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Abstract from the 7th Annual World Congress on Insulin Resistance (WCIR)

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GRAND HYATT HOTEL

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ULTRASONOGRAPHIC MEASUREMENT OF INTRABDOMINAL VISCERAL FAT IN OBESE MEN. ASSOCIATION WITH ALTERATIONS IN SERUM LIPIDS AND INSULINEMIA.

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Abdominal obesity and specifically visceral fat (VF) leads to increases in cardiometabolic risk (CMR) factors, independently of the body mass index (BMI). To examine CMR factors associated with the presence and amount of VF, determined by ultrasound, in individuals with overweight/obesity, 154 men, 20-60 years of age, attending the preventive annual examination at an Industrial Clinic in Venezuela, were evaluated. It was observed that VF was associated positive and significantly with age, abdominal circumference and the degree of insulin resistance in subjects with normal weight as well as in those with overweight and obesity. However, BMI was correlated with VF only in those with normal weight or overweight. A correlation was observed between VF with glycemia and triglycerides in the obese, while insulin was correlated with VF only in subjects with normal weight. Taking 6 cm as the cut-off point for VF, it was possible to predict the presence of hyperglycemia with a 58.6 % of sensitivity and 77% of specificity, presence of insulin resistance with 54 % of sensitivity and 78 % specificity, hypertriglyceridemia with 39 % of sensitivity and 78 % specificity and low HDLc with 45 % sensitivity and 77 % specificity. The ROC curve for CMR factors, revealed that VF was better in predicting alterations as hyperglycemia and hypertriglyceridemia, while abdominal circumference was better predicting alterations as insulin resistance and low HDLc. Moreover it was shown that ultrasound could be a useful image method to quantify VF and its possible relation with CMR factors.

RELATIONSHIP BETWEEN ADIPONECTIN AND LEFT ATRIUM SIZE IN UNCOMPLICATED OBESE PATIENTS: ADIPONECTIN, A LINK BETWEEN FAT AND HEART

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Background:

It is well known that obesity is a risk factor for severe cardiovascular complications, such as coronary heart disease, heart failure, stroke and venous thromboembolic disease and atrial fibrillation. Left Ventricle (LV) and Left Atrium (LA) enlargement is a characteristic

feature of these patients with the consequent cardiovascular risk. Factors other than hemodynamic may influence LA remodelling.

Aim of the study:

To evaluate the relationship between adiponectin and LA size in uncomplicated obese patients.

Methods:

74 asymptomatic obese patients and an age and sex-matched control group (N=70) were recruited. A detailed clinical, echocardiographic and analytical study was performed. Insulin resistance was assessed using the HOMA-IR method. Insulin sensitivity was assessed measuring serum total adiponectin concentrations.

Results:

Adiponectin levels were lower in the obese group (P<0.001) and particularly so in those obese participants with enlarged LA (32%; P<0.0005). LA sizes were higher in the obese group (P<0.0005). Adiponectin displayed significant correlations with: BMI, glucose, insulin, HDL-cholesterol and triglyceride concentrations as well as HOMA-IR, (P<0.001, for all). Adiponectin displayed significant correlations with LV mass and LA size, diastolic and systolic cardiac volumes and diameters, cardiac output (P<0.001, for all). Adiponectin correlations with LA size (r=-0.429; P<0.001) persisted after adjustment for HOMA-IR, age, sex and LV mass.

Conclusions:

A novel inverse relationship between adiponectin and LA size independent of age, sex, insulin resistance and LV mass appears in our series. Adiponectin could be a link between adipose tissue and the heart, having an influence on cardiac remodelling.

CHARACTERISTICS AND PREVALENCE OF METABOLIC SYNDROME AMONG THREE ETHNIC GROUPS IN CAMEROON

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Objective:

To compare the characteristics and prevalence of the metabolic syndrome (MetS) in three Cameroonian population: Beti, Bamiléké, Sawa.

Methods:

The study was based on four cross-sectional studies conducted between 2006 and 2008. Among the participants received during the study, originate from three ethnic groups living in the urban city of Yaounde were selected to underwent anthropometric measurement and biochemical test. The MetS was identified among participants according to the National Cholesterol Education Program (NCEP) definition.

Results:

The age-standardized prevalence of the MetS varied by ethnic group, ranging from as high as 16.8 % among Bamiléké women to

as low as 2.7% among Beti men. Compared with MetS components overall prevalence in Cameroon, Sawa had a worse metabolic profile, while Bamiléké had a better metabolic profile except for a high rate of abdominal obesity.

Conclusions:

The results indicate that the MetS is prevalent in diverse ethnic groups in Cameroon but varies in the pattern of phenotypic expression. Preventive measurements must take into account these ethnic variations for the efficient reduction of metabolic syndrome frequency in Cameroonian population.

EVIDENCE FOR A ROLE OF OXIDATIVE STRESS ACTIVATED SIGNALING PATHWAYS IN MEDIATING MUSCLE INSULIN RESISTANCE AND GLUCOSE UPTAKE DYSFUNCTION

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Abstract:

Evidence indicates that both stress activated kinases pathway and reactive oxygen species (ROS) are involved in oleate-induced insulin resistance in skeletal muscle model. In the present study, we examined the effects of free fatty acids (FFAs) on insulin sensitivity and signaling cascades in the C2C12 skeletal muscle cell culture system. We compared the effects of a monounsaturated fatty acid, oleate (C18:1) and a saturated fatty acid, palmitate (C16:0). We tested the hypothesis that elevated FFAs can cause oxidative stress that mediates the induction of insulin resistance. Earlier, we have reported that FFAs activate the IKK α/β , c-jun N-terminal kinase (JNK), the stress kinases S6 kinase p70 (p70SK), (SAPK), and p38 MAP Kinase (p38MAPK) as seen in our proteomic kinases screen. Interestingly, the antioxidants, Tempol (4-hydroxytetramethylpiperidine-1-oxyl) at (0.5mM) and Taurine at (10mM) concentrations were capable of reversing the oleate-induced insulin resistance in myocytes as manifested from the glucose uptake data. In conclusion, our data, demonstrate that oxidative stress is one of the key players in FFAs-induced insulin resistance in the skeletal muscle model (C2C12).

Key Words:

Free Fatty Acid (FFA); Muscle Insulin Resistance, C2C12; Oxidative Stress and Reactive Oxygen Species (ROS).

CHANGES ON THE PHYSIOLOGICAL LACTONASE ACTIVITY OF SERUM PARAOXONASE 1 IN HEALTHY OVERWEIGHT AND OBESE WOMEN AFTER WEIGHT LOSS

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Obesity is a metabolic and cardiovascular risk factor and is compounded with insulin resistance. Paraoxonase 1 (PON-1) is associated with the anti-atherogenic functions of high-density lipoprotein (HDL). We investigated the effects of a sole LCD intervention for weight loss on serum PON-1 activity (lactonase, arylesterase and tri-esterase) and HDL cholesterol (HDL-C), and their association with low-density lipoprotein cholesterol (LDL-C), in obese but otherwise healthy subjects. A total of 30 Japanese women (mean age, 50.3 \pm 8.5 years) with a body mass index (BMI, mean 28.5 \pm 3.3 kg/m²) participated in this study. During the intervention period of 2 months, they were placed on a LCD (Diet's™, 5023kJ/day) with meal replacement every dinner. Serum PON-1 lactonase activity with 5-(thiobutyl)butyrolactone (TBBL), its tri-esterase activity was determined using paraoxon and its mono-esterase activity with phenylacetate as substrates. PON-1 lactonase levels decreased by 5.8%. This change was paralleled by its arylesterase (7.2%) and triesterase (6.9), $p < 0.001$. In multiple regression analysis adjusted for age, the percent change of PON-1 was significantly, positively, and independently correlated to that of LDL-C ($\beta=0.51$), HDL-C ($\beta=0.40$), and BMI ($\beta=0.37$). This plausibly reflects less need for PON-1 activity to prevent LDL oxidation suggesting that reduced PON- activity as well as HDL-C in response to LCD may not be detrimental.

EFFECTS OF FEMALE SEX STEROIDS ON BODY WEIGHT AND INSULIN SENSITIVITY IN RATS

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Introduction:

Sex steroids play considerable roles in insulin physiology. The main purpose of the present study was to examine the effects of female sex steroids on body weight and insulin sensitivity through ovariectomy and progesterone or estradiol replacement or administration in rats.

Material and Methods:

7 week old female albino (Wistar) rats were used in our study. Progesterone (20 mg/kg/day) or estradiol valerate (200 μ g/kg/day) were injected subcutaneously. After 4 weeks, insulin sensitivity and body weight were measured and compared between groups (ANOVA).

Results:

Insulin sensitivity and body weight were increased in both bi-ovariectomised and uni-ovariectomised rats compared with

control group ($P < 0.01$). Progesterone or estradiol replacement in bi-ovx rats was followed by increased or decreased body weight and increased or decreased insulin sensitivity compared with bi-ovx rats, respectively ($P < 0.05$). In non-ovariectomised rats, administration of progesterone resulted in increased and of estradiol led to decreased body weight and insulin sensitivity compared with control animals ($P < 0.01$).

Conclusion:

Conclusively, our findings indicate that progesterone is enhancer and estradiol is reducer of insulin sensitivity in rats. In addition, weight gain after ovariectomy or progesterone treatment and weight loss following estradiol treatment did not probably contribute in acting on insulin sensitivity.

Key words:

Insulin sensitivity, Body weight, Ovariectomy, Progesterone, Estradiol, Rat.

EFFECT OF AN A54T POLYMORPHISM IN INTESTINAL FATTY ACID BINDING PROTEIN ON RESPONSES TO DIET IN MEXICAN SUBJECTS WITH OVERWEIGHT OR OBESITY.

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Introduction:

A polymorphism in *FABP2* that result in an alanine-to-threonine substitution at amino acid 54 of IFABP protein is associated to insulin resistance (IR), obesity, and mellitus diabetes type 2. The allele T54 of *FABP2* has 2-fold greater affinity by the fatty acid compared to allele A54. This greater affinity cause increased absorption and processing of fatty acids. Therefore, *FABP2* gene could is under diet control.

Objective:

To Value anthropometry and biochemistry parameters in Mexican subjects with overweight (OW) or obesity (OB) with A54T polymorphism on responses to a diet.

Methods:

Patients with BMI ≥ 25 kg/m² were recruited. The diet consisted of 55% carbohydrates, 15% proteins, 30% lipids (Guide ATPIII). Before and after 2 months of implemented diet anthropometric and biochemical measurements were performed. The *FABP2* genotype was realized by PCR-RFLP's

Results:

The 37.6% had OW, 32.1% OB type 1, 21.1% OB type 2, 7.3% OB type 3 and 1.8% morbid obesity. The 97.2% had cardiovascular risk (CVR). The 34.9% of patients showed hypercholesterolaemia, 45.9% hypertriglyceridaemia. The IR was found in the 58.6% of subjects. To 2 months nutritional intervention 6.3% had normal weight, 48.1%

OW, 22.8% OB type 1, 16.5% OB type 2, 5.1% OB type 3 and 1.3% morbid obesity. The CVR diminished to 88.6%, hypercholesterolaemia to 27.5%, hypertriglyceridaemia to 38% and the IR to 39.2%.

Conclusions:

The subjects with OW and OB with genotype AA and AT/TT improved significantly with the implemented diet. However, the subject's carrier of AT/TT polymorphism had better responses to implemented diet.

NORTH EAST OF IRAN PREVALENCE IN MASHHAD DIABETIC PATIENT 2I INFECTION IN TYPE - PREVELENC OF HTLV

Objective:

To evaluate the prevalence of Human T Cell Leukemia virus type 1 (HTLV-I) infection among patients with Type 2 diabetes mellitus (DM) in Mashhad in northeastern Iran and the levels of basal insuliniemia in them.

Methods:

A total of 266 consecutive diabetic patients (86 Male and 180 Female, with a mean age of 54.36 ± 11.58 years) attending our unit were compared with 60,892 non diabetic blood donors. Serologic testing for HTLV-I was done using an Enzyme-linked immunosorbent assay, then Polymerase chain reaction (PCR) performed in positive HTLV-I samples. Insulin level measured in patients with positive serologic tests for HTLV I . Statistical analysis was done using the Student's t-test by statistical software SPSS version 13.0.

Results:

PCR confirmed HTLV-I infection detected in ten patients (prevalence 3.75%). A higher prevalence of HTLV-I infection was observed in diabetic patients in comparison with blood donors (3.75 vs. 0.663%; $P < 0.001$). There was no correlation between HTLV-I infection and age, sex, body mass index, diabetes duration or glycaemic control. Basal insulinemia values were 26.2 ± 7.3 (mu/ml) in these patients.

Conclusions:

A high prevalence of HTLV-I infection was detected in diabetic patients. It is a possible hypothesis that diabetic patients are at increased HTLV-I infection risk. Moreover, basal insulinemia values are higher in these patients, which can be explained by presence of insulin resistance in them.

Key Words:

Human T Cell Leukemia virus type 1 (HTLV-I), Type 2 diabetes, Iran, insulin resistance.

IMPAIRED INSULIN-SIGNALING MAY BE A FORERUNNER TO HYPERGLYCEMIA IN ESSENTIAL HYPERTENSION

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Recent evidence indicates that impaired glucose tolerance is common in essential hypertension. We recently highlighted the role of heme oxygenase (HO) in diabetes. However, the effects of HO on insulin sensitivity and glucose metabolism in spontaneously-hypertensive rat (SHR), a model of essential hypertension with characteristics of metabolic syndrome including insulin resistance/impaired glucose metabolism remains largely unclear.

