 2.2 ± 0.2, p=1.0). The primary pathology of human diabetic neuropathy is paranodal and segmental demyelination without axonal atrophy or axonal degeneration and fibre loss. The early presence of endoneurial capillary abnormalities provides strong support for the role of microangiopathy in the pathogenesis of human diabetic neuropathy.

Prognostic factors of outcome in hyperosmolar nonketotic diabetic coma.

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Hyperosmolar nonketotic diabetic coma (HNDC) is an acute complication of predominantly NIDDM. It is associated with high mortality rate ranging from 30-50%. The aim of this study was to assess the prognostic value of invasive hemodynamic variables on the outcome. Thirty one patients with HNDC underwent right heart catheterization with the purpose of pressure-guided fluid replacement. The catheterization was performed to avoid frequent complications of fluid overload or insufficient fluid repletion, both of which occur if this condition is managed empirically or by central venous pressure. The decision to insert catheter was made if patient was hemodynamically unstable. The hemodynamic data were collected upon catheterization and 24 hours later. The overall mortality rate at the seventh day upon admission was 35%. The receiver-operating characteristic curve was constructed for each hemodynamic finding regarding outcome of disease. Log-rank analysis was performed for each cut-off point to see whether it may separate significantly survivors from fatalities. The best prognostic indicator was the ratio of left ventricular stroke work index and pulmonary capillary wedge pressure after 24 hours of catheter insertion. Its value > 4 was associated with the survival rate of 84%, while only 22% patients with considered as one of the best parameters of myocardial function in the critically ill patients. Our data allow conclusion that myocardial dysfunction has a significant role in determining the outcome of disease.

Hyperglycemia causes oxidative stress, inositol depletion and maldevelopment in the embryo

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Glucose-induced teratogenesis is related to oxidative stress and hampered prostaglandin biosynthesis. Previously, addition of the antioxidant N-acetylcysteine (NAC) and prostaglandin E- 2 (PGE2) was shown to diminish glucose-induced embryonic maldevelopment in vitro, in which also a decreased inositol metabolism was implicated. The aim was to investigate putative interrelationships between these different teratological pathways. We exposed embryos in vitro to 30 mM glucose (30G), and to 500 uM or 750 uM of scylloinositol (500SI and 750SI), a competitive inositol inhibitor, with the intent to cause embryonic dysmorphogenesis. We found that 30G, 500SI and 750SI embryos had fewer somites (16.3±1.1, 21.5±1.2 and 19.5 ± 1.0), shorter crown-rump length (CR: 2.8±0.2 mm, 3.3. ± 0.1 mm and 3.2 ± 0.1 mm) and higher malformation score (MS; 9.4, 6.4 and 6.9) than control embryos cultured in 10 mM glucose (10G) (somites: 28.7 ± 0.3, CR: 3.4 ± 0.2 mm, MS: 0.1, p < 0.05 vs. 30G, 500SI and 750SI, ANOVA and (chi)2 - statistics). Adding 1600 uM inositol to the 30G or 750SI, culture medium partly corrected embroyo development (somites: 23.6-23.9, CR: 3.3-3.5 mm, MS: 3.7-4.2, p<0.05 vs. 30G and 750SI), and completely normalized the 500SI embroyo development (somites: 26.8 ± 0.7, CR: 3.5 ± 0.1 mm, MS: 1.8), whereas addition of 280 nM PGE2 failed to diminish the 500SI-disturbed embryonic maldevelopment. We conclude that high glucose concentration suppresses the embryonic metabolism of inositol and prostaglandins. The inositol depletion is associated with oxidative stress, but seems to be parallel with the inhibition of prostaglandin metabolism, thereby increasing the number of compounds with antiteratogenic potential in diabetic pregnancy.

TREATMENT

GLYCEMIC CONTROL

The Steno type-2 study: intensive multifactorial intervention delays progression in diabetic micro-and macroangiopathy in microalbuminuric type 2 diabetic patients

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Aim and Methods : To asses the effect of intensified multifactorial intervention on diabetic complications over a 4 yr period we performed an open, parallel, randomized intervention trial with 160 type 2 diabetic patients with persistent microalbuminuria randomized to a standard group (n=80) continuing conventional treatment or an intensively treated group undergoing behaviour modification (diet, exercise smoking habits) and aggressive, stepwise pharmacological treatment focusing on glycaemia (metformin, sulphonylureas, insulin), hypertension (ACE-inhibitors, diuretics, calcirumantagonists, beta blockers), dyslipidemia (statins, fibrates) and secondary cardiovascular disease prevention with aspirin. Results : A separation of 1.4% in HbA (1C) (mean (Se)) (7.6(1.0) vs. 9.0 (0.1)%. <p0.001 (ANOVA) was obtained. The decline in systolic blood pressure 9 (2) vs. 4 (2) mm Hg, p=0.01), fasting scholesterol (0.7 (0.1) vs.0.2 (0.1) mmol/1, p<0.00005, fasting s-triglycerides (0.5(0.2) vs. 0.4 (0.4) mmol/l, p<0.005) and albumin excretion rate (median (range)) (23(-1091,231) vs. 0 (-

