

## PL1: The Role of Thermogenesis in the Aetiology of Obesity

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In the standard equation for body weight balance, the delta (the increase or decrease in body weight) is obtained as the difference between energy intake and energy utilization. Most discussions of the cause for the development of obesity focus on the energy intake part of the equation, and most drugs against obesity are being developed with a reduction in energy intake as the target. However, the other part of the equation is obviously mathematically equally important, but the general interest here has focussed on the issue whether the reduction in physical activity resulting from the conveniences of modern life is a significant cause of obesity. However, the amount of energy that is spent on physical activity is fairly limited (and has perhaps always been), as compared to the energy utilized in the broad phenomenon of resting metabolism. The issues to be discussed here are thus: to what extent can differences in resting metabolic rate, in man and mouse, account for differences in obesity susceptibility? And what are the causes of such differences? Perhaps of even more interest are the questions as to whether we can alter the resting metabolic rate. Issues concerning the efficiency of mitochondrial energy transfer to ATP are central to this issue, and an ability to alter this, e.g. by activating proteins with an uncoupling activity, may be an important tool to combat obesity. Particularly an ability to transform energy-storing white adipose tissue into energy-utilizing thermogenic brown adipose tissue would dramatically alter the prospects for curtailing the current obesity epidemic.

## T5: Lifestyle Interventions

### O001

**The effects of three diets with varying calcium contents on 24-hour energy-expenditure, 24-hour fat oxidation and adipose tissue mRNA expression**

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**Background:** Recent evidence from both molecular and animal research and epidemiological investigations indicates that calcium intake could be inversely related to body weight, possibly through alterations in the calcitriol metabolism. The present study was designed to investigate these effects under strictly controlled isocaloric conditions.

**Subjects and methods:** 12 healthy males ( $28 \pm 8$  years, BMI  $25.2 \pm 2.1$  kg/m<sup>2</sup>) were provided with three different isocaloric diets [high calcium/high dairy (H/H), high calcium/low dairy (H/L) and low calcium/low dairy (L/L)] in a randomised, crossover design. At the end of the 7-day controlled dietary periods, measurements of 24-hour energy expenditure (EE) and substrate metabolism were done in a respiration chamber, fat biopsies were also obtained for determination of mRNA expression of proteins involved in the lipolytic/lipogenic pathways.

**Results:** 24-hour energy expenditure was  $8.19 \pm 0.21$ ,  $8.04 \pm 0.20$  and  $8.11 \pm 0.20$  kJ/min in the H/H, H/L and L/L conditions. The absolute 24-hour fat oxidation in these conditions was  $108 \pm 7$ ,  $105 \pm 9$  and  $100 \pm 5$  g/day. mRNA concentrations of UCP<sub>2</sub>, FAS, GPD2, HSL and PPAR $\gamma$  did not differ. Calcitriol metabolism was significantly changed by the diets, with a  $37 \pm 13$  pmol/l decrease in the H/H diet and a  $33 \pm 15$  pmol/l increase in the L/L condition ( $P < 0.05$ ).

**Conclusion:** Altering the dietary calcium content for a 7-day period influences neither 24-hour energy expenditure nor 24-hour fat oxidation to a substantial extent as well as gene expression of different proteins related to fat metabolism, despite significant alterations of the serum calcitriol concentration.

**Acknowledgment:** This study was supported by a grant of the Dutch Dairy Association, Zoetermeer, the Netherlands.

### O002

**Cognitive behavioral therapy guided-self-help and orlistat for the treatment of binge eating disorder: a randomized double-blind placebo-controlled trial**

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**Introduction:** Cognitive behavioral therapy (CBT) has efficacy for binge eating disorder (BED) but not obesity. No controlled studies have tested whether adding obesity medication to CBT facilitates weight loss. We performed a randomized, placebo-controlled study of orlistat (an approved obesity medication) administered concurrently with guided-self-help CBT (CBTgsh).

**Patients and methods:** Fifty obese (body mass index of 30 or greater) patients with BED were randomly assigned to 12-week treatments of either orlistat + CBTgsh (120 mg tid) or placebo + CBTgsh, and were followed in double-blind fashion for 3-months after treatment.

**Results:** 78% of patients completed treatments without differential dropout between orlistat + CBTgsh and placebo + CBTgsh. Intent-to-treat remission rates (zero binges for past 28 days on Eating Disorder Examination Interview) were significantly higher for orlistat + CBTgsh than placebo + CBTgsh (64% versus 36%) at post-treatment but not at 3-month follow-up (52% in both). Intent-to-treat rates for achieving 5% weight loss were significantly higher for orlistat + CBTgsh than placebo + CBTgsh at post-treatment (36% versus 8%) and 3-month follow-up (32% versus 8%). Significant and comparable improvements in eating disorder psychopathology (eating-, weight-, and shape concerns, body image) and psychological distress (depression) occurred in both treatments.

**Conclusion:** Our findings provide further support for the efficacy of CBTgsh for BED. The addition of orlistat to CBTgsh was associated with greater weight loss than the addition of placebo to CBTgsh. Clinical improvements were well maintained at three-month follow-up after treatment discontinuation.

## O003

**Short-term effects of two popular dietary interventions for weight loss (versus a control group) on lipid peroxidation, LDL oxidation and antioxidant balance****L BROWN\***, **C van BLERK\***, **N FINER†**, **J McENENY†**, **T ASHTON\*** and **C REAVELL\****\*Department of Sport Sciences, De Montfort University, Bedford, †Wellcome Research Facility, Addenbrooke's Hospital, ‡Centre for Clinical and Population Sciences, Queen's University Belfast, Belfast, UK*

**Introduction:** Low-carbohydrate diets are increasingly used to promote weight loss. This study investigated the short-term effects of the Atkin's Diet (low-carbohydrate/LowCD) and Slimming World (high carbohydrate, low fat, conventional/ConvD) (versus control) diet on oxidant stress/antioxidant parameters in overweight women.

**Patients and methods:** Subjects (age:  $40 \pm 8$  years, BMI:  $30 \pm 2.9$  kg/m<sup>2</sup>) were randomly assigned to either LowCD ( $n + 12$ ), ConvD ( $n + 12$ ) or control group (CtrlG) ( $n + 6$ ). All subjects completed a 2-week baseline and 4-week intervention period. Measures included lipid hydroperoxide (LH), LDL oxidation (LDLOx), superoxide dismutase (SOD), erythrocyte glutathione (GSH) and total antioxidant status (TAS).

**Results:** LH levels increased after 1 week on LowCD *vs* baseline ( $1.389 \pm 0.5$   $\mu$ m vs  $1.025 \pm 0.31$   $\mu$ m;  $P < 0.026$ , respectively), then decreased during the remaining 3 weeks, but continued to be higher than baseline measurements ( $1.25 \pm 0.4$   $\mu$ m *vs*  $1.025 \pm 0.3$   $\mu$ m;  $P + 0.096$ , respectively). TAS, SOD and GSH were higher at the end of the 4-week LowCD intervention *vs* baseline measurements ( $638 \pm 132$  *vs*  $493 \pm 115$   $\mu$ mol/L,  $P < 0.001$ ;  $3994 \pm 1276$  Hb *vs*  $3033 \pm 733$  U/g Hb,  $P + 0.066$ ;  $6.05 \pm 1.47$  Hb *vs*  $5.60 \pm 1.36$  micromoles/gram Hb,  $V + 0.075$ , respectively). In comparison to baseline measurements, LDLOx decreased after 2 weeks on LowCD ( $56.4 \pm 6.24$  mins *vs*  $48.5 \pm 7.4$  mins,  $P < 0.01$ , respectively), but then increased above baseline levels by the end of the intervention, although this was not statistically significant ( $60.4 \pm 14.6$  mins,  $P + 0.16$ ). No significant changes in LH, LDLOx, SOD, GSH and TAS were identified following ConvD or CtrlG.

**Conclusion:** Short-term compliance to LowCD increased oxidant stress, an effect which was not observed following ConvD. Oxidant/antioxidant status during long-term LowCD should be examined to assess the potential risk to cardiovascular health.

## O004

**Detection of short walking episodes in daily life by means of a new accelerometric approach****P TERRIER**, **M CHALOKH** and **Y SCHUTZ***Department of Physiology, University of Lausanne, Lausanne, Switzerland*

**Introduction:** The aim was to objectively assess walking activities during daily life with a new method based on accelerometry. Indeed, the profile of spontaneous walking during occupation has not been previously analyzed by objective methods. The hypothesis was that a substantial part of the daily walking activities was constituted by short walking 'bursts', which can play an important role in body weight regulation through Non-Exercise Activity Thermogenesis (NEAT).

**Subjects and methods:** The physical activity level of 29 healthy young subjects with variable BMI ( $18\text{--}41$  kg/m<sup>2</sup>) was explored during their habitual occupation, with a triaxial accelerometer fixed on the lower back. The duration and frequency of walking episodes were assessed by analyzing the 3D-accelerometric signals (60 Hz sampling rate) with a new signal processing method based on the recognition of the gait pattern.

**Results:** The subjects spent  $18.7 \pm 8.7\%$  of the day-time (8 h) in walking activities, i.e.  $90 \pm 42$  min. About one third of this activity (28 min.) was explained by very short walking episodes ( $n + 151 \pm 77$ ) of an average duration of 11 s ( $6\text{--}17$  s), and two third (62 min) by walking episodes of duration greater than one minute (average: 3.4 min).

**Conclusion:** Intermittent short walking episodes were spontaneously performed by all subjects; this presumably is a very energetically inefficient process and may account for a substantial part of NEAT when integrated over a whole day. Whether or not the classical exercise prescription by health authorities (30–60 min walking per day) should take into account the spontaneous walking activities (in particular short bursts) is a matter of debate.

## O005

**Physiological determinants of exercise adherence and physical activity in weight-reduced men****P BORG**, **K KUKKONEN-HARJULA** and **M FOGELHOLM***UKK Institute, Tampere, Finland*

**Introduction:** Physiological factors may affect adoption of physical activity (PA). Also, the effect of weight-loss and exercise intervention on long-term physical activity is mostly unstudied. The aim was to identify factors predicting adherence to prescribed exercise and subsequent free-living PA.

**Subjects and methods:** Ninety middle-aged, sedentary, obese men (BMI 30–40, mean 33.0) started a very-low-energy-diet (VLED) producing a 14.2 kg (4.0) weight-loss. After VLED they were randomised into 3 weight maintenance (WM) groups (walking, W; strength training, S; control) for 6 months. Exercise groups trained  $3 \times 45$  min/week. WM was followed by 23-month unsupervised follow-up (FU).

**Results:** During WM group W adhered better to prescribed exercise volume (80% *vs.* 66%,  $P + 0.07$ ). In combined exercise groups, abdominal strength and greater weight-loss during VLED predicted exercise adherence. PA during FU (55 men remaining) was predicted by baseline PA and leg strength, PA and improved back strength during WM and abdominal strength after WM ( $r^2 + 0.89$ ). Adherence to prescribed exercise or weight-loss did not predict long-term PA.

**Conclusion:** Weight-loss improves short-term adherence to exercise, but weight-loss or greater exercise adherence did not predict long-term free-living PA. Long-term PA was mostly explained by previous PA, but also by strength gains during WM. Our results imply that PA behavior is hard to change, but improved fitness gains from exercise intervention may have a small role in increasing or maintaining long-term PA.

## O006

**Long-term weight maintenance with two carbohydrate restricted diets****J KEOGH**, **N LUSCOMBE**, **P FOSTER**, **M NOAKES** and **P CLIFTON**

**Introduction:** High protein diets for weight loss are popular but there is limited evidence of their long-term efficacy. The aim of this study was to determine long term maintenance of weight loss following energy restriction on moderate carbohydrate diets high in either protein or fat.

**Subjects and methods:** Following a parallel study of a high protein (HP) (34% protein) or standard-protein, high fat (HF) (45% fat) diet of 16 weeks of energy restriction (6 MJ/day) subjects were asked to maintain the same dietary pattern for the following 36 weeks.

**Results:** Weight loss from baseline for the 38 completers was  $6.2 \pm 7.3$  kg ( $P < 0.01$ ) with no diet effect,  $7.6 \pm 8.1$  (LP) *vs*  $4.8 \pm 6.6$  kg (HP). There was no difference in weight loss when the group was divided on the basis of their reported protein intake at the end of the study. No diet effect was seen with fasting plasma insulin or triglyceride which were reduced by 25–27% and with HDL cholesterol which rose by 20%. 25 subjects who had body composition measured by dual energy X-ray absorptiometry had a mean weight loss of  $8.1 \pm 6.9$  kg ( $2.1 \pm 2.7$  kg lean mass and  $5.2 \pm 5.5$  kg fat) ( $P < 0.001$ ).

**Conclusion:** Irrespective of initial diet composition there was a clinically significant weight loss at the end of a year of a reduced carbohydrate diet which was associated with improvements in cardiovascular disease risk markers.

## T1: Adipose Tissue Development and Function

O007

**Hormone-sensitive lipase is the rate limiting step for human. Adipocyte lipolysis and is defective in human obesity**  
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**Introduction:** The role of hormone-sensitive lipase (HSL) in obesity and as a rate limiting step for adipocyte lipolysis has been the topic of recent discussion due to the characterization of a novel human triglyceride lipase. We investigated the importance of HSL.

**Methods:** Fat cells from mouse (wt and HSL<sup>-/-</sup>) and human subjects were used. In addition human preadipocytes were isolated from 81 obese and 42 non-obese subjects. Effects of a selective HSL inhibitor (BAY) was determined in both cell types.

**Results:** BAY counteracted stimulated but not basal lipolysis in mouse fat cells. No effect on lipolysis was observed in adipocytes from HSL-null mice. In human adipocytes, basal as well as catecholamine- and natriuretic peptide-stimulated lipolysis were almost completely blunted by the HSL inhibitor. In human adipocytes catecholamine-induced lipolysis was decreased by 40% ( $P + 0.002$  or better) while leptin secretion was increased by 80% ( $P < 0.001$ ) in cells from obese humans. For differentiated pre-adipocytes derived from obese and non-obese subjects, leptin secretion was normal but catecholamine-induced lipolysis and HSL protein expression were 60–70% decreased ( $P < 0.001$ ) in obesity.

**Conclusion:** We conclude that HSL is the major lipase and the rate limiting step for basal and stimulated lipolysis in human fat cells whereas other lipases also are important for lipolytic regulation in mouse fat cells. Furthermore, decreased catecholamine-induced lipolysis, unlike leptin hypersecretion, is an early defect in subcutaneous adipocytes of obese individuals, most probably due to a low expression of HSL.

O008

**The antilipolytic effect of the alpha-2 adrenoceptor and phosphodiesterase varies between human freshly isolated adipocytes, differentiated preadipocytes and mesenchymal stem cell derived-adipocytes**

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**Introduction:** Both the  $\alpha_2$ -adrenoceptor ( $\alpha_2$ -AR) and the enzyme phosphodiesterase-3B (PDE3B) are of importance in the regulation of lipolysis as inhibitory factors. We studied and compared the  $\alpha_2$ -AR and PDE3B in relation to lipolysis in human adipocytes of different origin i.e. freshly isolated adipocytes, differentiated preadipocytes and mesenchymal stem cell (hMSC) derived-adipocytes (hMSC-DA).

**Methods:** For freshly isolated adipocytes and preadipocyte cultures, adipose tissue was obtained from the subcutaneous abdominal or mammary depot. hMSC were isolated from bone marrow aspirates from the iliac crest of healthy donors. The preadipocytes and hMSC were differentiated into adipocytes *in vitro*. Lipolysis experiments were performed and PDE-activity was measured. RNA was isolated for the measurement of  $\alpha_2$ -AR or PDE mRNA levels.

**Results:** Noradrenaline (NA) stimulated lipolysis in freshly isolated adipocytes and differentiated preadipocytes, but reduced lipolysis in hMSC-DA. Co-incubation with yohimbine ( $\alpha_2$ -AR blocker) increased NA-induced lipolysis with the greatest relative effect in the hMSC-DA. Incubation with 8bcAMP increased lipolysis in all types of adipocytes. Co-incubation with cilostamide (PDE3 blocker) increased 8bcAMP-induced lipolysis in freshly isolated adipocytes and differentiated preadipocytes, but had no effect in hMSC-DA. PDE activity was: freshly isolated adipocytes > differentiated preadipocytes > hMSC-DA. Levels of PDE or  $\alpha_2$ -AR mRNA followed the same pattern.

**Conclusion:** Our study shows that the order of  $\alpha_2$ -AR potency is: hMSC-DA > differentiated preadipocytes > freshly isolated adipocytes, whereas for the PDE3B activity it seems to be the opposite. There might be a developmental regulation of lipolysis with a marked  $\alpha_2$ -AR and a less pronounced PDE3B effect in adipocytes from immature precursors.

O009

**Functional studies of mesenchymal stem cells derived from adult human adipose tissue**

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**Introduction:** Recent evidence suggests that a small number of human mesenchymal stem cells (hMSCs) can be derived from adult peripheral tissues including adipose tissue, muscle and dermis. However, although these studies have assessed morphological differentiation and mRNA expression no functional analysis of these cells has been performed.

**Material and methods:** We isolated hMSCs from the stromal-vascular portion of subcutaneous adipose tissue (AT-hMSCs) from adult subjects undergoing cosmetic lipoaspiration and from bone marrow aspirates from the iliac crest of healthy adult donors (BM-hMSCs). Both types of hMSCs were differentiated into chondrogenic, osteogenic and adipogenic lineages in specific defined media.

**Results:** Differentiation of AT-hMSCs into the different lineages demonstrated their multipotency when incubated in the appropriate media. The functional properties of differentiated adipocytes from AT-hMSCs were compared with those derived from BM-hMSCs. The two cell types increased lipolysis upon three-hour incubation with 0.1 mM adrenaline alone ( $167 \pm 33\%$  over basal in AT-hMSCs and  $51.4 \pm 7.6\%$  in BM-hMSCs) which was potentiated with the  $\alpha_2$ -AR antagonist yohimbine (0.1 mM) ( $1561 \pm 1039\%$  over basal in AT-hMSCs and  $449 \pm 64.4\%$  in BM-hMSCs), demonstrating a strong  $\alpha_2$ -adrenergic effect. Both cell types secreted the fat cell-specific factors leptin and adiponectin in a time dependent manner in comparable amounts.

**Conclusion:** hMSCs derived from adult human adipose tissue can be differentiated into fully functional adipocytes with a similar phenotype as that observed in cells derived from BM-hMSCs.

O010

**Strong co-regulation of hormone-sensitive lipase and the novel adipocyte triglyceride lipase in human adipose tissue**

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**Introduction:** Alterations in human adipocyte lipolysis are common in insulin resistant conditions. Until recently, hormone-sensitive lipase (HSL) was considered as the only rate-limiting step for adipocyte lipolysis. However, a novel adipocyte triglyceride lipase (ATGL) seems to play an additional rate-limiting role for lipolysis in mouse fat cells.

**Methods:** We presently investigated the mRNA expression of these two lipases in subcutaneous adipose tissue of 80 healthy obese women set in relation to the lipolytic capacity of the fat cells, which was defined as the maximal lipolysis stimulation of a lipolytic agent.

**Results:** A high ability of noradrenaline and different selective beta-adrenergic agonists to stimulate lipolysis was correlated with a high mRNA level for HSL ( $P$  from 0.008 to 0.028) or ATGL ( $P$  from 0.007 to 0.01). The relative ATGL expression was higher than that of HSL ( $P < 0.001$ ). Both mRNAs correlated weakly and inversely with body mass index ( $r + 0.22$ – $0.32$ ). However, a strong linear and positive correlation between the mRNA expression of both lipases was demonstrated ( $r + 0.76$ ,  $P < 0.0001$ ).

**Conclusion:** These data show a marked co-regulation of the expression of HSL and ATGL in man suggesting synergistic roles of the two corresponding genes in regulating lipolysis in human fat cells.

## O011

**C/EBP $\beta$  over-expression rescues PGC-1 $\alpha$  gene expression in a white adipose tissue (3T3L1) cell line****G KARAMANLIDIS<sup>†</sup>, D HAZLERIGG<sup>†</sup> and M LOMAX<sup>\*</sup>**<sup>\*</sup>Imperial College, DAS, Wye Campus, <sup>†</sup>University of Aberdeen, School of Biological Sciences, Scotland, UK

**Introduction:** The transcription factor C/EBP $\beta$  and the co-activator PGC-1 $\alpha$ , are involved in adipose tissue cellular proliferation, differentiation and regulation of energy homeostasis. We have previously demonstrated that PGC-1 $\alpha$  expression is stimulated by cAMP stimulation in brown (HIB1B) but not in white (3T3L1) adipocytes. In this study we tested the hypothesis that C/EBP $\beta$  over-expression in 3T3L1 cells can rescue PGC-1 $\alpha$  responsiveness to cAMP stimulation through a specific binding site on the PGC1 $\alpha$  promoter.

**Materials and methods:** Luciferase reporter constructs containing 264 bp of the proximal PGC-1 $\alpha$  promoter were co-transfected into HIB1B and 3T3L1 cells with a C/EBP $\beta$  expression vector. Transfected cells were exposed to cAMP stimulation. Site specific mutagenesis of -86 to -92 of the promoter was employed to demonstrate functionality of this element.

**Results:** Over-expression of C/EBP $\beta$  in 3T3L1 cells increased PGC-1 $\alpha$  promoter activity to the same levels as in HIB1B cells in the both control and cAMP stimulated cells ( $P < 0.001$ ). Mutation of the promoter at -86 to -92 reduced ( $P > 0.001$ ) promoter activity during C/EBP $\beta$  over-expression in both cell lines. C/EBP $\beta$  mRNA level were increased ( $P < 0.001$ ) during differentiation in HIB1B but not 3T3L1 cells. UCP1 expression was stimulated ( $P < 0.001$ ) by cAMP stimulation in HIB1B but not 3T3L1 cells except in the presence of the C/EBP $\beta$  expression vector.

**Conclusions:** The data suggest that C/EBP $\beta$  expression is a regulator of PGC-1 $\alpha$  transcription through a promoter specific site and that cAMP stimulation of C/EBP $\beta$  expression may be one of the key switches in the determination of preadipocytes to the white or brown adipocyte lineages.

## O012

**Role of CB2 receptor in the development of human adipocyte****L HOAREAU<sup>\*</sup>, S HOUTMANN-BES<sup>†</sup>, MP GONTHIER<sup>\*</sup>, P RAVANAN<sup>\*</sup>, P DELARUE<sup>‡</sup>, O HULARD<sup>‡</sup>, M CÉSARI<sup>\*</sup>, F FESTY<sup>\*1</sup> and R ROCHE<sup>\*1</sup>**<sup>\*</sup>Laboratoire de Biochimie et de Génétique Moléculaire, Faculté des Sciences, Université de La Réunion, <sup>†</sup>Cabinet de chirurgie plastique, <sup>‡</sup>Clinique des Orchidées, Ile de La Réunion, France <sup>1</sup>These authors equally contributed to the work.

**Introduction:** Cannabinoid receptor 2 (CB2) is usually described as an immune cell receptor while cannabinoid receptor 1 (CB1) is rather implicated in the regulation of food intake. We previously identified the presence of these receptors on the human adipocyte surface. According to these facts, we have measured levels of adiponectin and leptin on human mature adipocytes in primary culture after stimulation with CB1 and CB2 agonists. In order to determine if CB2 could play a role in the development of adipose tissue, we have also investigated the effect of CB2 agonist on human pre-adipocytes proliferation and apoptosis.

**Methods:** Dosage of leptin and adiponectin were realised by ELISA on human mature adipocytes media. Cell proliferation was determined by BrdU incorporation and FACS analysis. Apoptosis was analysed by Annexin-V staining. Specific signalling pathway was determined by inhibition and analysis of cAMP and MAP-Kinase pathway.

**Results:** On mature adipocytes, CB1 and CB2 agonists have no effect on adiponectin secretion and don't decrease leptin level. However, CB2 agonist strongly decreases pre-adipocyte proliferation, in a dose-dependent manner, and doesn't lead cells to apoptosis. This effect is specific to CB2 receptor signalling pathway.

**Conclusion:** Our results suggest that the endocannabinoid system could regulate human adipose tissue development by acting on adipocyte precursors proliferation. This brings new perspectives on the regulation of adipose tissue expansion, and provides new data for an inter-relation between the endocannabinoid system and the adipocyte.

**T2: Morbidity and Life-Years Lost: the Relationship to Obesity**

## O013

**Obesity in young adulthood is a risk factor for disability pension later in life. Cohort study of 371 106 men born in Sweden 1952–1959****F RASMUSSEN<sup>\*†</sup>, N KARNEHEID<sup>\*</sup>, T NORDQVIST<sup>†</sup> and M KARK<sup>†</sup>**<sup>\*</sup>Child and Adolescent Public Health Epidemiology Group, Department of Public Health Sciences, Karolinska Institute, <sup>†</sup>Division of Epidemiology, Stockholm Centre of Public Health, Stockholm, Sweden

**Introduction:** Obesity is a chronic disease with both medical and social consequences. The aim of this study was to investigate the relationship between body mass index at age 18 and later disability pension.