We evaluated the effects of the HO inducer, hemin, on insulin sensitivity in adult SHR with established hypertension. Adult SHRs were severely hypertensive, but had normoglycemia. The administration of hemin (15 mg/kg ip) normalized blood pressure in adult and enhanced insulin-sensitivity by improving glucose tolerance (IPGTT), reducing insulin intolerance (IPITT) and attenuating insulin resistance (HOMA-index). These insulin-sensitizing effects were accompanied by increased gastrocnemius HO-1, HO-activity, cGMP, cAMP alongside anti-oxidants including bilirubin, ferritin, superoxide dismutase, catalase and the total anti-oxidant capacity, whereas oxidative/inflammatory mediators like 8-isoprostane, nuclear-factor kappaB, activating-protein (AP-1), AP-2, c-Jun-NH2-terminal-kinase were suppressed. Furthermore, hemin therapy enhanced the depressed levels of adiponectin, adenosine-mono-phosphate-activated protein-kinase and GLUT-4 in SHR, suggesting that although SHRs were normoglycemic, insulin-signaling may be impaired. Contrarily, the HO-inhibitor chromium mesoporphyrin, exacerbated oxidative stress, aggravated insulin resistance, IPGTT and IPITT.

Hemin also enhanced HO-signaling in Wistar-Kyoto control rats and increased insulin-sensitivity albeit less-intensely than in SHR, suggesting greater selectivity of HO in SHR with dysfunctional insulin-signaling.

Our results suggest that perturbations of insulin-signaling may be a forerunner to hyperglycemia in essential hypertension. By concomitantly potentiating insulin-sensitizing pathways, suppressing insulin/glucose intolerance and abating oxidative stress, hemin therapy may prevent metabolic and cardiovascular complications in essential hypertension.

INSULIN RECEPTOR SUBSTRATE: ROLE IN INSULIN SIGNALLING IN OBESITY AND TYPE 2 DIABETES

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Introduction:

Obesity and diabetes mellitus are the most prevalent and serious metabolic disease worldwide. They affect more than 50% of adults in the USA. Reduced insulin sensitivity and increase in serine-307 phosphorylation of insulin receptor substrate-1 (IRS-1) is a common finding in insulin resistance. Obesity is associated with infiltration of macrophages in obese adipose tissues.

Objective:

To study the link between obesity and insulin resistance.

Materials and Methods:

An *in vitro* co-culture system composed of differentiated adipocyte and macrophage was developed. Co-culture of differentiated adipocyte with macrophage was compared with differentiated adipocytes prior and after treatment with linoleic acid and tumor necrosis factor- α . Serine 307 phosphorylation of IRS-1 was determined by ELISA while insulin sensitivity was measured by determining glucose uptake by radiometric assay.

Results:

It was found that linoleic acid (free fatty acid) promotes serine phosphorylation of IRS-1 in a dose and time-dependent manner and increase glucose uptake. Serine phosphorylation was induced at 100 μ M and the strongest activity was observed at 200 μ M. Serine phosphorylation of IRS-1 was higher in adipocytes co-culture with macrophages compare to adipocytes alone. Higher levels of glucose uptake were observed in adipocytes co-culture with macrophages compare to adipocytes alone.

Conclusions:

High level of macrophages in obese adipose tissues may link between obesity and insulin resistance.

RATIO OF FASTING GLUCOSE TO ADIPONECTIN IS AN IMPORTANT PREDICTOR FOR THE DEVELOPMENT OF TYPE 2 DIABETES

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Adiponectin and resistin are inversely associated with type 2 diabetes but it is not yet concluded whether adiponectin and resistin are the causal factors of diabetes. The present study was undertaken to evaluate the association of serum adiponectin and resistin with insulin secretory capacity and insulin resistance in subjects with impaired glucose regulation (IGR). Twenty four subjects with impaired fasting glucose (IFG), 58 with impaired glucose tolerance (IGT), 30 with IFG-IGT subjects were recruited in this study. Forty four non-diabetic healthy controls without family history of diabetes or prediabetes were also recruited. Serum insulin, adiponectin and resistin levels were measured using ELISA technique. Serum adiponectin (μ g/ml) and resistin levels (ng/ml) were not significantly differed among the study groups. Ratios of fasting insulin with adiponectin and resistin were increased both in IGT and IFG-IGT subjects. Binary logistic regression analysis have shown that fg:adiponectin ratio was significantly associated ($\beta=1.085$, $p=0.031$) with IGR subjects when age and BMI were adjusted. Ratios of fasting glucose with adiponectin and resistin were also increased in IFG-IGT subjects. Multiple regression analysis have shown that fins:adiponectin ratio was negatively associated ($\beta = -0.201$, $p=0.034$) with insulin sensitivity (HOMA% S) and positively ($\beta=0.507$,

$p=0.0001$) with insulin secretory capacity (HOMA %B) in IGR subjects. On the other hand *fasting insulin* showed significant negative association ($\beta = -0.237$, $p=0.015$) with HOMA%S and positive association with HOMA%B ($\beta=0.506$, $p=0.001$) in IGR subjects. The findings indicate that ratios of fasting glucose to adiponectin may be an important predictor for the development of type2 diabetes.

STUDY OF OBESITY, INSULIN RESISTANCE, AND METABOLIC SYNDROME IN SOUTH INDIAN POPULATION

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Our objective was to investigate the relationship between obesity, as measured by body mass index (BMI), insulin resistance (IR), and components of the metabolic syndrome (MS). Cross-sectional study, a sample of 106 healthy male subjects (age: 35-65 years) from a primary health care outpatient clinic in Warangal (India) over a period of 1 year.

Measurements:

Body mass index (BMI), blood pressure (BP), total cholesterol, triglycerides, HDL-C, glucose, HbA1c, creatinine and insulin were measured by standard methods. IR was defined as HOMA-IR equal to or greater than 3.8. The prevalence of IR was 38.54%. Subjects were divided into groups according to BMI. A 'normal' BMI was defined as below 25 kg/m²; overweight was defined as a BMI equal to or above 25 kg/m². The prevalence of IR was 29.54% in the group with normal and 46.15% in the overweight group ($P<0.001$). The percentage of subjects with the MS (high BP, dyslipidemia or abnormal glucose tolerance) significantly increased ($P<0.001$) in subjects with overweight (46% vs. 16% in normal subjects). Pearson correlation analysis has shown a significant correlation between IR (HOMA-IR), insulin ($P<0.0001$), glucose ($P<0.01$), hypertension ($P<0.0001$), abnormal lipid profile ($P<0.05$), and insulin sensitivity ($P<0.0001$). Overweight, expressed as BMI, appears to be a good indicator of risk for IR and the MS, particularly in non-obese subjects (BMI<30). The main independent parameter of risk for IR is TG, whereas those for the MS are IR, obesity, and age.

Keywords:

Insulin resistance; overweight; obesity; metabolic syndrome; HOMA-IR.

HYPERTRIGLYCERIDEMIA/HYPERACIDEMIA: A CAUSE AND CONSEQUENCE OF HYPERINSULINISM/INSULIN RESISTANCE

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Hypertriglyceridemia and hyperacidemia could be cause and consequence of hyperinsulinism/insulin resistance.

Objective:

To diminish triglycerides and free fatty acids levels to break the vicious circle.

Design and methods:

Twenty-six patients with primary hypertriglyceridemia received, after six months of a non-pharmacological treatment, 500 mg of etofibrate retard. Before and after six months of treatment were determined: total C and TG, HDL-C, LDL-C, apos A1 and B, FFA, and glycemia and insulinemia during an OGTT. For statistical analysis ($p<0,05$) were applied the tests: Chi-Square, Friedman, Nemenyi, T-Test, U-Mann Whitney, Wilcoxon, and the trapezoidal rule. Using the HOMA index (cut-off point=2,5), were obtained two groups, thirteen patients each; nine indexes of insulin secretion and nine indexes of insulin resistance were calculated. All patients had from three to seven metabolic disturbances.

Results:

After treatment, total TG, FFA and C/HDL-C ratio diminished (40%, 19% and 20%, respectively), and apo AI increased (32%). Glycaemia, insulinemia, and total glycemid and insulinemic areas under the curve, diminished during the OGTT ($p<0,05$). One insulin sensitivity index and one insulin resistant index improved in the more sensitive group; four insulin sensitivity indexes and seven insulin resistance indexes improved in the less insulin sensitive group ($p<0,05$). There were not differences in the 24 hours of a typical day diet recalls.

Conclusions:

Etofibrate improved lipid profile, glucose tolerance, insulinemia and insulin sensitivity. Lipids improvement could break the vicious circle hypertriglyceridemia-hyperacidemia-hyperinsulinism-insulin resistance. Etofibrate is effective in the treatment of the dyslipidemia of the insulin resistance syndrome.

NON-OBESE PERSONS: OUT OF WEIGHT RISK?

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At the present pandemia of Diabetes mellitus type 2, the minority of affected persons is non-obese. In a genetic research looking for susceptibility alleles, we studied 499 non-obese persons (BMI ≥ 22 and < 30): 272 (54,5%) diabetic patients (92 males, 180 females) and 227 (45,5%) non-diabetic persons (55 males; 172 females) (n.s.); ≥ 40 and ≤ 70 years old. A clinical record was done and was determined: glycaemia, total cholesterol, total triglycerides and insulinemia (non-insulin treated patients). Leukocytic DNA was obtained for the genetic study. Medians from quantitative variables were compared by T-Student Test for independent samples and the association from quantitative variables were explored by Chi Square Test; significance level $p < 0.05$. There was a predominance of familial antecedents of Dm, and personal antecedents of high blood pressure, coronary heart disease, asthma and glaucoma in the diabetic persons (DG). At the physical examination there was a predominance of high blood pressure (systolic, diastolic and systo-diastolic) in the DG. There were not statistical differences between both groups in insulinemia, cholesterolemia and triglyceridemia. Grouping the persons in normal weight (≥ 22 and < 25), and pre-obese (≥ 25 and < 30), statistical differences were found in the pre-obese DG in: hypercholesterolemia, in females; hypertriglyceridemia, in both sexes; hyperinsulinism, hypercholesterolemia + hypertriglyceridemia and risk factor clustering, in male sex. Pre-obese non-diabetic women were hyperinsulinemic. Conclusion: Pre-obesity is risk factor of dysmetabolism in type 2 diabetic patients. Recommendations: In Diabetes mellitus type 2 is indispensable to get and maintain normal weight. Pre-obesity must be included in prevention programs.

PRE-OBESITY, IN PATIENTS WITH DM TYPE 2, IS A RISK FACTOR FOR HYPERINSULINISM

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Dm type 2 is determined by genetic and non genetic factors. There have been found differences in the candidate genes determining Dm in different populations. We studied 499 non obese Cuban citizens (BMI ≥ 22 and < 30), ≥ 40 and ≤ 70 years of age: 272 (54.5%) diabetic patients and 227 (45.5%) non diabetic persons (n.s.) Polymorphisms Ala513Pro and Gly972Arg of gene IRS 1 and Gly1057Asp of gene IRS 2 were studied. The frequencies were compared by the Chi Square Test ($p < 0.05$), and the strength of association was quantified by the ODD ratio. There was a preponderance of familial DM, HBP and risk factor clustering in the diabetic patients ($p < 0.05$). Comparing normal weight and pre-obese persons, there were differences in hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia and risk factors clustering. There were no statistical differences in the polymorphisms studied of the IRS-1 gene. The frequency of the allele Asp1057 from the Gly1057Asp polymorphism of the IRS 2 gene was 49.8%, DG and 58,8% NDG; its behavior related to heredity suggest protection against Dm2. When the person is overweight, the allele Asp1057 protective role is not expressed.

Conclusions:

The polymorphisms studied of the IRS 1 gene does not participate in the etiology of DM type 2. The IRS 2 allele Asp1057 gives protection, that is modified when pre-obesity is present and in persons when their parents have DM, and is associated to hyperinsulinism in pre-obese people. Pre-obesity is associated to an increment in dysmetabolism.

Recommendations:

Health intervention programs should include pre-obesity.

INSULIN RESISTANCE CONTRIBUTED TO CARDIOVASCULAR RISK FACTORS INDEPENDENT OF OBESITY IN SAUDI WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Objective:

To study the role of insulin resistance independent of body mass index (BMI) in contributing to cardiovascular risk (CVR) factors among women with polycystic ovarian syndrome (PCOS).

Methods:

All women presenting with infertility to King Abdulaziz University Hospital, Jeddah, Saudi Arabia were interviewed, had physical examination, and a standard infertility work-up to study the role of insulin resistance and CVR factors in our population. Women diagnosed to have PCOS from the clinical, biochemical, and ultrasonographic criteria were requested to have a 75 g oral glucose challenge test. Insulin, glucose, total cholesterol, triglycerides, LDL- and HDL-cholesterol levels were measured in the fasting state. This preliminary report compares 65 women with PCOS (age: 26.8 ± 6.6 years) to 130 healthy women (age: 26.4 ± 5.2 years) matched for age and ethnicity. CVR factors score was calculated for each woman including: waist circumference, total cholesterol, HDL-cholesterol, systolic and diastolic blood pressure measurements and the presence of diabetes mellitus.

Results:

Women with PCOS who were hyperinsulinaemic (n=28; insulin levels were 157 ± 39 pmol/L) exhibited higher CVR factors (composite score for CVR factors = 2.90 ± 1.32) than their normoinsulinaemic (n=37; insulin levels were 49.3 ± 18.8 pmol/L) counterparts, who in turn exhibited more CVR factors (composite score for CVR factors = 1.22 ± 1.09) than corresponding healthy controls (insulin levels were 48.9 ± 16.1 pmol/L with composite score for CVR factors = 0.62 ± 0.72), respectively ($P < 0.005$). Women with PCOS exhibited significantly abnormal lipid profile: increases in the levels of total cholesterol, LDL-cholesterol, triglycerides and decreases in HDL-cholesterol, respectively, as compared to corresponding control group. In addition, women with PCOS exhibiting variable BMI showed greater insulin resistance suggesting that PCOS *per se* together with BMI, both contributed to the observed insulin resistance.

