ABSTRACT SERVICE*

*Abstracts are excerpted from 59th annual ADA meeting held from June 19 to June 22, 1999, San Diego, California, USA.

EPIDEMIOLOGY

Mortality in persons with type 2 diabetes. The San Luis Valley diabetes study 1984-98.

Marian J Rewere, Carolyn Swenson, Susan Shetterly, Sharon Scarbro, Denver, CO University of Colorado, School of Medicine

It is unknown if excess mortality in type 2 diabetic patients is parimarily due to hyperglycemia, to the clustering of cardiovascular risk factors (hypertension, central obesity, dyslipidemia) or is associated with specific diabetes treatment (insulin, oral agents). In 1984-88, we examined a population-based group of 524 type 2 diabetic patients and 1,280 non-diabetic controls, matched for age and ethnicity, residing in two rural Colorado countries. Diabetes status was confirmed by OGTT. In 1998, after an average of 11 years of follow-up, 177 (33%) of diabetic patients were deceased – a relative risk RR=2.6 (95% CI 2.1-3.3), compared to the controls. Among diabetic patients age-adjusted mortality was higher in men (RR=1.5; 1.1-2.0), smokers (1.6; 1.1-2.5), and drinkers of > 50g alcohol per week (1.8; 1.1-3.0), but similar in Hispanics and non-hispanics and non-hispanic whites. Adjusting for these factors hypertension (2.5; 1.6-3.8) and higher waist/ hip ratio (1.4; 1.0-1.9 for 0.1 increase in ratio) predicted mortality, but LEL-HDL-Cholesterol, and triglyceride levels did not. Adjusting for all of the above factors, diabetes duration (.5; 1.2-1.7 for 10 years) and glycohemoglobin (1.4; 1.2-1.6 for 2% increase) strongly predicted mortality. Microalbuminuria (1.7; 1.2-2.4) and ratinopathy (1.7; 1.2-2.5) were additional independent predictors of mortality, which supports the pivotal role of hyperglycemia. Insulin or oral hypoglycemic agent therapy did not increase mortality risk. These results suggests that hypeglycemia and hypertension control as well as smoking and alcohol counseling may be useful areas for intervention to prevent excess mortality in type 2 diabetes. The limited impact of dyslipidemia on all cause mortality in this type 2 diabetic population requires further exploration.

Subclinical states of glucose intolerance and the risk of death in the United States.

Sharon H Saydah, Mark S Eberhardt, Catherine M Loria, Frederick L Brancati, Baltimore, MD, The John Hopkins Medical Institutions

Although clinically evident diabetes is a well-established cause of mortality, less is known about the subclinical states of glucose intolerance. We therefore performed a prospective cohort study using data from the second National Health and Nutrition Examination Survey (NHANES II) and the NHANES II Mortality Study (NH2MS), in which 9250 adults aged 30-74 years underwent a detailed health evaluation in 1976-80 (NIHANES II), and were then followed through 1992 for overall and causespecific mortality (NH2MS). Vital status was determined by computerized matching to the National Death Index and Social Security Administration Master Death File. This analysis includes 3246 adults who were randomly selected for oral glucose tolerance testing (OGTT) and had complete data. Participants were grouped into four categories according to WHO criteria: diagnosed (dx) diabetes, undiagnosed (undx) diabetes, impaired glucose tolerance (IGT) and normal glucose tolerance. Proportional hazards models including age, sex, race, education, body mass index, systolic blood pressure, high density lipids and smoking, were performed using SUDAAN statistical software to account for the complex sample design of NHANSE II. Of the 3246 adults, 262 had previously dx diabetes, 190 had undx diabetes, 496 had IGT and 2298 had normal glucose tolerance. The cumulative mortality at age 75 was greatest for adults with dx diabetes (36%, 95% Confidence Interval (CI) = 29%-42%)followed by adults with undx diabetes (26%, 95% CI=20%-33), IGT (22%, 95% CI=18%-26%) and normal glucose tolerance (20%, 95% CI = 17%-22%). Compared to those with normal glucose tolerance, the fully adjusted relative risk (RR) for all cause mortality was greatest for adults with dx diabetes (RR = 2.75, 95% VI = 2.03-3.73), followed by people with undx diabetes (RR=1.75, 95% CI = 1.12-2.75) and adults with IGT (RR=1.32, 95% CI =1.00-1.74). ± similar pattern of risk was observed for cardiovascular disease (CVD) mortality. These data suggest that, in the United Stages: 1) There is a gradient of mortality associated with abnormal glucose tolerance, ranging from a 30% greater risk in people with IGT, to a 2.7-fold greater risk in people with clinically evident diabetes, 2) These associations are independent of established CVD risk factors which commonly accompany abnormal glucose tolerance. These findings support the need for improved detection and treatment of subclinical states of glucose intolerance.

A population-based study of the risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in people with older-onset diabetes.