**Material and methods:** In 2001 men resident in Sweden and born 1952–1959 were located. Data on disability pension was available 1990–2001. Height and weight were measured at age 18 years. Education and marital status were measured in 1990. 371 106 men were complete on all variables used (67% of all identified). The hazard ratio for attaining disability pension was calculated with Cox regression controlling for education, childhood socioeconomic status, marital status and municipality.

**Results:** Men who were obese at age 18 years had higher risk for disability pension later in life (1.47, 95% CI: 1.30, 1.66) compared to normal weight counterparts. The relationship between BMI and disability pension was J-shaped with higher risks for underweight (1.17, 95% CI: 1.11, 1.23) as well as overweight individuals (1.07, 95% CI: 1.00, 1.13). Low attained education was an important risk-factor (3.71, 95% CI: 3.50, 3.94). Marital status, municipality and childhood socioeconomic status also showed significant contributions ( $P < 0.001$ ). **Conclusions:** Obese men in Sweden are at higher risk for attaining disability pension. The relationship between BMI and disability pension is J-shaped. Individuals that attain disability pension very rarely return to working life. Since the prevalence of obesity is increasing in Sweden the number of disability pensioners might also increase, with increasing costs for the society as a consequence.

## O014

**Age and cohort effects on body weight and BMI in Dutch adults: the Doetinchem cohort study****ACJ NOYENS<sup>\*†</sup>, TLS VISSCHER<sup>\*†</sup>, WMM VERSCHUREN<sup>\*</sup>, AJ SCHUIT<sup>\*</sup>, HC BOSHUIZEN<sup>\*</sup>, W VAN MECHELEN<sup>‡</sup> and JC SEIDELL<sup>†‡</sup>**<sup>\*</sup>National Institute for Public Health and the Environment, Bilthoven, <sup>†</sup>Institute for Health Sciences, VU University, <sup>‡</sup>EMGO Institute, VU University Medical Center, Amsterdam, the Netherlands

**Introduction:** Cross-sectional studies show that older age groups have higher mean BMI than younger age groups and that BMI tends to decrease after age 60 years. This can be explained by a mixed effect of ageing per se, characteristics of subsequent birth-cohorts and selective survival. Purpose of the present study is to evaluate age and cohort effects on body weight and BMI in Dutch adults, based on longitudinal data.

**Subjects and methods:** Population based cohort study with an 11-year follow-up period with three measurements of body height and weight (1987–1991, 1993–1997 and 1998–2002). Complete data was available from 4065 healthy subjects aged 20–59 years at baseline.

**Results:** Highest increase in body weight and BMI over follow-up was observed in young adults, aged 20–29 years at baseline (7.0 kg or 2.1 kg/m<sup>2</sup> gain). Also in subjects aged 50–59 years at baseline, an increase in body weight and BMI was observed (2.5 kg or 1.1 kg/m<sup>2</sup> gain). Both age and cohort effects were observed: older subjects and younger cohorts had higher body weight and BMI.

**Conclusions:** Findings based on our longitudinal data suggest that the effect of age on body weight and BMI based on cross-sectional surveys may underestimate the actual increase in weight with ageing, because of cohort effects. Highest weight gain was observed in young adults. Weight gain was still present after age 60 years, in contrast to findings based on cross-sectional data. This indicates that prevention of weight gain is still useful in subjects aged 60 years.

O015

**Six-year weight changes, 19 year-mortality and cause-of-death analysis in the Finnish twin cohort****M KORKEILA\***, **A RISSANEN<sup>†</sup>**, **TIA SÖRENSEN<sup>‡</sup>** and **J KAPRIO\***\*Department of Public Health, University of Helsinki, <sup>†</sup>Obesity Research Unit, Helsinki University Hospital, Helsinki, Finland, <sup>‡</sup>Institute for Preventive Medicine, Copenhagen, Denmark

**Introduction:** Overweight is related to increased mortality whereas results from studies on weight changes and mortality are conflicting. We examined six-year weight changes in relation to subsequent 19-year mortality in adult Finns. We also studied twin pairs discordant for death to assess whether the relationship between body weight, weight changes and mortality is explained by genetic or shared environmental factors.

**Materials and methods:** Body mass index (BMI) and six-year weight changes for 15 904 healthy subjects from the Finnish Twin Cohort were calculated from self-reports in 1975 and 1981. Mortality from 1976 until 2001 was ascertained from national registries. 407 twin pairs were discordant for death.

**Results:** Overweight (BMI  $\leq$  27) at baseline was related to risk for death from all causes (RR + 1.37, 1.08–1.74), CHD (2.16, 1.26–3.70) and combined CHD and cerebrovascular disease (CVD) (1.81, 1.12–2.93). Among obese subjects only, both weight gain (RR + 4.18, 1.11–15.78) and loss (3.76, 1.10–12.90) predicted increased mortality. Compared to subjects with stable weight at baseline, six-year weight gain doubled the risk for CVD (2.36, 1.11–5.03) and for violent death (1.50, 1.06–2.10), whereas weight loss was not significantly related to any particular cause-of-death. BMI at baseline was similar among death discordant twin members, but significantly higher among those members of pairs ( $n$  + 54) where one died of CHD ( $P$  + 0.05 for all pairs and 0.02 for DZ pairs).

**Conclusion:** While confirming the relationship between overweight and cardiovascular mortality our results suggest that long-term weight gain may predispose to violent and CVD death.

O016

**Age of menarche and adult BMI in the Aberdeen children of the 1950s cohort study****M PIERCE** and **DA LEON**

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**Background:** Few studies have looked at whether the inverse association of age at menarche with adult body mass index (BMI) is due to the tendency for BMI to track between childhood and adult life, with BMI playing a causal role in determining age at menarche. We aimed to investigate whether the inverse association of age at menarche and BMI (obesity) in middle life is due to confounding with early childhood BMI.

**Patients and methods:** Historical cohort study of 3743 females born 1950–1955, Aberdeen (Scotland). Height and weight in early childhood measured at primary school entry. Age at menarche, and height and weight in adulthood, obtained by postal questionnaire.

**Results:** The age adjusted change in mean adult BMI per additional year of age at menarche was  $-0.64$  (95% CI  $-0.78, -0.50$ ) kg/m<sup>2</sup>. Adjustment for early childhood BMI (between 4 and 6 years) reduced this to  $-0.57$  ( $-0.71, -0.43$ ) kg/m<sup>2</sup> per year. Additional adjustment for childhood and adult social class, parity, smoking and alcohol intake had little effect. The odds ratio for being obese vs. not obese in adulthood was 0.82 (0.76, 0.86) per year increase in age at menarche. Adjustment for childhood BMI, and other covariates did not change this estimate.

**Conclusions:** Early childhood BMI explains little of the inverse relationship between age of menarche and adult BMI and none of the association with adult obesity. Instead, age at menarche may simply be a proxy marker for the pace of sexual maturation which itself leads to differences in adiposity (and BMI) in the peri-pubertal period that track into adult life.

O017

**Relationship between obesity and reproductive dysfunction in men – data from the florey adelaide male ageing study****G WITTERT\***, **M HAREN\***, **G COMIN\***, **W TILLEY\***, **V MARSHALL<sup>†</sup>**, **P O'LOUGHLIN<sup>‡</sup>** and **J HILLER<sup>§</sup>**\*Department of Medicine, University of Adelaide, <sup>†</sup>Department of Surgical Specialties, Royal Adelaide Hospital, <sup>‡</sup>Division of Clinical Biochemistry, IMVS, <sup>§</sup>Department of Public Health, University of Adelaide, Adelaide, South Australia, Australia

**Introduction:** This study determined the relationships between BMI and waist circumference and various measures of testosterone, erectile function (EF), sexual desire (SD), and lower urinary tract symptoms (LUTS) in men.

**Subjects and methods:** 568 men aged 35–80 years were recruited by random telephone dialing of households in Northwest Adelaide. EF was assessed by the International Index of Erectile Function (IIEF). Dyadic and solitary SD was assessed by Sexual Desire Inventory (SDI-2). Obstructive and irritative LUTS were assessed using the International Prostate Symptom Scale (IPSS). Morning serum samples were assayed for total T (TT), SHBG and bioavailable T (BT). Free T (FT) was calculated. Height, weight, waist circumference and blood pressure were measured. Chronic disease, prior urogenital surgery, social, demographic and behavioural factors, and medication use were determined by questionnaire.

**Results:** Independent of age larger waist circumference and BMI were associated with lower T (both  $P$ s < 0.0001), BT (waist  $P$  + 0.004, BMI  $P$  + 0.033) and FT (both  $P$ s < 0.0001). BMI was independently associated with LUTS ( $P$  + 0.023). Diabetes mellitus ( $P$  + < 0.05) and hypertension ( $P$  < 0.05), but not obesity per se were associated with erectile dysfunction. Higher levels of testosterone were independently associated with greater solitary (T,  $P$  + 0.025; BT,  $P$  < 0.001; FT,  $P$  < 0.001) and dyadic (T,  $P$  + 0.027; FT,  $P$  < 0.001) sexual desire. Moreover, irritative LUTS and ED are positively associated with each other independent of obesity, age and hypertension.

**Conclusion:** Obesity and the metabolic disturbances associated with obesity are associated with adverse consequences for sexual and reproductive health in men.

O018

**Obesity, mortality rates and life-years lost****TLS VISSCHER\*<sup>†</sup>**, **JC SEIDELL\*<sup>‡</sup>**, **WGC WENDEL-VOS\***, **WJ BEMELMANS\*** and **WMM VERSCHUREN\***\*Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, <sup>†</sup>Institute for Health Sciences, Vrije Universiteit, <sup>‡</sup>Prevention centre Overweight Zwolle, the Netherlands

**Introduction:** Obesity in adulthood has recently been associated with a decreased life-expectancy. Although the number of life-years lost due to obesity has been debated, and the impact of different periods of follow-up is relatively unclear, increased mortality in the obese is now commonly used to stress the public health impact of obesity. The present study assessed obesity in adulthood in relation to all-cause mortality rates and life-years lost, taking into account different periods of follow-up.

**Methods:** A total of 16 000 Dutch men and 17 500 women aged 37–43 years were followed from baseline (1974 to 1980) to the end of 1999 (maximum follow-up 25 years). Body weight and height were measured at baseline and BMI categories were defined according to the WHO-guidelines. Mortality during the first five years was excluded.

**Results:** For obesity, increased hazard ratios of mortality for obesity became apparent after 15 years of follow-up. Hazard ratios of mortality for obesity were 1.7 (95% confidence interval: 1.4–2.1) for both men and women, during the 25 years of follow-up. Obese subjects did not have more life-years lost compared to normal weight subjects during the first 15 years of follow-up. Among women, 0.2 life-years lost could be attributed to obesity during the 25 years of follow-up. Among smoking men, 0.5 life-years lost and among never smoking men, 0.2 life-years lost could be attributed to obesity.

**Conclusion:** Obesity at age 37–43 years is related to mortality, but only when follow-up is long, and the impact on life-years lost during adulthood is small. Increased mortality should not be used as the most important marker for the public health impact of obesity in adulthood. Instead, the few life-years lost during adulthood are likely to imply large direct and indirect costs due to non-fatal obesity related morbidities and disabilities.

## T5R1: Lifestyle Interventions

### Low-carbohydrate vs low-fat diets for treatment of obesity

#### A ASTRUP

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Despite reported decreases in dietary fat the proportion of obese individuals in the population continues to rise. A general decrease in the level of daily physical activity, more sugar-sweetened soft drinks, increased portion sizes, and underreporting of consumed fat are likely explanations. Alternative dietary solutions, such as the Atkins diet, glycemic index (GI) of foods etc., have been proposed. However, dietary fat is still one of the important lifestyle factors contributing to the rise in obesity, a fact that is supported by evidence from meta-analyses of randomised trials comparing ad libitum low-fat, high-carbohydrate diets with normal-fat diets. These studies have consistently shown that a 10% reduction in dietary fat produces weight loss of 3–4 kg in overweight subjects, and of 5–6 kg in obese subjects. In long-term trials with good adherence diets providing 25–30% energy from fat combined with slightly increased physical activity have produced 2–5 kg weight loss, sustained over 4–5 years, and substantial reductions in cardiovascular events. This combined intervention, with modest weight loss, reduces the incidence of diabetes by 58%. Dietary fat should be replaced by high fibre, starchy carbohydrate foods and by protein. There is little evidence that low GI foods are better than high GI foods for weight control. In mixed meals GI is not predictable from GI tables, but requires detailed information about total calories, fat and protein contents. Contrastingly, sugars in soft drinks seem to have a very low satiating effect and may produce weight gain. Randomised trials show that restriction of carbohydrates, as in the Atkins diet, produces weight loss and risk factor improvements in obese subjects in the first 6 months, but no difference compared with fat-reduced diets after 12 months. Although weight loss occurs and no adverse effects on cardiovascular risk factors are observed, it is not clear what happens with risk factors when weight loss subsides.

### Lifestyle activity vs structured exercise in body weight management

#### MA VAN BAAK

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It is generally accepted that a high level of energy expenditure is of importance for the prevention of body weight gain and maintenance of body weight loss after weight reduction. Substantial increases in energy expenditure can only be attained by becoming more active. Current consensus is that prevention of weight regain in formerly obese individuals may require 60 to 90 minutes of moderate-intensity activity daily, and that 45 to 60 minutes may be required to prevent the transition to overweight or obesity. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise, on the other hand, is a subcategory of physical activity defined as planned, structured movement undertaken to improve or maintain one or more aspects of physical fitness. With the paradigm changing from fitness to health, from exercise to physical activity, the term lifestyle activities has been introduced. These are self-selected activities, which include all leisure, occupational, or household activities that are at least moderate to vigorous in their intensity and could be planned or unplanned activities that are part of everyday life (Dunn *et al.*, 1998). In contrast, structured exercise is usually prescribed, of a fixed composition and performed at specific times during the week in discrete bouts. Although the effectiveness of structured exercise programs for weight management is not disputed, long-term adherence to such programs is problematic. An interesting question is therefore whether lifestyle activities can combine a similar effectiveness with respect to weight management with better long-term adherence. It has been suggested that lifestyle-based physical activities are more acceptable in the general population and even more so in special populations with chronic health problems. There are no studies that have directly compared the two types of interventions, but in the presentation data on short- and long-term adherence and effectiveness of programs that aimed to increase total physical activity through lifestyle activities or structured exercise with respect to body weight management will be discussed.

### Behavioural strategies that work

#### A GOLAY

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Binge eating disorder is frequent in patients suffering from obesity. This eating disorder must be taken into account during the weight loss programme in order to diminish the relapse and the 'yo-yo' phenomenon. Eating disorders can be detected and treated by GPs. They assess patients' expectations and negotiate weight loss objectives (1–3 kg/month). They can detect eating disorder not only through the DSM IV criteria but also by asking questions regarding physical and emotional hunger, satiety, alimentary restriction, cognitive restriction, snacking, bulimia and binge. They help find emotional as well as alimentary stimuli. The strategies can be worked out after the detection of stimuli. The most important is to let patients find themselves their own strategies. Strategies can be divided into short-term strategy to avoid binge and long term strategy to prevent binge. Patients will find simple strategies for cooking, eating and shopping. Then, GPs will encourage them to structure their meals. Finally, GPs will motivate patients to change, to search for success, to use the mistake, to cope with difficulties and to work on solving problems. In conclusion, GPs can detect and prevent binge eating disorder in order to improve weight loss but mostly avoid the relapse. They motivate patients to change their behaviour and help them find binge stimuli and their own strategies.

## T1R1: Adipose Gene Regulation in Obesity and its Complications

### New aspects on metabolic regulation

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Obesity which is characterized by an excess of fat stores is the most important risk factor for type 2 diabetes. Triglycerides stored in white adipocytes are the most important fuel store in the body. Elevated concentrations of plasma free fatty acids (FFA) have long been seen as a major contributor to the metabolic abnormalities found in obese subjects. Understanding the mechanisms controlling adipose tissue lipolysis is essential both for a better appreciation of the complications seen in obese subjects and for the design of drugs limiting FFA efflux from adipose tissue to the plasma. The relative importance of hormone-sensitive lipase (HSL) and the recently identified adipose triglyceride lipase (ATGL) in adipose tissue lipolysis was investigated. We show that a novel HSL inhibitor did not inhibit other lipases and entirely counteracted stimulated lipolysis in mouse fat cells. It had no effect on residual ATGL-mediated lipolysis in HSL-null mice. HSL and ATGL mRNA were induced concomitantly during human adipocyte differentiation. Moreover, HSL and ATGL mRNA levels were highly correlated in human adipose tissue suggesting common regulatory mechanisms for the two genes. HSL appears as the major lipase and the rate limiting step for stimulated lipolysis whereas ATGL participates in basal lipolysis. Brown adipose tissue (BAT) plays an opposite physiological function as it allows dissipation instead of storage of energy. In humans, there are no BAT depots in adults. In rodent BAT, the transcriptional coactivator PGC-1 $\alpha$  activates the expression of mitochondrial genes incl. the gene encoding UCP1, an uncoupling protein essential for adaptive thermogenesis. We have shown that adenovirus-mediated expression of human PGC-1 $\alpha$  in human subcutaneous white adipocytes stimulates palmitate oxidation and produces a gene expression profile resembling that of brown adipocytes. PPAR $\gamma$  agonists potentiated the effect of PGC-1 $\alpha$  on UCP1 expression and fatty acid oxidation. Hence, PGC-1 $\alpha$  is able to direct white adipose tissue PPAR $\gamma$  towards a transcriptional program linked to energy dissipation. However, pangenomic microarray analysis revealed that a large fraction of genes are regulated by PGC-1 $\alpha$  independently of PPAR $\gamma$ . Therapeutic strategies aimed at altering the phenotype of human white adipocytes may be conceivable for the treatment of obesity.

### Functional role of human mutations and adipose specific genes

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Most of our knowledge about adipose tissue function is derived from studies of various animal models. However, important species differences are at hand when the metabolic and protein secretion functions of adipose tissue are concerned, making it sometimes hard to make firm conclusions from animal experiments only. In addition, the structural variances in several of the genes that are involved in adipocyte regulation of metabolism, in particular lipolysis, are human specific and have consequences for human fat cell function. Some genes with clear importance for rodent fat cells are not expressed in human fat cells (for example resistin) or even completely absent in man (for example insulin receptor substrate 3). Finally, the expression and functions of genes encoding for important adipocyte functions such as adrenoceptors, insulin signalling transduction molecules, leptin and testosterone receptors are differently expressed in various human adipose tissue regions (in particular subcutaneous versus visceral region). This has among other things pathophysiological consequences for serious forms of obesity such as visceral obesity. Such variations are not common among laboratory animals or the animals (in particular rodents) display different types of adipose regional variations than humans.

### Novel modulators of adipocyte biology Hunting for new pieces to the complicated puzzle of obesity

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Disentangling the neuroendocrine systems which regulate energy homeostasis and adiposity has been a long-standing challenge in pathophysiology, with obesity as an increasingly important public health problem. It has been shown that sophisticatedly integrated mechanisms operate in an orchestrated manner in adipocyte biology enabling the organism to adapt to a wide number of different metabolic challenges. Adipose tissue is no longer considered a passive bystander in body weight regulation since it actively secretes a large number of hormones, growth factors, enzymes, cytokines, complement factors and matrix proteins, at the same time as expressing receptors for most of these elements, which influence fuel storage, mobilization and utilization at both central and peripheral sites. Moreover, compelling evidence gathered during the last decades has revealed adipose tissue as an extremely dynamic endocrine organ playing a relevant role not only in metabolism control, but also in reproduction, immunity, blood pressure, fibrinolysis, coagulation, and angiogenesis, among others. Thus, an extensive cross-talk at a local and systemic level in response to specific external stimuli or metabolic changes underpins the multifunctional characteristics of adipose tissue, which relies on its vast secretome. In addition to the already known adipokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukins (IL-1 $\beta$ , IL-6, IL-8, IL-10), angiotensinogen, plasminogen activator inhibitor-1 (PAI-1), C-reactive protein (CRP), tissue factor, transforming growth factor- $\beta$  (TGF- $\beta$ ), leptin, resistin, adiponectin, etc., attention has been more recently devoted to 'newcomers' to the 'adipose tissue arena', which include adrenomedullin, serum amyloid A (SAA), vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 (HIF-1) and visfatin, among others. While *in vitro* and *in vivo* experiments have provided extremely valuable information, the advances in genomic, proteomic and metabolomic methodologies are offering a level of information not previously attainable to help unlock the molecular basis of obesity. The potential and power of combining pathophysiological observations with the wealth of information provided by the Human Genome, SNP databases, haplotype maps, knock-out models, overexpression experiments, DNA microarrays, RNA silencing and other emerging technologies provide a new and unprecedented view of a complex disease conferring new insights into old questions by identifying new pieces to the unfinished jigsaw puzzle of obesity.

## T2R1: Advances in Genetic Epidemiology

### Gene–environment interactions in obesity and the metabolic syndrome

P FROGUEL (UK)

Not received

### Translation of evidence from primary prevention trials into public health action

WPT JAMES

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The recent understandable demand that all policy changes should first have their proof of efficacy established with Cochrane analyses of several trials in different circumstances reflects current medical practice appropriate for evaluating medical tests, drugs and procedures. Cochrane insisted on the use of impartial evidence collected in a transparent manner. Should public health policies and actions be based on the same set of principles? Ideally this is desirable but in relation to obesity and other major public health problem e.g. diabetes, hypertension and ischaemic heart disease one needs to recognise the fundamental determinants of the public health problem. Recent diabetes prevention trials have illuminated the opportunity for prevention but this does not automatically determine the public health response. Similarly with hypertension there is clear value in reducing salt and fat intakes but the proven prevention actions go far beyond suggesting individual behavioural change. Analyses of heart disease highlight other key factors but their determinants are also complex. The main causes relate to government and industrial policies affecting the availability and cost of food as well demonstrated with alcohol and smoking prevention. Current short term intervention trials on children and adults need to take account of the magnitude of the effect, the demands and costs of the intervention and the pervasiveness of their impact before – as in Australian proposals – a portfolio of options is set out. The variety of demands which each initiative requires e.g. in Swinburn's four arenas: physical, economic, regulatory/legislative and socio-cultural domains needs a staged and semi-quantitative analysis taking account of the costs and efficacy of different measures. Since food costs and availability are not determined by individuals then economist Wanless has demanded the use of rigorous economic and social policy analyses in tackling both obesity and physical inactivity with rigorous evaluations of the range of initiatives underway. WHO Europe has also set out a cross-governmental approach which doctors need to support as part of a programme for obesity prevention.

### Are there independent health benefits of wide hips?

BL HEITMANN

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**Introduction:** Both obesity and fat distribution are associated with adverse health effects. Abdominal obesity has been found to be an independent risk factor for both early death and for cardiovascular morbidity.

**Materials:** It has been argued that waist circumference is a better predictor of premature death than the waist to hip circumference ratio. Subsequently it has been advocated, to discard the hip measurement and concentrate on waist circumference only, on the grounds that waist circumference provides a more practical correlate of abdominal fat distribution and associated ill health than the waist to hip ratio. However, a number of cross sectional studies have shown that both men and women with small hips have an excess risk of being diabetic, suffering from hypertension or gall bladder disease. This is in keeping with a number of findings of separate and opposite associations of waist and hip circumference, both with lifestyle and other cardiovascular disease risk factors. Recently, also prospective studies have examined associations between hip circumference and both morbidity and mortality. Generally, these studies report that narrow hips seem to increase the risk for morbidity and early death. Indeed, this protection from a wide hip circumference appears to be independent of both general overweight and of android fat patterning, characterized by a wide waist circumference. Furthermore, the protection seems greater for women than for men.

**Methods:** That narrow hip circumferences related to increased health risk may reflect reduced femoral fat, small pelvic bone structure, muscle atrophy or combinations hereof in the gluteo-femoral region. A direct athero-protective effect of the peripheral fat mass, mediated via differences in endogenous glucocorticoid tone, increased plasma adiponectin, or high lipoprotein lipase activity has been suggested as a possible mechanism. Also, reduced insulin sensitivity of the large gluteal muscle may play an important role.

**Conclusion:** Our recent data have suggested a critically low hip circumference threshold of approximately 100 cm that appears to be present for both genders. Our data indicate that there may be no additional benefit to having large hips above this threshold.

## T1: Regulation of Adipose Tissue Function

### O019

**Impaired fat-induced thermogenesis in obese subjects: the NUGENOB study**

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[NUGENOB: Nutrient-gene interactions in human obesity-implications for dietary guidelines, www.nugenob.com supported by EU (QLRT-2000-00618)].

**Introduction:** Obesity may be associated with a reduced thermic effect of food potentially leading to the development or maintenance of large adipose tissue stores.