Conclusion:

Insulin resistance contributed to the extent of CVR factors independent of obesity in Saudi women with PCOS.

EXCESS WEIGHT IN CHILDREN AND RISK FACTORS FOR CVD: DOES BIRTH WEIGHT INFLUENCE?

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Abstract:

Background: Low birth weight is associated with increased risk of developing cardiovascular disease (CVD), especially in children with rapid catch-up of weight. Aim: Our purpose was to assess whether birth weight is associated with risk factors for CVD in excess weight children. Methods: We analyzed 223 (mean age 9 ± 1.4 years old) excess weight children (142 overweight and 81 obese). Subjects were divided in groups according to birth weight: Adequate (≥ 3000 g: ABW), Insufficient (2500-2999g: IBW) and Low Birth Weight (< 2500 g: LBW). The variables: abdominal circumference (AC), systolic and diastolic blood pressure (SBP, DBP), lipids profile and Insulin Resistance (IR) using HOMA (Homeostasis Model Assessment) index were evaluated. Results: Overweight former LBW children showed statistically significant associations with SBP ($p < 0,001$), DBP ($p < 0,001$) and IR ($p = 0,007$) (Table 1). Statistical difference in SBP and DBP was observed between overweight former IBW and ABW ($p < 0,005$). Obese former LBW children demonstrated increasing values of SBP, DBP, triglycerides and decreasing HDL levels compared to ABW group. 14% of obese former LBW children showed 4 risk factors for CVD. Conclusions: Low birth weight was associated with risk factors for CVD: higher blood pressure and IR in excess weight children. Supported by: FAPESP

Table 1. Clinical Variables of Overweight Children

	ABW (n=81)	IBW (n=33)	LBW (n=28)
SBP (mmHg)	90.29 \pm 1.18	100.79 \pm 2.11	100.64 \pm 1.35
DBP (mmHg)	58.09 \pm 0.99	64.09 \pm 1.45	66.25 \pm 1.45
HOMA -IR	1.60 \pm 0.12	2.31 \pm 0.22	2.71 \pm 0.53

Key Words:

Insulin Resistance; children; birth weight; overweight

EXERCISE IN EARLY STAGES OF DEVELOPMENT PROTECT TO DOWN-REGULATION OF PPAR INDUCED BY HIGH FAT DIET IN MUSCLE OF RATS

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Recent studies suggest that PPAR δ , pivotal to control the fatty acid oxidation in skeletal muscle, is a key target for intervention in obesity and type 2 diabetes. The aim of this study was evaluate the effect of physical activity/inactivity, in early stages of development, on dysregulation of PPAR δ gene induced by high fat diet. Sixty male Wistar rats (postnatal day 23) were distributed in three groups (standard group (STD), movement restriction (MR) and exercise (Ex). Between days 23 and 70, MR group was kept in small cages and Ex group run in treadmill five days per weeks. From day 70 to 102, half of rats of each group were fed with control diet (CD) and others with high fat diet (HFD). During this period, all rats were kept in similar conditions. Body weight did not show significant differences induced by diet between groups on day 103; nevertheless high fat diet produced a significant increase in weight of epididymal fat pad when compared group fed with control diet. Differences in plasmatic levels of glucose or insulin between groups were not observed. Levels of TNF α were significantly higher in group MRHFD ($p < 0.05$). Glucose uptake stimulated by insulin show a significant reduction ($p < 0.05$) in MRHFD group. Real time RT-PCR analysis show decrease PPAR δ gene expression in response to high fat diet in STD and RM ($p < 0.05$) but not in Ex group. In conclusion, physical activity in early stages of development can control of PPAR δ gene dysregulation induced by high fat diet in adulthood.

CARDIO METABOLIC RISK FACTORS DOCTORS V/S GENERAL POPULATION**Introduction:**

With emergence of lifestyle disorders in India and paucity of data on the same among medical personnel, we assessed the health profile of a group of young doctors and general population specifically focusing on prevalence of diabetes and other cardio metabolic risk factors.

Materials and Method:

Cardio metabolic risk factors were assessed by interview method using a structured, pre-tested questionnaire amongst 50 subjects each, from the medical personnel and general population belonging to 20-40 years age group. Pregnant females were excluded. Personal data, height, weight, BMI, waist circumference, blood pressure, FBS, lipid profile, past history, drug history and family history were recorded. The data were analyzed according to NCEP: ATP III guidelines for metabolic syndrome.

Results:

Doctors had significantly higher prevalence of hypertension (66% v 18%, $p < 0.003$). Other risk factors among the cases compared with the controls were Diabetes (2% v 10%), BMI (38% v 32%), Waist circumference (34% v 20%), S. Cholesterol (22% v 16%), S. TG (20% v 22%), S. HDL (34% v 48%) and S. LDL (4% v 2%). Metabolic Syndrome was found to be equal amongst both the groups (16%).

Conclusion:

Cardio metabolic risk factors were found more among the medical personnel in comparison to the general population, amongst which blood pressure levels were statistically significant. A further study on a larger group of subjects would be conclusive for all the risk

factors and Metabolic Syndrome. This study is helpful in primary prevention, early detection and management of lifestyle disorders in young population especially medical personnel.

DIETARY REDUCTION OF POST-PRANDIAL HYPERGLYCEMIA WITH MULBERRY TEA SEEN IN METABOLIC SYNDROME AND TYPE-2 DIABETES

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Aim:

In management of metabolic syndrome and type 2 diabetes the role of diet is important. Indian diet contains large amount of sugar & starches that set off unpredictable blood sugar fluctuations, increasing the risk of diabetic complications. The aim is study the effect of Mulberry tea as it is known to contains 1-deoxy-ynojirimycin (DNJ), a potent glycosidase inhibitor and has been hypothesized to suppress abnormally high post prandial blood glucose levels .

Method:

The study is designed in follow-up diabetic patients, 20 diabetics as controls were given plain tea and 28 patients were given mulberry tea containing DNJ to measure effect based on FBS and PPBS.

Fasting blood glucose sample was collected, followed by standard breakfast and one cup of 70ml tea with 1 teaspoon of sugar. The postprandial blood glucose was measured again at 90minutes in all 48 patients.

Results:

Fasting value in control group 178.55 ± 35.61 and cases 153.50 ± 48.10 . After consumption of plain tea and mulberry tea the post-prandial value was 287.20 ± 56.37 and 210.21 ± 58.73 respectively the significance is $t=4.492$; $p<0.001^{**}$ and the effect size is very large (1.31).

Conclusion:

Mulberry tea suppresses post prandial rise of blood glucose levels.

Table 3. Levels of FBS and PPBS in controls and Cases

Variables	Controls	Cases	Significance	Effect size
FBS	178.55 ± 35.61 (129-262)	153.50 ± 48.10 (93-278)	$t=1.972$; $p=0.055+$	0.57(M)
PPBS	287.20 ± 56.37 (159-380)	210.21 ± 58.73 (118-341)	$t=4.492$; $p<0.001^{**}$	1.31(VL)

PREVALENCE OF METABOLIC SYNDROME IN POSTMENOPAUSAL WOMEN USER AND NONUSER OF HORMONE REPLACEMENT THERAPY

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Background:

The prevalence of Metabolic Syndrome (MetS) increases with age and after the onset of menopause with the increase of risk factors of Cardiovascular Disease (CVD); which may explain in part the apparent acceleration of CVD in postmenopausal women.

Aim:

Our purpose was to assess the prevalence of MetS in postmenopausal women user and nonuser of Hormone Replacement Therapy (HRT). Methods: In this cross-sectional study, 317 postmenopausal women were divided in two groups: 182 HRT users and 135 HRT nonusers. We evaluated the HRT effects in the components of the MetS in 274 women between one and ten years of menopause period according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria.

Results:

The mean ages, menopause age and menopause period of HRT users and nonusers, were 52.9 ± 5.4 ; 46.9 ± 5.4 and 5.9 ± 5.2 years respectively. The frequencies of MetS in the two groups were statistically different : 29.6% nonusers and 19.2% users ($p=0.031$). Between the groups, the waist circumference was the only marker of the MetS statistically significant ($p=0.035$). There were not significant changes in these parameters: HDL-Cholesterol; fasting serum glucose; triglycerides and systolic and diastolic blood pressure.

Conclusions:

These findings indicate that postmenopausal women have a high prevalence of MetS, which were significantly higher in women nonusers of HRT. The abdominal obesity was the most frequent feature observed among the components of MetS, principally in nonusers women of HRT.

Key Words:

Metabolic Syndrome, Menopause, Hormone Replacement Therapy

PAPILLARY THYROID CANCER IS LESS AGGRESSIVE IN PATIENTS WITH INSULIN RESISTANCE

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We have reported that patients with insulin resistance (IR) have larger thyroid glands and a higher incidence of thyroid nodules

(*Thyroid*, 2008, 18:461-464). Moreover, we subsequently showed that patients with papillary thyroid cancer (PTC) also have a higher frequency of IR (*Metab Syndr Relat Disord*, 2009, 7:375–380). The aim of the present study is to compare, at diagnosis of PTC, the TNM stage between 14 women with IR [Group 1 (G1)], mean age 45.1 ± 11.1 yrs., vs 16 women without IR [Group 2 (G2)], mean age 43.4 ± 13.9 yrs. The diagnosis of IR was made when the HOMA-IR index was higher than 2.5. To facilitate analysis, T (tumor size) was grouped as follows: T 1+2 and T 3+4.

Results:

Age was not different between groups. Weight was higher in G1 than in G2 as expected (75.9 ± 17 Kg, vs 59.9 ± 8.1 Kg, respectively; $p < 0.01$). T 1+2 was observed in 92.9% of G1 vs 87.5% of G2 ($p = ns$), T 3+4 in 7.1% of G1 vs 12.5% of G2. Lymph node metastasis were present in 14.3% of G1 and in 50% of G2 ($p < 0.04$), while distant metastasis were 7.1% in G1 vs 12.5% in G2 ($p = ns$).

Conclusion:

patients with PTC and IR have a lower frequency of lymph node metastasis when compared with no IR patients. This situation would suggest that those “genuine” PTCs (not stimulated by IR) might behave more aggressively, perhaps due to intrinsic mutations, than those generated only by the proliferative stimulus of insulin in a relatively rather normal thyroid epithelium.

EVALUATION OF SOME MARKERS OF SUBCLINICAL ATHEROSCLEROSIS IN EGYPTIAN YOUNG ADULT MALES WITH ABDOMINAL OBESITY

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Young adults with abdominal obesity are liable to have high burden of subclinical atherosclerosis which may contribute to increased risk of cardiovascular disease later in life. This study aims to evaluate subclinical atherosclerosis and its possible correlation with some inflammatory and biochemical markers in Egyptian young adult males with abdominal obesity. The current study included fifty young adult males aged 19-29 years, they were divided into: group I of 20 non obese subjects as controls. Group II of 30 apparently healthy obese subjects. Carotid intima media thickness (IMT) was estimated using B mode ultrasonography of the common carotid arteries, abdominal ultrasonography was also done to assess the presence of fatty liver. Laboratory investigations included determination of fasting levels of serum glucose, triglycerides (TG), cholesterol [total (TC), high density (HDL-cholesterol) and low density (LDL-cholesterol) lipoprotein fractions], high sensitive C-reactive protein (hs-CRP), neopterin, lipoprotein-a [Lp(a)], activities of gamma glutamyl transferase (GGT), aspartate and alanine aminotransferases (AST, ALT) and plasma levels of plasminogen and fibrinogen. Results showed that carotid-IMT, serum hs-CRP, neopterin, Lp(a), plasma fibrinogen, plasminogen, TC, TG, LDL-cholesterol and liver enzymes were significantly elevated ($p < 0.001$) in obese subjects as compared to controls. All obese subjects showed fatty liver. A significant positive correlation was found between carotid-IMT and body mass

index (BMI), waist circumference (WC), waist/hip ratio (WHR), cholesterol, triglycerides, neopterin, hs-CRP, AST, ALT and GGT. In conclusion, young adult males with abdominal obesity are liable to develop subclinical atherosclerosis, and hence they are prone to increased risk for future cardiovascular disease. The elevated serum levels of inflammatory biomarkers; neopterin, hs-CRP and plasma fibrinogen as well as the elevated activities of hepatic transaminases (ALT&AST), and GGT; biomarkers for NAFLD may be useful predictors of subclinical atherosclerosis.

Key words: Abdominal obesity, subclinical atherosclerosis, carotid IMT, neopterin, hs-CRP, NAFLD.

ASSOCIATION OF SERUM FETUIN-A AND PARAMETERS OF INSULIN RESISTANCE IN TYPE 2 DIABETIC PATIENTS

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Background:

Fetuin-A (α_2 -Heremanschmid glycoprotein), (AHSG) is a 59 KDa multifunctional hepatic secretory protein that can inhibit insulin receptor autophosphorylation and subsequent downstream insulin signaling in vitro.

Aim:

Study of human fetuin-A and its possible role in insulin resistance (IR) observed in type 2 Diabetes mellitus patients.

Subjects and Methods:

Thirty five subjects were divided into two groups: A patient group included 20 patients with type 2 diabetes mellitus and a control group included 15 healthy volunteers. Detailed history taking, clinical examination, body mass index (BMI) calculation and laboratory investigations included evaluation of serum levels of fetuin-A, tumour necrosis factor- α (TNF- α), leptin, insulin, C-peptide, fasting (FSG) and postprandial serum glucose (PPG), glycated haemoglobin (HbA_{1c}), lipid pattern and high sensitive C-reactive protein (hs CRP). Homeostasis model assessment of insulin resistance (HOMA-IR), insulin/glucose and C-peptide/glucose ratios were estimated.