Charles T Valmadrid, Ronald Klein, Scot E Moss, Barbara EK Klein, Medison, WI University of Wisconsin Medical School

Despite many studies on the relation of proteinuria with increased risk of all-cause mortality in type 2 diabetes, it remains uncertain whether microalbuminuria and gross proteinuria are independent risk factors for cardiovascular disease mortality. Moreover, the role of albuminuria in cardiovascular death has not been well described in population-based studies of type 2 diabetes. To examine the associations of microalbuminuria and gross proteinuria with cardiovascular mortality in prople with type 2 diabetes, we followed 840 older-onset diabetic participants of the Wisconsin Epidemiologic Study of Diabetic Retinopathy from 1994 to 1996. Microbuminuria was determined by an agglutination inhibition assay and gross proteinuria by a standard reagent strip. The main outcome variable was time to death from cardiovascular disease, define as any mention of ischemic heart disease, heart failure, and cerebrovascular disease as the underlying or contributory cause on death stated on the death certificates. Of the 840 individuals, 54.8% had normoalbuminuria while 24.8% had microalbuminuria and 20.5% had gross proteinuria. There were 364 deaths from cardiovascular disease during the 12-year follow-up (6127 person-years). As compared to persons with

normoalbuminuria, those with microalbuminuria and gross proteinuria had significantly higher risks of cardiovascular death. The hazard ratios (and 95% confidence interval [CI] – as adjusted for age, gender, glycemic control, insulin use, alcohol intake, physical activity, cardiovascular disease history, antihypertensive use and retinopathy severity—were 1.84 (1.42-2.40) and 2.61 (1.99-3.43) for those with microalbuminuria and gross protenuria, respectively. Further control for other factors, including total cholesterol and high-density lipoprotion cholesterol in a subset of the cohor who had complete data on these lipids, did not change the relations we found. When the end point used was coronary heart disease mortality (n=242 cases), the increased risks were significant for both microalbuminuria (adjusted hazard ratio =1.96% CI=1.42-2.72) and gross proteinuria (adjusted hazard ratio=2.73, 95% CI=1.95-3.81). Results from our population-based study strongly suggest the independent associations of both microalbuminuria and gross proteinuria with subsequent mortality from cardiovascular and coronary heart disease.

MONITORING AND NON INVASIVE GLUCOSE TESTING

Non-invasive continuous glucose monitoring during physiological blood glucose changes in volunteers and diabetic patients

Lutz Heinemann, Uwe Kraemer, Hans-Martin Kloetzer, Marcus Hermann, for the Non-Invasive Task Force, Duesseldorf, Germany. Heinrich-Heine-University Duesseldort

Continuous glucose monitoring by means of optical glucose sensors would allow diabetic patients to check their metabolic control at their convenience. In experimental glucose clamp studies with patients with type 1 diabetes mellitus we have demonstrated that non-invasive glucose monitoring is possible by registration of the scattering coefficient of human skin. In order to evaluate if physiological changes in glycemia can also be detected, we monitored we monitored blood glucose in five healthy volunteers (age 26 ± 1y, 22.3 ± 2.4kg/m^2 consuming a large breakfast and in 13 patients with type 2 diabetes mellitus (age 57 ± 8y, BMI 29.2 ± 2.0 kg/ m^2) receiving an oral glucose tolerance test (75g) for four hours. Two simultaneous measurements of the skin tissue scattering coefficient were carried out in each volunteer/patient by means of a portable system in order to evaluate reproducibility. An optic sensor head was attached directly to the skin and light was applied for registration of reflected light intensity. Additionally measurements of the interstitial fluid glucose concentration were performed simultaneously by means of the microdialysis technique (CMA catheter and analyzer). Blood glucose increased from baseline levels of 3.9 ± 0.4 mmol/l to maximal values of 12.3 ± 0.7 mmol/l after 122 ± 12 min in healthy subjects (with low-dose somatostatin infusion) and from 8.8 ± 0.8 17.1 ± 2.2 mmol/l after 114 ± 17 min in diabetic patients. In 8 of the 10 measurements with the volunteers the observed changes in scattering coefficient correlated well with the changes in glycemia (linear regression coefficient r = 0.75). No correlation was observed in 2 measurements. Reproducibility was good in three of the five volunteers. In the diabetics, 16 of the 26 measurements showed a good correlation (r =0.77). Two measurements showed a moderate correlation and 9 measurements no correlation. Reproducibility was good in 11 patients. The interstitial glucose concentration showed a good correlation with the intravasal measurements in the patients (r=0.84). This study shows that in principle physiological changes in blood glucose can be monitored by registration of scattering coefficient changes in volunteers and diabetic patients in most, but not all experiments.