1038, 162), p<0.005) were all significantly greater in the intensively treated group. the progression to overt diabetic nephropathy (7 patients vs. 18, p=0.01 (multiple logistic regression), the progression in retinopathy (19 vs. 33, p=0.04) and progression in autonomic neuropathy (8 vs. 22, p=0.01) was lower in the intensive group compared to the standard group. The number of patients with peripheral vascular disease events was significantly smaller in the intensive group (13 vs. 29, p=0.02). The combined incidence of fatal and non-fatal macrovascular events was smaller in the intensively treated group (25 vs. 42, p=0.03). Conclusion: Intensive multifactorial intervention over a 4 yr period delays the progression in micro-and macrovascular diabetic complication in type 2 diabetic patients with persistent microalbuminuria.

Self-adjustment of bedtime insulin (SABI) : A key to successful insulin therapy in NIDDM.

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We reasoned, based on analysis of our previous multicenter study, and on meta-analyses of insulin treatment trials that use of insufficient insulin does is due to adjustment of insulin doses exclusively at outpatients visits. In a new Finish multicenter study we randomized 96 patients with NIDDM (age 58 ± 1 years, HbA (1C) 9.9 ± 0.2 % BMI 29 ± 0.5 kg/m2, for treatment with various bedtime NPH regimens for 12 months. The patients were given oral and written instructions of how to adjust the bedtime NPH dose. The patients were instructed to increase the insulin does every 3 days by 4 IU/day if the fasting plasma glucose concentration exceeded 8 mmol/L and by 2 IU/day if the fasting plasma glucose exceeded 6 mmol/L. The glycemic target was to mmol/1. This was predicted to lower HbA-(1c) to less than 7.5%. The dose of bedtime insulin required to lower fasting glucose from 10.5±2.1, 11.2±2.3, 10.0±2.3 and 12.1 ± 3.1 mmol/1 in groups treat with bedtime NPH and glibenclamide, metformin, both or another injection of NPH in the morning to 6.4±0.3, 6.2±.02, 6.4±0.3 and 6.7±0.3 mmol/1 (p<0.001 for 12 vs. 0 months in each group) varied over 20-fold from 8-168 IU/day. HbA- (1c) decreased to 7.2±0.2, 7.7±0.3, 7.8±0.2 and 7.9±0.3% (p<0.001). No severe hypoglycemias occurred, although the frequency of biochemical hypoglycemias significantly increased at fasting glucose concentrations below 6 mmol/L. In summary: Glycemic targets can be reached safely by instructing the patients to self-adjust their insulin dose. We attribute the better results of this as compared to our previous multicenter study to self adjustment of insulin dose. These data emphasize the need to not only instruct the patients to perform homeglucose monitoring but also to change treatment according to glucose concentrations.

Blood glucose self-monitoring in insulin treated type 2 diabetes

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Up to the present there is controversy about blood glucose self-monitoring in type 2 diabetes. In 842 insulin-treated type 2 diabetic patients (age 60.1±10.9 years, diabetes duration since diagnosis 12.6±7.6 years, BMI 28.6±5.1 kg/m2, HbA1c9.34±1.98%(HPLC, Diamat^{r}), normal range 4,4-5, 9%), a cross-sectional study was conducted to assess blood-glucose self-monitoring and interactions with quality of diabetes care. Among the patients studied, there were 90% of all insulin-treated type 2 diabetic patients aged 16 to 60 years and living in a large city (100424 inhabitants) and all patients consecutively attending our hospital clinic since 1991. Additional 91 patients were studied, treated at district hospitals. There was a negative correlation (r=0,16 p<0,001) between the frequency of blood glucose self-test/week and HbA1c,. Performing multivariate analysis the most important parameters associated with HbA1c (r-sqared=0.09) were: The frequency of blood glucose self-test/week (c=0.006, p<0.001), the insulin dose/kg body wt (c=0.003, p<0.001) and participation in a 5-day structured teaching and treatment programme for patients with conventional insulin therapy according to Berger et al. (5 - TTP, c=0,078, p<0,001). Other factors investigated in the model (age, diabetes duration, number of insulin injections/day, sex) showed no associations, Performing a subgroup analysis in patients older than 60 year (n=396) important parameters associated with HbA1c (R-squared=0.16) were the participation in 5- TTP (c=0.004, P<0.001) and the frequency of blood-glucose self-tests/week (c=0.006, p<0.001) too. In an other sub-group analysis patients (n=249) were studied who have not participated in a 5-TTP. In this sub-group there were no correlation and no association between the frequency of blood-glucose self-monitoring and HbA1c. Then, an intervention was started: 33 of the 249 patients participated in a 5-TTP. At the time of re-examination 1 year after participating in the 5- TTP, HbA 1c decreased from 9.5±1.9% to 8.3±1.6% (p=1.036) and there was a strong association between the frequency of blood glucose self-monitoring is not only important to prevent asymptomatic hypoglycaemia, but also to improve quality of diabetes care and to achieve glycaemic goals. Participation in a 5- TTP and regularly blood glucose self-monitoring is mandatory for all insulin treated patients with type 2 diabetes mellitus.