Results:

Serum fetuin-A was significantly higher in type 2 DM patients than that in the control group. A significant positive correlation was found between serum fetuin-A and serum levels of insulin, HOMA-IR, C-peptide, C-peptide/glucose ratio, insulin/glucose ratio, Leptin, TNF- α , BMI, LDL-C and hs-CRP.

Conclusions:

High human serum fetuin-A has a strong association with IR in type 2 diabetic patients thus raising the possibility that fetuin-A could be a target for treatment of type 2 diabetes. Future studies with longitudinal cardiovascular outcomes are needed to establish the possibility of using fetuin-A as a predictor of cardiovascular events in diabetic patients.

Key words:

Fetuin-A, Insulin resistance, type 2 diabetes mellitus.

SERUM LEPTIN LEVEL IS ASSOCIATED WITH INSULIN RESISTANCE INDEPENDENT OF OBESITY INDICES

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Background:

Studies of the association between serum leptin concentration and insulin resistance are contradictory. We studied serum leptin level and the homeostasis model assessment of insulin resistance with adjusting for several indicators of obesity.

Methods:

This population-based study was conducted in the Guangzhou Biobank Cohort Study in 702 older adults aged 50 or above. Serum levels of leptin, both fasting and 2 hour oral glucose-load (2hOGTT) glucose and insulin, homeostasis model assessment insulin resistance index (HOMA-IR), and anthropometric indices were evaluated.

Results:

Leptin concentrations were positively significantly associated with indicators of insulin resistance after age and sex adjustment, including body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), body fat percentage (BFP), high density lipoprotein cholesterol (HDL), triglyceride, fasting and 2hOGTT glucose and insulin and HOMA-IR, but less so with to glycosylated hemoglobin A1c. The association between leptin (ng/ml) and fasting/ 2hOGTT insulin (μ U/ml) or HOMA-IR remained significant after controlling for age, sex, BMI, physical activity, smoking, mean arterial pressure, HDL and triglyceride (regression coefficient (95% confidence interval): fasting insulin 0.17 (0.10, 0.24), 2hOGTT-insulin 0.28 (0.01, 0.55), HOMA-IR 0.04 (0.02, 0.05)). Similar results were obtained if BMI replaced by WC, WHR or BFP. Same models were performed in subgroups analysis by sex and diabetes status. No significant difference between sex or different diabetes status was observed.

Conclusions:

Our study showed a highly correlation between leptin and hormonal indices of IR in older adults independent of general/central obesity or body fat percentage. Further studies will be important to determine whether serum leptin concentration has a role in the diabetes and the other metabolic abnormalities associated with insulin resistance.

STUDY OF PREVALENCE OF RETINOPATHY AND ITS RISK FACTORS IN TYPE 2 DIABETES PATIENTS WITH INSULIN RESISTANCE IN ANANTAPUR SOUTH INDIA.

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Background and Aims:

Retinopathy is not only related to glycaemic control and diabetes duration, but also to blood pressure and B.M.I, as was shown by the UKPDS and the HOORN study.

Materials and Methods:

500 type2 diabetic patients with insulin resistance from the O.P. of our Diabetes center, Sainagar, Anantapur, India are taken up for the study. But 25 patients with major cardiovascular disease, amputation or serum creatinine level >1.5 mg/dl were excluded (M/F:265/210, mean age : 41+or- 12 yrs, duration of diabetes 19+or-11 yrs, HbA1c 7.8+or-1.1%). Retinopathy was examined by fundoscopy (Airlie House classification), neuropathy by electromyography, blood pressure was taken 5 min. rest and a mean of 4 measurements was used. B.M.I and HbA1c are measured to all patients.

Results:

Retinopathy was present in 53%, Hypertension ($>130/80$ mm Hg.) in 41%, neuropathy in 41%. Retinopathy is more prevalent in over weight subjects than in normal weight (62% Vs 45% $P<0.0001$). Patients with retinopathy were older (46+ - 11 vs 36+ - 11 yrs $p<0.0001$), had longer diabetes duration (25+ - 10 vs 13+ - 9 yrs $p<0.0001$), a higher HbA1c (8.0+ - 1.0 vs 7.7+ - 1.2% $p=0.004$) and a higher B.M.I (26.0+ - 4.2 vs 24.8+ - 4.4 $p=0.005$) than those with out retinopathy. Logistic regression analysis showed that diabetes duration ($p<0.0001$), blood pressure ($p=0.013$), HbA1c ($p=0.019$) were independent risk factors for retinopathy.

Conclusions:

Retinopathy is present in 53% of type 2 diabetic patients and is more prevalent in patients who has hypertension ($>130/80$ mm Hg), longer diabetes duration (24+ - 5 years), higher HbA1c (8.0+ - 1.0%) and higher B.M.I (>25).

POSTPRANDIAL INSULIN AND TRIGLYCERIDE LEVELS AFTER DIFFERENT BREAKFAST MEAL CHALLENGES – MEASUREMENT IN DRIED BLOOD SPOTS (DBS)

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The metabolic conditions that predispose individuals to atherosclerosis are thought to be a postprandial phenomenon, termed “postprandial dysmetabolism”. In non-diabetics, high postprandial insulin and triglycerides are independent risk factors for coronary artery disease and cardiovascular events. Pre- and postprandial serum testing for insulin and triglycerides is inconvenient for patients and practitioners, limiting routine application of these tests and their use in large scale clinical studies. We developed finger stick DBS tests for insulin and triglycerides that correlate highly with venous serum values ($r=.93$ and $r=.91$ respectively), and evaluated these analytes in DBS from 19 healthy volunteers after an overnight fast, before and 2 hours after eating 5 different breakfast meals. Meals consisted of: 1) glazed donuts, fruit smoothie; 2) boiled eggs, sausages, 2% milk; 3) bagel, cream cheese, boiled egg, 2% milk; 4) pancakes, syrup, tea with cream/sugar; 5) oatmeal, almonds, apple, skim milk.

Postprandial insulin levels $>8 \mu\text{U/mL}$ were classified as “non-optimal” while $>15 \mu\text{U/mL}$ were “abnormal”; triglyceride levels $>100 \text{ mg/dL}$ were “non-optimal” and $>150 \text{ mg/dL}$ “abnormal”. For insulin, meal 2 (lowest carbohydrate, highest protein) produced the best (significantly fewer abnormal/non-optimal) postprandial results and meal 4 (highest carbohydrate, lowest protein) the worst (significantly more abnormal/non-optimal) postprandial results. For triglycerides, no meal differed significantly from the others in the number of abnormal or non-optimal classifications. The convenience of in-home collection and analyte stability offer much wider scale use of the DBS tests for routine clinical assessment and large scale epidemiological studies of postprandial dysmetabolism.

SOME MEDICINAL PLANTS USED AGAINST INSULIN SECRETION BY THE ALTERNATIVE MEDICINAL PRACTITIONERS IN DHAKA CITY OF BANGLADESH

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Today a person is very much preoccupied. Modern lifestyle has contributed to serious increase in killer disease like insulin secretion. Currently, most medications or therapies for treatment of insulin secretion have serious side-effects, which sometimes can be more life-threatening than the disease itself. It is important, therefore, to turn to medicinal plant sources for discovery of novel yet safe compounds, which has less or no side-effects to treat insulin secretion. We accordingly conducted an ethnomedicinal survey of several areas within Dhaka city of Bangladesh to learn more about medicinal plants used by the alternative medicinal practitioners to treat insulin secretion. Interviews were conducted with the help of a semi-structured questionnaire and medicinal plant specimens as pointed by the alternative medicinal practitioners were photographed, collected, deposited and identified at the Bangladesh National Herbarium. Some of the medicinal plant names obtained in our survey included *Lepidagathis hyalina*, *Plantago major*, *Nigella sativa*, *Aconitum napellus*, *Olea europaea*, *Bacopa monnieri*, *Spondias dulcis*, *Psidium guajava*, *Andrographis paniculata*, *Tamarindus indica*, *Zingiber officinale*, *Cinnamomum tamala*, *Curcuma longa*, *Withania somnifera*, *Embllica officinalis*, *Maranta arundinacea*, *Ocimum tenuiflorum*, *Morinda angustifolia*, *Ficus racemosa*, *Eclipta alba*, *Kalanchoe pinnata*, *Punica granatum*, *Murraya koenigii*, *Dillenia indica*, *Citrus acida*, *Aloe barbadensis*, *Syzygium cumini*, *Camellia sinensis*, and *Vigna mungo*. Since the city patients appeared to be generally satisfied with the treatment offered through these medicinal plants, it is important to conduct proper scientific studies towards discovery of compounds of interest in these medicinal plants, which can be used as safe and effective medicines.

ROLE OF MACROPHAGES IN OBESITY WITH INSULIN RESISTANCE

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Introduction:

Obesity and diabetes mellitus are the most prevalent and serious metabolic diseases worldwide. Together they affect more than 50% of adults in developed countries. Subjects who are obese or have diabetes mellitus show insulin resistance. Reduced insulin sensitivity and increase in serine-307 phosphorylation of insulin receptor substrate-1 (IRS-1) is a common feature of insulin resistance. Free fatty acid and tumor necrosis factor (TNF)- α are major factors that contribute to insulin resistance. While obesity is associated with infiltrations of macrophages in obese adipose tissues.

Objective:

To study the molecular link between obesity and insulin resistance.

Materials and Methods:

An *in vitro* co-culture system composed of differentiated 3T3-L1 adipocyte fortified with macrophage was developed. Co-culture of differentiated 3T3-L1 adipocyte with macrophage was compared with differentiated 3T3-L1 adipocytes prior to and after treatment with linoleic acid (free fatty acid) and TNF- α for 0-24 hours. Serine 307 phosphorylation of IRS-1 was determined by ELISA while insulin sensitivity was measured by determining glucose uptake by radiometric assay.

Results:

It was found that linoleic acid promotes serine-307 phosphorylation of IRS-1 in a dose and time-dependent manner. Serine phosphorylation was induced at $100 \mu\text{M}$ and the strongest activity was observed at $200 \mu\text{M}$ ($p < 0.05$) prior to linoleic acid treatment. A similar phosphorylation pattern was observed in co-culture with serine phosphorylation of IRS-1 was higher in this group compared to adipocytes alone prior to linoleic acid ($p > 0.05$) and TNF- α treatment ($P < 0.05$). Within this group, higher level of serine IRS-1 phosphorylation observed in differentiated 3T3-L1 alone after treatment with TNF- α for 4 and 8 hours ($p < 0.05$). Prolonged treatment with TNF- α (12-24 hours) in differentiated adipocytes, caused significant reduction in phosphorylation. The same result was found in co-culture, where a significantly higher level of serine phosphorylation ($P < 0.05$) observed at 4 hour of TNF- α treatment and reduced after for 8 to 24 hours. Higher levels of glucose uptake were observed in co-culture compared to adipocytes alone at the basal level and prior to linoleic acid and TNF- α treatment ($p < 0.05$ and $p < 0.01$).

Conclusions:

High level of macrophages in obese adipose tissues may be a link between obesity and insulin resistance. Linoleic acid, TNF- α and macrophages infiltration may play a role in the development of insulin resistance by increasing serine IRS-1 phosphorylation and glucose uptake.

ADIPOKINE CONCENTRATIONS IN RELATION TO INSULIN SENSITIVITY IN TYPE 1 DIABETES

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Background:

A number of adipokines, especially adiponectin, have been related to insulin sensitivity (SI)/resistance in type 2 diabetes. Although insulin resistance also occurs in type 1 diabetes, such associations have not been so extensively explored. We thus assessed the cross-sectional association of adiponectin, TNF- α , IL-6 and CRP with SI.

Methods:

SI was assessed by hyperinsulinemic-euglycemic clamp studies in 30 participants of the Epidemiology of Diabetes Complications study, a 20-year prospective investigation of childhood-onset type 1 diabetes. Mean participant age at the time of these assessments was 48 years and diabetes duration 39 years. Total body fatness measurements, assessed by dual x-ray absorptiometry, were also available for 26 of the 30 participants who underwent clamp studies. Univariate associations were assessed with Spearman correlation coefficients, whereas linear regression models were constructed to evaluate the relationship between each adipokine of interest and SI, adjusting for diabetes duration, gender, height, total fat mass, HbA_{1c} and daily insulin dose per body weight.

Results:

No significant correlations were observed between SI and adiponectin ($r=0.29$, $p=0.15$), TNF- α ($r=0.03$, $p=0.86$), or IL-6 ($r=-0.23$, $p=0.25$). However, a strong inverse correlation was observed with CRP ($r=-0.63$, $p=0.0004$). In multivariable analyses, no independent association was observed for any of the adipokines studied. The most important (inverse) correlate of SI was daily insulin dose per body weight.

Conclusions:

No association between SI and adiponectin, TNF- α , IL-6 or CRP was observed in this group of individuals with a long duration of type 1 diabetes, in whom insulin dose was the major correlate of SI.

CHARACTERIZATION OF SEX-DEPENDENT DEVELOPMENT OF INSULIN RESISTANCE IN ZUCKER DIABETIC FATTY RATS USING TRANSCRIPT AND PROTEIN PROFILING.

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Objectives:

The aim of this study was to find sex-dependent hepatic gene products that correlate with insulin resistance in Zucker diabetic fatty (ZDF) rats.