Development of a rapid, non invasive test for diabetes using fluorescence spectroscopy

Richard Bergenstal, Eugene Oddone, David Edelman, James Long, John F Price, Indianapolis, IN Roche diagnostics

We will be describing a new tabletop instrument designed to non-invasively measure optic lens fluorescence. The instrument is used to detect elevated advanced glycosylated end products (AGEs) in the crystalline lens of the patient. Elevated AGEs area significant symptom of diabetes. The crystalline lens of the eye is excited with blue laser (473 nm), and the fluorescence and scattering intensities are measured. These measurements require only 20 seconds and are used as inputs to a mathematical screening model, which generates an output. The output is used to determine whether or not the measurement subject has a low or high probability of having diabetes. The instrument uses low-density, eye-safe light to measure changes in the fluorescence and scattering properties of the lens related to the glycosylation to the proteins in the lens of the eye. These glycosylation and products build up at faster rates in patients with elevated glucose levels and can be used to distinguish patients with diabetes. The results of multi-site clinical studies using preproduction instrumentation on a population of 800 patients will be presented. Screening for diabetes is difficult since it typically requires a Screening for diabetes is difficult since it typically requires a lengthy fasting period and an invasive blood collection. By evaluation the fluorescence products that accumulate in the lens of the eye, one can rapidly screen a patient for diabetes with similar sensitivity and specificity as existing screening approaches. Since no invasive blood collection in required, many of the infection control issues are reduced. As with any screening method, follow-up confirmatory tests will be required to make a final diagnosis.

Glycaemic control, as measured by HbA_{1C} is a poor predictor of macrosomia in pregnancy in type 1 diabetes

Rosemary C Temple, Vivian Aldrige, Katherine Duffield, Richard Greenwood, Philip Heyburn, Michael Sampson, Norwich, United Kingdom, Norfolk and Norwich Health Care NHS Trust

Studies of glycaemic control in type 1 diabetes suggest good glycaemic control reduce incidence of macrosomic infants but also that glycaemia control in early rather than later pregnancy has a greater influence on birthweight. We have investigated the relationship between infant birthweight (BW) and glycaemic control (HbA_{1C}) at booking and in first, second and third trimesters of pregnancy to establish whether HbA_{1C} may be a useful predictor for marcrosomia. Type 1 diabetics who delivered at 32 weeks gestation or later, 1995 to 1998, were included. HbA_{1C} (normal range 3.6-5.8%) was measured monthly. Macrosomia was defined as infant birthweight above 90^{th} centile. Infant birth weight ratio (IBR) was defined as infant BW divided by 50^{th} centile BW matched for gastation and sex. We report results of 62 live births. 30(48%) of infants were macrosomic. There was no significant difference between macrosomic and non-macrosomic pregnancies in parity (43% primps vs 47% primps), duration to diabetes [10.6 (7.7) vs 12.9 (7.3) years] and maternal weight at booking [69.4

(12.7) vs 67.7 (10.9) Kgs.] There was no significant difference in HbA $_{1C}$ between macrosomic and non-macrosomic pregnancies at booking [6.7(1.1) vs 7.2 (1.9) %], at 12 weeks gestation [6.1 (0.8) vs 6.6 (1.7)%], at 24 weeks [5.7 (0.8) vs 5.9 (1.5)%] and 34 weeks [5.9 (0.7) vs 6.0 (1.4) %). No significant correlation was demonstrated between IBR and HbA1C at booking (e =0.12, p = NS), 12 weeks (r=0.22, p=NS), 24 weeks (r=0.09, p=NS) or 34 weeks (r = 0.04, p = NS). These results suggest that HbA 1C at all stages of pregnancy is a poor predictor of macrosomia.

Correlation of Gluco Watch (R) biographer glucose values with Hemocue (R) blood glucose results in young subjects with type 1 diabetes

Satish K Garg, Janet Tamada, Russell Potts, Steve Fermi, Kathy Jennings, Seth Perry, Michele Pennington, Julie Robinson, Peter Chase, Denver, CO University of Colorado Health Sciences Center

Frequent blood glucose monitoring is an integral is an integral part of intensive diabetes management and has resultsed in improved glycemic control. Reverse inotophoresis is used to extract interstitial fluid in the Gluco Watch ® non-invasive monitor and the extracted glucose is measured electrochemically. Seventy-six (76) Gluco Watch biographers were used in 39 young adults (two biographers malfunctioned) with type 1 diabetes (mean ± SD age 31 ± 6.9 years and mean ± SD duration of diabetes 18.4 ± 8.6 years) to determine the accuracy of the glucose values. All subjects (25 females and 14 males) wore two biographers each on the forearm (ventral aspect) three inches away from the wrist and the elbow joints. Subjects reported fasting to the clinic and began the study by 7:30 am. After a 3-hour period there was calibration with finger-stick blood glucose values using the Hemocue (R). Subjects were then asked to check blood glucose values on the Hemocue two times an hour for the next 12 hours. Hemocue blood glucose values correlated well with the interstitial glucose values from the biographer (r=0.9) and throughout the ranges (40-4000mg/dL). The error grid analysis (Table) depicted >96% of blood glucose values in the A and B regions. In addition, 11 subjects wore biographers for three days at home and the correlation with One Touch (R) glucose values was r=0.86. This confirms the reproducibility of glucose values in the clinic and at home and a good correlation of Gluco Watch biographer glucose values with Hemocue blood glucose results.

Region	# of patients	%
A	1148	73.87
B	352	22.65
C	1	0.06
D	53	3.41
E	0	0
Mean % Error	14.5 %	

PATHOGENESIS

PPAR [alpha] suppresses insulin secretion.