**Aim:** Of the present study was to study energy expenditure (EE) before and for 3 hours after a high fat load in a large cohort of obese subjects ( $n = 701$ ) and a lean reference group ( $n = 113$ ).

**Methods:** Subjects from 7 European countries underwent a 1-day clinical investigation with a liquid test meal challenge containing 95 en% fat, (energy content was 50% of estimated REE). Fasting and postprandial EE, as well as metabolites and hormones were determined.

**Results:** Obese subjects had a reduced postprandial EE after the high fat load (adjusted postprandial EE; lean vs obese:  $1000 \pm 31$  vs  $992 \pm 32$  kJ\*180 min,  $P < 0.01$ ), independent of body composition, age, gender, center and resting energy expenditure (REE). Within the obese group thermogenesis increased again with BMI-category. Additionally, insulin resistance ( $HOMA_{IR}$ ,  $P < 0.01$ ), habitual physical activity ( $P < 0.01$ ), postprandial plasma triacylglycerols (TAG,  $P < 0.05$ ) and insulin ( $P < 0.01$ ) were all independently positively related to the postprandial EE. REE, adjusted for FFM, increased with degree of obesity, a difference that disappeared after adjustment for fat mass. Furthermore,  $HOMA_{IR}$  ( $P < 0.01$ ), fasting plasma FFA ( $P < 0.01$ ) and cortisol ( $P < 0.05$ ) were positively associated, whilst fasting plasma leptin ( $P < 0.01$ ) and IGF-1 ( $P < 0.05$ ) were negatively associated with REE.

**Conclusion:** The 3 hour fat-induced thermogenic response is reduced in obesity. It remains to be determined whether this blunted thermogenic response is a contributory factor or an adaptive response to the obese state.

### O020

**Adipose tissue gene expression in obese subjects during low-fat and high-fat hypocaloric diet**

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¹NUGENOB is the acronym of the project 'Nutrient-Gene interactions in human obesity – implications for dietary guidelines' supported by the European Community (Contract no. QLK1-CT-2000-00618).

**Introduction:** Adaptation to energy restriction is associated with changes in adipose tissue gene expression. It is unknown to what extent these changes depend on the energy restriction as such or on the macro-nutrient composition of the diet.

**Methods:** We determined the expression of 38 genes expressed in adipose tissue that encode transcription factors, enzymes, transporters and receptors which are known to play a critical role in the regulation of adipogenesis, mitochondrial respiration, and lipid and carbohydrate metabolism. Two groups of 25 obese subjects following 10-week hypocaloric diet programs with either 20–25% or 40–45% of total energy from fat were investigated. mRNA levels were measured using reverse transcription-real time PCR on subcutaneous fat samples obtained before and after the diets.

**Results:** The two groups of subjects lost 7 kg during the diets. Ten genes were regulated during energy restriction. However, none of the genes showed a significantly different response to the diets. PPAR $\gamma$  coactivator 1 mRNA level was increased while expression of leptin, osteonectin, phosphodiesterase 3B, hormone-sensitive lipase, receptor A for natriuretic peptides, fatty acid transporter, lipoprotein lipase, uncoupling protein 2 and peroxisome proliferator-activated receptor  $\gamma$  mRNAs were decreased. Clustering analysis revealed new potential coregulation of genes, e.g. between adiponectin receptors and the liver X receptor  $\alpha$ .

**Conclusions:** In accordance with the comparable loss of fat mass between the diets, this study shows that energy restriction and/or weight loss rather than the fat/carbohydrate ratio of a low-energy diet is of importance in modifying the gene expression in the human adipose tissue.

### O021

**Noradrenaline stimulates glucose uptake in brown adipose tissue through the activation of UCP1 and AMP kinase**  
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**Introduction:** Sympathetic stimulation activates glucose utilization in parallel with thermogenesis in brown adipose tissue (BAT). We have shown the sympathetically stimulated glucose uptake is independent of the action of insulin, but dependent on the activation of a thermogenic molecule, uncoupling protein (UCP) 1. The aim of this study was to clarify the mechanisms of UCP1-linked glucose utilization, with special references to the role of AMP kinase.

**Methods:** UCP1-knockout (KO) and wild-type (WT) mice were starved overnight, anesthetized, and injected with noradrenaline (0.2 mg/kg, ip). Glucose utilization in BAT was estimated from the tissue uptake of 2-deoxyglucose (2-DG). The AMP kinase activity and adenine nucleotide levels were measured for freeze-clamped BAT.

**Results:** In WT mice, noradrenaline injection increased 2-DG uptake (+213%), AMP kinase activity (+210%), site-specific phosphorylation of AMP kinase (+226%) and the AMP level (+208%) in BAT, while it decreased the ATP level (–55%). The AMP kinase activity and adenine nucleotide levels in skeletal muscle and heart were little influenced by noradrenaline. The effects of noradrenaline were greatly attenuated or undetected in BAT of UCP1-KO mice. Similar but weaker responses to noradrenaline were also found in white fat pads of WT mice acclimated to cold, which expressed significant amounts of UCP1.

**Conclusion:** Our results, together with the previously reported role of AMP kinase for glucose transport in myocytes, suggest that sympathetically stimulated glucose utilization in BAT is due to the serial activation of UCP1 and AMP kinase, and may contribute to the recovery of intracellular energy (ATP) levels.

### O022

**Adipose tissue disturbances in response to HIV infection and anti-retroviral treatment: from inflammation to mitochondrial toxicity**  
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**Introduction:** Profound adipose tissue disturbances (peripheral lipodystrophy, visceral accumulation, lipomatosis) appear in HIV-infected patients under highly active anti-retroviral treatment (HAART-associated lipodystrophy). The etiopathogenic basis of these alterations is poorly known and highlights an unexpected sensitivity of the adipose tissue to either antiretroviral drugs, HIV-infection or the combination of both. To distinguish among these aspects, a genomic (transcriptomics) approach was followed to establish major disturbances in adipose tissue from patients under different conditions.

**Patients and methods:** We obtained biopsies of subcutaneous abdominal adipose tissue of at least 10 patients from every one of the four following groups: untreated HIV-infected patients (naive), HIV-infected patients under HAART with no signs of lipodystrophy, with evident lipodystrophy, and healthy controls. The mRNA expression of 26 gene markers corresponding to mitochondrial function, adipose differentiation and metabolism, adipokines were quantified using quantitative real-time PCR (TaqMan, Applied Biosystems).

**Results:** Around 50% of the genes analyzed showed significant differences at least in one group respect to others. Most of the differences were already present when naive patients were compared with controls. Minor changes were associated to HAART treatment or to the diagnosis of lipodystrophy. The genes more profoundly affected corresponded to some adipokines (down-regulation of adiponectin and leptin; up-regulation of TNF $\alpha$ ) and mitochondrial gene markers.

**Conclusion:** Major disturbances in adipose tissue gene expression are already present in HIV-infected, non HAART-treated, patients thus indicating a major role of HIV infection itself in eliciting adipose tissue alterations leading to lipodystrophy.

## O023

**Meal-induced thermogenesis and macronutrient oxidation are not different between lean and obese women after two separate isoenergetic meals, one rich in fat and one rich in carbohydrates**

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**Introduction:** The effect of meal composition on meal-induced thermogenesis (MIT) and substrate oxidation (SO) has been well-documented, but there is little data comparing directly lean and obese subjects. In this study we investigated the potential differences in MIT and SO between lean and obese women who were fed two different isoenergetic meals, one rich in fat (FM) and one rich in carbohydrates (CM).

**Methods and subjects:** 15 lean (BMI:  $22.4 \pm 2.4$  kg/m<sup>2</sup>) and 15 obese (BMI:  $35.9 \pm 4.6$  kg/m<sup>2</sup>) women, matched for age, were fed on two different occasions and in random order with two isoenergetic meals, one FM and one CM. Energy expenditure was measured by indirect calorimetry at baseline and for 3 hours after the test meals. Postprandial changes in SO and MIT were quantified by the area under the respective 180 min plots.

**Results:** Protein oxidation was higher in both groups after the CM compared to the FM (lean:  $\Delta + 9.3 \pm 2.9$  mg/min,  $P < 0.01$ ; obese:  $\Delta + 6.7 \pm 2.0$  mg/min,  $P < 0.004$ ). Glucose oxidation increased after the CM and declined after the FM (lean:  $\Delta + 500 \pm 55$  mg/min,  $P < 0.0001$ ; obese:  $\Delta + 447 \pm 49$  mg/min,  $P < 0.0001$ ). Fat oxidation declined after the CM and increased after the FM (lean:  $\Delta + 160 \pm 23$  mg/min,  $P < 0.0001$ ; obese:  $\Delta + 159 \pm 21$  mg/min,  $P < 0.0001$ ). Finally, MIT was significantly higher after the CM compared to the FM (lean:  $\Delta + 1.03 \pm 0.33$  kJ/min,  $P < 0.01$ ; obese:  $\Delta + 0.74 \pm 0.22$  kJ/min,  $P < 0.004$ ). In all the above parameters no significant differences were observed between the two groups.

**Conclusion:** Lean and obese women demonstrate similar responses in terms of macronutrient oxidation and MIT following two different isoenergetic meals, one rich in fat and one rich in carbohydrates.

## O024

**Polyunsaturated fatty acids of marine origin induce mitochondrial biogenesis and beta-oxidation in white fat**

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**Introduction:** Omega-3 polyunsaturated fatty acids (PUFA) of marine origin limit accretion of body fat and improve metabolic syndrome. We investigated in mice whether a stronger effect on adiposity of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acid, as compared with their precursor, alpha-linolenic acid (ALA), could involve modulation of gene expression and metabolism of white fat.

**Methods:** Oligonucleotide microarrays, cDNA PCR-subtraction and quantitative real time RT-PCR were used to identify genes that are modulated by EPA/DHA. Antigens of mitochondrial proteins and COX activity were estimated in cell membranes. Isolated adipocytes were analyzed by live cell imaging of active mitochondria with MitoTracker Red dye. Fatty acid (FA) oxidation was measured in adipose tissue fragments.

**Results:** EPA/DHA concentrate admixed to a semisynthetic high-fat diet rich in ALA up-regulated genes for mitochondrial proteins. Predominantly in epididymal fat, this was associated with a 3-fold induction of regulatory factors for mitochondrial biogenesis, transcriptional coactivator PGC-1 and nuclear respiratory factor-1 (NRF-1). Expression of carnitine palmitoyltransferase 1, which regulates FA entry into mitochondria, was increased. FA oxidation was stimulated while lipogenic genes were down regulated. The effect on gene expression was also apparent in adipocytes from epididymal fat, when DHA/EPA intake limited development of obesity induced by high-fat chow-based diet. Expression of PGC-1 and NRF-1 was also stimulated by omega-3 PUFA in 3T3-L1 cells.

**Conclusion:** Antiadipogenic effect of EPA and DHA involve enhancement of mitochondrial biogenesis and lipid utilization in adipocytes.

## T2: Preventive Measures for Obesity and Related Risk Factors

## O025

**Prevention of overweight: 2-year results of ICAPS (intervention centred on adolescents' physical activity and sedentary behaviour)**

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**Objectives:** To evaluate the 2-year impact of ICAPS, a physical activity (PA) multilevel intervention, on activity patterns and overweight among adolescents and at providing social support and environmental conditions that encourage PA of adolescents inside and outside school.

**Design:** A controlled, ongoing field trial, initiated in 2002 in middle-school's first-level students from four intervention and four control matched schools randomly selected in Eastern France. Participants were 954 adolescents (92% of the eligible students) aged  $11.7 \pm 0.6$  years. Longitudinal 2-year data were collected from 834 students. Outcomes were participation in leisure organised PA (LPA%), active commuting to/from school  $> 20$  min/day (COM%), high sedentary (SED%) behaviour (television viewing  $> 2$  h/day), and overweight status (international references). Analyses used mixed models, taking into account the cluster randomisation design and controlling for baseline measures, age, puberty stage and socioeconomic status.

**Results:** After 2 years, an increase of LPA% (OR + 2.2;  $P < 0.0001$ ) and of COM% (OR + 1.5;  $P < 0.02$ ) associated with a decrease of SED% (OR + 0.6;  $P < 0.001$ ) was observed in intervention adolescents compared to controlled adolescents. Simultaneously the risk of being overweight was reduced by 21% (OR + 0.79;  $P < 0.05$ ) in intervention adolescents.

**Conclusion:** Two-year evaluation of ICAPS indicates effectiveness in improving PA patterns behaviour of adolescents and preventing overweight. It remains to be demonstrated that these effects will be long lasting.

## O026

**Impact of Mediterranean diet intake on cardiovascular risk factors and circulating adipokines**

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**Introduction:** Cardiovascular diseases (CVD) represent the main cause of death in developed countries, with dietary habits playing a key role to determine their occurrence. The aim of this study was to assess the beneficial effects of habitual consumption of a Mediterranean diet (MD) on anthropometric and metabolic factors associated with CVD.

**Subjects and methods:** Food-frequency questionnaires were used to appraise dietary habits. Two comparable groups of healthy young men and women ( $35 \pm 1$  years;  $n = 10$  males + 10 females/group) either highly adherent to a MD or a Western diet (WD) were selected. Body fat was measured by Bod Pod<sup>®</sup>, serum resistin and adiponectin by ELISA, and other variables were determined by conventional biochemical/endocrine methods.

**Results:** Despite similar age and BMI ( $23.6 \pm 0.3$  kg/m<sup>2</sup>) in both groups, the MD group exhibited significantly lower body fat ( $33.4 \pm 1.6$  vs  $23.8 \pm 1.6$ %;  $P < 0.001$ ) and waist/hip ratio ( $0.94 \pm 0.02$  vs  $0.82 \pm 0.01$ ;  $P < 0.001$ ). Moreover, individuals in the MD group presented lower circulating triglycerides ( $131 \pm 11$  vs  $79 \pm 5$  mg/dl;  $P < 0.001$ ), glucose ( $92 \pm 2$  vs  $82 \pm 1$  mg/dl;  $P < 0.001$ ), insulin ( $12.9 \pm 1.4$  vs  $5.1 \pm 0.4$  mU/l;  $P < 0.001$ ), insulin resistance (HOMA,  $2.9 \pm 0.3$  vs  $1.0 \pm 0.1$ ;  $P < 0.001$ ), leptin ( $26.3 \pm 3.6$  vs  $10.3 \pm 1.9$  µg/l;  $P < 0.001$ ) and resistin ( $7.5 \pm 0.8$  vs  $5.6 \pm 0.4$  ng/ml;  $P < 0.027$ ) concentrations as compared to the WD group. Furthermore, MD subjects exhibited higher adiponectin ( $5.6 \pm 2.0$  vs  $13.5 \pm 1.3$  µg/ml;  $P < 0.001$ ) and HDL-cholesterol ( $40 \pm 2$  vs  $54 \pm 3$  mg/dl;  $P < 0.001$ ) concentrations. In addition, the MD group showed significantly lower homocysteine ( $14.3 \pm 3.2$  vs  $7.1 \pm 0.6$  µmol/l;  $P < 0.010$ ) and C-reactive protein concentrations ( $0.76 \pm 0.13$  vs  $0.18 \pm 0.04$  mg/l;  $P < 0.001$ ).

**Conclusion:** MD favourably affects body composition and circulating concentrations of adipokines.

**Acknowledgment:** Supported by INIA (CAL01-067-C4-1/2/3/4).

O027

**Comparison of two physical activity questionnaires in obese subjects – the NUGENOB study****B TEHARD<sup>†</sup>, W SARIS<sup>‡</sup>, A ASTRUP<sup>§</sup>, A MARTINEZ<sup>¶</sup>, MA TAYLOR<sup>\*\*</sup>, P BARBE<sup>††</sup>, B RICHTEROVA<sup>‡‡</sup>, B GUY-GRAND<sup>\*</sup>, TIA SORENSEN<sup>§§</sup> and JM OPPERT<sup>\*</sup>**

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**Introduction:** Simple instruments are needed to assess habitual physical activity (PA) in obese subjects. This was a comparative study of PA data obtained using two questionnaires in the multi-centre NUGENOB obesity project ('Nutrient-Gene interactions in human obesity – implications for dietary guidelines', EU QLK1-CT-2000-00618, www.nugenob.org).

**Patients and methods:** In 757 obese subjects (75% female; mean age 37.1 years, BMI 35.5 kg/m<sup>2</sup>) assessment included: the Baecke PA questionnaire (assessing work, sport, and non-sport leisure activity), the short last-7 day version of the International Physical Activity Questionnaire (IPAQ, assessing vigorous, moderate-intensity, walking activity, and sitting), body composition (percent body fat by bio-impedance), waist circumference, and fasting plasma concentrations of glucose, insulin, leptin and FFA.

**Results:** Total habitual PA assessments by the Baecke and IPAQ were significantly related (Spearman rho + 0.51 and 0.49 in women and men respectively, both  $P \geq 0.0001$ , with adjustment for age and center). Using principal component analysis on obesity-related variables, we built two uncorrelated indices corresponding to general obesity (determined by high percent body fat and leptin) and abdominal obesity (determined by high waist circumference and HOMA index for insulin resistance). PA scores from both questionnaires were negatively related to general and abdominal obesity indices, except for abdominal obesity with the IPAQ in men.

**Conclusion:** This study shows reasonable agreement between IPAQ and Baecke questionnaires for assessment of total PA in obese subjects. The IPAQ may capture less of the relationships between PA and abdominal obesity than the Baecke questionnaire, especially in men, compared to consistent associations between PA and general obesity.

O028

**Knowledge of food energy content is related to social stratum and obesity****JR SPEAKMAN<sup>†</sup>, H WALKER<sup>‡</sup>, L WALKER<sup>‡</sup> and DM JACKSON<sup>†</sup>**

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**Introduction:** The prevalence of obesity is greater in lower social classes. The reasons for this effect however are unclear. Since there is also a link between education and social class, and an association between education and prevalence of obesity, one hypothesis is that lack of education about energy contents of foods may contribute to the effects of social class on obesity.

**Methods:** We tested the hypothesis that knowledge of food energy contents is associated with differences in body mass index (BMI) in a sample of 346 people aged between 18 and 45, living in Scotland, UK, of variable body mass index and drawn from different social strata.

**Results:** Knowledge of food energy contents was very poor in all sub-populations of this sample. We found that subjects of different BMIs did not differentially estimate the energy contents of foods high in carbohydrate, but low in fat and protein (fruit and bread). However, foods that contained high fat contents, independent of the other macronutrients present, were perceived to have significantly lower energy contents by obese people than non-obese subjects. Overall this effect interacted with social class, such that the influence of BMI was exaggerated in the lower social stratum but abolished in the higher social class.

**Conclusion:** Underestimating the energy contents of high fat foods may contribute to the development of obesity in lower social strata – suggesting public health education programmes directed at these people may help alleviate the obesity epidemic.

O029

**Development of fatness from adolescence to adulthood: a determinant of the metabolic syndrome and arterial stiffness in young adults. The Amsterdam growth and health longitudinal study****I FERREIRA<sup>†</sup>, JWR TWISK<sup>‡</sup>, WILLEM VAN MECHELEN<sup>§</sup>, HCG KEMPER<sup>†</sup> and CDA STEHOUWER<sup>††</sup>**

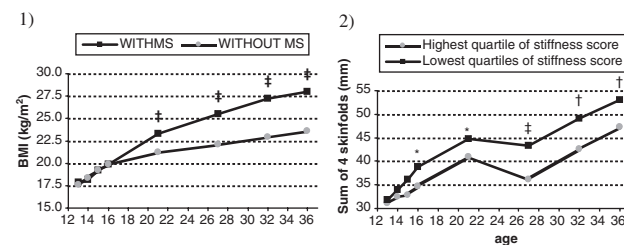
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**Introduction:** Information on the time-course of adiposity, from young age to adulthood, in adults identified with the MetS or high arterial stiffness is lacking; such information is needed in order to provide a better insight into the early pathophysiological mechanisms of these obesity-related diseases.

**Methods:** Longitudinal data on body fatness (BMI and skinfolds) were derived from the Amsterdam Growth and Health Longitudinal Study, a prospective cohort study ( $n = 364$ , 189 women; 8 follow-up measures between the ages of 13 and 36 years), and analyzed with the use of generalized estimating equations. The MetS (defined based on the NCEP definition and prevalent in 10.4% of the study population) and arterial stiffness (measured with non-invasive ultrasonography at the carotid and femoral arteries) were assessed at the age of 36 years only (main outcomes).

**Results:** Body fatness increased significantly from adolescence to the age of 36 years ( $P < 0.001$ ); these increases were considerably more marked in subjects who, at the age of 36, had the MetS (Fig. 1) and higher arterial stiffness (i.e., a lower stiffness score; Fig. 2).

**Conclusion:** The development of fatness, starting already from young age, is an important determinant of the MetS and arterial stiffness in young adults. Intervening early in life, may be a fruitful area for prevention of these obesity-related complications.



Development of BMI/sum of 4 skinfolds, from adolescence to adulthood in subjects: 1) with vs. those without the MetS; 2) within the upper vs. 3 lowest sex-specific quartiles of arterial stiffness score;

\* $P < 0.05$ ; <sup>†</sup> $P < 0.01$ ; <sup>‡</sup> $P < 0.001$ .

O030

**Parenting styles and practices and adolescent soft drink consumption****KA VAN DER HORST<sup>†</sup>, S KREMERS<sup>‡</sup>, I FERREIRA<sup>†</sup>, AS SINGH<sup>‡</sup> and J BRUG<sup>†</sup>**

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**Introduction:** Parents largely provide the eating environment of their children. Considering the increase in soft drink consumption by adolescents and its association with obesity, the present study aimed to investigate whether dimensions of parenting styles (strictness and involvement) and specific parenting practices are associated with adolescent's soft drink consumption. A combined a contextual model of parenting style with the Attitude, Social influences, Self-efficacy (ASE) model was used.

**Participants and methods:** Secondary school students ( $n = 383$ , mean age 13.5  $\pm$  SD years) from five schools completed a self-administered questionnaire on soft drink consumption, ASE variables, habit strength and parenting variables. Data were analyzed with the use of multiple linear regression models.

**Results:** Parenting practices were significantly related to soft drink consumption so that the more restrictive parental practices, the less soft drink were consumed ( $\beta + -38.0$  ml/day, 95% CI + -48.1; -28.0). Although this association was highly mediated (about 50%) by habit strength, attitudes and parental modeling, parenting practices nevertheless remained independently associated with soft drink consumption ( $\beta + -17.1$  ml/day; 95% CI + -27.2; -6.90). Significant interactions between parental style dimensions and parenting practices further indicated that parenting practices were associated with less adolescents' soft drink consumption in those who considered their parents to be high in strictness and low involved.

**Conclusion:** Parenting practices and styles play a key role on adolescent's soft drink intake, especially through modeling and parenting. Strict rules within an involved and not too strict parenting style have the most positive effects on adolescents' soft drink consumption. These findings highlight the importance of involving parents in obesity prevention campaigns and interventions aiming at the young.

## T6: Adipose Tissue Biology

O031

**Adipose-tissue infiltration with monocytes in humans**  
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**Introduction:** The infiltration of adipose tissue by monocytes has recently been demonstrated in animal models of obesity. This raises the question how adipocytes and macrophages influence each other, and challenges the common belief that adipocytes importantly contribute to systemic levels of proinflammatory cytokines.

**Patients and methods:** We studied the genes expression of macrophage markers (CD14 and CD68), chemokines (M-CSF1, MCP-1), and cytokines (IL-6 and TNF $\alpha$ ) in subcutaneous adipose tissue of 65 postmenopausal women (BMI 20–44 kg/m<sup>2</sup>). In a second study, obese hypertensive subjects were divided by high and low levels of CD11b expression on circulating monocytes, and microdialysis data in subcutaneous adipose tissue and skeletal muscle were compared between both groups. CD11b is necessary for monocytes to migrate from blood vessels into tissues, and is expressed only in response to stimuli such as MCP-1. An oral glucose load served to describe systemic insulin sensitivity in these subjects as well.

**Results:** All six genes were expressed at higher levels in adipose tissue of obese subjects. Strong correlations (independent of BMI) were found between chemokine and macrophage marker genes. Gene expression of IL-6 and TNF $\alpha$  was also correlated with markers of macrophage infiltration in adipose tissue. Obese hypertensive subjects with high levels of peripheral CD11b expression demonstrated striking impairments in adipose-tissue glucose handling and lipolysis. These differences occurred despite similar anthropometric and metabolic characteristics.

**Conclusion:** These results suggest an important pathophysiological role for macrophage infiltration of adipose tissue in obese subjects, before systemic deteriorations in insulin sensitivity are detectable.

O032

**A human-specific role of CIDEA in adipocyte lipolysis and obesity**  
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**Introduction:** Cell death-inducing DFFA-like effector A (CIDEA) is expressed in brown, but not white, mouse adipose tissue and CIDEA null mice are resistant to obesity and diabetes. However, the expression and action of CIDEA in human white adipose tissue have so far not been investigated.