Methods:

Non-diabetic obese ZDF female rats were compared with either diabetic obese male ZDF rats or obese ZDF female rats with diet-induced diabetes. Diabetes-related hepatic gene products were identified using genome-wide transcript profiling and confirmed by RT-PCR. Interesting gene products were selected for antibody-based protein profiling in rat plasma using Luminex and validated in liver and plasma using immunoblotting.

Results:

During the course of this study, glucose and insulin sensitivity was reduced in males and females on high-fat diet, with males showing the highest degree of glucose intolerance and insulin resistance. One hundred twenty four transcripts were identified as significantly different between healthy and diabetic female rats, whereas two hundred thirty eight were different between diabetic males and females. Overlapping differences included genes involved in different pathways of cellular metabolism. The protein profiling identified nine proteins that were significantly different between the healthy and diabetic females and twenty eight that were different between the diabetic males and females. Interestingly, these sex-different proteins found in serum correlates to the sex-different hepatic gene products in terms of function linked to insulin sensitivity and type 2 diabetes. Further insight into the relationship between sex-dependent development of insulin resistance and the findings in this study using the ZDF rat as a model, may help improve individual treatment options and mitigate disease development in males and females with type 2 diabetes mellitus.

PIOGLITAZONE THERAPY IMPROVES SUBCUTANEOUS ADIPOSE TISSUE FAT STORAGE IN INSULIN RESISTANCE, OVERWEIGHT INDIVIDUALS

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The correlation between obesity and insulin resistance has been well established. However, the pathogenesis of insulin resistance remains to be determined as obesity alone does not cause insulin resistance. One explanation has been the failure of adipose tissue to differentiate normally, resulting in excess fat that must be stored in visceral and other secondary tissues. The goal of this work was to promote adipocyte differentiation by the administration of pioglitazone, a thiazolidinedione known to improve insulin sensitivity, in a group of overweight insulin resistant and insulin sensitive patients. Methods Thirty-seven overweight (BMI >27, <35), otherwise healthy, non-diabetic patients were stratified into insulin resistant and sensitive subgroups and administered 30 mg of pioglitazone daily for 12 weeks. CT of the abdomen was performed prior to pioglitazone therapy and at the conclusion of the 12-week course. Results All results were adjusted for gender. CT imaging of the abdomen showed that insulin-resistant individuals had significantly more subcutaneous ($p=0.005$) and visceral ($p<0.000$) abdominal fat

than equally overweight insulin sensitive patients at baseline. At the conclusion of twelve weeks of pioglitazone therapy, overweight insulin resistant patients had significantly less visceral fat ($p=0.008$) as compared to before therapy, and subcutaneous fat had increased after pioglitazone administration, but not significantly ($p=0.23$). Equally overweight insulin sensitive subjects, however, did not have a significant change in either visceral or subcutaneous fat. Conclusions These findings support the theory that pioglitazone therapy promotes improved insulin sensitivity via increasing fat storage in physiologic subcutaneous adipose tissue and decreases abnormal fat storage in visceral tissue.

TREATMENT WITH A SOLUBLE ACTIVIN RECEPTOR TYPE IIB FUSION PROTEIN INDUCES A THERMOGENIC PROFILE IN WHITE FAT AND PROMOTES RESISTANCE TO DIET INDUCED OBESITY IN MICE FED A HIGH-FAT DIET

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Obesity is a pervasive condition which, among other health risks, contributes to development of insulin resistance. Growth factors that signal via activin receptor type IIB (ActRIIB) negatively regulate muscle mass and may also mediate adipose mass. Previous work demonstrated that inhibition of ActRIIB signaling with a soluble ActRIIB increases muscle mass and decreases adiposity in wild-type mice. To determine if inhibition of ActRIIB signaling can alleviate the adverse effects of diet-induced obesity (DIO), we tested ACE-435, a protein comprised of an optimized form of the ActRIIB extracellular domain linked to a human Fc, in mice fed high-fat diet (HFD). HFD-fed mice were treated with vehicle (HFD-VEH) or ACE-435 (HFD-ACE; 10 mg/kg 2X/week for 8 weeks). Chow-fed mice were followed as a diet control. NMR analysis demonstrated that lean mass was significantly increased ($p<0.001$) and fat mass gain reduced ($p<0.01$) in the HFD-ACE mice compared to the HFD-VEH group. Furthermore, ACE-435 prevented HFD-induced increases in serum lipid levels and liver steatosis. ACE-435-treated mice were also resistant to HFD-associated changes in serum hormones. ACE-435 prevented the reduction in adiponectin and increase in insulin that were observed in HFD-VEH mice. Moreover, adiponectin and insulin levels of the HFD-ACE mice were comparable to chow-fed controls. Surprisingly, white fat from HFD-ACE mice had a gene expression profile consistent with thermogenesis, including significantly upregulated UCP-1 and PGC-1 α expression ($p<0.05$) compared to control animals. These data demonstrate the beneficial effects of ACE-435 on DIO and introduce a role for in inducing a thermogenic program in white fat.

TO ASSESS THE ASSOCIATION OF LONG-TERM SODIUM VALPROATE MONOTHERAPY AND POLYCYSTIC OVARIAN SYNDROME (PCOS) IN SOUTH INDIAN WOMEN WITH EPILEPSY.

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Methods:

The study was conducted in 30 newly diagnosed and untreated female epileptic patients, diagnosed as per the criteria defined by International League against Epilepsy. 30 patients were enrolled for this study and followed-up for one year. Clinical parameters, like transabdominal ultrasonography and venous blood sampling after an overnight fast for the analysis of serum testosterone and insulin were collected at baseline and at the end of study. Hirsutism was evaluated and scored by modified Ferriman Gallway system. Menstrual diary cards were distributed among all patients at the time of enrolment to record information about menstrual cycles. Follow-up were done at the end of 3rd, 6th, 9th and 12th months.

Results:

The 25 women who completed 1 year follow-up, we observed clinically relevant weight gain in 60%, hirsutism in 12%, menstrual abnormalities in 16%, polycystic ovaries (PCO) in 8%, polycystic ovarian syndrome (PCOS) in 20% and a significant increase in mean serum testosterone ($p<0.001$). A significant positive correlation existed between weight gain and the development of menstrual abnormalities ($r = 0.45$, $p<0.05$), hirsutism ($r=0.56$, $p<0.008$) and PCO ($r = 0.51$, $p<0.02$). No correlation existed between weight change and serum testosterone. However positive correlation definite existed between weight gain and hyperinsulinaemia ($r=0.66$, $p<0.0001$).

Conclusions:

Long-term valproate therapy in south Indian women with epilepsy is associated with development of hirsutism, significant weight gain, alterations in reproductive hormonal function, and ultimately a higher occurrence of PCOS.

PPAR INDEPENDENT MECHANISMS OF THIAZOLIDINEDIONE INHIBITION OF PAI-1 EXPRESSION IN VASCULAR ENDOTHELIAL CELLS

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Increased levels of Plasminogen Activator Inhibitor Type-1 (PAI-1) are observed in patients with insulin resistance (IR). The thiazolidinediones (TZDs), peroxisome proliferator-activated receptor gamma (PPAR γ) agonists, have been shown to decrease IR. Inhibition of

increased PAI-1 production may account, in part, for the putative therapeutic effects of the TZDs. We previously reported PPAR γ independent inhibition of TNF α induced PAI-1 expression by rosiglitazone in human vascular endothelial cells (HVEC). This effect was associated with PPAR γ independent inhibition of orphan nuclear receptor Nur77 protein expression and binding of nuclear proteins to the PAI-1 promoter *cis*-acting response element for Nur77 (NBRE). Nur77 binding to the PAI-1 NBRE has previously been identified as crucial for TNF α -mediated up-regulation of PAI-1 expression in HVEC. Here we report that rosiglitazone treatment inhibits TNF α -mediated induction of Nur77 mRNA expression in HVEC. Use of the specific PPAR γ inhibitor SR-202 had no effect on rosiglitazone-mediated inhibition of induced Nur77 mRNA expression suggesting this effect was PPAR γ independent. Rosiglitazone treatment inhibited, in a PPAR γ independent manner, TNF α stimulation of a 1.4 kb Nur77 promoter construct transfected into HVEC confirming the transcriptional nature of this effect. Rosiglitazone treatment attenuated binding of nuclear proteins to the NF- κ B binding site of the Nur77 promoter in HVEC in a PPAR γ independent manner. These observations suggest a PPAR γ independent mechanism for the effects of TZDs on inhibition of PAI-1 expression and possibly IR via modulation of Nur77 expression, which may allow for the development of specific, novel PPAR γ independent agents.

ROLE OF SENSORY NEURONS ON THE PANCREATIC BETA CELL FUNCTION AND ON THE DEVELOPMENT OF INSULIN RESISTANCE

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Aim:

To investigate the role of capsaicin-sensitive sensory afferent nerves on the pancreatic beta cell function and on the development of insulin resistance in genetically obese, insulin resistant Otsuka Long Evans Tokushima Fatty (OLETF) rats.

Methods:

At the age of 6 weeks, OLETF rats were divided into two groups. The control group was treated with the vehicle for capsaicin, and the capsaicin group was treated with a single subcutaneous dose of 50 mg/kg capsaicin. The next 19 weeks, the metabolic variables (body weight gain, ingested food and water, stool and urine production) were measured by means of metabolic cage. At the end of the treatment period glucose stimulated insulin response was determined by oral glucose tolerance test (OGTT), whole body insulin sensitivity was determined by means of hyperinsulinaemic euglycaemic glucose clamping and the hepatic glucose production (HGP) as well as insulin stimulated peripheral glucose uptake (PGU) was determined by means of 3 H-glucose infusion. Fasting plasma insulin level was determined by RIA and fasting blood glucose value by glucose oxidase method. Pancreatic beta cell function was characterized by HOMA-%B index based on fasting insulin and glucose level.

Results:

The body weight of the capsaicin treated group was significantly lower than the control group. There were no changes in the other metabolic parameters. During the OGTT, the control treated group had reduced glucose stimulated response compared to capsaicin treated group and the area under the curve values were 1844 ± 124 , and 1287 ± 87 , respectively ($p < 0.5$). The whole body insulin sensitivity improved (from 9.4 ± 1.8 to 15.6 ± 2.1 mg/kg/min) significantly according to the improvement in HGP (from 7.5 ± 1.5 to 12.9 ± 3.1 mg/kg/min) and PGU (from 6.7 ± 1.2 to 2.8 ± 1.1 mg/kg/min). There was no difference in the pancreatic beta cell function between the two treatment groups.

Conclusion:

The capsaicin-sensitivity sensory afferents play role in the development of obesity and insulin resistance in OLETF rat. To explore the interaction between the CCK-1 and TRPV-1 receptor in the vagal afferent, further experiments are needed. (The work was supported by the No. 74162 Hungarian Scientific Research Fund.)

CAN A GREEN BASED DIET, COUPLED WITH NUTRICEUTICALS, REVERSE THE METABOLIC SYNDROME IN WOMEN?

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Aims:

Obesity and the metabolic syndrome is a worldwide epidemic fostered in part by changing food consumption and depleted soil nutrients secondary to industrial fertilizers. We tested whether a green food based diet, coupled with simple supplements, could potentiate weight loss in women.

Methods:

100 women volunteers with BMI's ≥ 30 (range 30-45), aged 18-78, were enrolled in a high green based diet (Diet Evolution) which consisted of sharp curtailment in refined or whole grains, unlimited access to salads and green vegetables, liberal use of olive oil, and avoidance of starchy vegetables, while allowing small portions of animal products. Pts were given 1000mg of Garcinia, 400 mcg of Chromium Picolinate, 200mcg of Selenium, and 200 mg of Potassium twice daily. Pts were followed for 6 months to 2.5 years (mean 1.5 yrs). Baseline blood work was repeated at 3-month intervals and sent to a core lab, Berkeley Heart Labs, Alameda, CA.

Results:

Weight loss ranged from 8 to 65 pounds (mean 24 lbs). BMI decreased from 35 ± 5 to 27 ± 5 over the study period. Serum Insulin levels fell from 18 ± 5 to 8 ± 3 uU/dl. Fasting serum glucose fell from 115 ± 10 mg/dl to 94 ± 5 mg/dl. Serum Triglycerides fell from 165 ± 36 to 56 ± 24 mg/dl. Systolic BP fell from 140 ± 10 to 110 ± 6 mmHg.

Conclusions:

A diet high in green vegetables, with reductions in refined or whole grain products (a grain-less Mediterranean diet), coupled with simple nutraceutical supplements, effectively treats obesity and the metabolic syndrome in a broad age range of women.

CAN NIACIN BE USED SAFELY TO ELEVATE HDL LEVELS IN PATIENTS WITH THE METABOLIC SYNDROME?

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Aims:

Niacin is one of the few compounds capable of raising low HDL cholesterol levels in patients with the Metabolic Syndrome (MS), but it is often avoided owing to its purported adverse effects on serum glucose levels. Little is known about Niacin's effects on serum insulin or HbA1C levels, which would more accurately gauge its true effect on MS. As part of a comprehensive treatment program for pts with MS, we studied whether the introduction of Niacin would have beneficial effects on HDL cholesterol without adverse effects on Insulin or HbA1C in 450 pts.

Methods:

Four hundred fifty consecutive MS pts (aged 23 to 82) were enrolled in the Diet Evolution program, which we have described previously, and given Extended Release Niacin 1,000-1,500 mg per day, if baseline HDL levels \leq 40 mg/dl in males or \leq 50 mg/dl in females. Fasting serum Glucose, Insulin, HbA1C levels were drawn at baseline, and at 3-month intervals for 1 year, and sent to a core lab, Berkeley Heart Labs, Alameda, CA.