TREATMENT

NEWER INSULINS

Insulin Lispro : safe and effective treatment option for gestational diabetes.

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Postprandial hyperglycemia is strongly associated with increased fetal and neonatal morbidity, and the main goal of management of the gestational diabetes should be the achievement of normoglycemia. Therefore we designed our study to compare regular insulin with lispro insulin for the effectiveness of the treatment of women with gestational diabetes mellitus (GDM).

We followed 35 women with GDM who failed to achieve good glucose control with diet alone. Study was open labeled, and patients were randomized to receive either regular or lispro insulin at the dose of 0.719 U/kg body mass. Patients kept an eight-point daily diary ad were evaluated for HbA1c and antibody testing bi-weekly. All data were analysed using descriptive statistics, and a 2-sample t-test assuming equal variance. Results were shown in the table:

	HbA(1c) at enrollment	Hba(1c) 6 w after	Change in HbAlc	Antibody testing
LISPRO	5.49±0.38	5.12±0.50	0.29±(5.66%)**	1.26±0.69
REGULAR	5.33±0.36	5.31±0.57	0.05±(2.67%)	1.96±0.31
P value	NS	<0.05	<0.05	<0.05
p=0.008				

As shown above, women with GDM on lispro therapy achieved good glucose control defined by significantly lower levels of HbA1c, while regular insulin did not. Based on all glucose records, the lispro group had fewer hypoglycemic events with overall better glucose control. At the same time the antibody testing showed that insulin lispro is less immunogenic, although levels in both groups were within reference range. According to data shown above, we may conclude that lispro insulin should be considered the optimal treatment in patients with GDM.

Pre - versus postprandial insulin lispro : a comparative long-term crossover trial in 30 type a diabetic patients

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In a previous study in type I diabetics we demonstrated that insulin lispro administered shortly after the start of a low-caloric standard meal displays a glucodynamic control at least as good as regular insulin injected 40, 20 or 0 minutes prior to the meal. the current study was designed to investigate the impact of routine postprandial injection of insulin lipro compared to the standard preprandial administration on efficacy and safety using a crossover design where each period lasted for 3 month. 30 type I diabetic patients (between 19-55 years, HbA1c ,=8, informed consent), were randomized to one of the two sequence groups (prepostprandial or post-/preprandial). In addition all patients performed a time-action profile with a high caloric standard meal at the end of each period-to compare the glucodynamic control of pre-versus postprandial insulin lispro in this setting. 20 patients were already on intensified treatment with insulin lispro, 10 patients were changed from rugular to lispro and enrolled after a stabilisation period. Primary efficacy parameter for the long-term trial was HbA1c, secondary parameters were 8-point blood glucose profiles once monthly, serum cholesterol and lipid levels and fructosamine values, from baseline to last visit. Safety data comprised the number hypoglycemic episodes (<= 50 mg/dl) and adverse events as collected by patient diary. The overall satisfaction of the patients with their treatment was measured by quality -of-life instruments. Results for HbA1c and hypoglycemic events (mean ±SD) : HbA1c baseline value for both groups was 7.21 ±0.57. The change from baseline to end-point was:

A-HbA1c	Postprandial 0.09(±4.45)	Preprandial -0.09 (±0.45)	P = 0.071
Hypo events	Postprandial 31.8(±27.1)	Preprandial 32.4(±30.6)	p=0.725

No carryover effects were detected, neither for the HBA1c analysis nor for hypoglycemic episodes. In fold decrease in fasted FFA[HS+FO: 0.29±0.02 mmol.1]. While the fasted level of ketone bodies remained unchanged [HS + FO:9.7±1.4 mg/dl], the ration of ketone bodies to FFA was increased 1.8-fold [HS: 18.6 HS+FO:33.2] Hepatic CPT I activity was slightly increased after n-3 PUFA (HS:2.6±0.1, HS+FO: 3.2±0.09 mkil.min protein]. On the other hand, the CPT II activity was induced more than 3-fold in comparison to the HS diet [5.9±0.5, HS±FO 19.4±2.0 nmol.min mg protein] We conclude from these data that an increased hepatic fatty acid oxidation may contribute to the decrease in plasma lipids after treatment with n-3 PUFA in dietary induced hypertriglyceridemia and insulin resistance.