**Materials and methods:** Using real-time PCR, CIDEA mRNA levels were determined in subcutaneous adipose tissue of 43 non-obese and 155 obese subjects, of which 12 underwent weight reduction surgery. The results were correlated with previously determined clinical data. Comparative mRNA measurements from white and brown adipose tissue of mice were also performed. Potential *in vitro* actions of CIDEA were investigated by treatment of human preadipocytes with tumour necrosis factor alpha (TNF- $\alpha$ ) and CIDEA siRNA.

**Results:** CIDEA mRNA was expressed in white human fat cells and in brown mouse adipocytes. However, CIDEA was not detectable in white adipose tissue of mice. CIDEA expression was decreased 2-fold in obese humans and levels were normalised after weight reduction. A low CIDEA expression was associated with several features of the metabolic syndrome. CIDEA expression in brown adipocytes of mice was not influenced in different models of obesity. Human adipocyte depletion of CIDEA by RNAi stimulated lipolysis in itself and augmented TNF- $\alpha$  action on lipolysis. In addition, TNF- $\alpha$  treatment decreased adipocyte CIDEA expression.

**Conclusion:** CIDEA appears to play an important and human-specific role in lipolytic regulation and possibly in metabolic complications of obesity. This is at least in part mediated by interactions between CIDEA and TNF- $\alpha$ .

O033

**Neonatal androgenization in female rats results in insulin resistance, increased intra-abdominal fat-depot, adipocyte size and altered immune- and adipogenetic profiles**

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**Introduction:** Neonatal events might contribute to the development of disorders such as type 2 diabetes and obesity at adult age. The aim of this study was therefore to examine the effects of a neonatal injection with testosterone (T) on insulin sensitivity and endocrine characterization of the adipose tissues in the adult female offspring.

**Methods:** Newborn pups received one injection of T. At 16 weeks of age the rats were exposed to a euglycemic hyperinsulinemic clamp. Realtime-RT-PCR was used to study the mRNA expression of the sex steroid receptors and immune- and adipogenetic markers in four different fat-depots. Adipocyte size was analysed with a computerized-image-analysis-system.

**Results:** The adult T-rats had an increased mesenteric adipose tissue weight, decreased serum T and adiponectin levels. They also decreased their insulin sensitivity but increased the mRNA expression of insulin and androgen receptor as well as adipocyte size in the mesenteric adipose tissue only. The immune- and adipogenetic profiles were also altered compared with controls ( $P < 0.05-0.001$ ).

**Conclusions:** The insulin resistance seen in the neonatal T-exposed female rats might be due to the altered expression of adipokines in the hypertrophied adipocytes in the mesenteric fat depot. These results point to an important role of adipose tissue in the development of insulin resistance which can be programmed at early age.

O034

**Identification of distinct expression profiles during adipogenesis in human preadipocytes isolated from different fat depots**  
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**Introduction:** Fat depots vary in size, function, and potential contribution to disease, including metabolic syndrome. Fat tissue turns over throughout life, with preadipocytes undergoing adipogenesis to replace fat cells. Lipid accumulation and adipogenic transcription factor expression varies among differentiated preadipocytes cultured from different depots, suggesting that depot-specific preadipocyte properties contribute to regional variation.

**Methods:** To define mechanisms and consequences of regional variation in adipogenesis, we conducted expression array analyses (9600 transcripts) at 21 time points over 30 days during differentiation of human abdominal subcutaneous, mesenteric, and omental preadipocytes cultured in parallel from 3 subjects (216 arrays; 2.1 million data points). Results were compared to genome-wide arrays at days 0 and 30 in differentiating primary preadipocytes and telomerase-expressing strains derived from single preadipocytes from different fat depots, as well as previously reported profiles of human subcutaneous and omental fat tissue.

**Results:** 503/9600 transcripts varied as a function of depot and time (FDR < 0.1). Generally, the extent, rather than timing, of differentiation-dependent changes in expression varied among depots. PPAR gamma was higher early during differentiation and achieved a higher peak in subcutaneous than visceral preadipocytes. During late adipogenesis, regional differences in expression of PPAR gamma target genes, including aP2, became apparent. These depot-dependent differences in expression were reflected in telomerase-expressing strains, indicating that regional differences in adipogenesis do not result from presence of other cell types in primary cultures and are inherent.

**Conclusions:** The process of adipogenesis differs inherently among human fat depots, potentially contributing to regional variation in fat cell function.

O035

**Elevated serum resistin causes insulin resistance in mice implanted with resistin-overexpressing cells****Y SAITO\***, **Y KITAGAWA\***, **H BUJO†** and **K TAKAHASHI\****\*Department of Clinical Cell Biology and Department of Genome Research and Clinical Application, †Graduate School of Medicine, Chiba University, Chiba, Japan*

**Introduction:** Obesity is frequently associated with metabolic disorders through insulin resistance. Adipose tissue secretes some bioactive molecules, which may play important roles in the development of insulin resistance. Resistin, whose expression is suppressed by thiazolidinedione treatment in adipocytes, is one of key molecules for tightly linking between adiposity and insulin resistance. Here, we show the *in vivo* effects of resistin on insulin sensitivities in mature mice using a cell implantation method.

**Materials and methods:** The resistin cDNA was transfected into 3T3-L1 preadipocytes, and the cells were implanted into subcutaneous areas of athymic mice of BALB/C strain. The metabolic analyses were performed at 6 weeks after implantation.

**Results:** The mice implanted with resistin-overexpressing 3T3-L1 cells (R-mice) showed significantly increased serum resistin levels. Serum insulin levels were significantly increased after glucose loading in R-mice, compared to the mice implanted with mock-transfected cells (M-mice). Decreased glucose response after insulin injection was observed in R-mice, compared to M-mice. Insulin-induced phosphorylation level of IRS-1 was significantly lower in muscles of R-mice than M-mice. TNF- $\alpha$  mRNA expression in intra-peritoneal fat was significantly increased in R-mice, compared to M-mice, although no difference in subcutaneous fat between them. Serum concentration of TNF- $\alpha$  was positively correlated with resistin level in R-mice.

**Conclusion:** Resistin, when actually secreted from the cells in mature mice, causes the disturbed glucose metabolism, possibly based on the decreased insulin sensitivity in muscle. The *in vivo* effects of resistin on insulin sensitivities might be in part mediated by the increased TNF- $\alpha$  expression in visceral fat tissues.

O036

**PPAR gamma activating Angiotensin Receptor Blockers exhibit differential cofactor recruitment and induce altered gene expression in 3T3-L1 adipocytes****M SCHUPP\***, **R GINESTE**, **M CLEMENZ\***, **H WITT†**, **J JANKE†**, **S HELLEBOID‡**, **N HENNUYER§**, **P RUIZ‡**, **T UNGER\***, **B STAELS§** and **U KINTSCHER\****\*Center for Cardiovascular Research (CCR), Institut für Pharmakologie und Toxikologie, Campus Charité-Mitte, Charité-Universitätsmedizin Berlin, Hessische Str. 3/4, 10115, †HELIOS Klinikum Berlin, Franz Volhard Klinik, Campus Berlin-Buch, Charité-Universitätsmedizin Berlin, Wiltberg Str. 50, 13125, ‡Max-Planck Institute for Molecular Genetics, Ihnestr. 73, 14195 Berlin, Germany, §UR 545 INSERM, Departement d'Atherosclerose, Institut Pasteur de Lille and the Faculte de Pharmacie, Universite Lille II, Lille, 59019 France, ¶GENFIT, Parc Eurasante, Loos, France*

**Introduction:** The nuclear transcription factor Peroxisome Proliferator Activated Receptor Gamma (PPARgamma) is a major regulator of lipid and glucose metabolism. Recently, a subset of Angiotensin Type 1 Receptor Blockers (ARBs) has been identified as PPARgamma activating compounds. We studied the interactions between the PPARgamma- ligand binding domain and ARBs, and their impact on gene expression in 3T3-L1 adipocytes.

**Methods:** We used partial trypsin digestion of the recombinant receptor for testing ligand binding, and GST – pull down and Fluorescence resonance energy transfer (FRET) – assays to detect protein – protein interaction. Transient transfection assays were used to confirm results in COS-7 cells with ectopic TIF-2 expression. Furthermore, we carried out gene expression profiling using Oligochips in 3T3-L1 adipocytes treated with ARBs and the TZD Pioglitazone.

**Results:** Irbesartan and Telmisartan released the corepressor NCOR and recruited the coactivator DRIP205 to PPARgamma in a concentration dependent manner. Surprisingly, Telmisartan did not recruit TIF-2, a coactivator implicated in the PPARgamma mediated lipid uptake and storage which was confirmed in cells due to the lack of increased transactivation of Telmisartan with ectopic TIF-2 expression. Gene expression profiling showed a large overlap of genes regulated by TZDs and ARBs but also revealed differentially expressed genes in regard to fat cell function.

**Conclusion:** We provide the molecular basis for a dissociation of beneficial PPARgamma-mediated effects such as insulin sensitization from side effects (e.g. weight gain) elicited by TZD-activation. These data may also help to design future ligands which exhibit antidiabetic action without the use-limiting side effects of TZDs.

## PL2: Heterogeneity in Causes and Development of the Obesity Epidemic

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An epidemic is defined as occurrence of a disease greatly in excess of expectation within a particular population. The term 'the obesity epidemic' refers to the rising prevalence of obesity (BMI  $\leq$  30) or overweight (BMI  $\leq$  25) in most populations of the world. The prevailing interpretation of its causes is that the societies have created a more and more 'obesogenic' environment, because the genetic causes, as the only alternative explanation, cannot change so rapidly. The 'obesogenic' environment is assumed to be continuous exposure to living conditions that eventually creates a positive energy balance of the body by increasing energy intake and reducing energy expenditure by physical activity, leading to deposition of the surplus of energy as fat in the adipose tissue. It is generally assumed that those who become obese in this environment are those susceptible to the environmental changes due to their genetic predisposition. If this paradigm is true, meaning that it is an exclusive and exhaustive interpretation of the epidemic, then the public health challenges to combat the epidemic is huge and perhaps impossible unless fundamental dimensions of the societies – through political and cultural (r)evolutions – are transformed. There is obviously a need to review the components of the paradigm of the obesity epidemic to see which are based on observational or experimental scientific evidence and which are implicit assumptions. There are several elements of circular reasoning in the paradigm, but it seems as if the main missing link is the lack of support to the assumption that the changes of the 'obesogenic' environment, as conceived, provides an adequate explanation of the development of the epidemic. Very few attempts to generate this evidence have apparently been undertaken, and when done they do not provide an unambiguous support. Studies that can address the development of the epidemic in time and space in sufficient detail suggest that an environmental conditioning may take place very early in life, adding to the genetic susceptibility. If this is true, it will pave the way for a preventable target in a limited time window at an age, where preventive actions are commonly accepted, such as vaccinations.

## T1R2: Role of the Brain in the Pathogenesis of Obesity and Metabolic Syndrome

Peripheral signaling to the brain

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Over the past decade, we have seen a steady increase in the number of molecules that signal the body's energy status to the brain. Most short-term acting signals lead to meal termination and include nutrients and factors released by the liver and gastrointestinal tract such as cholecystokinin and PYY3–36. In contrast to satiety factors, ghrelin is released by the stomach and has orexigenic effects. Insulin and leptin signal energy intake and storage and are involved in long-term control of the energy balance. Central interpretation of this complex signalling network occurs in the hypothalamic neurocircuitry leading to properly adapted food intake and energy expenditure via the release of neuropeptides including NPY, orexin and melanocortins. Leptin is a blood-borne protein released by adipocytes and functions via specific receptors on hypothalamic neurons. Since the discovery of leptin, adipose tissue is considered as a complex endocrine organ, also releasing other cytokines, acylation-stimulating protein, adiponectin and resistin. Hypothalamic interpretation of circulating leptin levels leads to appetite suppression and enhanced energy expenditure. Obese people however generally show elevated leptin levels and little response to leptin administration, a phenomenon referred to as leptin resistance. This can be explained by inappropriate transport over the blood-brain barrier, but evidence is accumulating for dysfunctional signal transduction via the hypothalamic leptin receptor. Suppressor-of-cytokine-signalling-3 (SOCS-3) emerges as an important player since reduced SOCS-3 levels lead to elevated leptin sensitivity and to resistance against diet-induced obesity in mice. Leptin receptor signal control is however complex and also CIS and SOCS-2, two other members of the SOCS family and the SHP2 phosphatase can interact with the leptin receptor. Interestingly, the same molecules that convey the energy status to the brain, also have important roles on peripheral tissues. Leptin for example appears to act as a metabolic switch controlling high energy demanding processes such as reproduction and immune function. The marked resistance of leptin-deficient ob/ob mice against various autoimmune diseases illustrates this link to the immune system. A recently developed leptin antagonist is currently being tested in experimental models for autoimmune diseases. Here, a major challenge will be to suppress peripheral leptin activity, without interfering with its hypothalamic function.

## Genetic variation and appetite regulation

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The identification and characterization of patients with morbid obesity due to mutations in single genes has shed light on the molecular mechanisms underlying the hypothalamic regulation of appetite, body weight and endocrine axes. We have identified eight obese children who have undetectable levels of serum leptin and were homozygous for a frameshift mutation in the *ob* gene. These children were severely hyperphagic, constantly demanding food and developed severe disabling obesity, impaired T cell mediated immunity and hypogonadotropic hypogonadism. Treatment with recombinant human leptin for up to seven years led to sustained, beneficial effects on appetite, fat mass, hyperinsulinaemia and hyperlipidaemia. The major impact of leptin was on food intake with a marked reduction in caloric consumption during a test meal. Leptin administration permits the full progression of appropriately timed puberty but does not appear to cause precocious activation of puberty in younger children. Mutations in the leptin receptor result in a similar phenotype. We have recruited over 1500 patients with severe, early onset obesity as part of the Genetics of Obesity Study (GOOS). Complete loss of pro-opiomelanocortin derived peptides results in isolated ACTH deficiency, red hair, pale skin and obesity. Common variants in this gene may also contribute towards obesity at a population level. We have recently identified a third patient with a mutation in pro-hormone convertase-1 which results in a complex endocrinopathy and enteropathy due to a failure of prohormone processing. Loss of function mutations in the melanocortin 4 receptor (MC4R) cause a dominantly inherited obesity syndrome that accounts for up to 6% of patients with severe, early-onset obesity. MC4R deficiency is characterised by hyperphagia, severe hyperinsulinaemia and increased linear growth. These studies provide evidence for the pivotal role of the leptin-melanocortin system in energy balance and neuroendocrine function in humans.

**Dissecting neuronal pathways for appetite control****ML AUBERT, DD PIERROZ and PD RAPOSINHO***Division of Paediatric Endocrinology and Diabetology, Department of Paediatrics, University of Geneva School of Medicine, 1211 Geneva 14, Switzerland*

Ingestive behavior and body weight (BW) homeostasis are controlled by multiple, interacting neuroendocrine circuits involving neuropeptides such as Neuropeptide Y (NPY), Melanocortins (MCs), AGRP, CART, Orexin, etc. These circuits are sensitive to peripherally produced hormones such as leptin, insulin and ghrelin that relay metabolic messages to the brain. Knowledge of the neuronal circuits that control food intake and related hormonal regulations has extended our understanding of *energy homeostasis*, the process whereby energy intake is matched to energy expenditure over time. Also to help the design of drugs targeted for pharmacological interventions in the field of obesity. Catabolic neuronal pathways are those that both reduce food intake and increase energy expenditure (MC neurons producing  $\alpha$ -MSH), pathways that are *stimulated* by input from insulin and leptin. In contrast, anabolic pathways (neurons containing NPY or AGRP) are those that stimulate food intake and decrease energy expenditure, and these pathways are strongly *inhibited* by insulin and leptin. Set points for the balance of neuronal stimulation of food intake and energy expenditure regulating BW homeostasis may have changed with the new trend of increase in food availability and energy intake. Once set to regulate a neuronal system adapted to scarcity of food, the new abundance of food dictates an adaptation of this system that may have been slow to occur, therefore biased toward weight gain. The epidemic of obesity could be at least partly explained by this lack of adaptation to the recent abundance of food. Since in many situations, neuroendocrine axes are highly dependent upon nutritional status, the question arises whether the different hypothalamic neuropeptides known to control feeding may be involved in the control of hypothalamic-pituitary endocrine axes. NPY is known to modulate sexual behavior and gonadotropin secretion and the concept prevails that NPY acts as an inhibitory factor on GnRH release when metabolic conditions are altered and dictate temporary reduction in reproductive activity.  $\alpha$ -MSH is a key satiety factor that acts through the receptor subtypes MC3/MC4. Disruption of synthesis of POMC or MC4-R ends up in obesity *but normal fertility*. A better knowledge of the physiology of these factors is needed for the understanding of such diseases like anorexia nervosa, cachexia, or bulimia that are mixed metabolic and endocrine pathologies.

**T2R2: Prevention of Obesity****Environmental determinants of overweight and obesity****S KUMANYIKA***University of Pennsylvania School of Medicine, USA*

Obesity is determined by eating behaviors and physical activity patterns, which are in turn influenced by the interactions between environmental and lifestyle options and obligations and personal choices in the relevant domains. Several conceptual models are available to assist with systematically thinking about the different types of environmental determinants, how they impact on behaviors of populations and individuals, and possible ways to modify environments or environmental pathways that lead to obesity. The general nature of the problem is considered similar across societies, e.g., excess exposure to and promotion of high calorie foods and disincentives to daily physical activity, interacting with people's predispositions towards overeating and inactivity. However, the nature of the problem and of potential solutions will vary according to social policies, cultural context, infrastructure in urban and rural areas, and population characteristics. The development of ways to assess these environmental variables is progressing. The ability to demonstrate differences in food or physical activity patterns according to environmental variations is still limited, in part because of the complexity of the pathways involved but also because the theoretical relationships between individual choices and environmental options have not been well articulated. Most lacking is confirmation of hypothesized causal pathways from controlled trials in which environmental determinants are altered, partly because many pathways involving societal level phenomena cannot be studied experimentally, and also because no single environmental intervention is likely to be successful. The relevant environmental determinants involve fundamental social processes and will require comprehensive approaches in multiple levels and across multiple sectors. Effecting changes on such a broad scale may seem impossible, especially to those of us in the health sector, since many of the determinants of interest are controlled by other sectors such as commerce, transportation, politics, education, agriculture, economics, and media. Retrospective analyses of large scale changes in environmental determinants of other public health problems can be useful for envisioning what forms success in addressing environmental determinants of obesity might take.

**Evidence on the effectiveness of public health interventions****J TUOMILEHTO (FINLAND)****Not received**

**Health economics of obesity: new insights****AM WOLF***Department of Health Evaluation Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA*

The prevalence of overweight and obesity continues to rise at an alarming rate throughout Europe and the world. Economics play a role in the causes and consequence of obesity. Increased rates of obesity in the United States has been linked to food supply trends and the growing consumption of energy-dense foods. Drewnowski recently linked obesity to dietary energy density and the energy costs of foods. Chou explored how the number of fast food and full service restaurants, the price of food consumed at home, the price of cigarettes as well as the hours of work and hourly wage rate shapes individual food choices and are the primary economic variables responsible for the increase rate of obesity in the US. Having knowledge of economic causes of obesity may help researchers develop interventions infused with economic theory that may help reduce obesity rates. Examples from tobacco will be used. Obesity, in addition to having economic causes has economic consequences. Obesity accounts for 2 to 6% of a nation's health care costs in North America and Europe. Overweight accounts for an additional 3.7%. The effects of obesity on health care costs already exceed those of smoking and problem drinking. Increases in obesity prevalence alone accounts for 12% of the growth in health care spending in the US. Health care costs increase by grade of obesity but in a non-linear fashion and the pattern of increase differs by gender. Age and race also influence how obesity impacts health care costs with the greatest health care costs observed among Caucasian people ages 55–64. Comorbid conditions, especially diabetes, cardiovascular disease and osteoarthritis, explain most of the increased health care costs but an independent effect of obesity on health care costs has been documented. In the US, a higher BMI is associated with prescription medication, outpatient, inpatient and emergency room expenditures. Prescription medication use appears to be the primary driver of increased health care expenditures. Higher grades of obesity are also associated with lost productivity and disability. Understanding economic consequences of obesity may help direct treatment prioritisation.

**T6R1: Mechanisms Involved in the Development of Metabolic Syndrome****Genetic of the metabolic syndrome****M LAVILLE and E HERRIOT***Lyon-France*

Although the precise definition of the metabolic syndrome is still under discussion, it appears that insulin-resistance is a major feature of the metabolic syndrome. One could thus consider that the basis of the metabolic syndrome insulin-resistance and thus that genetic of the metabolic syndrome is those of insulin-resistance. In contrast, as the metabolic syndrome was introduced as a diagnostic category to identify individuals that satisfy three of five relatively arbitrarily chosen criteria, the value of the notion of the metabolic syndrome must be considered not in pathophysiologic terms, but as a pragmatic approach. Consequently, genetics factors involved in each component of this syndrome should be considered. Role of adipose tissue glucocorticoid production appears to have a role in both the regional repartition of adipose tissue and the genesis of hypertension. The local production of angiotensinogen also plays a role both in the recruitment of preadipocytes and hypertension. Transcriptional factors from PPAR family are also involved in adipose tissue differentiation, lipid profile, and lipid oxidation and insulin sensitivity and should also be considered. Defect in adiponectin secretion has also been suggested as involved in the metabolic syndrome. The possible implication of all this parameters will be reviewed and considered with regards to insulin resistance. Whether mechanisms involved in insulin resistance or able or not to explain all the features of the metabolic syndrome will be discussed.

**Differential functions of visceral, subcutaneous and ectopic fat****B RICHELSEN***Dept. of Endocrinology and Metabolism, Aarhus University Hospital,**Tage Hansensgade, Aarhus C, Denmark*

Recent findings indicate that the metabolic syndrome (MS) is mainly linked to the amount of visceral adipose tissue (VAT) and that the subcutaneous adipose tissue (SAT) in the gluteal-femoral region may even have protective effects. Moreover, MS is related to accumulation of fat in other tissues than the AT (e.g. liver, muscle and  $\beta$ -cells). Thus, the different health effects of AT in various topographic locations may be due to inherent differences in the functions of the AT/adipocytes in the various depots. We and others have found that adipocytes from VAT is more lipolytic active and insulin less antilipolytic active in these cells as compared with adipocytes from SAT and s.c. gluteal adipocytes, and high levels of FFA is a known mediator of MS. Comparison of several adipocyte-derived proteins has generally shown a higher expression and higher protein production of substances mediating or positively related to MS (such as PAI-1 and several cytokines – TNF $\alpha$ , IL-6, IL-8) in adipocytes from VAT as compared with SAT. Moreover, adiponectin which may improve insulin sensitivity is expressed to a lesser extent in VAT. Many of these differences between VAT and SAT seem to be due to the different amount of infiltrating macrophages in the two depots with higher amount of macrophages in VAT as compared with SAT. Why macrophages accumulate to a higher extent in VAT is still unknown but we have found a higher expression of MCP-1 in VAT which is an important chemoattractant substance and may play a role for attracting macrophages preferentially to VAT. Thus, VAT may be looked upon as an inflammatory fat depot. Still new adipocyte-derived proteins are discovered and very recently a protein, visfatin, has been shown to be highly expressed and produced from VAT and rather surprisingly it seems that visfatin has insulin mimetic effects maybe through interaction with the insulin receptor. The importance of visfatin is, however, still unknown. In conclusion AT-derived compounds (FFA and various proteins) may be involved in the health complications of obesity and differential function of the AT in various regions may explain why some fat depots are positively related to MS whereas others are not or even protective.

**Inflammation, obesity and the metabolic syndrome****JS YUDKIN***University College London, London N19 5LW, UK*

Adipose tissue expresses cytokines which inhibit insulin signalling pathways in liver and muscle. Obesity also results in impairment of endothelium-dependent vasodilatation to insulin. We have previously suggested that adipocytokines expressed and secreted by adipose tissue might contribute to the coexistence of insulin resistance and endothelial dysfunction, and ultimately to atherothrombotic vascular disease. However the best characterised of the adipocytokines which contributes to insulin resistance is tumour necrosis factor- $\alpha$ , a molecule which under normal circumstances circulates in low concentrations and is likely to be inactive in the systemic circulation because of association with binding proteins. We now propose a vasoregulatory role for local deposits of fat around blood vessels, which may contribute both to insulin action and to vascular endothelial dysfunction. In particular, we propose that the localised fat depot around the origin of arterioles supplying skeletal muscle may play a physiological role in blood flow distribution. Isolated first order arterioles from rat cremaster muscle are under dual regulation by insulin, which activates both endothelin-1 mediated vasoconstriction and nitric oxide mediated vasodilatation. In obese rat arterioles, insulin-stimulated nitric oxide synthesis is impaired, resulting in unopposed vasoconstriction. We propose this to be the consequence of production of the adipocytokine tumour necrosis factor- $\alpha$  from the cuff of fat seen surrounding the origin of the arteriole in obese rats – a depot to which we ascribe a specialist vasoregulatory role. We suggest that this cytokine accesses the nutritive vascular tree to inhibit insulin-mediated capillary recruitment – a mechanism we term ‘vasocrine’ signalling. We also suggest a homology between this vasoactive periarteriolar fat and both periarterial and visceral fat, which may, through outside-to-inside signalling, play a direct role in producing the inflammatory changes found in atherosclerotic plaques. These observations may help explain relationships between visceral fat, insulin resistance and vascular disease.