Karen M Tordjman, Trey Coleman, Fengjuan Zhang, Clay F, Semenkovich, St. Louis, MO Washington University School of Medicine

PPAR (alpha) appears to affects both lipid and glucose metabolism. The purpose of this study was to examine the putative role of PPAR [alpha] on b -cell function. When fed a high fat, high carbohydrate diet, the LDLR-/- mouse rapidly develops hyperlidemia, hyperisulinemia, obesity, and hyperglycemia. By breeding the PPAR [alpha] knockout into the LDLR-/- background, a double knockout (PPAR [alpha]-/- LDLR-/-) was generated that was compared to the LDLR-/- model. Baseline characteristics were identical for both groups. At age eight weeks, all mice were fed the diabetogenic diet. Over the course of three months, weight gain was similar in both groups. However, in contrast to LDLR-/- mice, and despite higher circulation free fatty acid levels, PPAR [alpha] -/- LDRL-/- mice appeared to be protected from diet-induced hyperglycemia. After two months on the high fat high carbohydrate diet, blood glucose was 271 ± 15 mg/dl in LDRL-/- mice, but only 115 ± 13 mg/dl in PPAR [alpha] -/- LDRL-/- mice (p< 0.0001). Next, a recombinant adenovirus containing mouse PPAR (alpha) cDNA (AdPPAR[alpha] was generated. Two month old PPAR [alpha] -/- mice received a single injection of either AdPPAR [alpha] or vehicle. Two weeks after injection, liver acyl-CoA oxidase activity was increased by 26% in AdPPAR [alpha]-injected animals compared to control. More significantly, islet cells isolated from AdPPAR[alpha]-injected animals exhibited a dramatic decreases in glucose-stimulated insulin secretion (GSIS) from 1.08 ± 0.1 to 0.37 ± 0.07 ng/slet/30 min (p=0.02) when compared to control islets. The determine if these findings represented direct effects of PPAR [alpha] on B-cells, we studied the rat insulinoma INS-1 cell line. Cells were infected with either 1010 pfu/ml of AdPPAR [alpha] or AdB-Gal. PPAR[alpha] ,RNA was induced by more than 10-fold within 24 h in AdPPAr [alpha]-treated cells. In parallel, basal insulin secretion was suppressed by 22% (from 2.1 ± 0.2 to 1.63 ± 0.1 ng/m g DNA/h, p<0.05) at 24 h, and by 48% at 72 h (from 0.99 ± 0.05 to o.52 ± 0.03 mg/m g DNAh, p < 0.0001). The effect of GSIS was comparable or greater. In conclusion, PPAR[alpha] exerts a direct negative effect on basal and GSIS, both in islets of PPAR. [slpha]-/- mice and in INS-1 cells. Elucidation os the target genes for PPAR [alpha] in the b -cell, particularly those involved in lipid metabolism, could shed light on the mechanisms of insulin secretion.

Low cellular IRS 1 gene and protein expression predict insulin resistance and type 2 diabetes.

Eugenia Carvalho, Per-Anders Jansson, Mette Axelsen, Jan W Eriksson, Xudon Huang, Leif Groop, Cristina Rondinone, Lars Sjostrom, Ulf P Smith, Gothenburg, Sweden, Sahlgrenska University Hospital

No celluar markers of individuals at risk for insulin resistnce and type 2 diabetes have been identified. We recently reported that IRS-1 protein expression and associated Pi3-kinase activity were markedly reduced (~70%) in fat cells from individuals with NIDDM (PNAS 94: 4171, 1997). This was not seen in cells from individuals with IDDM suggesting a relationship with insulin resistance rather than hyperglycemia per se. We now examined two groups of healthy, non-diabetic individuals with high risk of type 2 diabetes: those with at least two first-degree relatives with type 2 diabetes (n=22) and a carefully matched control group lacking heredity (n=22) as well as a group of massively obese subjects (n=20). Careful metabolic characterization was performed and adipocyte IRS-1 gene and protein expression measures. Low cellular IRS-1 protein expression was defined as < =50% of that of the healthy controls, -30% of both high-risk groups had low IRS-1 protein expression. This abnormality identified the two subjects with previously unknown type 2 diabetes. Low IRS-1

protein expression was related to low Mrnalevels, suggesting an impaired transcription, but not to the common Gly 972 Arg polymorphism of the IRS-1 gene. Individuals with this perturbation were insulin resistant (insulin sensitivity during a euglycemic clamp reduced –50%, $p < 0.01$) and they had significantly higher fasting insulin and triglyceride levels in spite of similar age, BMI and amount of body fat as the group with normal IRS-1 expression. Conclusion : A low adipocyte IRS-1 expression predicts insulin resistance and type 2 diabetes in healthy but high-risk individuals (both genetic and environmental) suggesting a relationship to common pathogenetic factor (s).

Are sex hormones and leptin involved in the pathogenesis of type 2 diabetes?