High fibre diet improves long glucose control in insulin dependent diabetic patients

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Several short term studies have demonstrated that a high fiber diet improves glucose and lipid metabolism in diabetic patients. However ADA dietary recommendations have questioned the beneficial effects of dietary fibre on glucose control in diabetic patients, since they have never been demonstrated in long-term studies. Therefore, the aim of our study was to evaluate the long term (six months) compliance and metabolic effects of a high fibre diet in IDDM patients. A randomize study with parallel groups was undertaken in 63 IDDM patients of both genders. After 4 weeks of an isoenergetic low fibre diet (CHO 58%, Protein 17%, Lipid 25%, Fibre 9g/1000 kcal/d) patients were randomized to either high fibre diet (HF) CHO 58%, Protein 18%, Fat 24%, fibre 26g/1000 kal/d) or a low fibre diet (LF) (CHO 58%, Protein 17%, Fat 25%, Fibre 9 g/1000 kcal/d) to be followed for 6 months. Of 31 and 32 participants treated with HF and LF diet, 28 and 27 concluded the study, respectively. Mean age was 32±12 and 26.±7yrs. BMI 24±0.6 and 24±0.5 kg/m2, duration of diabetes 11±7 and 10±5 yrs, HbA1c 8.9±1.4 and 8.7±1.4% (M±SD). Dietary compliance was, in general, satisfactory: beside dietary fibre (42±8 g/d and 15±3g/d, respectively), diet composition was similar in the two groups (seven - day

- food records). Compliance to the diet was not satisfactory in 7 patients in the HF group (fibre<30g/d) and in 4 patients in the LF group (fibre>20g/d). After 6 months of treatment, the HF diet, compared with the LF, reduced significantly 2h postprandial plasma glucose (195±92 vs 255±91) mg/dL, p<0.04) and HbA1c (8.6±1.0 vs 9.1±1.3%; p<0.03) without changes in insulin dose. No effect on plasma lipids was observed. the number of hypoglycemic events per patient was significantly lower in the HF than in LF diet (4.4±3.7 vs 8.8±7.5; p<0.01). this study definitely demonstrates that, also in the long term, compliance to the HF diet is satisfactory and that HF diet improves plasma glucose control in IDDM patients and reduced the frequency of hypoglycemia.

Type 2 diabetic patients have to exercise every day.

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Exercise is considered a cornerstone in the treatment of diabetes. Scientific studies in this field are quite rare, poorly controlled patients are usually enrolled so statistically significant differences are easily pointed out. The aims of our randomized study were to: 1)evaluate the effects of a moderately intense physical activity program on well controlled (HbA10 < 130% of upper limit of normal) non-insulin treated type 2 diabetic patients, and, 2) assess the metabolic evolution during the 3 days following the last exercise session. Twenty five subjects (experimental group (E) n=12, control (C) n=13) were enrolled in a 10-wk aerobic exercise program (3 X 60 min/wk, 69.5% maximal heart rate, with medical supervision). The two groups were similar in terms of age (E: 54.1±6.1/C: 54.3±6.5), BMI (31.4±5.1/32.4±5.2), Hba10 (7.7±1.6/6.9±1.0%), fasting glycemia (8.6±2.9/7.1±1.9 mM), and VO2 max (25.0±6.3/23.8±6.4 ml. kg-1 min-1; Lipids profile was optimal: cholesterol (4.94±0.76/5.01±0.78mM), HDL (1.06±0.34/1.02±0.34 mM), LDL (2.90±0.63/3.14±0.79 mM), TG (2.30±1.55/2.36±1.66 mM). At the end of the program, there was a statistically significant difference for VO2max (E:±4.1, C:±0.2 ml.kg-1 min-1; p<0.05) and LDL (E:±0.19, C:-0.06 mM; p<0.05) between the two groups. Moreover, the metabolic evolution 3 days after the last exercise session (D1, D2, D3) showed three significant differences: and increase in LDL (D1=3.16±0.73/D2=3.30±0.77,p<0.005), an increase in fasting insulinemia (D1=118.9±91.0/D3=324.7±609.3, p<0.002) as well as an increase in the insulin/glucose ratio (D2=15.8±9.1/D3=45.0±47, p<0.003). In these patients, moderately intense physical exercise had no effect on glycemic control but the interruption of exercise worsened LDL concentrations and insulin sensitivity within 36 hours. These data, suggest that well controlled non-insulin treated type 2 diabetic patients should exercise every day.