**PL4: Childhood Obesity and Adult Risk of Disease****W.H. Dietz***Centers for Disease Control and Prevention, Atlanta, GA, USA*

We initially postulated that the three periods of risk for adult disease between conception and adulthood were the prenatal period, the period of ‘adiposity rebound’, and adolescence. More recent data confirm that increased birthweight is associated with an increased risk of subsequent overweight, whereas reduced birthweight is not. The period of ‘adiposity rebound’ refers to the increase in body mass index (BMI) that occurs at approximately six years of age, after BMI reaches its nadir. A more accurate description of this period is the period of BMI rebound, because it is not completely clear that increases in adiposity are what determine the increase in BMI. Some data suggest that early BMI rebound is associated with an increased BMI in later life. However, as the growth curves indicate, children with increased BMIs tend to have an earlier BMI rebound, suggesting that BMI at the time of rebound may be a more important determinant of subsequent BMI than the timing of BMI rebound. Most data now suggest that an increased BMI in early childhood is associated with an increased risk that BMI will be increased later in life. For example, in the Bogalusa Study, half of all adults with a BMI  $\leq 40$  had onset of overweight prior to eight years of age. This observation suggests that early childhood onset overweight rather than the period of adiposity rebound may increase the risk of later obesity and its complications. In the Bogalusa cohort, the risk of adult cardiovascular risk factors appeared related to the severity of obesity rather than the age of onset. The final period of risk appears to be adolescence. This risk may be compounded by the gender-related patterns of fat deposition that occur in adolescence; males tend to deposit fat centrally, whereas females tend to deposit fat gluteally.

### T3: Somatic Consequences of Obesity

O037

**Obesity, fat distribution and upper airways size evaluated by acoustic pharyngometry in women**

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**Introduction:** Visceral obesity is a risk factor for Obstructive Sleep Apnoea (OSA). A reduction of pharyngeal size caused by fat deposition around the pharynx has been described in men with visceral obesity and OSA. In women, the relationships between obesity, fat distribution and pharyngeal morphology are less clear.

**Patients and methods:** BMI, waist, neck circumferences, and sagittal abdominal diameter (SAD) were measured in 90 women (BMI range 18.4–45.9 kg/m<sup>2</sup>). Upper airways size were evaluated by acoustic pharyngometry in clinostatic and orthostatic position. The cross-sectional area of the pharynx at the oro-pharyngeal junction, the area at the glottis and the mean pharyngeal area in between were measured.

**Results:** The cross-sectional area at the oro-pharyngeal junction in the orthostatic position (OPJ) was negatively related to BMI ( $r = -0.28$ ;  $P < 0.01$ ), waist ( $r = -0.25$ ;  $P < 0.05$ ), SAD ( $r = -0.32$ ;  $P < 0.005$ ), and neck ( $r = -0.25$ ;  $P < 0.05$ ). In multiple regression analysis, the only variable found to be correlated to OPJ was SAD ( $P < 0.05$ ). Patients were divided in three groups: non obese women (BMI  $< 30$  kg/m<sup>2</sup>), subcutaneous obese women (BMI  $> 30$  kg/m<sup>2</sup> and SAD  $< 25$  cm) and visceral obese women (BMI  $> 30$  kg/m<sup>2</sup> and SAD  $> 25$  cm). OPJ was lower in women with visceral obesity ( $1.37 \pm 0.29$  cm<sup>2</sup>) than in subcutaneous obese ( $1.67 \pm 0.26$  cm<sup>2</sup>;  $P < 0.05$ ) and non obese women ( $1.71 \pm 0.31$  cm<sup>2</sup>;  $P < 0.01$ ).

**Conclusion:** We demonstrated an inverse association between upper airways size and adiposity and visceral fat distribution in women. The anthropometric measurement more strictly related to a low cross-sectional area of the pharynx was SAD, the most reliable index of visceral fat accumulation.

O038

**The effects of weight reduction in paf-acetylhydrolase and paraoxonase activities in obese subjects**

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**Introduction:** Platelet-activating factor acetylhydrolase (PAF-AH or Lp-PLA<sub>2</sub>) is a Ca<sup>2+</sup>-independent phospholipase A<sub>2</sub> primarily associated in plasma with LDL. Increased plasma PAF-AH levels have been associated with increased cardiovascular risk in large clinical trials. Paraoxonase 1 (PON1) is an esterase associated with HDL and substantially contributes to its antiatherogenic effects. In this study we examined the effect of weight reduction in PAF-AH and PON1 activity in obese subjects.

**Patients and methods:** 28 obese women participated in a weight reduction program. All subjects received a low-calorie diet. Body weight (BW), serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) levels as well as PAF-AH and PON1 activities were measured at baseline and after 4 months of weight loss.

**Results:** At baseline BW was  $99 \pm 15$  kg and BMI  $38 \pm 4.9$  kg/m<sup>2</sup>. Program patients lost  $10.2 \pm 5$  kg ( $P < 0.001$ ). A significant decrease of TC, LDL-C and TG levels was observed after weight loss (all  $P < 0.05$ ). Moreover, PAF-AH activity was reduced from  $49 \pm 15$  nmol/ml/min to  $44 \pm 14$  nmol/ml/min ( $P < 0.01$ ), while PON1 activity did not change significantly. Patients with the highest PAF-AH activity at baseline presented the greatest decrease after weight loss ( $r = 0.49$ ,  $P < 0.01$ ).

**Conclusion:** Weight loss may result in a significant reduction of PAF-AH activity whereas it does not affect PON1 activity in obese patients.

O039

**Sympathovagal balance and metabolic correlates in obesity and sleep apnea**

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**Introduction:** Heart rate variability (HRV) has been indicated as an indicator of cardiovascular risk. Since primary obesity and obstructive sleep apnea (OSA), have a cardiovascular risk higher than normal weight population, we have studied the role of autonomic balance in relation to the degree of overweight, fat topography and metabolic parameters in these two pathological conditions.

**Patients and methods:** One hundred and twenty six men with obstructive sleep apnea (OSA, BMI  $+ 31.7 \pm 4.6$  SD) and 90 obese men (OB, BMI  $+ 34.8 \pm 4.7$  SD), were consecutively studied by evaluating metabolic profile, blood pressure, BMI, waist (W) and hip (H) circumference and sagittal abdominal diameters. In very selected subgroups obtained according to the absence of any condition or medication able to influence autonomic balance, the study of HRV was performed by spectral analysis on a 24 h ECG Holter.

**Results:** In spite of a lower BMI, OSA subjects showed values of sagittal abdominal diameters similar to the ones of OB men; a prevalent fat accumulation was demonstrated in both groups. A significant relation linked BMI and W to blood pressure. OSA subjects showed a significant increase of LF/HF ratio (sympathovagal balance), and a significant decrease of pNN50 (parasympathetic/vagal activity).

**Conclusion:** Weight excess and visceral obesity are the main factors involved in the onset and progression of cardiovascular disease. In OSA subjects a relative increase in sympathetic tone parallel to a well evident decrease of the parasympathetic drive may play an additive role in the pathogenesis of cardiovascular diseases.

O040

**Waist circumference, quality of life, and gender differences in overweight and obese persons**

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**Introduction:** Abdominal obesity as measured by waist circumference has been associated with increased cardiovascular risk and decreased general health-related quality of life (QOL). This study (1) assesses the relationship between waist circumference and a measure of QOL previously validated for obese persons (IWQOL-Lite), and (2) determines whether waist circumference adds additional predictive information about QOL over and above BMI.

**Patients and methods:** 1033 participants were analyzed retrospectively from a data base of a clinical trial assessing waist circumference variation and QOL (mean age  $+ 47.8$ ; BMI  $+ 34.0$  kg/m<sup>2</sup>; 60.6% female; 96.8% Caucasian). At baseline and one year, participants completed the IWQOL-Lite. **Results:** Higher waist circumferences at baseline were associated with lower total QOL scores for men ( $r = -0.43$ ) and women ( $r = -0.35$ ), as well as lower scores on all subscales (all  $P$  values  $< 0.001$ ). One-year decreases in waist circumferences were associated with statistically significant improvements in QOL for both men and women (all  $P$  values  $< 0.01$ ), with changes in physical function, self-esteem, and total score being most pronounced. In predicting baseline QOL and one-year changes in QOL, waist circumference provided additional information over and above BMI for men but not for women.

**Conclusion:** In persons with abdominal obesity, waist circumference decrease is related to an increase in QOL. The IWQOL-Lite, previously validated with respect to degree of obesity, demonstrates baseline differences among waist circumference categories as well as responsiveness to improvements in waist circumference in this population.

O041

**Changes of heart rate variability in primary obesity: correlations with fat topography and metabolic features**

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**Introduction:** Cardiovascular diseases are important causes of morbidity and mortality in obese subjects, and changes in autonomic nervous system have been proposed as one of the possible pathogenetic mechanisms. The aim of this study was the evaluation of the relationships between changes in heart rate variability (HRV) and primary obesity.

**Subjects and methods:** Twenty nine obese women (BMI + 34.1 ± 3.2 SD) and 16 normal weight controls (BMI + 20.8 ± 2.1) were carefully selected according to the absence of any condition or medication able to affect autonomic balance. In each subject we evaluated: anthropometric and metabolic parameters, and insulin resistance (HOMA). The study of HRV was performed by spectral analysis on a 24 h ECG Holter.

**Results:** The LF/HF ratio (sympathovagal balance), was significantly increased in obese patients during the night when compared to controls (slight increase of sympathetic tone and decrease of the parasympathetic one) and it was significantly related to waist circumference, WHR and HOMA index. The analysis in time domain revealed a significant impairment of diurnal and nocturnal parameters of parasympathetic/vagal activity, being negatively related to weight excess visceral obesity and insulin resistance.

**Conclusions:** In obese women, without any clinical evidence of cardiovascular or metabolic diseases, it is already present at night time an autonomic imbalance, with a relative prevalence of the sympathetic tone on the parasympathetic drive and a significant impairment of parasympathetic tone. Weight excess, visceral obesity and insulin resistance seem to play a primary role in the occurrence of changes of HRV

O042

**Effect of weight loss on biochemical parameters in hypertensive obese**

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**Introduction:** Obesity which is a common problem in both developed and developing countries, is an established risk factor for cardiovascular disease and also associated with other cardiovascular risk factors such as hypertension, diabetes and hyperlipidaemia. In this study we evaluated the effect of weight loss with a combination of diet, orlistat therapy and exercise on biochemical parameters in hypertensive obese.

**Material and method:** Data of 340 obese (BMI ≤ 30) patients (98 men and 242 women, mean age 51.5 ± 12.4) who visited the outpatient obesity clinic were evaluated. There were 205 hypertensives (145 women and 60 men). After the initial visit consisting of clinical evaluation (demographic characteristics, physical examination, weight, height) and biochemical work up (blood glucose, HbA1C, lipids, CRP, fibrinogen) all patients were given an 18 months weight loss program consisting of 3 × 120 mg orlistat, exercise (3 × 1 h/week) and a 1000–1200 kC diet. Biochemical work up was repeated every third month. Medication for diabetes or hyperlipidaemia were not changed during the follow up period.

**Results:** Hypertensive patients had a more prominent weight loss compared to normotensives (20 ± 11 vs 10.9 ± 8,  $P < 0.0001$ ). After 18 months of therapy total cholesterol decreased from 209.6 ± 43 to 154 ± 23 mg/dl ( $P + 0.007$ ,  $r + 0.93$ ), LDL-c decreased from 133.5 ± 32.9 to 86 ± 23 mg/dl ( $P + 0.031$ ,  $r + 0.85$ ), triglycerides decreased from 157 ± 137 to 58.3 ± 18.2 mg/dl ( $P + 0.0007$ ,  $r + 0.98$ ), fasting glucose decreased from 123.3 ± 52.8 to 87 ± 10.6 mg/dl ( $P + .0011$ ,  $r + 0.97$ ), HbA1C decreased from 6.2 ± to 5.4 ± 0.9% ( $P + 0.0083$ ,  $r + 0.92$ ), CRP decreased from 1.5 ± 2.6 to 0.4 ± 0.1% mg ( $P + 0.021$ ,  $r + 0.88$ ) and fibrinogen decreased from 373 ± 59 to 328 ± % mg ( $P + 0.0002$ ,  $r + 0.99$ ). Although there was a substantial increase in HDL-c (45 ± 12 to 57 ± mg/dl), the negative correlation with weight loss was not statistically significant ( $r + -0.044$ ,  $P + NS$ ).

**Conclusion:** Weight loss with a combination of drug therapy with orlistat, diet and exercise causes significant positive changes in lipid and blood glucose levels as well as on CRP and fibrinogen levels in hypertensive obese so that we can conclude that weight loss itself causes a significant risk reduction when coronary artery disease is concerned.

## T4: The Epidemiology of Childhood Obesity

O043

**Concurrent increases in the prevalence and incidence of obesity among Danish schoolchildren**

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**Introduction:** Worldwide, the prevalence of childhood obesity is increasing dramatically. In Denmark, the increase in the prevalence among schoolchildren, aged 7–13 years, followed a distinct pattern for the 1930–1970 birth cohorts. We investigated if the increase in prevalence was mirrored by increases in the incidence and the persistence of overweight and obesity.

**Materials and Methods:** 108 513 girls and 108 513 boys born from 1930–1970 attending primary school in Copenhagen underwent compulsory health examinations at ages 7–13 years. The examinations included measurements of height and weight. We calculated body mass index (BMI; kg/m<sup>2</sup>) and defined overweight and obesity according to international criteria. For each sex and birth cohort, we computed the incidence as the percentage new cases of overweight and obesity and persistence as the percentage of cases continuing in the state of overweight and obesity. The secular trends of the incidence, persistence and prevalence of overweight and obesity were compared.

**Results:** For each gender, the prevalence, incidence and persistence of overweight and obesity followed the same secular trend. The incidence was approximately 5% for overweight and 0.3% for obesity, although it increased across time and was always higher for girls than for boys. Approximately 40 to 60% of overweight children remained overweight. A similar pattern was evident for obesity.

**Conclusion:** The obesity epidemic is already evident among 7-year-old children, and new cases of overweight and obesity emerge before age 13 years. Therefore, the obesity epidemic is explained by an increasing incidence and through an increasing persistence of overweight and obesity.

O044

**The stability of the association between birth weight and childhood overweight during the development of the obesity epidemic**

**S RUGHOLM\***, **LW OLSEN\***, **JL BAKER\***,  
**L SCHACK-NIELSEN<sup>†</sup>**, **J BUA\*** and **TIA SØRENSEN\***

\*The Danish Epidemiology Science Center, Institute of Preventive Medicine, Copenhagen University Hospital, <sup>†</sup>Department of Human Nutrition, The Royal Veterinary and Agricultural University, Denmark

**Introduction:** Birth weight is associated with the risk of developing overweight in childhood. However, it is unknown whether this association has remained stable before and during the current childhood obesity epidemic. Therefore, we investigated the association between birth weight and overweight among Danish girls and boys, ages 6–13 years, who were born from 1936–1983.

**Materials and Methods:** Subjects were 252 961 children with birth weight and annual measurements of height and weight available from school health records. Birth weight was divided into categories of 500 g increments. A body mass index (BMI; kg/m<sup>2</sup>) was calculated for each child, and overweight was defined using IOTF age- and sex-specific criteria. Time was divided into three periods based on the year of birth: 1936–1951, 1952–1967 and 1968–1983. Using the birth weight categories, the relative risk of being overweight was calculated separately for each age, sex and time period.

**Results:** As birth weight increased, the relative risk of overweight increased in a nearly linear manner. Additionally, high birth weight (≤4.0 kg) was consistently associated with an elevated risk of childhood overweight. There were no notable differences in the relative risk observed for every age, among boys and girls, and in every time period.

**Conclusion:** The association between birth weight and later risk of developing overweight during childhood remained stable during the development of the obesity epidemic. Given the recent increase in the numbers of high birth weight infants reported in several countries around the world, there is cause for concern about the future health of these children.

O045

**Alcohol consumption is related to abdominal obesity in adolescent boys, but not in girls, in the Greek population****C LOUPA, M KAKLAMANOY, D KAKLAMANOY, L LANARAS, T TZOTZAS and E KAPANTAS***Hellenic Medical Association for Obesity (HMAO), Athens, Greece*

Data from first national epidemiological large scale survey on the prevalence of abdominal obesity in Greece.

**Aim:** WHR is considered more reliable than BMI, because it is related to abdominal obesity. Aim of this study is to explore a potential relation of alcohol consumption to abdominal obesity in adolescents.

**Patients and methods:** Data was collected by a questionnaire given to a sample of households representative of the Greek population. WHR was calculated from waist and hip circumference. Alcohol consumption was calculated by adding number of units consumed weekly, multiplied by alcohol comprehensiveness of beverages. SPSS version 11.5 was used for statistical analysis.

**Results:** 5808 boys, age  $15.2 \pm 1.7$  and 6692 girls,  $14.1 \pm 0.9$  years were included. Data was not available for girls ages 17–19. 60.3% of boys vs. 80.9% of girls ( $P < 0.001$ ) drunk no alcohol. 23.1% boys, consumed 1–50 g/week, 12.2% 51–150 g, 3% 151–300 and 1.4% > 300. Girls 15.1, 3.3, 0.5 and 0.1%, respectively. WHR was  $0.89 \pm 0.31$  in boys and  $0.82 \pm 0.24$  in girls. In boys, WHR was associated to alcohol consumption ( $P + 0.006$ ). This was not the case with girls ( $P + 0.098$ , Kendall's tau-b).

**Conclusions:** In the Greek population, adolescent boys drink more alcohol than girls. In addition to the effects of alcohol consumption to risk factors of various diseases, alcohol is related to abdominal obesity in boys, but not in girls.

O046

**Obesity in primary school children in the Negev, desert area in southern Israel****N BILENKO<sup>†</sup>, I BELMAKER<sup>\*\*</sup>, L SEGEV<sup>†</sup> and D FRASER<sup>†</sup>**

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**Background:** Childhood obesity is a serious health problem. The objectives of this study were to define the extent of obesity and to identify risk groups in the first graders.

**Methods:** Clustered Socio-Economic Status (SES) stratified sample of 750 first grade children in the Negev. Children with Body Mass Index (BMI) at or above the 95<sup>th</sup> percentile of sex-age-specific BMI charts defined as obese, between 85<sup>th</sup> and 95<sup>th</sup> percentile- at risk for obesity.

**Results:** The overall prevalence of obesity was 8.8% and of risk for obesity – 7.5%. The rates of obesity or at risk for obesity reached 28% in Jews and 18% in Bedouins. In Jews 15.2% of girls and 7.7% of boys were obese ( $P + 0.01$ ), and 28.6% of girls and 19.3% of boys had BMI at 85<sup>th</sup> percentile or higher ( $P + 0.02$ ). Bedouins living inside towns had rates of obesity 3-fold higher than those living outside of towns ( $P + 0.007$ ). Female gender and Jewish origin were factors independently associated with obesity (OR + 2.0 95% CI 1.1–3.7,  $P + 0.02$  and OR + 6.1, 95% CI 2.6–14.6,  $P < 0.001$ , respectively).

**Conclusions:** One in six Negev first graders is obese or at risk for obesity. Intervention programs should address young children and should be gender, SES and culturally specific.

O047

**Prevalence of overweight in a national representative sample of Greek infants and preschool children: the Greek Infant Nutrition Survey (GINS)****Y MANIOS, E GRAMMATIKAKI, E OIKONOMOU, M BIRBILLIS, G MOSCHONIS and M MPARTSOTA***Department of Nutrition and Dietetics, Harokopio University of Athens, Greece*

**Introduction:** Infancy and early childhood are both critical periods of rapid physical growth, cognitive and emotional development. The Greek Infant Nutrition Survey (GINS) is the first study attempting to record the prevalence of overweight on a national representative sample of infants and preschoolers.

**Methods:** 2514 infants and preschool children (1294 boys, 1220 girls) from nursery schools in Greece took part in the study. The measurements conducted included recumbent length, height, weight and derived body mass index (BMI).

**Results:** The mean age of all children surveyed was  $42.4 \pm 11.7$  months. The percentage of children being overweight was increasing with age (11.6%, 14.7%, 16.0%, 18.3% for boys and 12.5%, 16.1%, 16.5%, 17.8% for girls at the age groups of 1–2 year, 2–3 year, 3–4 year, 4–5 year respectively). When the analysis was repeated for the total number of children participating in the study and taking into consideration maternal educational level the percentage of children being overweight was higher for those subjects with lower maternal educational level (<9 year), compared to those with further education (>12 years) (22.5% vs. 15.7%,  $P < 0.05$ ).

**Conclusion** The prevalence rates of overweight and obesity presented in the present study were found to be relatively high and to exceed those reported for other European countries. Due to the tracking phenomenon of obesity and its relation with many other chronic diseases, early prevention of this condition should begin early in life, in order to efficiently tackle these health and social issues.

O048

**Changes in shape and location of BMI-distributions in Swedish children. Interactions of genes and environment?****F RASMUSSEN<sup>\*†</sup>, M ERIKSSON<sup>\*†</sup> and T NORDQVIST<sup>†</sup>**

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**Introduction:** One aim was to disentangle how the shape and location of the BMI-distribution changed among Swedish children over a 12 year period. Another aim was to identify the age during childhood when changes occurred or became manifest.

**Material and methods:** Two population-based cohorts, 2469 children from Stockholm born 1985–1987 and 3650 from Gothenburg born 1973–1975, were compared with respect to BMI-distributions from 2 to 15 years of age.

**Results:** Differences between the BMI-distributions of the two cohorts were present from 5–6 years of age. From age 7, the children born 1985–1987 and belonging to the upper parts of the BMI-distribution, e.g. those above the 90<sup>th</sup> or 95<sup>th</sup> BMI percentiles, had much higher BMI mean values compared to their counterparts born 12 years earlier. Comparisons with respect to the 5<sup>th</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup> and 95<sup>th</sup> BMI percentiles showed that changes appeared above the 25<sup>th</sup> percentile and became increasingly pronounced in the upper parts of the BMI-distributions.

**Conclusions:** School aged children in the rightmost parts of the BMI-distributions may be more susceptible to 'obesogenic' environmental exposures than those in the middle or leftmost parts. The results support the suggestion that the period of BMI rebound is critical for development of obesity.

## T5: Pharmacotherapy

## O049

The 5-lipoxygenase activating protein gene is involved in the inflammatory reaction of adipose tissue and in the insulin resistance of the obese subjects

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**Introduction:** Inflammation in adipose tissue may link obesity to insulin resistance and to atherosclerosis. The inflammatory arachidonate 5-lipoxygenase activating protein (alox5ap) gene is involved in the pathogenesis of atherosclerotic cardiovascular disease. We investigated alox5ap in adipose tissue of obese and non-obese subjects.

**Methods:** ALOX5AP mRNA expression was compared in adipose tissue between 20 lean and 49 obese subjects, and nine women before and two to four years after gastric banding surgery. In addition ALOX5AP mRNA was compared between the various types of cells in adipose tissue. For measuring alox5ap mRNA levels quantitative real time PCR was used. Western blot was used for detecting flap and 5-lipoxygenase protein. Genotyping was performed on 231 non obese and 350 obese men.

**Results:** Alox5ap mRNA was expressed in the different cell types of adipose tissue. The alox5ap protein, 5-lipoxygenase activating protein, as well as 5-lipoxygenase itself were detected in isolated adipocytes. mRNA levels of alox5ap in subcutaneous adipose tissue were 80% higher in obese than in lean women, and was normalized after weight reduction in the obese. Among the obese women a high adipose mRNA expression of alox5ap associated with several features of the metabolic syndrome independently of age and body mass index. Alox5ap gene polymorphisms did not associate with obesity. In conclusion, the expression of alox5ap is increased in adipose tissue from obese subjects. A high expression is associated with metabolic syndrome phenotypes indicating that the gene may induce inflammation in adipose tissue of the obese by facilitating 5-lipoxygenase activity in fat cells leading to insulin resistance.

## O050

Safety, dose-tolerance, and weight-related effects of pramlintide in obese subjects with or without type 2 diabetes

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**Introduction:** In addition to its glucoregulatory effects in insulin-treated patients with diabetes, pramlintide (PRAM), an analog of the beta-cell hormone amylin, has shown various effects relevant to obesity in previous trials. These include meal-related satiety, food intake reduction, and sustained weight loss in overweight/obese subjects with insulin-treated type 2 diabetes mellitus (T2DM; 120 µg).