Jan W Eriksson, Stina Lindmark, Bjorn Eliasson, Per-Anders Jansson, Umea, Sweden, Dept of Medicine

To further examine early hormonal pertubations in the pathogenesis of type 2 diabetes we studied 50 young, healthy, non-obese subjects of whom 25 had either two first-degree or one first-degree plus two second-degree relative with type 2 diabetes (R) and 25 who had no known relatives with diabetes (C). The groups were matched for ge (R 33.3 ± 6.1 vs C 33.4 ± 6.2 yr, mean ± SD), BMI (23.9 ± 2.9 vs 23.4 ± 2.1) and sex (M/F 12/13). Body fat and lean body mass determine by bioimpiedance did not differ between the groups. Fasting serum glucose and insulin were similar and so were 2h-OGTT values. Insulin sensitivity assessed as the M-value during a hyperinsulinemic (~ 100mU/L), euglycemic clamp was similar 9R 91.0 ± 0.7 VS c 10.2 ± 0.4 mg/kg/min, mean ± SE). In male subjects R had significantly lower serum testosterone levels compared to C, 14.8 ± 1.2 vs 21.6 ± 1.8 nmol/l ($p < 0.005$). In females testosterone levels were similar between R and C (1.1 ± 0.1 vs 0.8 ± 0.2). In males, but not females, serum testosterone was strongly and positively associated with insulin sensitivity ($r=0.55$, $p<0.01$) and this relationship persosted also in multiple regression analysis including BMI and body fat. Serum levels of SHBG and prolactin did not differ significantly between the groups. Serum leptin was higher in R than C (9.9 ± 1.7 vs 5.7 ± 1.3 ng/ml, $p<0.005$), also when males and females were analyzed separately. In male R, leptin as inversely related to insulin sensitivity ($p<0.05$). Conclusion : Among subjects with a family history of type 2 diabetes, males have reduced serum testosterone levels, whereas leptin levels are elevated in both males and females. An altered interplay between sex steroids and leptin may be involved in the early development of insulin resistance and type 2 diabetes.

Celluar mechanism of nutritionally induced insulin resistance in Psammomys obesus: Overexpression of Protein Kinase C epsilon in skeletal muscle precedes the onset of hyperinsulinemia and hyperglycemia

Yukia Ikeda, Ehud Ziv, Lone L Hansen, Anna K Busch, Bo F Hansen, Eleazar Shafrir, Luitgard Mosthaf, Gentofte, Denmark, Hegedorn Research Institute

The sand rat (Psammomys obesus) is an animal model of nutritionlly induced diabetes. The objective of the study was to determine whether changes in the expression level and/or activity of Protein Kinase C (PKC) isoforms might be associated with the development of diabetes of these animals. We report here that several PKC isoforms alpha, epsilon, zeta which include members from all three subclasses of PKC, are overexpressed in the skeletal muscle of diabetic animals. This is most prominent for the epsilon isotype of PKC (82.2 % increase). Interestingly, increased expressin of PKC[epsilon] (59.3% increase) could already be detected in normoinsulinemic, normoglycemic (prediabetic) animals of the diabetes prone (DP) line when compared to a diabetes resistant (DR) line. In addition, plasma membrane (PM) associated fractions of PKC [epsilon] were increased in skeletal muscle of both diabetic and prediabetic animals, suggesting increased activation of this PKC isotype in the DP line. Altered expression/activity of PKC [epsilon] may thus contribute to the development of diabetes in these animals, possibly through inhibition of insulin receptor (IR) tyrosine kinase activity mediated by serine/threonine phosphorylation of the IR or IRS-1. However, overexpression of PKC[epsilon] also mediated downregulation of insulin receptor (IR) numbers in a cell culture model (293 cells). In accordance with this we detected decreased ^{125}l-insulin binding (14.3% decrease), probably reflecting a downregulation of insulin receptor numbers, in skeletal muscle of Psammomys from the DP line. The number of insulin receptors was inversely correlated to both the expression and PM associated levels of PKC[epsilon]. The data suggest that over expression and/or chronic activation of PKC[epsilon] may contribute to the development of insulin resistance in these animals, possibly by increasing the degradation of insulin receptors.

Size of birth, growth in childhood, and future risk of type 2 diabetes

Johan G Eriksson, Tom Forsen, Jaakko Tuomilehto, Anti Reunanen, Clive Osmond, David Barker, Helsinki, Finland, National Public Health Institute

Low birth weight has been associated with increased risk of type 2 diabetes later in life, hypothesized to originate through adaptations made in utero. Obesity is an important risk factor for type 2 diabetes. Since obesity may be entrained in childhood the combination of low birth weight and high childhood body mass index may be associated with increased rates of type 2 diabetes. The aim of this study was to test the association between fetal and childhood growth on diabetes prevalence among 7088 individuals born 1924-33. In men there was a highly significant trend between birth weight and diabetes prevalence ($p=0.008$) but in women this was not significant ($p=0.3$), although the prevalence of diabetes was lowest (4.8%) in the highest birth weight quintile and highest (6.9%) in the lowest birth weight quintile ($p=0.09$ between these quintiles). Body mass index (BMI) at 7 years was not related to diabetes prevalence, but BMI at 11 and 15 years predicted a higher prevalence of diabetes in both man and women. The cumulative incidence in males in the lowest birth weight quartile and highest BMI quartile at 11 years was 14.9% compared with children in the highest birth weight quartile and highest BMI quartile where the cumulative incidence was 4.9%, yielding an odds ratio of 4.4 (1.6-12.2). The corresponding cumulative incidence in females in the lowest birth weight quartile and highest BMI quartile at 11 years was 13.8 compared with children in the highest birth weight quartile and highest BMI quartile where the cumulative incidence was 4.5% and gave an odds ratio of 2.9 (1.2-6.9). There was no interaction between birth weight and BMI in childhood. In this study we have shown that low birth weight in men and childhood obesity in both men and women increase the risk of diabetes later in life. Our findings point to the importance of childhood obesity in the pathogenesis of type 2 diabetes and are consistent with an intrauterine