Results:

Follow-up was 100%. 11 women could not tolerate extended release Niacin and were switched to Inositol Hexanicotinate without difficulty. Weight loss was 21 lbs (range 5 to 65lbs). HDL increased from 43 ± 8 to 67 ± 4 mg/dl over one year. Serum Glucose went from 110 ± 20 mg/dl at baseline to 101 ± 12 mg/dl at one year. Serum Insulin fell from 17 ± 5 to 9 ± 3 uU/dl at one year, while HbA1C fell from 6.0 ± 0.3 to 5.7 ± 0.2 %.

Conclusions:

Extended release Niacin has important HDL raising properties for patients with the Metabolic Syndrome. When coupled with a high green food based diet with reduction of refined grain products (Diet Evolution), Niacin use has no negative impact on Glucose metabolism; in fact, all measures of glucose metabolism improved. Our study suggests that Niacin should be considered for all MS pts with chronically low HDL.

IDENTIFICATION OF NOVEL INSULIN RESISTANCE METABOLITES IN A NON-DIABETIC POPULATION BY GLOBAL BIOCHEMICAL PROFILING

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Insulin resistance is a risk factor for type 2 diabetes and cardiovascular disease progression. Current diagnostic tests, such as glycemic indicators, have limitations in the early detection of insulin resistant individuals. We sought to identify novel biomarkers for detecting at-risk subjects. Biochemical profiling was conducted on a cohort of 399 nondiabetic subjects representing a broad spectrum of insulin sensitivity and glycemic status based on the hyperinsulinemic euglycemic clamp and oral glucose tolerance testing, respectively. A mass spectrometric metabolomic technology enabled identification of 471 metabolites in the fasting plasma, with γ -hydroxybutyrate (γ -HB) being the one best separating (by random forest analysis) insulin resistant (lower third of the clamp-derived $M_{FFM} = 33 \mu\text{mol min}^{-1} \text{kg}_{FFM}^{-1}$, median [interquartile range], $n=140$) from insulin sensitive subjects ($M_{FFM} = 66 \mu\text{mol min}^{-1} \text{kg}_{FFM}^{-1}$). Independently and in an additive fashion, AHB also separated subjects with normal glucose tolerance from subjects with impaired glucose regulation (impaired fasting glycemia and impaired glucose tolerance). These associations were independent of sex, age and BMI. Furthermore, in 35 morbidly obese patients studied before and after surgically-induced major weight loss, insulin sensitivity improved by 1.8-fold in parallel with a 1.7-fold decrease in plasma γ -HB concentrations. A metabolomic technology demonstrated that γ -hydroxybutyrate is an early marker for both insulin resistance and dysglycemia. The underlying biochemical mechanisms may involve increased lipid oxidation and oxidative stress.

LONG AND MEDIUM TERM EFFECTS OF LEPTIN REPLACEMENT TREATMENT IN GENETICALLY LEPTIN DEFICIENT PATIENTS

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Leptin is an important regulator of food intake and energy expenditure. The effect of leptin on glucose homeostasis and insulin resistance in particular is a topic of active investigation and has been recently summarized as “paradoxical observations on the associations between leptin and insulin resistance”. We

developed minimally invasive methodology, mathematical model, and software for analysis of glucose homeostasis by deconvolution of insulin secretion, delivery and sensitivity from 24-hour standardized meals test with frequently measured blood glucose, insulin and C-peptide and applied it to the study of glucose homeostasis in a unique group of 3 genetically leptin-deficient patients before and after leptin replacement treatment. We showed that leptin replacement therapy had different time-dependent effects on the glucose homeostasis. In the long-term, leptin increased insulin sensitivity 10-fold and decreased insulin secretion 2-fold. Interestingly, in the medium-term, the 7 week interruption of leptin replacement therapy resulted in a moderate (50%) decrease of insulin sensitivity. To further investigate the time-dependent effects of leptin we performed a quantitative analysis of plasma proteome of our patients "before", "after", "on", and "off" leptin replacement. Around 500 proteins were reliably identified and quantitated for each of the patients. Synchronous dynamics of abundances of about 90 proteins was observed reflecting both long term and short term effects of leptin replacement treatment. Pathways and processes enriched with over abundant synchronous proteins were: cell adhesion, cytoskeleton remodeling, cell cycle, blood coagulation, glycolysis and gluconeogenesis. Plausible common regulators of the above synchronous proteins were identified through transcription regulation network analysis. Two of the transcription factors (c-Myc and androgen receptor) of the generated network are known to activate each other through the double positive feedback loop – a possible molecular mechanism of the long term effects of leptin replacement therapy. Among the differentially abundant proteins, 27 belonged to the insulin resistance network generated with Metacore 5.3 (GeneGo). In particular, adiponectin was about 2-fold overabundant in all 3 leptin replacement treatment stages in all 3 patients, thus confirming our observation that leptin decreases insulin resistance in leptin deficient patients. Studies of the short term effects of leptin injection and proteomics study of our patients' adipose tissue samples are in progress.

RELATIONSHIP OF -238G/A AND -308G/A TNF- GENE POLYMORPHISMS WITH CARDIOVASCULAR RISK FACTORS IN MEXICAN FAMILIES

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Abstract

Tumor Necrosis Factor alpha (*TNF-α*) is a cytokine involved in inflammatory process as well as in glucose and lipid metabolism. *TNF-α* has been associated with insulin resistance, type 2 diabetes and atherosclerosis. *TNF-α* gene polymorphisms in the promoter region can be related with the variation of serum cytokine levels.

Aim:

Analyze the relationship of -238G/A and -308G/A *TNF-α* gene polymorphisms with cardiovascular risk factors in families with obesity.

Materials and methods:

Ninety members of 30 Mexican families, in which an index case had obesity, were included in the study. The families were integrated by case-parents trios. We evaluated the body composition by bioelectrical impedance. Peripheral blood samples were collected to determine biochemical and hematological parameters. High sensitivity C- reactive protein levels were measurement for nephelometric analysis. Screening for -238G/A and -308G/A *TNF-α* polymorphisms was performed by PCR-RFLPs.

Results:

The genotype frequencies of -238G/A polymorphism were: 81.1% G/G, 17.8% G/A and 1.1% A/A, and for the -308G/A were: 97.8% G/G and 2.2% G/A. In the parents, both polymorphisms were in Hardy-Weinberg's equilibrium. The genotype -308G/A was associated with type 2 diabetes (OR=1.9, p=0.02), whereas the genotype -238G/A was not associated with any parameters.

Conclusion:

The G/A genotype of -308 *TNF-α* gene polymorphism can confer susceptibility for the development of type 2 diabetes in Mexican families.

HYPOCHOLESTEROLEMIC EFFECTS OF SOLUBLE DIETARY FIBER ON HEPATIC METABOLIC PATHWAYS IN HAMSTERS

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Hydroxypropyl methylcellulose (HPMC) is a well-characterized semi-synthetic cellulose derivative that has the structural and physiological properties of a soluble non-fermentable dietary fiber. A relationship of HPMC's viscosity with its hypocholesterolemic effects has been demonstrated in both animals and human clinical investigations. Concurrently, significant increases in fecal excretion of bile acids and sterols have been observed upon HPMC intake which may result indirectly in changes in hepatic lipid metabolism. However, our understanding of how soluble dietary fibers alter cellular cholesterol metabolism and regulate the molecular events at the gene/protein level have yet to be elucidated. In the present study, we measured mRNA levels of a series of hepatic genes involved in bile acid, cholesterol, and fatty acid metabolism to better understand the underlying mechanisms in hamsters. After four consecutive weeks of feeding hamsters supplemented with 5% HPMC resulted in significant reductions of total, VLDL and LDL cholesterol levels in plasma and cholesterol, triglycerides, and total lipids levels in liver.

Correlations of hepatic gene expression levels with the plasma lipoprotein concentrations were examined. The cholesterol levels were mediated by increased expression of genes involved in both bile acid and cholesterol synthesis, such as *CYP7A1* and *SREBP-2*. Interestingly, regulation of *CYP7A1* expression was not dependent on *FXR α* expression but dependent on *HNF-4 α* /*PGC-1 α* . Simultaneously, *LDLR* expression was significantly increased and inversely correlated with plasma cholesterol levels, indicating increased bile acid synthesis, in combination with an accelerated plasma LDL cholesterol clearance rate. Furthermore, reductions in both plasma and hepatic triglyceride levels were associated with an increase in *PPAR α* and a decrease in mRNA for *SREBP-1c*. This study supports the potential dietary use of HPMC for the prevention or management of dyslipidemia-related diseases such as cardiovascular disease and metabolic syndrome.

SERUM ISCHEMIA MODIFIED ALBUMIN LEVELS IN OBSTRUCTIVE SLEEP APNEA PATIENTS BEFORE AND AFTER TREATMENT: A PILOT STUDY

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Background:

Obstructive sleep apnea syndrome (OSAS) is associated with insulin resistance and the metabolic syndrome. It increases the rate of cardiovascular morbidity, which has been suggested to be partly related to increases in oxidative stress and a state of inflammatory cell activation. Ischemia-modified albumin (IMA) is proposed as a novel marker sensitive to cardiac ischemia with the potential to become a triage tool in suspected acute coronary syndrome patients. IMA is produced by oxidative attack on albumin by reactive oxygen species (ROS) at sites of ischemia.

Hypothesis:

We hypothesized that the cycles of hypoxia/reoxygenation in OSAS, may increase IMA levels. IMA levels measurement is inexpensive, quick and easily automated. If proven true, the biomarker could help monitor the effectiveness of the treatment of these patients.

Methods:

Ten patients (5 male, 5 female) with OSAS (more than 15 events of apnea-hypopnea/hour) and 20 age-matched controls were studied. The patients were studied at diagnosis and after 6 months of continuous positive airway pressure treatment (CPAP). All subjects were non smokers. Subjects with a history of diabetes, myocardial ischemia, renal, thyroid or systemic diseases were excluded. IMA was measured using a test based on the

ischemia-induced decrease in cobalt 2+ binding as previously described. All serum samples were kept at -80 C before analysis. We introduced minor modifications in the method to adapt it to a 96 well plate reader (Versa Max from Molecular Devices). All samples were run in duplicates on the same plate, 2 times. The intra-assay CV was 5%. Other parameters were measured using standard clinical laboratory methods.

Results:

During the observation period, no subjects experiences CV events. In OSAS patients under treatment the lowest saturation oxygen concentration during sleep measured by infrared methods, significantly recovered from 79.0 ± 7.5 to $90.0 \pm 5.5\%$ ($p=0.027$). IMA levels were 0.69 ± 0.08 in controls and 0.65 ± 0.1 in sleep apnea patients. The treatment of continuous positive airway pressure treatment had no significant effect on the marker (0.64 ± 0.1), although a trend to decrease was noted.

Conclusions:

Even within the limitations of small sample numbers, this is the first study measuring IMA in OSAS patients, a frequent comorbidity in insulin resistance. Our data show that IMA levels do not change in OSAS patients as compared to control subjects nor it changes with the CPAP treatment. IMA is produced by free radical attack on a terminal peptide of albumin, associated with focal ischemia. This pilot study seems to indicate that hypoxia/reoxygenation does not induced localized high fluxes of reactive oxygen species that could modify the molecule.

PREVALENCE OF INSULIN RESISTANCE AND ITS RELATIONSHIP WITH GLYCOSYLATED HEMOGLOBIN IN NEWLY DIAGNOSED GLYCEMIC ANOMALIES VISITING DIABETIC CLINICS OF LAHORE-PAKISTAN

Insulin is the primary hormone whose action is essential for the proper maintenance of glucose homeostasis. In this study a total of 508 subjects of both sexes (male $n=228$, female $n=280$) visiting diabetic clinic of Lahore during the year 2005-2006 were recruited. All subjects underwent a 75 g oral glucose tolerance test (OGTT) for the diagnosis of diabetes and IGT under the expert supervision of hospital management. The subjects were categorized using Diabetes Expert Committee criteria (2003) according to which fasting plasma glucose (FPG) > 100 -125 mg/dl were impaired glucose tolerant (IGT) subjects, and FPG > 126 mg/dl were diabetic (T2DM). Insulin was assessed by Immunoenzymometric Assay Homeostasis model assessment (HOMA-IR) was employed to estimate insulin resistance from simultaneous FPG and fasting plasma insulin levels (Matthew *et al.*, 1985):.

Marked hyperinsulinemia and insulin resistance were observed in the IGT subjects ($P<0.05$). Serum insulin concentration showed a positive and significant correlation with BMI in all the study groups ($r=0.435$, $r=0.474$, $r=0.247$; $P<0.0$). In T2DM group insulin had significant relationship with HbA1c, ($r=-0.240$, $P<0.05$). The relationship of insulin resistance has been worked out with the circulating levels of insulin, BMI and HbA1c in all the comparable groups. In the control, IGT and T2DM groups it was $r=0.967$,

$r=0.977$ and $r=0.729$, respectively ($p<0.01$). Significant gender differences were observed ($p<0.05$)

Key words:

Insulin resistance, BMI, HbA1c, OGTT.

ROLE OF SOCS2 IN GLUCOSE HOMEOSTASIS AND INSULIN SIGNALING

Fahad

SOCS2 have been shown to exert a negative feedback loop to the GH-activated JAK2/STAT5 signalling pathway. Accordingly, gigantism is observed in SOCS2 knockout (SOCS2-KO) mice. Interestingly, despite of the increased GH activity (SOCS2-KO) mice show normal glucose tolerance and insulin sensitivity.

Aim:

To investigate the role SOCS2 in regulating glucose homeostasis and insulin signaling in SOCS2-KO mice and in cell models.

Method:

Glucose and insulin tolerance test were performed in age-matched 25 male C57BL mice (SOCS2-KO and wildtype) after 4 months of normal or high fat diet. Insulin signaling was assessed in Huh7 cells after SOCS2 over-expression or SiRNA knockdown.