TREATMENT

DRUGS

Long-lasting antidiabetic effect of a dipeptidyl peptidase IV resistant analogue of GLP-1

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Glucagon like peptide one (GLP-1) stimulates insulin secretion in a glucose dependent manner. Its insulinotropic activity is preserved in non insulin-dependent diabetic patients and allows a complete correction of diabetic hyperglycemia. The therapeutic use of this peptide is however limited by its short half-life due to rapid in vivo degradation by dipeptidylpeptidase IV (DPPIV). To overcome this draw back we report that replacing alanine at position 8 of the peptide by glycine made the peptide (GLP-1-Gly8) resistant to proteolysis by DPPIV as monitored by HPLC and a biological assay. This change slightly decreased the affinity of the peptide for its receptor (IC50 0.4 ± 0.1 and 1.4±0.6 nM for GLP-1 and GLP-1-Gly8, respectively) but did not change the efficiency to stimulate accumulation of intracellular cAMP (EC50 0.25±0.5 and 0.36±0.06nM for GLP-1 and GLP-1-Gly8, respectively). To determine the in vivo effects of GLP-1-GLy8, we generated glucose intolerant C57B1/6J mice by feeding them a high-fat, sugar-free, diet. An acute intraperitoneal injection of GLP-1-Gly8 could efficiently normalize, glucose tolerance and fasting hyperglycemia even when injected up to 4 hours before initiation of glucose tolerance tests whereas the effect of GLP-1 was lost even when injected 10 minutes before glucose challenge. The effect of GLP-1-Gly8 has very significantly improved therapeutic capabilities as compared to that of the GLP-1, GLP-1-Gly8 represents a more promising peptide than GLP-1 for the treatment of NIDDM since it could be used at much lower doses and with a more flexible schedule of administration.

Continuous subcutaneous infusion of GLP-1 lowers blood glucose and reduces appetite in NIDDM patients

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The gut hormone GLP-1 has insulinotropic and anorectic effects during iv infusion and has been proposed as a new treatment for NIDDM and obesity. The effect of a single sc injection is short lasting due to rapid degradation. We, therefore, infused GLP-1 (1.2 or 2.4 pmol/kg/min) or saline subcutaneously for 48 h in randomised order in 11 patients with NIDDM to evaluate the effect on appetite during fixed energy intake, on plasma glucose (PG), insulin, glucagon, postprandial lipidemia, blood pressure (BP), heart rate (HR) and basal metabolic rate (BMR). The high rate infusion resulted in elevations of the plasma concentrations of intact GLP-1 similar to those observed after iv infusion of 1.2 pmol/kg/min, previously shown to effectively lower blood glucose in NIDDM patients. Fasting PG (day 2) decreased dose dependently from 13.2 ± 1.3 (saline) to 11.3 ± 1.0 mmol/L (GLP-1), p=0.001, during the high rate infusion, and from 12.2 ± 2.7 (saline) to 11.8 ± 2.9 mmol/L (GLP-1), NS, during the low rate infusion.

Correspondingly, 24 h mean PG decreased from 14.4 ± 1.5 to 12.1 ± 1.2 mmol/L, p = 0.005, high rate infusion), Fasting insulin and C0peptide levels were significantly higher during the high dose GLP-1 administration, whereas glucagon levels were unchanged. Neither triglycerides nor free fatty acids were affected. The GLP-1 administration decreased hunger (p<0.0001), increased satiety (p=0.001), increased fullness (p=0.004). No side effects during GLP-1 infusion were recorded except for a short lasting cutaneous reaction. BMR and HR did not change significantly during GLP-1 administration, but systolic and diastolic BP was slightly lower during the GLP-1 infusion. We conclude that a 48 h continuous subcutaneous infusion of GLP-1 in NIDDM patients 1) lowers fasting as well as meal-related PG, 2) reduced appetite, 3) has no gastrointestinal side effects, and 4) has a small positive effect on BP.