programming of type 2 diabetes independently of childhood obesity.

Decreased mitochondrial DNA content is a possible link between fetal undernutrition and insulin resistance

Kyong Soo Park, Suk Kyeong Kim, Yun Yong Lee, Ji Hyun Song, Hong Kyu Lee, Seoul, South Korea, Seoul National University Hospital

Fetal undernutrition is known to be associated with insulin resistance in later life although the link between them is uncertain. Recently we found that decreased mitochondrial DNA (mtDNA) content in peripheral blood precedes the development of diabetes and mtDNA content is inversely correlated with insulin resistance paramenters such as diastolic blood pressure and waist to hip ratio. We also found that mothers who have less mitochondrial DNA (mtDNA) content in peripheral blood would give birth to low birth weight baby. We extended this observation to an animal model, and examined if fetal undernutrition would bring low mitochondrial DNA content. In order to see the relationship between fetal undernutrition and mtDNA content, we compared mtDNA content in liver and muscle in rats born from mothers undernourishied during both pregnancy and lactation to those in rats born from normal mother. The deprived mothers were fed on a 80g casein/kg diet from 15 days before mating until the end of the suckling period. Rats born from deprived mothers were randomly distributed into two groups at weaning (week O): a group fed on 180g casein/kg diet (group 2) and a group fed on a 80g casein/kg diet (group 3). Rats born from normal mothers (180g casein/kg ere still fed on 180g casein/kg diet at weaning (group 1). mtDNA content was measured by quantitative PCR. Deprived mother rats shows lower mtDNA content in liver and muscle (778 ± 278 vs 1104 ± 394, 297 ± 87 vs 425 ± 105 amol/m g genomic DNA respectively) than normal mother rats. At week 1 and week 5, both liver and muscle mtDNA content of group 2 and 3 were lower than those of group 1. At week 13, muscle mtDNA content of group 2 (438.8 ± 152.0 amol/m g genomic DNA). However, muscle mtDNA content of group 3 (275 ± 79 amol/m g genomic DNA) were still lower than thoseof other groups. Liver mtDNA content of group 3 were lower than those of group 1 and group 2 at week 13. In summary, fetal undernutrition leads to low mitochondrial DNA content in metabolically active tissues in rat. Taking these data together, decreased mitochondrial DNA content may be a possible link between low birth weight and insulin resistance.

COMPLICATIONS :

Treatment of diabetic polyneuropathy (DPN) with recombinant human Nerve Growth Factor (rhNGF)

Aaron Vinik, Norfolk, Virginia, VI the Leonard Strelitz Diabetes Institute

DPN is a heterogeneous disorder withdifferential involvement of small and large nerve fibers. NGF targets high affinity TrkA and low affinity p75 receptors implicated in small nerve fiber function which is disturbed in DPN, rhNGF arrested or reversed these abnormalities in DPN preclinical studies. To test the safety and efficacy of rhNGF in DPN, a US study recruited 250 patients with stage-2 neuropathy. Subjects were randomly assigned to receive placebo or rhNGF (0.2m g/kg 3xwk or 0.3m g/kg 1xwk for 6m). Patients were assessed at baseline and at end point. There were no differences in age, sex, race, type or duration of diabetes, duration of neuropathy or NIS-LL at baseline. rhNGF was well tolerated but caused injection-site hyperalgesia in 93-94% of cases and myalgia in 11-16% of cases, both significantly greater than placebo. There was no effect on glycemic control or other complications of diabetes e.g. retinopathy. There was a significant improvement in cooling detection threshold (CDT P< 0.049) and a trend towards improvement in heat perceived as pain (HP5 p=0.15) and NIS-LL (p= 0.17). rhNGF groups reported a global improvement in symptoms (p= 0.001). rhNGF appears to be safe and showed preliminary evidence of efficacy in patients with symptomatic small fiber neuropathy (SEN). This led to larger phase 3 pivotal trials. Two groups of patients (n-1500/1019) have been enrolled into randomized, multicenter, double-blind, placebo-controlled studies (0.1m g/kg rhNGF 3xwk vs. 0.3m g/kg 1xwk vs. placebo or o.1m g/kg 3xwk vs. placebo for 48 wk). These were initiated in 6/97 and 10/97 with the primary endpoint being the NIS-LL with secondary efficacy parameters of CDS, HP5, and new foot ulcers. Subjects enrolled in the study were required to have abnormal CDT, HP5 and NC. Subjects in the US study (n=1019) were: 19-75y old; male:74% type 2 diabetics with NIS-LL score or 13.4 (range 0.52); mean duration of diabetes 15y, neuropathy 5y and 40% had good glucose control. Excellent correlations were found with the NIS-LL sensory component and duration of DM and neuropathy, microalbuminuria, CDT, HP5, automatic symptoms, weight, height and age butnot gender, ethnicity or glucose control. These studies suggest that SEN can be specifically targeted and that treatments beyond glycemic control may be necessary in the event of a successful outcome of the phase 3 studies.