Results:

On normal diet, SOCS2 KO and the wild type mice were similar in their perirenal fat mass and glucose tolerance. However, after high fat diet the knockout mice developed severe impairment in glucose tolerance and hyperinsulinemia with increased perirenal fat deposition. There was increased hepatic micro-vesicular fat deposition in the knockout compared to wild type, which shows a macro-vesicular pattern. Furthermore, there was a defect in the insulin mediated leptin release in the knockout mice. In contrast, Akt phosphorylation was attenuated in Huh7 cells overexpressing SOCS2 and slightly enhanced after SiRNA knock-down.

Conclusion:

These findings suggest that SOCS2 might play an important role in glucose homeostasis as well as type 2 diabetes. Further investigation is undergoing to identify SOCS2 point of action in the insulin signaling cascade.

XOMA 052, AN ANTI-IL-1 BETA MONOCLONAL ANTIBODY, IMPROVES GLUCOSE CONTROL AND BETA CELL FUNCTION IN THE DIET-INDUCED OBESITY MOUSE MODEL

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Abstract:

Aim:

Recent evidence suggests that interleukin-1 beta (IL-1 β)-mediated glucotoxicity plays a critical role in Type 2 diabetes mellitus (T2DM). While previous work has shown that inhibiting IL-1 β can lead to improvements in glucose control and β -cell function, we hypothesized that more efficient targeting of IL-1 β with a novel monoclonal antibody, XOMA 052, would reveal an effect on additional parameters affecting metabolic disease.

Methods:

In the diet induced obesity (DIO) model, XOMA 052 was administered to mice fed either normal or high fat diet (HFD) for up to 19 weeks. XOMA 052 was administered as a prophylactic treatment or as a therapy. Mice were analyzed for glucose tolerance, insulin tolerance, insulin secretion, and lipid profile. In addition, the pancreata were analyzed for β -cell apoptosis, proliferation, and β -cell mass.

Results:

Mice on HFD exhibited elevated glucose and HbA1c levels, impaired glucose tolerance and insulin secretion, and elevated lipid profile, which were prevented by XOMA 052. XOMA 052 also reduced β -cell apoptosis and increased β -cell proliferation. XOMA 052 maintained the HFD-induced compensatory increase in β -cell mass, while also preventing the loss in β -cell mass seen with extended HFD feeding. Analysis of fasting insulin and glucose levels suggests that XOMA 052 prevented HFD-induced insulin resistance.

Conclusions:

These studies provide evidence that targeting IL-1 β in vivo could improve insulin sensitivity and lead to β -cell sparing. Taken together, the data presented suggest that XOMA 052 could be effective for treating many aspects of T2DM.

IL-6 GENE POLYMORPHISMS: RELATIONSHIP WITH SYSTEMIC INFLAMMATION AND TYPE 2 DIABETES.

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Abstract.

Interleukin-6 has a key role in stimulating the acute-phase response which elevates the circulating levels of several plasma proteins such as C-reactive protein. Furthermore, IL-6 has effect on glucose and lipid metabolism. There is evidence that the increase in IL-6 levels is associated not only with type 2 diabetes but also with impaired glucose tolerance and insulin resistance. The -174 G/C and -572 G/C polymorphisms in IL-6 gene have been proposed as risk factors for type 2 diabetes based on studies of unrelated individuals.

Aim:

Analyze the association of -174 G/C and -572 G/C polymorphisms in IL-6 gene with cardiovascular risk factors in Mexican families.

Materials and methods:

Ninety members of 30 Mexican families, in which an index case had obesity, were included in the study. We evaluated the body composition by bioelectrical impedance. Peripheral blood samples were collected to determine biochemical and hematological parameters. High sensitivity C-reactive protein (hsCRP) levels were measurement for nephelometric assay. Screening for both polymorphisms studied was performed by PCR-RFLP.

Results:

In the parents, both polymorphisms were in Hardy-Weinberg's equilibrium. The genotypes -174 GC/CC were associated with type 2 diabetes (OR=1.23, IC_{95%} 1.01–1.5) and highest levels of hsCRP ($p=0.02$) whereas genotype -572 GG was associated with type 2 diabetes (OR= 1.24, IC_{95%} 1.04–1.47) and with an inflammatory state determined by the increase in the leukocyte count (OR=1.24, IC_{95%} 1.02–1.51).

Conclusion.

The genotypes -174 GC/CC and -572 GG may confer susceptibility for the development of systemic inflammation and type 2 diabetes in Mexican families.

INSULIN RESISTANT SUBJECTS ARE AT HIGHER RISK OF OBSTRUCTIVE SLEEP APNEA THAN EQUALLY OBESSE, INSULIN SENSITIVE SUBJECTS

Alice Liu¹, Clete Kushida², Gerald M. Reaven³

There is increasing evidence of an existing relationship between obstructive sleep apnea (OSA) and type 2 diabetes, although underlying pathophysiological mechanisms remain unclear. To evaluate the role of insulin resistance in mediating this association, we assessed risk of OSA in insulin resistant (IR), as compared with equally obese, insulin sensitive (IS) subjects.

Non-diabetic, overweight/ obese subjects underwent direct quantification of insulin sensitivity by determining steady-state plasma glucose (SSPG) concentrations during the insulin suppression test. Individuals whose SSPG values fell in the top and bottom tertiles of a previously defined reference range were considered IR and IS, respectively. The Epworth Sleepiness Scale (ESS) and the STOP and/ or Berlin Questionnaires to evaluate OSA risk were administered to 8 IR and 8 IS subjects.

By definition, mean SSPG values were significantly higher in IR than IS individuals (229 ± 46 vs 87 ± 12 mg/dL, $p<0.001$). The groups did not differ in BMI (33.1 ± 2.6 vs 31.7 ± 2.9 kg/m², $p=0.32$). 50% of IR versus 0% IS subjects met criteria for pathologic sleepiness by scoring ≥ 10 points by the ESS ($p=.077$). Mean ESS scores were also greater in IR than IS individuals (9.4 ± 5.2 vs 4.6 ± 2.1 , $p=0.03$). Finally, all 8 IR subjects were found to be at high risk of OSA by either the

STOP or Berlin Questionnaires, as compared with 1 IS subject ($p<0.001$).

In conclusion, apparently healthy, insulin resistant individuals are demonstrated using clinical predictor models to have an increased risk of OSA, independent of obesity.

PECULIARITIES OF INTERRELATIONS BETWEEN INSULIN RESISTANCE, CARBOHYDRATE METABOLISM DISORDERS AND SEX HORMONES SUPPLYING IN WOMAN WITH MENOPAUSAL METABOLIC SYNDROME

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Background and aims:

Peculiarities of interrelations between age-related changes in the system of sex hormones and decrease of insulin sensitivity in menopausal woman were investigated.

Materials and methods:

124 menopausal women aged 46-57 ($50,9\pm 0,3$) and 12 healthy women with saved ovarian function (control group) were analyzed. All menopausal women were divided into two groups: with menopausal metabolic syndrome (MMS) ($n=93$) and without it ($n=31$). The investigation includes serum fasting glucose, insulin, free testosterone (fT), sex hormone-binding globulin (SHBG), estradiol concentration, C-peptide, BMI and blood pressure. The insulin resistance (IR) was determined by means of HOMA-IR index.

Results:

Serum levels of plasma estradiol agreed to physiological range for this state in all investigative menopausal women (<82 pg/ml). Estrogen supplying did not differ between women with MMS and without MMS ($25,02\pm 1,66$ pg/ml and $22,36\pm 0,75$ pg/ml corresp. ($p>0,05$), which is several time less then in premenopausal women ($107,5\pm 17,3$ pg/ml, $p<0,001$). Decrease of estrogens level accompanied with increase of androgenization (level of fT $-1,37\pm 0,04$ ng/ml), HOMA-IR ($3,3\pm 0,06$), insulin secretion ($13,86\pm 0,21$ mIU/ml) in women with MMS comparing with subjects without signs of MMS ($1,10\pm 0,09$ ng/ml, $1,8\pm 0,05$, $8,27\pm 0,20$ mIU/ml, $p<0,05$). Significant lowering of SHBG ($72,38$ 6,09, $31,84\pm 0,82$ nmol/l, $p<0,001$) and C-peptide (1445 ± 30 , 591 ± 37 nmol/l) in women with MMS comparing to control group was revealed. SHBG is known to be both a regulator of sex steroids' bioavailability and an integral marker of insulin resistance and metabolic syndrome.

Conclusion:

It has been determined, that the changes of balance between sex hormones (increasing of free testosterone in condition of estrogen level decreasing) and insulin resistance enhancing, insulinemia and decreasing of SHBG could be suggested as related disorders

in the frame of single pathologic process, which needs further investigation and adequate pharmacological correction.

EFFECTS OF A LOW CARBOHYDRATE DIET ON INSULIN RESISTANCE IN OBESE SUBJECTS WITH PCOS

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Background:

Hyperinsulinemia is a prevalent and pathologic feature of PCOS, and has been shown to contribute to the reproductive hormonal abnormalities characteristic of the syndrome^{1,2,3}. Previous studies have demonstrated that carbohydrate restricted diets have a beneficial effect on daylong glucose concentrations and lipid profiles³ in non-PCOS patients. However to date no prospective studies have examined the effect of low carbohydrate diets on insulin resistance in PCOS.

Methods:

6 women with PCOS (mean age 30±3.1 yrs), elevated BMI (39.3±2.8 kg/m², weight 97.7±13.8 kg), and insulin resistance (SSPG 268±15) were enrolled in a 6-week crossover study comparing a 60% and 40% carbohydrate diet for 3 weeks. Both diets contained 15% protein but differed in fat content (25% vs 45%, both with 7% saturated fat). Diets were prepared by the Stanford GCRC dietitians and were isocaloric. After 3 weeks of each diet daylong glucose and insulin and fasting lipids were measured.

Results:

There was no difference in daylong glucose according to diet, however there was a significant difference in daylong insulin (644±174 uU/dL on 60% CHO vs 450±140 uU/dL on 40% CHO diet, p=0.02). No significant differences were seen between the two diets in fasting lipids or lipoproteins.

Conclusions:

Eucaloric, low carbohydrate diets are associated with a 30% decrease in daylong insulin concentrations in obese, insulin resistant women with PCOS. This is similar to the decline in daylong insulin concentrations seen with weight loss⁴ and thiazolidinedione treatment⁵, and suggests that dietary manipulation may be an important component of treatment of insulin resistance in PCOS.

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AMELIORATION OF INSULIN RESISTANCE BY THE NOVEL ANDROSTENE COMPOUND HE3286 (TRIOLEX[®]) IN OBESE, GLUCOSE INTOLERANT SUBJECTS AND POTENTIAL FOR GLYCEMIC CONTROL

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HE3286 (Triolex[™]) is a novel insulin sensitizer drug previously characterized in metabolic disease preclinical animal models. Feasibility of the pharmacological use of HE3286 was explored by studying its effect upon whole body insulin sensitivity in insulin-resistant humans under euglycemic hyperinsulinemic glucose clamp conditions. Non-diabetic, obese glucose intolerant subjects received a daily oral dose of placebo (N=11) or HE3286 in the 4-20 mg range (N=23) for 28 days. Two cohorts were defined according to their deviation from the average metabolic index M-value observed at baseline (5 mg/kg/min) and grouped into insulin-resistant (M<5; N=21) and insulin-sensitive (M>5; N=13) subjects. Insulin-resistant subjects (M<5) treated with 10 and 20 mg HE3286 showed significant improvement in insulin sensitivity with an overall increase in M of 0.78 mg/kg/min over baseline compared to a decrease of -1.48 mg/kg/min in placebo patients (p<0.001). From previous studies, HE3286 has been shown to possess broad anti-inflammatory activity. Accordingly, treatment with the highest dose of HE3286 (20 mg) is generally associated with decreased cytokine secretion from LPS-stimulated PBMC fractions prepared from M<5 subjects, as well as a significant drop in serum CRP levels after 28 days (p=0.046). Considering the existing link between inflammation and insulin resistance, these results suggest that the therapeutic effects of HE3286 may result from anti-inflammatory actions with possible cardiovascular benefit. Translation of these effects into improved glycemic control is currently being explored in patients with type

2 diabetes (T2DM). Preliminary results indicate a trend for HbA_{1c} lowering in T2DM subjects with demonstrable signs of insulin resistance.

PREVALENCE OF PRO12ALA POLYMORPHISM OF PPAR 2 GENE IN PATIENTS WITH METABOLIC SYNDROME

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Objectives:

Pro12Ala polymorphism of the peroxisome proliferators-activated receptor γ 2 (PPAR γ 2) has been shown to interact with obesity in the expression of insulin resistance. Aim of our investigation was to study prevalence of Pro12Ala polymorphism of PPAR γ 2 gene in patients with metabolic syndrome (MS) and healthy men of Uzbek nationality.

Design and Methods:

We have examined 110 ethnic Uzbek men with MS and 50 ethnic Uzbek healthy men. MS was defined according to IDF, 2005 criteria. Genomic DNA was extracted from peripheral blood using Diatom™ DNA Prep 200 Kit according to the manufacturer's protocol. Genotyping of Pro12Ala polymorphism of PPAR γ 2 gene was determined by PCR-restriction fragment length polymorphism-based methods.