**Patients and methods:** Randomized, triple-blind, placebo (PBO)-controlled study assessing safety, dose tolerance, and weight-related effects of PRAM, at doses >120 µg, in obese, non-insulin-treated subjects. After a 1-week PBO lead-in, 204 obese subjects [160 nondiabetic, 44 T2DM (metformin only), 80/20% F/M, age 48 ± 10 years, BMI 37.8 ± 5.6 kg/m<sup>2</sup>, mean ± SD], were randomized (2 : 1) to 16 weeks of treatment with PRAM or PBO TID (4-week dose escalation based on tolerability, 12-week dose maintenance, no lifestyle intervention).

**Results:** PRAM was well tolerated with ~90% of subjects able to escalate to 240 µg TID. No unexpected safety signals and no severe hypoglycemia were observed. The most common adverse event reported for PRAM vs. PBO was mild, transient nausea (36% vs. 22%). PRAM-treated subjects completing 16 weeks experienced progressive weight loss [mean ± SE PBO-corrected 3.6 ± 0.6% reduction in body weight (3.5 ± 0.6 kg,  $P < 0.0001$ )]. Approximately 31% (vs. 2% PBO) of these subjects achieved ≤ 5% weight loss ( $P < 0.0001$ ). The PBO-corrected weight loss with PRAM was observed in nondiabetic and T2DM subjects (3.4 ± 0.8 and 3.7 ± 1.0%), was most pronounced in subjects with a baseline BMI < 35 kg/m<sup>2</sup> (4.8 ± 1.0%), and was accompanied by reduction in waist circumference (3.4 ± 1.1 cm,  $P < 0.003$ ). PRAM-treated subjects not reporting nausea during the study experienced similar weight loss as those who did (3.5 ± 0.5 and 3.6 ± 0.7%).

**Conclusion:** These results provide additional insights into the safety and tolerability of PRAM and support further evaluation of PRAM as a potential obesity treatment.

µ = microgram

## O051

A phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of rising doses of AC162352 (synthetic human PYY<sub>3-36</sub>) in lean and obese subjects

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\*Amylin Pharmaceuticals, Inc., †Profil Institute for Metabolic Research, Ltd., San Diego, CA, USA, ‡University of Leeds, Leeds, UK

**Introduction:** Peptide YY<sub>3-36</sub> (PYY<sub>3-36</sub>), a gut peptide secreted in response to meals, has been reported in some studies to decrease food intake and body weight in rodents when administered peripherally. Studies in lean and obese humans showed that a 90-min infusion of PYY<sub>3-36</sub> prior to a buffet meal reduced ad-libitum food intake and hunger ratings. The anti-obesity potential of PYY<sub>3-36</sub> remains to be determined.

**Patients and materials:** This single-dose, dose-rising study examined the safety, tolerability, and pharmacokinetics (PK) of AC162352 in cohorts of 5 lean (BMI 18–25 kg/m<sup>2</sup>) and 5 obese (BMI 30–45 kg/m<sup>2</sup>) subjects. Within each cohort, subjects were randomized to receive a single, subcutaneous injection of either AC162352 or placebo in a 4 : 1 ratio. Immediately after injection, subjects ingested a standardized breakfast (20% of daily caloric requirements). Hunger ratings were assessed hourly using visual analogue scales.

**Results:** AC162352 appeared to be generally well tolerated over a wide range of doses. Doses from 2 µg up to 60 and 200 µg were tested in cohorts of lean and obese subjects, respectively. The dose-limiting adverse events were nausea/vomiting in lean and obese subjects. No safety concerns were identified relative to vital signs, ECG, laboratory parameters, or physical findings at the doses tested. Plasma PYY concentrations generally peaked ~30 min after injection, with dose-dependent increases in C<sub>max</sub> and AUC<sub>0-5h</sub>. In both lean and obese groups, there was a trend towards increased hunger suppression and satiety quotient (integrated measure of satiety and food intake) 1 h after breakfast with AC162352 vs. placebo.

**Conclusion:** The safety, tolerability, and PK results of this study support further investigation of AC162352 as a potential obesity treatment.

## O052

Pramlintide reduced ad-libitum food intake and meal duration independently of ghrelin, PYY, CCK, and GLP-1: further evidence for a physiological role of amylin agonism in human appetite control

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**Introduction:** We have reported that a single preprandial injection (120 µg) of pramlintide (PRAM), an analog of the beta-cell hormone amylin, reduced ad-libitum food intake in obese subjects and subjects with type 2 diabetes, a finding consistent with the well-established anorexigenic effect of amylin in rodents.

**Patients and methods:** To further elucidate amylin's role as a physiological satiety signal in humans, we studied a lower dose of PRAM (30 µg) in 15 healthy, normal-weight men (age 24 ± 7 years, BMI 22.2 ± 1.8 kg/m<sup>2</sup>, mean ± SD). In a randomized, double-blind, placebo (PBO)-controlled, crossover study, subjects underwent a standardized buffet meal test on two occasions. After fasting overnight, subjects received a single SC injection of PRAM (30 µg) or PBO, immediately followed by a standardized preload meal. After 1h, subjects were offered an ad-libitum buffet meal with measurement of total caloric intake (TCI) and meal duration.

**Results:** Compared to PBO, PRAM elicited significant mean ± SE reductions in TCI (1412 ± 94 vs. 1190 ± 117 kcal, Δ-221 ± 101 kcal, -14 ± 9%,  $P + 0.05$ ) and meal duration (36 ± 2 vs. 31 ± 3 min,  $P < 0.005$ ). Visual analogue scale (VAS) profiles of hunger trended lower and fullness trended higher in PRAM- vs. PBO-treated subjects during the 1<sup>st</sup> h after injection. Hunger and fullness profiles changed similarly during the buffet meal, despite subjects on PRAM consuming 14% fewer kilocalories. VAS nausea ratings remained near baseline, without discernible differences between treatments, and only one subject on PRAM reported nausea as an adverse event. Plasma ghrelin, PYY, CCK, and GLP-1 profiles revealed no evidence that reductions in food intake or meal duration with PRAM were mediated by other orexigenic or anorexigenic gut peptides.

**Conclusion:** These observations with PRAM add support to the concept that amylin agonism may have a physiological role in human appetite control.

O053

**Dietary lead-in weight loss not an accurate predictor of long-term success with orlistat****L VAN GAAL\***, **J HAUPTMAN†** and **P JAMES‡***\*Antwerp University, Antwerp, Belgium, †Roche Laboratories Inc., Nutley, USA, ‡London School of Hygiene and Tropical Medicine, London, UK*

**Introduction:** The original orlistat EU Summary of Product Characteristics (SmPC) required that patients lose  $\leq 2.5$  kg during a 4-week dietary lead-in before initiating orlistat treatment. This was based on the design of the trials supporting the Marketing Authorisation Application. However, those trials included lead-ins to balance groups for ability to lose weight using diet alone, and not to exclude patients from the trial. The SmPC also states that orlistat should be discontinued after 12 weeks if patients have not then lost  $\leq 5\%$  of bodyweight at start of drug therapy.

**Patients and methods:** We analysed data from the 6 MAA trials, to predict those patients most likely to lose 10% of their weight after 1 year's orlistat treatment, by 3 weight loss criteria: (1)  $\leq 2.5$  kg during diet lead-in; (2)  $\leq 5\%$  after 12 weeks' active treatment; and (3) both (1) and (2). Additionally, the XENDOS study, with no dietary lead-in, was analysed by criterion (2).

**Results:** Of the patients who lost  $\leq 10\%$  weight after 1 year, 28% would have been inappropriately denied access to treatment with orlistat by criterion (1). By criterion (2), only 16% would have been denied access. Using both criteria combined, the figure rose to 34%. Similarly, 91% of XENDOS patients would have continued drug access.

**Conclusions:** Patients who do not lose 2.5 kg during dietary lead-in still benefit from orlistat treatment. This requirement has now been removed from the EU SmPC. Weight loss after 12 weeks' orlistat therapy is the best predictor of weight loss at 1 year.

O054

**Sibutramine efficiency in metabolic control of obese diabetic patients****A MAZILU, A MIHAI, C SPIROIU and AE RANETTI***Central Clinical Emergency Hospital, Clinic of Endocrinology & Metabolism, Bucharest, Romania*

**Material and method:** This study compared the Sibutramine efficiency in two groups of diabetic patients using sulfonylurea or insulines, who had a relative good diabetes control (FPG less than 140 mg%, HbA1c less than 7.5%), who were admitted for periodical evaluation of diabetes or for other endocrine pathologies. We used the parameters obtained by physical exam (weight, BMI, waist, BP, HR), biologic assays: lipidogram, glucose, HbA1c, hepatic enzymes, Holter monitoring in the day before starting the therapy, first day of therapy and 6 months of therapy, questionnaire for patient satisfaction after 6 months of therapy.

**Results:** The weight loss was significantly important in the sulfonylurea group ( $4.6 \pm 1.6$  kg) compared to insulin group ( $2.4 \pm 0.95$  kg). Weight reduction more than 5% was obtained in 67.5% of patients treated with sulfonylurea and 52.5% in patients treated with insulin. BMI decreased with  $1.59 \text{ kg/m}^2$  in sulfonylurea group and  $0.97 \text{ kg/m}^2$  in insulin treated patients. The glucose level reduction was similar in both groups. HbA1c decreased by 0.07% in sulfonylurea group and by 0.058% in insulin group. The decrease in LDL cholesterol was more significant in sulfonylurea group, HDL cholesterol increase was reduced and similar in both groups. The increase in systolic BP was reduced in both groups (2.42 and 2.78 mmHg), diastolic BP was significantly increased in insulin group. The premature supraventricular beats increased significantly in the first day of treatment, but returned to near-normal values after 6 months of therapy. The adverse events were dry mouth, constipation, headache, insomnia, but their frequency diminished significantly after first week of treatment. There was no increase of hepatic enzymes. One case had an increase of urea and creatinine and was diagnosed with prostatic adenoma. 4 cases had a paradoxical increase in appetite. 92.5% of patients treated with sulfonylurea and 86.5% of patients treated with insuline were satisfied by this drug and wanted to continue the treatment.

**Conclusion:** Sibutramine is a good adjunctive in obtaining metabolic control.

## T3R1: Adipose Tissue Secretory Function and Obesity-related Co-morbidities

### Obesity, insulin resistance and atherosclerosis

E FERRANNINI (ITALY)

Not received

### Obesity and coagulations

D TSCHOPE (GERMANY)

Not received

### Obesity and male reproductive function

D MICIC

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It was demonstrated that obesity might have significant impact on male sexuality. High body mass index (BMI) may be associated with reduced semen quality. It was shown that obese men presented with less than 1/20th the number of normal-motile sperm cells in men with a normal BMI. Sperm quality decreased in men as their BMI increased, as demonstrated by DNA fragmentation index (DFI). Obesity imposes a risk to vasculogenic impotence by chronic diseases of diabetes, hypertension, heart disease and hyperlipidemia. In the Massachusetts Male Aging Study erectile dysfunction was more frequent among subjects with BMI greater than 29.9 kg/m<sup>2</sup>, reaching a cumulative incidence of 45%. Weight loss by reduced calorie intake and increased exercise lead to improvement of sexual function in obese men with erectile dysfunction. There seems to be an inverse relationship between BMI and testosterone levels and obesity seems to depress the production of testosterone. In obese older man there is increased aromatization of testosterone to estradiol and alteration of the hypothalamic pituitary-adrenal axis. Massive obesity in males is associated with decreased total and free testosterone levels as well as elevated estradiol levels. The decrease in testosterone occurs without the compensatory increases in gonadotropin and a progressive hypogonadotropic hypogonadal cycle develops. With increasing abdominal obesity and BMI, the hypogonadal state progresses and both the free and total testosterone continue to decline. Intervention studies demonstrate that correction of relative hypogonadism in men with visceral obesity seem to decrease the abdominal fat mass and reverse the glucose intolerance and lipoprotein abnormalities in the serum. Leptin, produced in adipocytes, plays an important role in the modulation of gonadal and reproductive function. Leptin missense mutation was described in male patient associated with hypogonadism and morbid obesity. Leptin replacement therapy in leptin-deficient adults with established morbid obesity results in profound weight loss and resolution of hypogonadism. Hyperinsulinemia that exist in obese males may have also a significant effect on the metabolic and gonadal function.

## T4R1: Critical Factors and Periods in the Development of Childhood Obesity

### Hypothalamic obesity syndromes

GP CHROUSOS (GREECE)

Not received

### Critical periods for the development of childhood and adolescent obesity

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Childhood obesity is an important public health problem, with a rapidly increasing frequency worldwide. Identification of critical periods for the development of childhood and adolescent obesity could be very useful for targeting prevention measures. Persistence, or tracking of fatness from childhood to adulthood has been demonstrated in a number of studies, although the magnitude of the effect depends on the cut-offs used to define overweight or obesity, the age at initial assessment and the length of follow-up. A wide range of correlation coefficients and relative risks has been reported. The magnitude of these estimates is inversely associated with the length of follow-up and the age at which the initial measurement is made. The prediction values potentials also differ according to the anthropometric predictors/indicators used. Weight status in childhood is a poor predictor of adult adiposity status and most obese adults were not obese as children. By contrast, most obese subjects had an early adiposity rebound (AR). The difference can be explained by the fact that an early AR, predicting high adult body mass index (BMI), is also associated with a low BMI in the first years of life. An early AR is associated with advanced bone age, and there is now increasing evidence that a rapid growth in infancy or early childhood can predispose to adult onset obesity and metabolic diseases. Various studies report that rapid growth is associated with high large subsequent weight gain, a android/central body fat pattern and cardiovascular diseases. The risk of Type 2 diabetes has been found to be associated with a rapid weight gain in the first weeks of life, and also with an early AR. Subjects with diabetes typically have a low BMI index followed by an early AR and an accelerated increase in BMI. This underlies the importance of BMI growth pattern rather than the absolute BMI level. In conclusion, while absolute fatness level in early childhood is a poor predictor of subsequent fatness, the association between growth pattern (early growth velocity or age at AR for example) and metabolic risks, confirms that early childhood is a critical period for the child's future health and development.

### Eating habits and risks for childhood obesity

I THORSDOTTIR

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The prevalence of overweight and obesity is increasing worldwide. Dietary intake during childhood and the possible influences of certain food groups and nutrients on the development of overweight and obesity in children will be discussed. Infant and childhood eating habits have been studied at the Unit for Nutrition Research in a longitudinal study and in cross sectional studies. Food intake, height, weight and biochemical measures were studied in two cohorts from birth to 1 year, and 2 years, with a follow up at 6 years of age ( $n = 180$ , part.rate = 75%). Fruit and vegetables consumption among 11-year-olds was studied in a cross sectional study (EU-5th FWP Prochildren,  $n = 1350$ , part.rate = 88%). Diet, anthropometry, biochemical measures, physical activity and fitness were studied in schoolchildren at the age of 9 y ( $n = 185$ , participation 95%) and 11 years ( $n = 180$ , part.rate = 89%). Additionally a retrospective study on the association between childhood and adult overweight has been performed at the Unit in co-operation with the Icelandic Heart Association (participants born: 1914–1935,  $n = 4800$ ). The studies show that early nutrition is important in the development of overweight. Six-year-old boys breast-fed <6 months had significantly higher BMI ( $18.0 \pm 2.5 \text{ kg/m}^2$ ) than boys breast-fed 8–9 months ( $15.8 \pm 1.2 \text{ kg/m}^2$ ,  $P = 0.006$ ) and boys breast-fed  $\leq 10$  months ( $15.7 \pm 1.2 \text{ kg/m}^2$ ,  $P = 0.005$ ). Boys in the highest quartile of protein intake (E%) at the age of 9–12 months had significantly higher BMI ( $17.8 \pm 2.4 \text{ kg/m}^2$ ) at 6 years than the lowest ( $15.6 \pm 1.0 \text{ kg/m}^2$ ,  $P = 0.039$ ) and the second lowest ( $15.3 \pm 0.8 \text{ kg/m}^2$ ,  $P = 0.01$ ) quartile. Results on food intake in other age groups and altered food supply in Iceland will be presented. These include for example added sugar, soft drinks, milk, fruit and vegetables and fish. The intake of added sugar is high in Iceland, on average 12.5E% among 2-year-olds and 13E% among 6-year-olds. Anthropometry, energy expenditure, food intake and physical activity among 9 and 15-year-old children and adolescents will be presented. Results from studies on the Heart Association cohort show that children who are overweight at school start are in great risk of becoming overweight as adults, while the risk is lower among children who are overweight at 2 years. Studies from Iceland suggest that lifestyle interventions should start early in life and dietary habits that are formed during the preschool years could be critical for the development of obesity.

## T5R2: Pharmacotherapy and Surgical Intervention

### Pharmacotherapy of obesity: whom and how to treat?

V HAINER

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Antiobesity drugs have been developed for (1) facilitation of weight loss during the lifestyle management, (2) improvement of weight loss maintenance and for (3) reduction of obesity related health risks. Such drugs affect different targets in central nervous system or peripheral tissues aiming to the normalization of regulatory or metabolic disturbances involved in the pathogenesis of obesity. It is expected that a lifelong treatment with antiobesity drugs will be required in order to affect specifically the target abnormality. Identical effectiveness of both continuous and intermittent treatment of obesity was demonstrated for several antiobesity drugs. Pharmacotherapy of obesity has been indicated for the treatment of obese adults ( $\geq 65$  years). However, several studies were conducted recently to evaluate efficacy and safety of antiobesity drugs also in children, adolescents and in the elderly. Pharmacotherapy of obesity should be applied as a part of the comprehensive obesity management which includes lifestyle modification. Our current potential to treat obesity by drugs is limited, as compared with the drug treatment of other diseases as hypertension, diabetes and dyslipidaemias. Currently only two drugs are licensed for the long-term weight management. Sibutramine, as a serotonin and noradrenaline reuptake inhibitor, induces satiety and prevents diet-induced decline in metabolic rate. Orlistat, as an inhibitor of lipase, reduces fat absorption in the intestine. Accessibility of modern antiobesity drugs is frequently limited by socioeconomic situation of obese patients. Among the drugs recently investigated, a special attention has been paid to cannabinoid receptor antagonist rimonabant, dopamine and noradrenaline reuptake inhibitor bupropion (marketed for depression and smoking cessation), anticonvulsant drug topiramate, lipase inhibitor ATL-962 and to intranasal peptide YY<sub>3-36</sub>. Rimonabant prevents addiction and exhibits also some favourable metabolic effects independent of weight loss. Future goals for the drug treatment of obesity include evaluation of: (1) predictors of drug-induced weight loss and its maintenance (as e.g. initial weight loss and genetic, metabolic, nutritional, and psychobehavioral factors), (2) primary drug effects on health risks, (3) efficacy and safety with combined drug treatment.

### How to approach weight loss in a diabetic patient

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**Background:** The relationship between obesity (visceral)-metabolic syndrome-type 2 diabetes-cardiovascular risk is already well defined. There is a great body of evidence demonstrating that weight loss is associated with important benefits for both prevention and control of cardiovascular risk in people with metabolic syndrome and type 2 diabetes. The mechanisms involved in weight loss-related benefits are extremely complex.

**Discussion:** Although a general agreement of weight loss benefits, there still are few aspects to be discussed and further studied:

1. Long-term data assessing the extent to which weight loss can be maintained in persons with type 2 diabetes;
2. Long-term data assessing the extent to which metabolic improvements following weight loss can be maintained;
3. Long-term data assessing the extent to which weight loss can be achieved and maintained in daily practice;
4. The optimal methods to achieve a persistent weight loss.

**Recommendations:** The practical approach to a person with obesity and type 2 diabetes consist of:

1. Global evaluation: cardiovascular and global risk assessment;
2. Personal and environmental assessment;
3. Individualized short/long – term goals setting;
4. Clinical management: 'THEME' Programs:
  - Therapy: lifestyle, behavioral changes
  - weight neutral hypoglycemic agents
  - weight loss pharmacotherapy
  - gastric surgery
  - Education (therapeutic, behavioral patient)
  - Monitoring
  - Evaluation
5. General strategy: initial and long-term approach;
6. Medical team;
7. Medical, social, community facilities.

### Comparison of short and long term outcomes of bariatric interventions

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Surgery for the morbidly obese patients was introduced half a century ago. Current bariatric surgical operations include gastric restrictive, malabsorptive, or combined restrictive/malabsorptive procedures. Currently, surgical treatment is the only long-lasting effective therapy for morbid obesity. The sustainable weight loss achieved by various surgical procedures results in amelioration and, in some cases, reversal of obesity related co-morbid conditions, such as diabetes, hypertension and heart diseases, asthma, osteoarthritis, gastrointestinal symptoms and various metabolic diseases. Currently, the number of reported studies that can provide evidence-based guidance regarding which type of surgery should be undertaken is limited. Thus there is need for randomized controlled trials. Bariatric surgeons still have to rely on the results of large series that have been reported. These studies confirm that bariatric surgery can be carried out safely and that it is associated with reproducible good results. There appears to be a trend for the more severely obese patients (super-obese, BMI > 50 kg/m<sup>2</sup>) to be treated with malabsorptive procedures (Gastric bypass, Bilio-pancreatic diversion, Duodenal switch) and the morbidly obese (BMI 40–50 kg/m<sup>2</sup>) with restrictive procedures, but in this context no clear guidelines exist. The aim of treatment is life long control of obesity and prevention and/or treatment of obesity related morbidity. This aim should be achieved with an acceptable quality of life, and low morbidity and mortality of the surgery.

## T4: Social Consequences and Management of Childhood Obesity

O055

**Ghrelin levels do not change after weight reduction in obese children and adolescents**

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**Introduction:** There are conflicting results for ghrelin changes in reduction of overweight. Increasing ghrelin levels in weight reduction are discussed to be responsible for compensatory mechanisms that make reducing of overweight unlikely to be sustained.

**Patients and methods:** We have analyzed fasting serum ghrelin levels, weighed dietary record and as biochemical markers of clinically relevant reduction of overweight leptin, adiponectin, insulin and insulin resistance measured by homeostasis model assessment (HOMA) at baseline and after a 1-year outpatient weight reduction program based on a high carbohydrate and low fat diet in 37 obese children (median 10 years, median SDS-BMI 2.4). Furthermore, we analyzed ghrelin levels in 16 lean age-matched children.

**Results:** Obese children demonstrated significantly ( $P < 0.001$ ) lower ghrelin levels compared to lean children (median 1754 pg/ml vs. 2760 pg/ml). Daily caloric intake ( $P + 0.004$ ) and percentage fat content decreased significantly ( $P < 0.001$ ), while percentage carbohydrate content increased significantly ( $P + 0.003$ ) between baseline and 1-year follow up in the obese children. Substantial reduction of overweight in 16 children (median decrease of SDS-BMI 29%) was associated with significant changes in insulin resistance (median decrease of HOMA 27%;  $P + 0.013$ ), adiponectin (median increase 15%;  $P + 0.003$ ), and leptin levels (median decrease 19%;  $P + 0.023$ ), while there were no significant changes in ghrelin levels (median increase 4%;  $P + 0.326$ ). In 21 children without weight change, there were no significant changes neither in insulin resistance, adiponectin, leptin nor ghrelin levels.

**Conclusion:** Low fat high carbohydrate diet induced weight loss does not change ghrelin secretion, but significantly decreases leptin levels, increases adiponectin levels and improves insulin resistance in obese children.

O056

**Quality of life of obese children – impact of severity of obesity**

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**Objective:** To assess the impact of obesity on quality of life (QOL) of children, and to compare QOL scores of obese children in a hospital versus community setting.

**Patients and methods:** QOL was assessed by the Pediatric Quality of Life Inventory™ questionnaire in 182 children recruited from the community and a hospital based obesity clinic. Subjects were divided into quartiles of BMI Z scores each containing 45–46 children. The first two quartiles correspond to normal BMI, 3<sup>rd</sup> and 4<sup>th</sup> quartiles represent moderate and severe obesity respectively.

**Results:** Obese children reported significantly lower QOL in physical, social and school domains compared with normal weight children ( $P < 0.01$ ). Analyzing results of QOL by BMI quartiles showed that the emotional and school domains scores of the moderately obese children were similar to the normal BMI quartiles. Only in the 4<sup>th</sup> quartile, that of children with severe obesity, were scores significantly lower. In contrast, in both physical and social domains scores decreased progressively with increased BMI Z scores. Parents' scores were lower than the children's in all domains. QOL scores of obese children assessed in the hospital clinic were similar to that of obese children assessed in the community.

**Conclusions:** Moderately obese children had similar emotional and school QOL scores as normal weight children, whereas in the physical domain a significant difference was documented even in moderate obesity. Parents of obese children perceived their child's QOL lower than the children themselves. Intervention programs aimed at improving QOL should be directed to both parents and children.

O057

**Changes in vital signs by BMI response category in a double-blind, placebo-controlled study to evaluate treatment of obese adolescents with sibutramine**

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**Introduction:** This double-blind, placebo (PLA)-controlled, 12-month study assessed efficacy/safety of sibutramine (SIB) in obese adolescents.