Topical Clonidine gel improves painful symptoms of diabetic neuropathy

Michael A Preifer, Douglas Allin, Robert Tanenbers, Mary schumer, Carolyn Knuckey, Katherine May, Lisa Hollen, Greenville, NC School of Medicine

Nine diabetic patients (age = 55 ± 4 yrs; diabetes duration =4.2 ± 1.3 yrs; mean ± SEM) with chronic (duration = 2.4 ± 0.6 yrs), bilateral, lower extremity, refractory painful diabetic neuropathy participated in a weekly dose-escalation (2.5, 3.75 and 5.0 mg/d) phase-1 trial. The analgesic effect (Numerical Graphic Pain Scale;NGPS); scale 0-10 with 10 being more symptoms, was assessed on a weekly basis. Safety was assessed by tracking reported adverse events and changes in blood pressure and pulse. NGPS decreased in a dose response pattern from the baseline evaluation (baseline = 7.9 ± 0.7; 2.5 mg/dose =5.0 ± 0.7; 3.75 mg/dose = 4.7 ± 0.9; 5.0 mg/dose = 3.1 ± 1.0; p < 0.01). Two patients became pain-free. Optimal pain relief was obtained at the 2.5 mg/d dose in three patients, at 3.75 mg/d in four patients and at 5.0 mg/d in two patients. Only one of the six patients experienced clonidine related adverse events (headaches [n = 4]; dizziness/light headness [n = 3]; dry mouth [n = 2]; nausea [n = 1]) sufficient of prematurely discotinued treatment. These effects are typical to those observe with oral clonidine. The side effects were minimal, were transient in all cases, except one and usually occurred shortly after the dose was increased. There were no treatment effects on blood pressure or pulse (all, p = NS) during the trial at any dose. Except for two plasma concentration values (0.0280 and 0.0399 ng/ml) all plasma concentrations of clonidine were reported as below the limit of quantitation (0.025ng/ml). Both of these values were just above the limit of quantitation and below the accepted lower

end of the range of antihypertensive concentrations (0.2 ng/ml). In summary, (1) daily doses to a maximum of 5 mg/d clonidine gel provide analgesic relief to patients with painful diabetic neuropathy, (2) daily doses to a maximum of 5 mg/d clonidine gel were well tolerated, and (3) the lack of cardiovascular changes and the lack of detectable plasma concentrations suggest the 0.1% formulation produces little systemic clonidine absorption. We conclude that topical clonidine gel may be a useful therapy for pain treatment in patients with diabetic neuropathy. Phase 2 trials are now indicated to confirm the efficacy and safety record.

Effect of Vitamin E(E) supplementation on lipid peroxidation (LP) and glutathione (GSH) levels in red cells (RBC) of diabetic patients (D).

Sushil K Jain, Robert McVie, John Jaramillo, Tiney Smith, Shreveport, LA Louisiana State, Univ Medical Center.

Elevated LP and lower GSH have been implicated in the pathophysiology of cardiovascular disease of D. This study has examined the effect of modest E supplementation on LP and GSH levels of RBC in D. Written informed consent to participate in this study was obtained from 29 D and 21 age-matched normal siblings (N) . D were supplement with DL-[alpha]-tocopherol (E) capsule (orally, 100 IU/day) or placebo (P) for 3 months in a double-blind clinical trials. Alternate D were assigned to E or placebo during regular visits to the clinic and fasting blood was collected from each D before the start and after E or P supplementation. GSH, malondialdehyde (MDA, a product of LP), and E were determined using HPLC. Data were analyzed satistically from 12 D on E and 12 D on P supplementation. RBC of D had 21% higher ($p<0.001$) LP and 15% lower ($p<0.05$) GSH levels in comparison to N.E had a significant correlation with the GSH levels in RBC ($r= 0.46$, $p<0.02$). E supplementation increased GSH levels by 9% ($p<0.02$) and lowered MDA levels by 23% ($p<0.001$) in D. there was no differences in these parameters before versus after P-supplementation. In conclusion, the blood GSH level is significantly related to the E level, and supplementation of modest E significantly increases GSH and lowers LP levels, and thus, may reduce risk of cardiovascular disease in D.