Results:

The frequency distribution of PPAR γ 2 gene variants and alleles in patients with MS was following: Pro/Pro genotype—82.5%, Pro/Ala genotype—in 16.5%, Ala/Ala genotype—in 1%, $\chi^2=174.63$, $df=2$, $p=0.000$. Wild-type Pro12 allele was revealed in 90.7% cases, Ala12 allele—in 9.3% one, $\chi^2=254.4$, $df=1$, $p=0.000$. Among healthy subjects the frequency of genotypes and alleles was: Pro/Pro—64%, Pro/Ala—36%, but there was no homozygous for Ala12 allele, $\chi^2=46.32$, $df=2$, $p=0.000$ and Pro12 allele—82%, Ala12 allele—18%, $\chi^2=79.38$, $df=1$, $p=0.000$. It has been noted that in spite of absence of Ala/Ala genotype among healthy subjects frequency of Ala12 allele of PPAR γ 2 gene was two times more in those than patients with MS, but not significantly ($p=0.052$).

Conclusion:

Results of our study have shown that similar frequency of Pro12 allele of Pro12Ala polymorphism of PPAR γ 2 gene in both patients with MS and healthy subjects.

METABOLIC SYNDROME IN A STUDENT POPULATION OF LIMA

Juan Lizaraburu, Jorge Samame

Objectives

To determine prevalence of the metabolic syndrome and components in a student population of Lima.

To determine in a short stature group compared to higher stature group, the prevalence of the metabolic syndrome, differences in the components and relation with body mass index.

Methodology

Descriptive study. 185 students of a health institute.

Inclusion Criteria:

Health institute students. Exclusion Criteria: Pregnancy, Diabetes mellitus diagnosis, cardiovascular disease, High blood pressure, Stroke, Subject does not accept to participate in the study.

Variables:

Short Stature (males \leq 160 cm, females \leq 150 cm), Body Mass Index (BMI), Metabolic Syndrome (MS) based on the IDF definition.

Results

Of the 185 student with mean Age 19,7 years, 87,6% were females. The Prevalence of Metabolic Syndrome was 4%. The mean of MS components were: Glucose 84mg%. HDL: 40,58mg% in males and y 42,3mg% in females. Triglycerides: 96.9mg%. Waist circumference: 77.8 in males and 75.71 in females. Blood pressure:101.19mmhg systolic and 66.39mmhg diastolic. BMI mean : 23.23 in males and 23.42 in females.

Short stature prevalence was 27%. The MS prevalence in short and not short stature groups were 4% .

Not short stature group: 49% with normal BMI (56% low HDL and 23% normal HDL)

Short stature group: 68% with normal BMI (60% low HDL and 8% normal HDL).

Conclusions

The metabolic Syndrome prevalence in the students is low (4%). The HDL levels are low although the students are young and without cardiovascular risk factors. The prevalence of short stature is moderately high (27%). More low HDL in the short stature subjects with normal BMI, compared to higher stature subjects.

FUNCTIONAL VARIANTS OF THE HMGA1 GENE CAUSE A MAJOR DECREASE IN INSULIN RECEPTOR EXPRESSION AND CONFER A HIGH RISK FOR TYPE 2 DIABETES MELLITUS

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Previously we found that high mobility group A1 protein (HMGA1) regulates insulin receptor (IR) gene expression. In several patients, functional variants in the HMGA1 gene have

been associated with decreased IR expression and type 2 diabetes (T2D). In the present study, we investigated the HMGA1 gene in 3 cohorts of T2D patients to determine the frequency of HMGA1 variants. Genomic DNA (n = 6902) from three populations (American, Italian, and French) was analyzed. It was either directly sequenced, or analyzed for specific HMGA1 mutations. Both mRNA and protein expression for HMGA1 and IR were measured in peripheral lympho-monocytes. The most frequent HMGA1 variant, IVS5 C-insertion, was associated with T2D in 7-8% of patients in all 3 cohorts. HMGA1 and IR mRNA and protein levels were decreased in patients with this variant. In the Italian cohort, the largest studied, the whole HMGA1 gene was sequenced, and 3 other functional variants were also observed. In the Italian cohort, where all 4 HMGA1 variants were analyzed, a variant was present in nearly 10% of T2D patients; in these patients IR expression was decreased by nearly 50%. In an Italian family with the IVS5 C-insertion variant, this variant was associated with either T2D or insulin resistance. These studies demonstrate that functional variants in the HMGA1 gene cause a decrease in IR content. In the 3 different populations examined, HMGA1 functional variants were present in over 7% of patients with T2D. These studies indicate therefore that the HMGA1 gene is a novel susceptibility gene for insulin resistance and T2D.

INSULIN RESISTANCE IN NON-OBESE SUBJECTS IS ASSOCIATED WITH LIPID ACCUMULATION AND ACTIVATION OF THE JNK PATHWAY

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The pathogenesis of insulin resistance in the absence of obesity is not well understood. In obesity, however, lipid related mechanisms have been identified whereby lipid accumulation disrupts insulin signaling. In obesity, stress kinases that negatively regulate the insulin signaling cascade are activated both by inflammatory molecules released from adipose tissue, and by increases in metabolic stress due to accumulation of lipid within skeletal muscle and other cells. We explored whether these same mechanisms contributed to the insulin resistance of non-obese individuals. Healthy, non-obese, normoglycemic subjects were evaluated for insulin sensitivity as determined by the euglycemic, hyperinsulinemic clamp. Total and regional adipose stores and intramyocellular lipids (IMCL) were assessed by DXA, MRI and MRS. Vastus lateralis muscle biopsies were examined for activation of both the insulin signaling, and the NF- κ B, JNK and P38MAPK stress kinase pathways. Insulin resistant subjects, when compared to insulin sensitive controls, displayed increased total fat, abdominal fat, and IMCL levels, and a trend toward increased visceral adipose tissue. Serum TNF- α levels increased with adiposity. In muscle of resistant subjects, IRS-1 serine phosphorylation was increased and insulin-stimulated tyrosine phosphorylation decreased. Activation of JNK, was observed, but not p38MAPK or IKK β . Thus, we find that insulin resistance in the non-obese is associated with higher total and abdominal adipose stores, and increased IMCL. Although the contributions of local lipid infiltration in muscle could not be separated from those of

generalized adiposity, the predominant effects on the activation of the JNK pathway suggests a significant effect of muscle lipid accumulation in impaired insulin signaling.

IMPACT OF MILD HYPERTHYROTROPINEMIA ON PHENOTYPIC EXPRESSION OF PCOS IN INDIAN WOMEN

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We aimed to study the impact of euthyroid hyperthyrotropinemia of subclinical origin on the clinical, biochemical and endocrine phenotype of PCOS. We studied 396 women with a diagnosis of PCOS on the basis of NICHHD 1990 consensus criteria (group A). Sixty one age matched girls having subclinical (elevated TSH with normal T3 and T4) and otherwise qualifying the NICHHD criteria for PCOS (group B).

Mean age of the subjects was 22.99 ± 4.93 (13-45) vs. 23.61 ± 4.93 (13-35) years and the mean number of menstrual cycles/ year were 8.23 ± 2.69 (2-15) vs. 6.34 ± 3.02 (1-12) years in euthyroid and hypothyroid PCOS subjects respectively ($p=0.9$). BMI, waist circumference, mean systolic blood, total serum cholesterol, triglycerides and uric acid were similar. OGTT with 75 gram oral glucose showed similar results ($p=0.8$). Serum insulin was also similar in the groups A and B respectively in the fasting (13.53 ± 10.14 vs. 12.91 ± 10.08 micro IU/L, $p=0.7$), 1 hour (96.45 ± 79.83 vs. 76.47 ± 48.08 micro IU/L, $p=0.2$) and 2 hour (66.36 ± 48.70 vs. 61.10 ± 34.938 micro IU/L, $p=0.6$) after glucose load respectively. Among the various insulin indices such as HOMA-IR; QUICKI, Matsuda index ($p=0.7$); Guttindex ($p=0.7$); Avignon Index ($p=0.7$) and Stumvoll index ($p=0.8$) the two groups didn't demonstrate any statistical difference. Serum LH (6.53 ± 4.8 vs. 6.35 ± 4.1 IU/l, $p=0.7$), FSH (4.96 ± 2.2 vs. 5.8 ± 2.3 IU/l, $p=0.008$), LH/FSH ratio (1.59 ± 1.5 vs. 1.34 ± 1.3 , $p=0.2$), serum prolactin (12.76 ± 6.1 vs. 10.48 ± 6.1 ng/ml, $p=0.06$) and serum total testosterone (77.97 ± 42.5 vs. 75.49 ± 42.7 , $p=0.6$) were similar. We conclude that mild TSH elevation in the face of a normal serum T4 does not alter the PCOS phenotype.

DIET-INDUCED WEIGHT LOSS DECREASES MACROPHAGE CONTENT IN ADIPOSE TISSUE OF OBESE WOMEN

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Objective:

Increased content of macrophages in adipose tissue is considered as a possible culprit of insulin resistance and obesity-related metabolic complications. The aim of this study was to investigate the effect of dietary intervention on adipose tissue macrophages (ATM) content in obese subjects.

Design and measurements:

16 obese women (age 39 ± 2 years, BMI 33.3 ± 0.5 kg/m²) underwent 6 month dietary intervention. At baseline and at the end of intervention samples of subcutaneous abdominal adipose tissue (SCAAT) were obtained by needle biopsy and blood samples were drawn. ATM content was analyzed by flow cytometry analysis using CD45, CD14, CD206 markers. Gene expression of macrophage specific markers was determined in SCAAT by real-time PCR.

Results:

Intervention induced a decrease of body weight (92.9 ± 1.7 vs 80.5 ± 2.2 kg, $p < 0.001$), plasma C-reactive protein (5.7 ± 1.4 vs 3.8 ± 1.5 mg/L, $p < 0.05$) and HOMA-IR (2.7 ± 0.4 vs 1.7 ± 0.2 , $p < 0.001$). ATM content defined by CD45+/14+/206+ decreased ($2.6 \pm 0.3\%$ vs $1.5 \pm 0.2\%$, $p < 0.01$). This decrease was associated with a decline of mRNA levels of macrophage markers (CD14, CD163, CD68, LYVE-1) in SCAAT.

Conclusion:

In moderately obese women, weight-reducing dietary intervention promotes a decrease of content of macrophages in SCAAT. The diet-induced decrease of ATM could be a mediator of beneficial metabolic changes brought in by weight-reducing diets.

Acknowledgement.

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ADIPOKINE GENE EXPRESSION IN HUMAN SUBCUTANEOUS AND VISCERAL ADIPOSE TISSUE IN RELATION TO INSULIN SENSITIVITY

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Objective:

Investigate gene expression of relevant adipokine markers in subcutaneous and visceral adipose tissue (AT) and its association with insulin sensitivity (IS).

Methods:

In 56 women with a broad range of BMI (20,2 to 48,9 kg/m²) undergoing elective abdominal surgery paired samples of subcutaneous (SCF) and visceral (VF) fat were obtained. Anthropometric measurements, euglycemic hyperinsulinemic clamp and blood analysis were performed. Expressions of leptin, IL-10, IL-18 and IL-1Ra in AT were identified by RT-qPCR.

Results:

Expressions of leptin and IL-1Ra were higher in SCF, IL-18 in VF and IL-10 was not different between the two depots. Expressions of leptin, IL-10, IL-1Ra in both fat depots and that of IL-18 only in SCF correlated positively with BMI and adiposity (%fat mass) and negatively with glucose disposal rate related to fat free mass.

Conclusions:

Expressions of leptin, IL-10 and IL-1Ra in both AT depot and that of IL-18 in SCF are related to insulin sensitivity. The results suggest that endocrine characteristics of SCF as well as those of VF may play a role in prediction of metabolic complications of obesity.

Acknowledgement.

This work was supported by grant 303/07/0840 of Grant Agency of Czech Republic and by projects HEPADIP (www.hepadip.org) and ADAPT (www.adapt-eu.net) of the Commission of European Communities.

HORMONAL BASIS FOR SEXUAL DIMORPHISM IN ADIPOCYTE SIZE AND ABDOMINAL FAT DISTRIBUTION

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Men have more visceral adipose tissue (VAT), smaller adipocytes, and, per kg muscle mass, have 45% decreased insulin-mediated-glucose-uptake (IMGU) compared to women. Transgender male-to-females demonstrate enlargement of adipocytes following estrogen treatment. Storage of fat in subcutaneous adipose tissue (SAT) may protect against insulin resistance (IR). To determine if sex steroid hormones explain these differences, we compared premenopausal (Pre), postmenopausal (Post) women, and men with regard to SAT mass, cell size, and IMGU.

Methods:

Healthy adults age 35-60 and BMI 25-35 underwent quantification of IMGU via the octreotide-modified-insulin-suppression test. Higher steady-state-plasma-glucose (SSPG) values indicate IR. SAT needle biopsy and abdominal CT scans were performed. Adipocyte size was determined by Multisizer III Coulter Counter. Comparison across groups of decreasing estrogen status (Pre, Post, Male) was done via ANOVA.

Results:

There was a trend towards increased %SAT (anova, $p = < 0.001$) and decreased %VAT (anova, $p < 0.001$) across groups of decreasing

estrogen. These correlations were unchanged after adjusting for BMI($p=0.38$) or age. Although SSPG did not differ significantly between groups($p=0.20$), correlation between %VAT (anova, $p<0.003$) and SSPG was significant in men($r=0.48$, $p<0.001$) and post($r=0.32$, $p<0.08$) but not premenopausal women($r=0.11$, $p<0.59$). Cell size was significantly greater in women combined($115 \pm 15 \mu\text{m}$) versus men($102 \pm 13 \mu\text{m}$, $p=0.0045$) and independent of BMI($p=0.65$).

Conclusions:

Increased cell size and relative volume of SAT in pre versus postmenopausal women and men suggests that sex steroid hormones play a role in regional abdominal fat distribution, possibly via increasing adipocyte size. Differences between relative SAT volume and IR also suggest this association is modified by sex steroid hormones. Further research should address the biological mechanisms underlying these observations.