**Patients and methods:** Patients ( $n + 498$ ), ages 12 to 16, mean BMI 36.1 kg/m<sup>2</sup>, with no history of cardiac disease received SIB 10 mg or PLA qd and lifestyle modification (3 : 1 ratio). Patients not meeting specific BMI criteria at Month 6 were titrated to SIB 15 mg or PLA, maintaining randomization. The primary efficacy variable was BMI change from Baseline to Endpoint (Month 12 or patient discontinuation). In a planned exploratory analysis, vital signs (VS) changes were analyzed by BMI change. **Results:** BMI reductions from Baseline to Endpoint of <5%, ≤5%, and ≤10% were observed in 137 (38%), 226 (62%), and 141 (39%) SIB patients, and 104 (82%), 23 (18%), and 7 (6%) PLA patients, respectively.

Mean vs changes by BMI reduction, baseline to endpoint

VS Variable	Treatment group	BMI reduction		
		<5%	≥5%	≥10%
Systolic blood pressure (mmHg)	SIB	0.0	-3.2	-4.5
	PLA	-1.9	-3.8	-4.7
Diastolic blood pressure (mmHg)	SIB	1.8	-1.2	-1.9
	PLA	-0.5	-3.5	-4.1
Pulse rate (bpm)	SIB	0.8	-0.9	-1.8
	PLA	-1.7	-2.0	-4.2

**Conclusion:** More SIB-treated patients achieved ≤5% and ≤10% reduction in BMI than did PLA-treated patients. SIB-treated patients with <5% BMI reduction had no change or small mean increases in VS, compared with the corresponding PLA-treated subset. In both treatment groups, mean reductions in VS at Endpoint were seen in patients with ≤5% BMI reduction, with the greatest reductions in the ≤10% BMI reduction subset.

O058

**Low health related quality of life in school-children with overweight and obesity: a Swedish population survey**

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**Introduction:** Overweight/obesity in adults has been associated with low ratings of health related quality of life (HQOL). Also clinical populations of children with overweight/obesity have shown depressed ratings of health related well-being and function. However, very few studies have addressed children in the general population, especially European children. This study survey HQOL in a general child population.

**Patients and methods:** The study was performed 2003/2004 in Umeå, a university city in northern Sweden. All children ( $n + 1660$ ) attending grade 3 and 6 in the schools of Umeå city completed the HQOL-questionnaire PedsQL. In grade 3 also parents ratings were included. Anthropometrics were collected from the school health records. Overweight was defined according to internationally accepted BMI reference values.

**Results:** Of all children, 21.6% were overweight/obese (overweight: 17.8%; obesity: 3.8%). The total scores of HQOL as well as scores of the subscales, physical functioning and psychosocial functioning (emotional-, social- and school function) were lower in children with overweight/obesity than in non-overweight children. The lowest ratings were found among children with obesity.

**Conclusion:** In this Swedish community based child population, children with overweight/obesity rated their health related quality of life lower than non-overweight children. The rating decreased with increasing level of overweight.

## O059

## Childhood obesity and metabolic syndrome

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**Introduction:** The prevalence of obesity is growing and has been shown to increase the risk of type 2 diabetes and Insulin Resistance Syndrome (IRS: obesity, abnormal glucose homeostasis, dyslipidaemia and hypertension), increasing the risk of cardiovascular disease. Recent studies have revealed the presence of its components in obese children and adolescents. The aim of this study is to assess the prevalence of IRS in obese Brazilian children seeking treatment.

**Methods:** The group consisted of 226 obese children (BMI + 31.57 ± 4.75; BMI Zscore + 4.98 ± 0.95), mean age 10.52 ± 0.35 years old, followed for 2 weeks on a dietary behavior intervention weight loss program. Blood samples were taken for measurement of metabolic profile. Children were randomized in four groups according to gender and age.

**Results:**

Age Gender n (%)	<10 years old		≤10 years old	
	Boys 30	Girls 43	Boys 55	Girls 88
Impaired fasting glucose	2 (6.67%)	5 (11.63%)	6 (10.91%)	1 (1.14%)
Type 2 diabetes	0	0	0	1 (1.14%)
Low HDLc	15 (50%)	9 (20.93%)	17 (30.91%)	24 (27.27%)
High triglycerides	6 (20%)	5 (11.63%)	9 (16.36%)	11 (12.50%)
Glucose intolerance	2 (6.67%)	2 (4.65%)	2 (3.64%)	2 (2.27%)
Hyperinsulinemia	19 (63.3%)	26 (60.46%)	33 (60%)	71 (80.68%)

**Conclusion:** The prevalence of IRS is high among obese children and adolescents. Biomarkers of an increased risk of adverse cardiovascular outcomes are already present in these youngsters. There is a need to establish international acceptable criteria for IRS in childhood.

## O060

## Five year trends in nutrition policies at school in Denmark

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**Introduction:** In 1999 as well as in 2002 the Danish Government included obesity and nutrition as one of the major public health issue in the plan on Health promotion. The hypotheses are that these initiatives may influence a positive change in nutrition policies in Danish schools. The purpose of the present study is to examine five-year trends in nutrition policies at private and public schools in Denmark.

**Population and methods:** Two surveys have been conducted by the National Institute of Public Health, Denmark one in 1999 (Lissau & Poulsen 2000) and one in 2004. In the first survey all public and private schools in Denmark received a self-administered questionnaire.

**Results:** In 1999 only 3% of schools had a written policy on nutrition, in 2004 it had increased to 17%. In 1999, 53% of the schools had refrigerators for the children to preserve their lunch during the morning until lunch break, in 2004 the prevalence increased to 78%. In addition, the following positive changes were seen from 1999 to 2004: fruits and vegetables available every day; 18% to 33%, breakfast served at school; 2% to 6%, and available iced water; 1% to 7%.

**Conclusion:** In conclusion, initiatives from Government on nutrition and obesity contribute in a positive way to an increased focus of nutrition policies in schools including a marked decrease of the prevalence of vending machines in Danish schools.

## T3: Psychological and Social Consequences of Obesity

## O061

## Smoking habits in Greek adults and their relation to body weight

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Data from first national epidemiological large scale survey on the prevalence of obesity in Greece.

**Aim:** The aim of our study was to estimate smoking habits in Greek adults and to possibly correlate them to body weight.

**Patients and methods:** Data was collected by a questionnaire from members of households. A sample of 17 403 adults (8090 males, age 44.6 ± 10.5 and 9313 females, age 41.5 ± 11.1) representing the entire population of Greece was selected. Anthropometry comprised waist circumference (WC), body weight and height for calculation of Body Mass Index (BMI). Statistical analysis used SPSS version 11.5.

**Results:** 60.9% males vs. 32.5% females ( $\chi^2 + 1409.4$ ,  $P + 0.000$ ) were reported as smokers and this significant difference was retained when smoking rates were estimated separately in the three main age groups (51.3% vs. 37.2%  $\chi^2 + 52.4$ ,  $P + 0.000$ , 64.1% vs. 34.4%  $\chi^2 + 1023.2$ ,  $P + 0.000$  and 55.7% vs. 12.2%  $\chi^2 + 520.6$ ,  $P + 0.000$  in the age groups 20–35, 36–50 and 50+ respectively). Male smokers had greater WC and BMI than non-smokers (95.65 ± 15.63 vs. 94.66 ± 15.84,  $P + 0.01$  and 27.38 ± 4.75 vs. 27.23 ± 4.92,  $P + 0.037$  respectively). Female smokers had smaller WC and BMI than non-smokers (84.63 ± 13.89 vs. 85.85 ± 14.79,  $P + 0.000$  and 25.42 ± 5.02 vs. 25.87 ± 5.28,  $P + 0.000$  respectively). When controlling for age, however, the above differences were vanished.

**Conclusions:** Greek males are greater smokers than females. Contrary to general belief, smoking habits are not in any way correlated to obesity indices.

## O062

## Alcohol consumption in the Greek population: is it related to abdominal obesity?

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Data from first national epidemiological large scale survey on the prevalence of abdominal obesity in Greece.

**Aim:** Waist-to-hip ratio (WHR) is considered more reliable than body mass index (BMI), because it is related to abdominal obesity. Alcohol consumption can have both deleterious (ex. hypertension, cardiomyopathy and liver cancer) and beneficial effects (the French paradox). Aim of this study is to explore a potential relation of alcohol consumption to abdominal obesity.

**Patients and methods:** Data was collected by a questionnaire given to a sample of households representative of the Greek population. WHR was calculated from waist and hip circumference. Alcohol consumption was calculated by adding number of units consumed weekly, multiplied by alcohol comprehensiveness of beverages. SPSS version 11.5 was used for statistical analysis.

**Results:** 8090 men, age 44.6 ± 10.5, and 9313 women, 41.5 ± 11.1 years, were included. WHR was 0.97 ± 0.3 and 0.87 ± 0.3 in men and women, respectively. 67.8% of men and 57.7 women had normal WHR ( $\geq 1$  and  $\geq 0.85$ , respectively). 22% of men vs. 54.6% of women ( $P < 0.001$ ) drunk no alcohol. In men, WHR was associated to alcohol consumption ( $P + 0.044$ ). This was not the case with women ( $P + 0.823$ , Kendall's tau-b).

**Conclusions:** In the Greek population, men drink more alcohol than women. In addition to the effects of alcohol consumption to risk factors of various diseases, alcohol is related to abdominal obesity in men only.

O063

**Obesity and attained education – are obese men discriminated against? A study of 762 376 Swedish men born 1952–1973****N KARNEHED\***, **F RASMUSSEN\*†**, **T HEMMINGSSON‡**, **I LUNDBERG‡** and **P TYNELIUS‡**

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**Introduction:** Stigmatization and discrimination of obese individuals have been reported in many affluent societies. The aim of this study was to disentangle the relationship between body mass index (BMI) at age 18 years and attained education with control for intelligence, parental education and parental occupation.

**Material and methods:** All Swedish men born 1952–1973 were followed in registers until 2001. High education was defined as more than, or equal to, 15 years of education. Intellectual capacity and BMI ( $\text{kg/m}^2$ ) were measured at compulsory conscription for military service at age 18 years. The hazard ratio (HR) for attaining high education was estimated with Cox regression controlling for intelligence, parental education and occupation, country of birth and municipality.

**Results:** The study population consisted of 762 376 men with complete data (63% of all identified). Young men who were obese ( $\text{BMI} \leq 30$ ) at age 18 years ( $n + 10\,782$ ) did not attain a high education as often as their normal weight ( $18.5 \geq \text{BMI} > 25$ ) counterparts, adjusted HR being 0.48 (95% CI: 0.45, 0.52). The adjusted HR when considering high education being more than 12 years of education was 0.63 (95% CI: 0.60, 0.66).

**Conclusions:** Obese men in Sweden are doing worse in the educational system than their normal weight counterparts even though adjustments were made for intelligence and parental education and occupation. Few obese individuals start a university education compared to normal weight counterparts but even fewer complete their degrees. We cannot exclude discrimination in the educational system as an explanation for this.

O064

**Impact of depression on adherence to dietary intervention in obese subjects****R RIENER, K SCHINDLER and B LUDVIK**

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**Introduction:** Even structured weight reduction programs in severely obese subjects are characterized by high drop-out rates. Since depression has a higher prevalence in these subjects, we aimed to investigate a potential relationship between symptoms of depression and adherence to a structured weight loss program over one year in obese and morbidly obese subjects.

**Patients and methods:** 18 obese and morbidly obese subjects ( $\text{BMI} 41.2 \pm 2.4 \text{ kg/m}^2$ ) participated in a structured weight reduction program including nutritional (meal replacement) and psychological (behaviour modification) intervention as well as regular supervised physical activity. Subjects were examined at baseline and after 12 months. Symptoms of depression were assessed by the Beck Depression Inventory (BDI) at baseline.

**Results:** 8 subjects (A) out of 18 finished the one year course. 10 subjects (B) dropped out during the first six months. At baseline, the groups did not differ regarding age (A:  $46.1 \pm 3.2$  years; B:  $47.3 \pm 2.9$  years, n.s.), weight at baseline (A:  $117.9 \pm 5.7$  kg; B:  $110.9 \pm 11.5$  kg, n.s.), and BMI (A:  $42.3 \pm 2.0 \text{ kg/m}^2$ ; B:  $40.4 \pm 4.0 \text{ kg/m}^2$ , n.s.). Subjects A significantly ( $P < 0.05$ ) reduced body weight by  $19.9 \pm 7.2$  kg. In addition, a significant ( $P < 0.05$ ) impact of the depression score (A:  $5.4 \pm 4.2$ ; B:  $11.1 \pm 5.9$ ) on adherence to therapy was observed.

**Conclusion:** Subjects with a higher depression score at baseline are more likely to drop out during a structured therapy including meal replacements. Thus, psychological evaluation with a major focus on depression could help to identify potential drop-out candidates, which should receive appropriate psychological treatment.

O065

**Weight loss strategies: a survey of 1000 overweight and obese subjects****JM LECERF\*†**, **B WAYSFELD‡**, **P KLEIN§** and **J Filipecki¶**

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**Introduction:** Losing weight is an important concern for overweight subjects. What strategies do those patients adopt to lose weight?

**Patients and method:** A survey of a representative sample of 1000 overweight (OW) [body mass index (BMI)  $+25$ – $29.9 \text{ kg/m}^2$ ] and obese (OB) ( $\text{BMI} \leq 30 \text{ kg/m}^2$ ) subjects aged 18 to 70 years was conducted.

**Results:** 75.8% of the subjects were OW and 24.2% OB. 76% of the OW subjects [men (M): 68.1% – women (F): 81.2%] and 85% of the OB subjects (M: 77% – F: 90%) had already experienced the need to lose weight (F > M;  $P < 0.01$ ). 66% of the OW and 83% of the OW subjects had already voluntarily tried to lose weight (OB > OW;  $P < 0.001$ ). For those attempts at their own initiative, 79% of the subjects went on a diet and 65% tried physical exercise (OB < OW,  $P < 0.05$ ). Among those who had voluntarily tried to lose weight, 49% had consulted a physician (general practitioner > specialist,  $P < 0.001$ ) or dietician (OB > OW,  $P < 0.0001$ ), (F > M,  $P < 0.05$ ). 63% of the entire population, (OB > OW,  $P < 0.0001$ ), had already attempted at least one diet. Among the subjects who had dieted, 57% experienced difficulty in complying with the diet regularly (OB > OW,  $P < 0.05$ ), 47% tended to discontinue the diet prematurely (OB > OW,  $P < 0.001$ ) and 26% considered that diets did not work for them (OB > OW,  $P < 0.05$ ). 37% of the entire population were aware that slimming drugs were available, but only 12% were considering using them.

**Conclusion:** Most of the OW and OB subjects had attempted to lose weight. Most had attempted dieting, but difficulties were frequently experienced. Few subjects were considering using a slimming drug. The strategies adopted appeared disappointing while the need to lose weight was very frequently experienced.

O066

**Coping, emotional adjustment, and weight change in obesity****M CONRADT\***, **J-M DIERK\***, **E RAUH\***, **P SCHLUMBERGER\***,**J HEBEBRAND‡** and **W RIEF\***

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**Introduction:** Obese subjects can experience high levels of emotional distress about being overweight since weight reduction efforts are mostly not successful. The chronic character of obesity underlines the need to investigate factors crucial for psychological adjustment. The aim of the present study is to identify coping strategies which are associated with a dysfunctional emotional adjustment in obesity.

**Patients and methods:** Subjects with a  $\text{BMI} > 30$  were recruited. The baseline survey comprised the administration of questionnaires and a telephone interview (time 1). After six months, the same measures were administered again (time 2). Altogether 101 obese subjects participated in our study (female: 70.3%; mean age  $+47.8 \pm 12.3$ ; mean  $\text{BMI} +36.7 \pm 5.1$ ). We defined emotional adjustment through obesity-related shame & guilt and depressive symptoms. We assessed four coping strategies (problem-/emotion-focused engagement/disengagement). Subjects described a typical weight-related stressful situation.

**Results:** There were no mean differences of emotional adjustment measures across levels of obesity. Concerning obesity-related stressful situations, 66% of the subjects reported social situations. Of the four coping strategies, emotion-focused disengagement at time 1 (self criticism, social withdrawal) was the only significant predictor for depressive symptoms (beta  $+0.35$ ;  $P < 0.01$ ) and shame & guilt feelings (beta  $+0.52$ ;  $P < 0.001$ ) at time 2. We could not find any significant linear or non-linear relationships between weight change and emotional adjustment or coping measures.

**Conclusion:** The emotional burden of obesity might be independent of the actual weight status and weight change over time. Social situations were identified as the most frequent stressors. Concerning the employed coping strategies, emotion-focused disengagement was substantially associated with dysfunctional emotional adjustment at follow-up.

## T6: Metabolic Syndrome: Clinical Implications

O067

**The cumulative number of metabolic syndrome components as a predictor for future stroke in diabetic patients**

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**Introduction:** Diabetes is one of the leading risk factors in stroke. Arterial hypertension, dyslipidemia, the insulin resistance syndrome, waist, and the race, are linked with increased incidence of stroke in diabetics.

**Patients and methods:** To investigate the impact of metabolic syndrome (MS) components (according to NCEP III criteria) in provoking stroke risk in type 2 diabetics.

**Material and methods:** In 600 diabetics with an average follow up of 10 years, baseline values of MS components (0–4), age, blood pressure, blood lipid levels and diabetes duration were determined. The progression to the end-point (stroke) was evaluated using Kaplan-Meier estimator, log rank test, and Cox proportional hazards models.

**Results:** 13% of diabetics presented stroke. We did not observe any statistically significant difference in stroke risk between diabetics with 0–1 and over 2 MS components. The Cox model shows that only waist and age exert an influence on time to stroke presentation. Waist increase of 5 cm associated with 2.9% higher risk (HR: 1.006, 95% CI: 1.002–1.010) but age increase of 10 years was associated with 81% higher stroke risk (HR: 1.06, 95% CI: 1.002–1.125).

**Conclusions:** MS components do not seem to affect the risk of stroke in diabetic patients. However the effect of both age and waist was significant. Future prospective studies are required to confirm these correlations.

O068

**Weight reduction increases skeletal muscle and adipose tissue but not myocardial insulin sensitivity. Study with positron emission tomography**

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**Introduction:** Very-low-calorie diet (VLCD) has been shown to decrease weight and improve whole body insulin sensitivity. In this study we evaluated the tissue specific effect of weight reduction on insulin stimulated glucose uptake (GU) using <sup>18</sup>F-labelled fluorodeoxyglucose (FDG) and positron emission tomography (PET).

**Subjects and methods:** 16 healthy obese (BMI 33 kg/m<sup>2</sup>) subjects underwent VLCD for 6 weeks. Femoral skeletal muscle and subcutaneous adipose tissue and myocardial glucose uptake were measured during euglycemic clamp and FDG-PET before and a week after diet intervention.

**Results:** In comparison to the baseline, VLCD significantly decreased weight (from 96 to 85 kg,  $P < 0.0001$ ). Whole body insulin sensitivity increased by 33% ( $P < 0.01$ ). This was mostly explained by the increase in skeletal muscle GU (+48%,  $P < 0.02$ ). Higher improvement in insulin sensitivity was observed in subcutaneous adipose tissue GU (+69%,  $P < 0.03$ ). In contrast, myocardial GU remained unchanged. Increase in whole body insulin sensitivity was associated with increase in subcutaneous adipose tissue GU ( $r + 0.71$ ,  $P + 0.002$ ), and increase in skeletal muscle GU ( $r + 0.90$ ,  $P < 0.0001$ ).

**Conclusions:** Rapid weight reduction enhances whole body insulin sensitivity by enhancing adipose tissue and skeletal muscle glucose uptake whereas myocardial glucose uptake remains unchanged.

O069

**Strength training improves the functional balance between beta- and alpha2- adrenergic pathways in subcutaneous adipose tissue of insulin-resistant obese**

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**Introduction:** This study investigates whether dynamic strength training modifies the control of lipolysis, with a particular attention paid to the involvement of antilipolytic alpha2-adrenergic receptors (AR) pathway. **Materials and methods:** Twelve male obese insulin-resistant subjects (age: 47.4 ± 2.8 years; BMI: 32.7 ± 0.9) were investigated during a 3-hour euglycemic-hyperinsulinemic clamp before and after 3 months of dynamic strength training. Before and during the third hour of the clamp, the effect of a perfusion of isoproterenol (1 μmol/l) or epinephrine (10 μmol/l) alone or associated with the alpha2-AR antagonist phentolamine (100 μmol/l) on the extracellular glycerol concentration (EGC) in subcutaneous abdominal adipose tissue (SCAT) was evaluated using the microdialysis method. In addition, biopsies of SCAT were carried out before and after training for subsequent mRNA analysis.

**Results:** Training resulted in an increase of whole body glucose disposal. After training, the decrease of EGC during the clamp was more pronounced compared with pre-training conditions. Before as well as after training, catecholamines induced an increase in EGC; the increase being lower during the third hour of the clamp. Isoproterenol-induced increase in EGC was higher after training. The epinephrine-induced lipolysis was potentiated by addition of phentolamine after but not before training. There were no training-induced changes in mRNA levels of key genes of lipolytic pathways.

**Conclusion:** The results demonstrate that, in insulin-resistant obese subjects, dynamic strength training improves whole body and adipose tissue insulin responsiveness. It improves as well responsiveness to beta-AR stimulation of lipolysis and to antilipolytic action of catecholamines mediated by alpha2-ARs in SCAT. The study was supported by grants of Ministry of Health of Czech Republic IGA NR 8066–3/2004 and IGA 6836–3.

O070

**Effect of pioglitazone treatment on adipose tissue glucocorticoid (GC) metabolism in adult rats with postnatal diet-induced overweight and metabolic syndrome**

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**Introduction:** Local reactivation of inert into active GC in visceral adipose tissue (VAT), driven by 11 beta-hydroxysteroid dehydrogenase type 1 (11 beta-HSD-1), plays a pivotal role in the pathophysiology of obesity and the metabolic syndrome. The metabolic actions of pioglitazone are well documented; however, their underlying mechanisms are only partially known. Some experimental studies (*in vivo* using a genetic model of obesity or *in vitro*) suggest that 11 beta-HSD-1 can be implicated. We studied the effects of pioglitazone in a model of environmentally (postnatal overfeeding) induced overweight and metabolic syndrome.

**Materials and methods:** Early postnatal (P3–P21) normofed (NF) or overfed (OF) adult rats were treated with pioglitazone for 5 weeks (3 mg/kg/day per os; Takeda Chemical Industries, Japan).

**Results:** In NF rats pioglitazone treatment induced a body weight increase but did not affect metabolic and hormonal parameters. OF rats were overweighted, showed glucose intolerance together with increased VAT mass and 11 beta-HSD-1 mRNA expression (44.48 ± 3.08 vs 35.20 ± 0.64 nCi/g in untreated NF;  $P < 0.001$ ). Pioglitazone treatment induced a body weight increase, normalized glucose tolerance, enlarged subcutaneous AT mass, and decreased VAT mass and 11 beta-HSD-1 mRNA expression (37.58 ± 0.64 nCi/g;  $P < 0.05$  vs untreated OF rats).

**Conclusion:** These results show that pioglitazone treatment down-regulates adipose tissue 11 beta-HSD-1 expression in a postnatal diet-induced model of overweight and metabolic syndrome. They suggest that drug-induced alterations in local GC metabolism, specifically in VAT, induces, at least in part, fat mass changes and insulin sensitivity improvement.

O071

**Angiotensin type 1 receptor antagonists stimulate human *in vitro* adipogenesis via PPAR $\gamma$ -Activation****J JANKE\***, M SCHUPP<sup>†</sup>, S ENGELI\*, K GORZELNIAK\*, FC LUFT\* and AM SHARMA<sup>‡</sup>\*Medical Faculty of the Charité, Franz Volhard Clinic, <sup>†</sup>Medical Faculty of the Charité, Center for Cardiovascular Research, Berlin, Germany, <sup>‡</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada**Introduction:** Angiotensin type 1 receptor antagonists (sartans or ARBs) have anti-diabetic effects. To investigate the mechanism, we studied the *in vitro* effects of several sartans on human adipogenesis and PPAR $\gamma$  target gene expression (eg. adiponectin, lipoproteinlipase).**Methods and materials:** The influence of the sartans on adipogenesis was tested by supplementing the differentiation medium with each sartan, conversion to the adipocyte phenotype was quantitated by measuring Oil red O stained lipid accumulation. Expression analysis of PPAR $\gamma$  target genes in differentiated preadipocytes after a 24 h incubation with each sartan were performed by real time TaqMan PCR and western blot.**Results:** Whereas three sartans increased lipid accumulation, one sartan did not influence adipose conversion. These findings were paralleled by adiponectin and lipoproteinlipase expression. Incubation with adipogenic sartans lead to increased expression levels, whereas the sartan without adipogenic potential was without effect.**Conclusions:** As exogenous angiotensin II was not added in our experiments, an activation of PPAR $\gamma$  by some sartans must be assumed. In addition, the PPAR $\gamma$  agonist Pioglitazone showed similar target gene expression patterns in our analysis. This may explain the observation that ARBs substantially lower the risk for the development of type 2 diabetes compared to other antihypertensive drugs. The distinct adipogenic potential of the sartans requires further comparative investigations of the antidiabetic effects *in vivo*.