Losartan modifies glomerular hyperfiltration and insulin sensitivity in type 1 diabetes

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The effect of the angiotensin II receptor antagonist, losartan on renal hemodynamics and insulin mediated glucose disposal was examined in normotensive, normoalbuminuric Type 1 diabetics patients using a doubleblind, placebo controlled, cross-over design. Diurnal blood pressure, GFR^{125} I-iothalamate), RPF131I-hippuran), UAE were measured and a hyperinsulinaemic, euglycaemic clamp with indirect calorimetry was performed in 9 patients (age 30±7 years (mean±SD), HbA 8.1±1.1%) following 6 weeks losartan 50 mg/day and 6 weeks placebo. Diurnal blood pressure was significantly reduced after losartan compared with placebo (122/70±118/ vs 130/76±12/6 mmHg, p<0.05). A significant decline in GFR (133±23 vs 140±22 ml/min, <0.05) and filtration fraction (GFR/RPF) (24.6±3.5 vs 26.2±3.6%, p<0.05) was observed during losartan vs placebo. RPF and UAE did not change. Isotopically determined glucose disposal rates were similar after losartan and placebo in the basal (2.61±0.53 vs 2.98±0.93 mg/kg/min) and insulin stimulated states 6.84±2.52 vs 6.97±3.11mg/kg/min). However, glucose oxidation rate increased significantly after losartan vs placebo in the basal state (1.72±0.34 vs 1.33±0.18, mg/kg/min, p<0.01) and during insulin stimulation (2.89±0.75 vs 2.40±0.62 mg/kg/min, p<0.03). Basal and insulin stimulated non-oxidative glucose disposal tended to decrease, however not significantly, after losartan. Endogenous glucose production and lipid oxidation were unchanged after treatment and similarly suppressed during hyperinsulinaemia. Glycaemic control, total cholesterol, HDL cholesterol and triglycerides were stable during losartan and placebo. In conclusion, losartan reduces blood pressure, glomerular hyperfiltration and filtration fraction and improves basal and insulin stimulated glucose oxidation in normotensive, normoalbuminuric Type 1 diabetic patients.

A randomized, placebo-controlled, double-blind fixed-does study of repaglinide.

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The safety and efficacy of repaglinide (REP) at 2 dose levels vs placebo was assessed in a multicenter, randomized, double-blind study. Eligible patients with type 2 diabetes were randomized to 1 of 3 groups: REP 1-mg (n=140), REP4-mg(n=146), or placebo (n=75). Study medications were administered preprandially (with 3 meals) for 24 weeks. Both REP doses were well tolerated. Adverse events (AEs) possibly or probably related to study drug were reported for 24% of placebo patients and 21% of all REP patients. The most frequent AE was dizziness. occurring in 4% of placebo patients. and in 1% and 5% of the 1 - and 4-mg REP patients, respectively. Hypoglycemic episodes increased with increasing doses of REP: 11% in the placebo group. 27% in the REP 1-mg group, and 36% in the REP 4-mg group. Most events were mild; none were severe. This frequency of hypoglycemic episodes is expected in a fixed-dose clinical trial, and is normally lower in clinical practice. For OHA-naive patients, mean decreases in the proportion of total HbA for both REP groups from baseline(1-mg: 0.093; 4-mg: 0.092) to end of treatment (1-mg:0.076; 4-mg: 0.074) were observed (change from baseline: 0.013 and 0.019); vs an increase from 0.085 to 0.092 for the placebo group (change from baseline: 0.01). for previously treated patients, mean decreases in the proportion of total HbA- from 0.087 and 0.085 for REP 1 - and 4-mg respectively to 0.082 were noted (change from baseline: 0.004 and 0.002); vs an increase from 0.087 to 0.1 for the placebo group (change from baseline: 0.014) REP was safe and effective in reducing HbA- vs placebo by the end of the study.

Nateglinide (A-4166), A new insulinotropic agent, controls prandial hyperglycemia in type 2 diabetic patients

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Main objective: to evaluate the prandial effects of 4 dose levels of nateglinide and placebo (PL) administered before main meals. Method: double-blind randomized. 12 week, parallel group study. A Sustacal^{r} challenge (liquid meal, 250 kcal) was performed at week 0, 4 and 12. Blood samples were obtained at baseline (BL), 15 min, 30 min, 1 hr, 2 hr and 4 hr after the challenge. Subjects: 243 subjects were tested at week 12. Results: The mean glucose and insulin levels at selected time points, and the area under the curve for 0-4 hours (AUC-0-4h adjusted for insulin/glucose at baseline were:

A rapid, dose-dependent increase in insulin secretion was observed 15 min post-challenge with a return to baseline values 4 hr post-challenge. This rapid prandial increase of insulin induced a significant reduction of post-prandial glucose excursions in a dose-dependent manner. Conclusions: nateglinide exerts its blood glucose lowering

effect by restoring early prandial insulin secretions and diminishing meal-related glucose fluctuations.