Aspirin use among Americans with diabetes: estimates from NHANES III

Deborah B Rolka, Anne Fagot-Campagna, Venkat Narayan, Atlanta, GA Centers for Disease Control and Prevention

The American Diabetes Association (ADA) recently recommended aspirin therapy (81-325 mg/day) as secondary prevention for people with diabetes with cardiovascular disease (CVD) and as primary prevention for those with CVD risk factors. We examined the prevalence and determinants of regular aspirin use in a representative sample of 1,503 U.S. adults aged \.=20 with self-reported diabetes who participated in the Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III). Persons who reported taking aspirin 15-30 times in the last month were defined as regular users. CVD included myocardial infarction, stroke, claudication, and angina. CVD risk factors were family history of heart disease, smoking, hypertension (SBP > = 140 mmHg, DBP > =90 mmHg, or ever prescribed medication), obesity (BMI > =27.3 kg/m2 in men, >=28 kg/m^2 in women), albuminuria (albumin >=30 m g/ml), and lipid abnormalities (HDL < 40, total cholesterol > =200, TGL > = 250, LDL \.= 130 mg/dl, or ever prescribed medication). Of the 5.1 % of U.S. adults with diagnosed diabetes, 27% (95% CI: 23-31%) had evidence of CVD, and 71% (67-74) had at least one risk factor but no CVD, only 2% (0-4%) had neither CVD nor any risk factor. Aspirin was used regularly by 32% (25-40%) of those with CVD and by 12% (7-16%) of those with CVD risk factors. Race, CVD, and age were significant predictiors of regular aspirin use in the recommended group (people with diabetes and either CVD or a risk factor). The odds of use were higher for non-Hispanic whites than for all others (OR = 3.6; 95% CI: 2.3-5.6), for people with CVD than for those without (OR = 3.6; 2.0-0-6.4), and for people 40 years or older than for those aged 20-39 (35.6: 7.7-163.6). The ADA recommendation for aspirin therapy appears to have included nearly every American adult with diagnosed diabetes during 1988-1994. However, fewer than 1 in 5 eligible persons took aspirin regularly. The potential for increasing utilization of this effective and inexpensive treatment is considerable.

Protein kinase C b -selective inhibitor LY333531 ameliorates abnormal retinal hemodynamics in patients with diabetes

Loyd Paul Aiello, Sven Buresell, Todd Devries, Carlos Alatorre, George King, Kirk Ways, Boston, MA Joslin Diabetes Center- Harvard Medical School

Diabetes-associated vascular dysfunctioin is partially mediated by activation of protein kinase C b (PKC- b). LY 333531, a selective inhibitor of the b isoform of PKC, prevents and reverses functional vascular abnormalities in diabetic animal models. This study evaluated the safety and retinal cascular pharmacodynamic effects of LY333351 in patients with diabetes. Patients (n=29) with type 1 or 2 diabetes of < 10 years duration and with no or minimal retinopathy were evaluated in a double-masked, randomized, parallel, 3-dose regimen, placebo-controlled study of one month duration. Patients received either placebo or LY333531 administered orally at 8mg BID, 16 mg/d or 16 mg BID, Standardized techniques were employed for all laboratory, clinical, and photographic evaluations. Rential blood flow was determined by dye dilution techniques. LY333531 was well tolerated and did not alter FBS or HbA_{1C}. Adverse event reporting was similar in incidence and type between placebo and drug groups. Laboratory and ocular evaluation did not reveal clinically significant adverse effect. Mean circulation time and retinal blood flow abnormalities were ameliorated in a dose responsive manner by 69-84% and 71-84%, respectively ($0.01 < p < 0.04$). Serum concentration of active drug was independently associated with normalization of rential hemodynamics even when baseline MCT and Hba_{1C} and diabetes type and duration were considered in multivariate analysis. In summary, Ly333531 was well tolerated for 30 days at doses up to 16mg BID in patients with diabetes. The orally administered drug induced retinal effects consistent with those expected following inhibition of PKC-b . These observation, in the absence of altered blood glucose, suggest that LY333531 might prove an effective intervention for diabetic retinopathy.

Octreotide retards progression of diabetic retinopathy in patients treated with thyroid hormone

Maria B. Grant, Robert n. Mames, Constance Fitzgerald, Kaushik M. Hazariwala, Sergio Caballero, Jkerry S. Estes, Gainesville, FL College of Medicine

The ability of the somatostation analogue, octreotide (OCT), to prevent progression of diabetic retinopathy (DR) was examined in a 2-phase open label prospective trial in patients with either severe non-proliferative or non-"high risk" proliferative DR. In Phase-I, 16 patients were randomized to either OCT treatment with highest tolerated doses (600-3000m g/day, s.c. continuous infusion or QID, n=8) or conventional diabetes management (control, n=8). Previously published results indicated that OCT improved glycemic control, diminished neuropathy and proteinuria. However, there was no difference between groups with regard to DR progression. Phase-II was designed after noting those patients on levothyrcxine (T_4) for hypiothyroidism and receiving OCT did not require laser therapy. Patients (n=230 with severe non-proliferative or non-"high risk" proliferative DR were randomized to control (conventional diabetes management, n=12) or OCT treatment (200-5000m g/day, s.c. infusion, n=11) in combination with T_4 (100-200m g/day). Patients were followed for 15 months or until laser photocoagulation was required for both eyes. Seven of 12 patients in the control group were