			PL	30 mg	60 mg
Insulin	BL	(fU/ml)	17.3	15.8	18.3
Insulin	15 min	(fU/ml)	28.1	34.1	43.3
Insulin	1 h	(fu/ml)	39.1	53.5	56.2
Insulin	4h	(fu/ml)	16.7	17.3	18.7
AUC (0-4h) insulin (hr.mU/L			±6.2	±16.8	±25.5
Glucose	BL (mmol/L)		10.4	10.2	9.6
	1h (mmol/L)		14.9	13.5	12.4
	2h (mmol/L)		12.7	11.1	9.9
	4h (mmol/L)		9.4	8.5	7.6
AUC (0-4h)glucose (hr.mmol/1)			±0.6	-2.7*	-6.4***

			120 mg	180 mg
Insulin	BL	(fU/ml)	22.5	15.5
Insulin	15 min	(fu/ml)	46.6	32.4
Insulin	1 h	(fu/ml)	64.9	58.3
Insulin	4 h	(fu/ml)	18.7	20.2
AUC {0-4h} insulin (hr,mU/L)			±32.6*	±39.5**
Glucose	BL (mmol/L)		9.8	9.9
Glucose	1h (mmol/L)		12.7	13.1
Glucose	2h (mmol/L)		9.8	10.4
Glucose	4h (mmol/L)		7.0	7.4
AUC {0-4h}glucose (hr.mmol/1)			-5.0***	-6.4***

Change vs placebo (ANOVA model): * p<0.05, **p<0.01, ***p<0.001

Cointraindications to metformin therapy are generally disregarded

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Metformin is well established in the therapy of NIDDM due to its antihyperglycaemic effect and its positive influence on insulin resistance. Nevertheless, the application of the substance is limited due to the known contraindications (CI), especially renal impairment and tissue hypoxia, in a cross section analysis, we evaluated, if metformin therapy in practice was critically proceeded and sufficiently monitored. 221 consecutive NIDDM patients (111 female, 110 male; age 66 q 11.5 yrs; BMI 29 q 5.6 kg / m2; HbA1c 9.3 q 5.6%; daily dosage 1200 q 540 mg) pre-treated with metformin were examined on CI of biguanide administration. All patients were hospitalized between January 1995 and December 1997 in a general district hospital due to acute medical problem or for improvement of diabetic treatment. A medical history, a complete physical examination, ECG and an elaborate laboratory profile were done and 30% underwent coronary angiography. This examination revealed the definite CI of renal impairment in 21% of all patients (creatinine > 1,2 mg /dl or creatinine clearance < 30 ml/min); 24% had cardiac failure (NYHA II - IV x). 23% showed coronary heart disease with the immediate need of intervention (lysis, PTCA, stent or ACVB). 6% had respiratory and 2% hepatic insufficiency; arterial occlusion, chronic alcohol abuse and pregnancy were present in another 6%. During the therapy with metformin, 14% of all diabetics developed cerebral ischaemia, in 6% an acute malignant tumor was diagnosed. Moreover in only 22% of all patients no CI were present. 52% of the diabetics exceeded the age of 65. The CI of biguanides were generally neglected in the presented cohort; furthermore, co-morbidity and old age of NIDDM patients were at risk for obtaining a lactic acidosis due to metformin therapy. Further education for physicians is needed for the treatment of patients with NIDDM.

Orlistat (Xenical[r]) reduces cardiovasular disease risk factors in obese patients with type 2 diabetes

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Type 2 diabetes mellitus and obesity are linked frequently with hypertension and hyperlipidaemia as the key components of insulin resistance syndrome, a condition which predisposes to major cardiovascular risk. To determine the independent effect of weight loss and orlistat (a lipase-inhibitor which blocks about 30% of dietary fat absorption) on risk factors, 321 obese diabetic patients treated with sulphonylureas, were randomised to a mildly hypocaloric diet plus orlistat (Orl) 120 mg tid or placebo (Pla) in a 1-year, double-blind, multicenter study. Weight loss at 1 year was significantly greater in the Orl vs Pla group (6.2% vs 4.3%, p<0.05). Changes in risk factors were calculated for 3 categories: weight loss<5%, 5-10%or>10% initial body weight. Total cholesterol was reduced in Orl patients (-0.31, -0.38 and -0.71) mmol/L, respectively) and in Pla was elevated over baseline (±0.01, ±0.31 and ±0.18 mmol/L, respectively; p<0.05), indicating an independent beneficial effect of Orl treatment. HbA1c showed progressive decrease across the weight categories from - 0.10 to -2.29% in both Orl and Pla (p<0.05) with no additive drug effect. Likewise, systolic blood pressure decreased progressively by -2, -3 and -15 mmHg across the weight loss categories in both Orl and Pla (p<0.05). Gastrointestinal adverse events such as fatty/oily stools, oily spotting and faecal urgency were mild and transient, and only 10% of Orl patients had more than 2 episodes of GI AEs. The drop-out rate for ORL was only 15% compared to PLA28%. The results of the study show that

ORL is an effective adjunct to diet, has an independent beneficial effect on lipid profile, leads to improved glycemia and blood pressure as related to weight loss and is well tolerated in obese patients with type 2 diabetes.

Sibutramine induces weight loss and improves glycemic control in obese patients with type 2 diabetes mellitus.

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Sibutramine (Sib, MERIDIA Reductill), a novel serotonin and norepinephrine reuptake inhibitor, was recently approved in the US for managing obesity. This 24-wk, randomized, double-blind, placebo (Pcb)-controlled, parallel-group study evaluated the effect of Sib (20 mg/d) on weight loss and glycemic control in obese patients with type 2 diabetes uncontrolled by diet or oral antidiabetic therapy. After a 5-wk run-in period (all received Pcb), patients were randomized to Sib ro Pcb; Sib patients started with 5 mg and were titrated up by 5 mg every 2 wk through wk 6. Sib patients received 20 mg in wk 6-24. Analysis for completers and categorical data were performed using the Kruskal-Wallis test (*indicates p<.05 vs Pcb). Of 175 patients (93 M, 82 F) randomized (89 Sib, 86 Pcb; mean characteristics: ge, 54.2 yrs; weight, 99 kg; BMI, 34 kg/m2; fasting plasma glucose, 182 mg/dL; HbA-10, 8.34%), 60 Sib (67%) and 61 Pcb (71%) patients completed the study. For 24-wk completers, mean actual and percent changes from baseline weight for Sib and Pcb patients, respectively, were - 4.3 kg* and -4.5%*, and -0.3 kg and -0.4%. The proportion of patients achieving >=5%and >=10% weight loss in Sib and Pcb groups, respectively, were 33%* and 8.3%* , and 0% and 0%. Mean changes in BMI were - 1.5 kg/m2 for Sib vs - 0.1 kg/m2 for Pcb. Sib produced larger mean reductions in waist circumference than Pcb (-3.4 cm vs - 2.0 cm). Weight loss (>-5%) with Sib was associated with improvements in glycemic control; mean changes from baseline in Hba10 and fasting plasma glucose (mg/dL) for Sib (>=5% weight responders) vs all Pcb patients, respectively, were -0.28 and -8.2* vs $\pm$ 0.25 and $\pm$ 15.8. Sib was well tolerated. The type incidence, and severity of reported adverse events were comparable between Sib and Pcb. Quality of life assessments showed significant* improvements with Sib in general health, social functioning, and bodily pain scales. Conclusion: Sibutramine at 20 mg/d is safe and produces significant weight loss associated with improved glycemic control in obese patients with type 2 diabetes.

Postmenopausal hormone replacement therapy and lipid parameters in women with type 2 diabetes

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Hormone replacement therapy (HRT) has a significant beneficial effect on lipid parameters in non-diabetic postmenopausal women. Little is known, however, of its effect in women with Type 2 diabetes. The aim of this study was to determine the effect of combined continuous HRT on lipid parameters and glycaemic control in these women. The study design was a randomised double-blind, placebo-controlled trial. Subjects were randomised to receive either combined continuous HRT (conjugated equine oestrogen 0.625 mg/day and medroxy-progesterone acetate 2.5 mg/day) or placebo. Fasting blood samples were drawn at 0. $\pm$ 13 and $\pm$26 weeks, and analysed for lipoprotein profile, Lp (a), fibrinogen, PAI-1, glucose and HBA_{1C}. 61 subjects (mean age 64 years) enrolled into the study, 32 in the placebo group and 29 in the HRT group. At baseline there were no significant differences in any variable between the 2 groups. 8 subjects did not complete the study period (1 placebo, 7 HRT). Total cholesterol levels at $\pm$26 weeks were 6.76q1.21 mmol/i in the placebo group and 5.59q0.97mmol/1 in the HRT group (p<0.001). LDL cholesterol was 4.64q1.12 mmol/1 in the placebo group and 3.52q0.78 mmol/1 in the HRT group (p<0.001). There were no significant differences in HDL cholesterol, triglyceride, Lp (a), fibrinogen, PAI-1, fasting glucose or HbA_{1C}. Patient weight increased significantly in the HRT treated group. In conclusion, combined continuous HRT use in postmenopausal women with Type 2 diabetes results in a significant reduction in total and LDL cholesterol without impairing glycaemic control or elevating triglyceride levels. Tolerability of HRT remains a problem.