O072

**Metabolic syndrome and neurometabolic asymmetry of hippocampus in adult bonnet monkeys****JG KRAL\***, SJ MATHEW<sup>†</sup>, DK SHUNGU<sup>‡</sup>, X MAO<sup>‡</sup>, ELP SMITH\*, D KAUFMAN\*, S BAPTISTE\*, JM GORMAN<sup>†</sup>, MJ OWENS<sup>§</sup>, CB NEMEROFF<sup>§</sup>, LA ROSENBLUM\*, MA BANERJI\* and JD COPLAN\*\*Primate Behavior Laboratory, Departments of Surgery (JGK, DK), Psychiatry (ELPS, LAR, JDC.), Medicine (MAB), SUNY Downstate Medical Center, Brooklyn, <sup>†</sup>Department of Neuroscience, Mount Sinai Medical Center, <sup>‡</sup>Departments of Radiology, Psychiatry and Biophysics, Weill Medical College of Cornell University, New York, New York, <sup>§</sup>Department of Psychiatry & Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, USA**Introduction:** The insulin resistance metabolic syndrome of obesity is postulated to be mediated by stress-induced alterations within the hypothalamo-pituitary-adrenal (HPA) axis and central corticotropin-releasing factor (CRF) systems. We examined relationships between juvenile bonnet macaque cerebro-spinal fluid (CSF) CRF, a marker of stress, and adult neurometabolic asymmetry within the hippocampus, a marker of negative emotional states in humans, and the appearance of components of the metabolic syndrome in adult macaques.**Patients and methods:** Eleven adult male monkeys who had undergone CSF CRF analysis as juveniles had magnetic resonance spectroscopic imaging of bilateral hippocampus, morphometry (body mass index, BMI; sagittal abdominal diameter, SAD) and determination of fasting plasma glucose, insulin and HOMA-IR as adults. Neurometabolite ratios included N-acetyl-aspartate as numerator (NAA; a marker of neuronal integrity) and choline (Cho; cell turnover marker) and creatine (Cr; a reference analyte) as denominators.**Results:** Juvenile CSF CRF levels positively predicted adult BMI, SAD and insulin resistance and were associated with right > left shift of NAA/Cho within the hippocampus. Adult visceral obesity and insulin resistance correlated with right > left shift in hippocampal NAA concentrations, controlling for age and denominator.**Conclusion:** Juvenile CSF CRF levels predict adult visceral obesity and insulin resistance, and asymmetry (right > left) of NAA concentrations in the hippocampus. These primate data support the hypothesis that the metabolic syndrome may be stress-driven.

### PL3: Psychological and Personality Disorders: Cause or Consequence of Weight Gain?

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Obesity is widely believed to be associated with psychological problems. A variety of causal processes have been hypothesised: stress and distress could promote weight gain through effects on eating, and excess weight might cause distress as a result of the experience of prejudice and discrimination. This paper reviews the literature on associations between obesity and depression, self-esteem and body image. The observation that obese patients in treatment have high rates of depression has lent credence to the idea that obesity and depression are associated. However, because community samples of obese adults or children typically have normal rates of depression, this must be largely a selection effect. The association is hypothesised to be stronger among women or higher SES groups, but there is limited support for this. Where associations are found, they are small and tend to be restricted to the super-obese of both sexes. Few studies have specifically investigated the causal processes, but results are consistent with depression being a consequence of associated physical disease, although some depressed patients may also be at risk of weight gain. Obese patients who are depressed should receive appropriate treatment, while recognising that weight loss, like any positive event, could facilitate psychological wellbeing. Self-esteem is assumed to be compromised in obesity as a consequence of the rampant prejudice and discrimination directed towards obese people. However, most studies carried out with community samples of obese adults and adolescents find normal levels of self-esteem. As with depression, the association has been predicted to be stronger in women and those from white, more affluent, backgrounds, but while there is evidence for moderation by gender, most obese adolescent girls have self-esteem scores within the normal range. Despite the social adversities, obese people appear to be successful in maintaining their sense of self-worth; an observation that gains support from studies of people with other stigmatised conditions. The strongest evidence for adverse psychological effects is on body image. Many obese people are profoundly dissatisfied with their bodies, whether this is assessed with a simple rating of dissatisfaction or more elaborate measures of appearance distress. Body dissatisfaction should not be assumed to be either trivial or inevitable. It may have important implications for prognosis and deserves greater attention in terms of aetiology, management and prevention. Obese people are neither notably depressed nor markedly low in self-esteem. The persistence of the idea that obesity is associated with significant psychological problems may derive from prejudice rather than scientific evidence. In contrast, body dissatisfaction can be high, with implications for lifestyle and happiness. Promoting awareness of the value of weight control without increasing unhealthy weight concern will be a significant challenge for nutritional public health.

### T4R2: How to Achieve Effective Prevention and Management of Obesity in Children

Obesity prevention in children

T LOBSTEIN

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Twenty percent of the EU's school-age children are estimated to be overweight and at a raised risk of adult disease. Of these children, one in five is obese and may show the early signs of cardiovascular disease, diabetes and liver disease. Child obesity substantially raises the risk of adult obesity, and is a risk factor for later chronic disease even if the child does not become an obese adult. The treatment of child obesity can involve a wide range of professional services including family counselling, behaviour modification, sports and activity training, nutrition and dietetics and, where necessary, surgical and possibly pharmaceutical interventions. Obesity treatment in children is costly and has a low success rate: practitioners generally aim to prevent further weight gain and reduce the risk of co-morbidities. Prevention is a priority. The number of overweight children has risen substantially in the last two decades and is likely to continue to rise unless major prevention programmes are initiated. But how should a prevention programme be designed? The various actors involved in the prevention of child obesity include the child, the family, the school, the health services, the community, businesses and society at large. A child's environment contains many inducements that encourage weight gain, and the child cannot be expected to resist these alone. Healthier choices need to be easy ones for a child to make, and need to be fully supported by all those responsible for children's health. Policies for preventing child obesity start in the home and extend throughout the child's social environment and the determinants of that environment, including national and international strategies for food production and the production of the built environment. Methods for assessing the effectiveness of interventions are frustrated by a lack of scientific evidence. Policy-makers recognise that a public health approach is needed which acts on a precautionary basis, using available evidence from controlled and uncontrolled interventions. The target is to support the optimum health for children, and it is the responsibility of various members of society to ensure that children can achieve such optimum health. In order to make progress, new tools for evaluating public health interventions are needed. Some examples of these new tools are presented.

**Definitions and assessment for overweight and obesity in children****TJ COLE***Centre for Paediatric Epidemiology and Biostatistics Institute of Child Health, University College London, UK*

Obesity is simply excess adiposity, and to define it we need some way to measure adiposity and a cut-off to identify excess. In childhood normal adiposity changes with age, so the definition needs to establish normal age-related adiposity then set the cut-off relative to normal to identify obesity with high sensitivity and specificity. Ideally the gold standard should be long-term outcome. These requirements are almost impossible to meet. Firstly adiposity is difficult to measure – expensive laboratory-based methods like DEXA and isotope dilution are impractical for large scale population use. Weight and height are simple and available alternatives, usually summarised as the body mass index  $BMI = \text{weight}/\text{height}^2$ . But BMI fails to distinguish between fat mass and lean mass. Secondly, the basis for deciding the cut-off is difficult. BMI chart centiles such as the 85th, 91st, 95th or 98th centile have been proposed to define overweight and/or obesity, but the justification for any particular centile is *ad hoc*. The evidence suggests a linear relation between child BMI and later risk, which means that shifting the cut-off up or down simply trades off sensitivity against specificity. In addition the later risk of a high BMI in childhood may or may not depend on the child's obesity status as an adult. So BMI change at different stages in childhood, and its relationship to outcome, may be at least as critical as BMI level for assessing risk. For example rapid weight gain in early infancy is emerging as a risk factor for later obesity. The talk will use these ideas to advocate two parallel approaches to BMI assessment: epidemiological classification based on the IOTF international BMI cut-offs, which link to the adult cut-offs of 25 and 30 kg/m<sup>2</sup>, and longitudinal assessment based on BMI centiles and BMI change over time. Waist circumference is also a promising measure of central adiposity that may prove to be more informative than BMI of later outcome.

**Strategies for obesity management in childhood and adolescence****K WIDHALM***Dept. of Pediatrics, Med. Univ. Vienna, Austria*

Prevalence of Overweight and Obesity in children and adolescents are worldwide increasing, in some countries the number of obese children has been doubled in the last 10–15 years. Up to 80% of the young obese subjects maintain obese as adults; problems with these age group are very well known, very few successful therapeutic regimen are available. Thus, it is pivotal to prevent obesity and to find out successful therapeutic regimen in the pediatric age group. The second problem is the fact that pediatric obesity is commonly not recognized as a disease which needs treatment. However, today it is well established that even in children and adolescents obesity is associated with insulin resistance, impaired glucose tolerance, dyslipidemia, fatty liver, endothelial dysfunction, joint problems and marked psychological disturbances. An appropriate management of childhood obesity therefore must include a diagnostic procedure by which comorbidities can be diagnosed adequately. After this procedure an individualized therapeutic regimen based on the entire pathological and psychological situation should be initiated: characteristics of these programs are multidisciplinary, family approach and longterm follow-up regimen. If in some patients no longlasting weight reducing or weight maintaining effect (1 to 2 points BMI per year seem to be a good goal) can be achieved, more sophisticated regimens like drugs or admission at special obesity clinics should be considered. It should be emphasized that it is fundamental, that special trained pediatricians, psychologists, dieticians, sport therapeutics and appropriate structures should be available. As a very last chance for morbidly obese adolescents bariatric surgical procedures after careful consideration and with longlasting follow-up programs can be used in special centers. For all programs a careful evaluation is mandatory. Beyond all therapeutic regimens much energy should be put into implementation of prevention programs which should start as early as possible – probably during pregnancy. National programs to combat obesity are urgently needed.

## T3R2: Psychological and Social Burden of Obesity

### Obesity, weight loss, and health-related quality of life

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Interest in the associations between obesity and health-related quality of life (HRQL) has increased rapidly since the late 1990's. Today, both generic and obesity-specific questionnaires are available to examine HRQL. The questionnaires explore functioning and well-being in physical, mental, social, and obesity-specific domains. In population-based observational studies, normal weight is associated with the best HRQL. Obese individuals report deteriorated HRQL. Higher BMI is associated with lower HRQL. Obesity has a greater impact on physical HRQL than on mental or social HRQL. Mental and social HRQL seem to be affected only among the morbidly obese and the obese with other chronic conditions, pain, or disordered eating. Several factors, such as sex, age, socio-economic status, and life-style factors modify the associations between obesity and HRQL. Among the obese individuals seeking weight loss, increasing degree of obesity is associated with broad-range deterioration of HRQL (physical, mental, social, and obesity-specific). Especially manifest are the various obesity-specific problems. Women seem to be more affected than men. Not only the treatment-seeking status but also the intensity of treatment influences HRQL responses: the obese seeking surgical treatment report worst HRQL. The psychosocial problems among the treatment-seeking morbidly obese can be quite severe, and symptoms of depression and anxiety are common. In this population it is especially important to measure perceived functionality and well-being, since perceived and measured disability may correlate only poorly. In the intervention studies (life-style, diet, drug, and/or surgical) weight loss seems to improve poor HRQL, and this improvement is dependent on the amount of weight loss. 5–10% weight loss may not be enough to improve poor HRQL in obese patients. Larger weight loss is associated with greater improvement in HRQL. Some of the improvements may be transient: Mental and social domains may improve in the short term, whereas physical and obesity-specific domains seem to improve also in the longer term. Other factors, such as participating in the intervention, improvement in comorbid conditions, or increase in physical activity may also improve HRQL. Weight loss surgery produces marked and sustained weight loss and HRQL improvements. The effects of weight loss drugs on HRQL are largely unknown.

### Genetic influences on eating behaviour

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**Introduction:** More than 430 genes, markers, and chromosomal regions have been associated or linked with human obesity phenotypes (Snyder *et al.* 2004). Since the brain adjusts eating behaviour to energy requirements of the body, genes expressed in the brain that are involved in processes as diverse as sensing food palatability, food reward, hunger and satiety, are all candidates to explain the genetic variability in development of obesity. Thus, a better understanding of how genes are affecting feeding behaviour may help to explain why some become obese whereas other remain lean when exposed to cafeteria diets. The identification of leptin was key towards unravelling the molecular processes that linked peripheral energy status to central regulation of energy balance. One major target of leptin is the hypothalamic melanocortin and NPY system.

**Methods:** In order to understand how the leptin signal is further transmitted in the brain a gene-therapy approach was used to overexpress Agouti (a melanocortin receptor inhibitor) or NPY. Local injections of recombinant adeno-associated viral particles in selected brain nuclei of adult rats were used to address where in the brain NPY and Agouti induce obesity and how obesity is caused.

**Results:** Agouti expression in the paraventricular nucleus (PVN), a hypothalamic region with a high density of MC receptors, induced acute-onset hyperphagia and rapid weight gain. In contrast, obesity and hyperphagia developed with a three weeks delay when Agouti was expressed in the dorsal medial hypothalamus (DMH). Agouti expression in the lateral hypothalamus (LH) did not affect food intake and body weight during regular diet, but on a high fat diet, animals with Agouti expression in the LH exhibited a marked increase in body weight. Thus, the LH is important for the protection against diet-induced obesity by controlling caloric intake during consumption of a high fat diet. Overexpression of NPY in the posterior hypothalamus also induced obesity in a characteristic manner.

**Conclusion:** Distinct brain regions confer hyperphagia and diet-responsiveness. This opens challenging opportunities for further understanding of patho-physiological processes in the development of the obesity syndrome [Kas *et al. J. Neurosci.* (2004) 24: 10176–10181].

### Obesity and sleep

A VGONTZAS (GREECE/USA)

Not received

## T6R2: New Insights in Clinical Presentation of Metabolic Syndrome

### Liver as a target of metabolic syndrome H YKI-JARVINEN (FINLAND)

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Obesity is not necessary to observe insulin resistance in humans since severe insulin resistance also characterizes patients lacking subcutaneous fat such as those with HAART (highly active antiretroviral therapy) – associated lipodystrophy. Both obese and lipodystrophic patients have, however, an increase in the amount of fat hidden in the liver. Liver fat content can be non-invasively accurately quantified by proton magnetic resonance spectroscopy. It is closely correlated with fasting insulin concentrations and direct measures of hepatic insulin sensitivity while the amount of subcutaneous adipose tissue is not. An increase in liver fat content has been shown to predict, independent of other cardiovascular risk factors, type 2 diabetes. This is easily explained by the fact that the liver, once fatty, indeed produces most of the known cardiovascular risk factors such as VLDL, glucose, CRP, PAI-1, fibrinogen and coagulation factors. The causes of interindividual variation in liver fat content independent of obesity are largely unknown but could involve differences in signals from adipose tissue such as in the amount of adiponectin produced and differences in fat intake. Adiponectin deficiency characterizes both lipodystrophic and obese insulin resistant individuals, and serum levels correlate with liver fat content. Liver fat content can be decreased by weight loss and by a low as compared to a high fat diet. In addition, treatment of both lipodystrophic and type 2 diabetic patients with PPAR $\gamma$  agonists but no metformin decreases liver fat and markedly increases adiponectin levels. The fatty liver may help to explain why some but not all obese individuals are insulin resistant and why even lean individuals may be insulin resistant, and thereby at risk of developing type 2 diabetes and cardiovascular disease.

### Dysregulation of lipid metabolism in metabolic syndrome E MANZATO

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According to the National Cholesterol Education Program (NCEP) the metabolic syndrome is defined as the association of three or more of five criteria: (1) abdominal obesity (waist circumference, >102 cm in men and >88 cm in women), (2) hypertriglyceridemia (>150 mg/dL), (3) low HDL (<40 mg/dL in men and <50 mg/dL in women), (4) hypertension (>130/85 mmHg), and (5) elevated fasting glucose (>110 mg/dL). Both abdominal obesity and diabetes are frequently associated to lipid alterations. The mechanism responsible for these lipid abnormalities is the insulin resistance state present in both these conditions. Abdominal adiposity per se is associated with several changes in lipid metabolism including hypertriglyceridemia (elevated very low density lipoproteins, VLDL), reduced HDL cholesterol (almost exclusively HDL2 cholesterol, the large buoyant anti-atherogenic subfraction of total HDL), and increased numbers of small, dense LDL particles, while elevated LDL cholesterol is not a feature of the abdominal obesity. LDL particles are different in size, density, chemical composition, and atherogenic potential. An increased number of small, dense LDL particles is frequently observed in the dyslipidemia of abdominal adiposity. In presence of elevated triglyceride concentrations the LDL particles become enriched in triglycerides and depleted of cholesteryl esters. Hepatic lipase hydrolyzes these triglyceride-rich LDL, forming smaller, denser LDL particles. HDL and VLDL metabolism are closely linked, which explains why increased plasma triglycerides are almost always associated with reduced HDL levels. An increased flux of cholesteryl ester from HDL to triglyceride-rich lipoproteins in hypertriglyceridaemia causes a tendency to low HDL-cholesterol concentrations. Diabetic dyslipidemia is a complex cluster of abnormalities, with low HDL-cholesterol, elevated serum triglycerides, excessive postprandial lipemia, a preponderance of small, dense LDL, and a preponderance of small, dense HDL. The NCEP guidelines recommend a non-HDL cholesterol goal of less than 130 mg/dL in hypertriglyceridemic patients (>200 mg/dL). The large population of individuals with the metabolic syndrome appears to be comprised of a heterogeneous group of disorders, and the identification of disease subtypes at high vascular risk can help identify candidates for aggressive lipid lowering interventions.

### PPAR agonists: targeting insulin resistance and atherosclerosis in the obese B STAELS

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Cardiovascular disease is significantly increased in visceral obese patients with metabolic syndrome and type 2 diabetes. A clustering of risk factors, including dyslipidemia, insulin resistance, hypertension, inflammation and coagulation disorders are likely to promote cardiovascular events in these patients. Peroxisome proliferator-activated receptors (PPARs) are transcription factors that influence vascular function both directly and indirectly by altering gene expression. Indeed, PPAR activation displays beneficial effects not only on glucose homeostasis and lipid metabolism but also on endothelial function and vessel wall inflammation. PPAR $\alpha$  agonists such as fibrates, and PPAR $\gamma$  agonists such as the insulin-sensitizing thiazolidinediones, are in clinical use and may alter the process of atherosclerosis, especially in subjects with metabolic syndrome and type 2 diabetes. This presentation will highlight the emerging evidence for PPAR $\alpha$  and PPAR $\gamma$  beneficial effects in prevention and treatment of atherosclerosis in such high-risk patients.

## PL6: Regional Fat Accumulation and Atrophy: Dysregulation of Adiponectin Pathway as a Central Player

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Adiponectin is a hormone secreted by adipocytes that acts as an antidiabetic and antiatherogenic adipocytokine. Levels of adiponectin in the blood are decreased under conditions of lipotrophy, obesity, insulin resistance and type 2 diabetes. Administration of adiponectin causes glucose-lowering effects and ameliorates lipotrophy- or obesity-linked insulin resistance in mice. Transgenic overexpression of adiponectin ameliorates insulin resistance and diabetes of ob/ob mice and also atherosclerosis of Apo E knockout mice. Conversely, adiponectin knockout mice exhibit insulin resistance and features of metabolic syndrome and also show increased neointimal formation. Polymorphisms of human adiponectin gene are associated with decreased levels of adiponectin in the blood, insulin resistance and type 2 diabetes. The insulin sensitizing effect of adiponectin seems to be mediated by an increase in fatty-acid oxidation through activation of AMP kinase and PPAR $\alpha$ . We have recently cloned cDNAs encoding adiponectin receptors 1 and 2 (Adipo R1 and Adipo R2) by expression cloning. Adipo R1 is abundantly expressed in skeletal muscle and Adipo R2 is predominantly expressed in liver. Expression of Adipo R1/R2 or suppression of Adipo R1/R2 expression by small-interfering RNA supports our conclusion that they serve as receptors for globular and full-length adiponectin. Adipo R1/R2 are abundantly expressed in vasculature, islets and hypothalamus. Adiponectin receptors are downregulated in obesity, which is associated with adiponectin resistance and hence insulin resistance. Studies on elucidation of molecular mechanism of adiponectin actions through Adipo R1/R2 and determination of pathophysiological roles of Adipo R1/R2 as well as development of new treatment strategy targeted to adiponectin/adiponectin receptors are underway in our laboratory.

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## T4: The Big Threat: Childhood Obesity and Metabolic Syndrome

O073

**Analysis of the Ala54Thr FABP2 polymorphism in obese children (OC): effect on obesity and insulin resistance**

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**Introduction:** The T54 allele of the intestinal fatty acid-binding protein 2 (FABP2) gene has been associated with impairment in lipid and carbohydrate metabolism in susceptible populations. Ala54Thr functionally alters the protein's ability to bind and transport dietary fatty acids. We wanted to screen-in our population of OC with the Ala54Thr FABP2 polymorphism. **Patients and methods:** Our 223 children from 6.91 to 14.33 years old were recruited on a BMI > 95<sup>th</sup> percentile age chart basis. They were followed for 20 weeks in a weight loss and balanced diet education program. All patients were divided in two groups: Ala54Ala and 54Thr variant after PCR-RFLP. **Results:** The allele frequency in our OC whole population of 223 is 0.22 but rises at 0.23 when considering the children less than 11 years old (21.8% older group). This younger population of 145 OC (6.91 to 11 years old) (BMI: 29.5  $\pm$  4.2) with BMI zscore 4.7  $\pm$  1.3 has been screened for the metabolic profile. We found no significant differences between the A54 and T54 genotype groups in BMI, Zscore, and weight loss but they have a strong tendency to have a higher fasting glycemia 89  $\pm$  1.1; 86  $\pm$  0.8 mg/dL ( $P$  + 0.058) and HOMA: 3.9  $\pm$  0.3; 3.2  $\pm$  0.2 ( $P$  + 0.067) in T54 and A54 respectively, and 48.2% of the T54 variant have a fasting insulin >15  $\mu$ UI (37.9% of A54).

**Conclusion:** The T54 genotype group presents a metabolic profile generally worst but not significantly than the A54. The Ala54Thr FABP2 polymorphism is not a major contributing factor but still is a risk factor for earlier obesity and insulin resistance.

O074

**Metabolic re-modelling in pre-pubertal children – testing the lipid flux hypothesis**

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**Introduction:** The behaviour of insulin resistance and its metabolic correlates in response to changes in body fat has not been well characterised in children. Frayn's lipid flux hypothesis proposes that adipose tissue buffers the flux of fatty acids in circulation by 'trapping' them and by increasing triglyceride clearance. We tested this hypothesis by examining trends in adiposity, insulin resistance (IR) and metabolic risk variables in healthy pre-pubertal children.

**Patients and methods:** Data were obtained from the EarlyBird cohort of healthy children (130 boys, 100 girls) who attended at 5, 6, 7 and 8 years. Measures included the sum of 5 skinfolds (correlation with DEXA % fat  $r$  + 0.92), HOMA-IR, triglycerides, HDL cholesterol (HDL-C), HOMA-beta. **Results:** Adiposity rose progressively and significantly between 5 and 8 years (+18%,  $P$  < 0.001), while HOMA-IR unexpectedly fell (–24%,  $P$  < 0.05). Consistent with the reduction in HOMA-IR, HDL-C rose (+17%,  $P$  < 0.001) and triglycerides fell (–8%, ns). Fasting glucose rose (+12% or 0.5 mmol,  $P$  < 0.001), while HOMA-beta fell (–35%,  $P$  < 0.001).

**Conclusion:** The fall in HOMA-IR and rise in HDL-C with increase in adiposity are consistent with the lipid flux hypothesis, and suggest fat re-modelling with significant metabolic impact. Growth deceleration and the GH/IGF1 axis may be implicated in the fall in IR. An acceleration of beta cell apoptosis, occurring independently, could explain the rise in glucose. These observations are novel, and need explanation to establish whether they are physiological and programmed, or pathological and ultimately harmful.

O075

**Does insulin resistance impair losing weight?****CYM NICOLAU, ICM GUAZZELLI, MDB RODRIGUES and SMF VILLARES***Childhood Obesity League – LIM 25 – Endocrinology Department – Hospital das Clínicas – Faculdade de Medicina da Universidade de São Paulo, Brazil*

**Introduction:** Insulin is an anabolic hormonal mediator of energy storage. In fed state, insulin levels are increased stimulating anorexigenic signals, muscles glucose uptake and inhibiting liver gluconeogenesis. In fasting state insulin levels are low, which results in increased feeding behavior and energy store. Obese subjects are hyperinsulinemic, but insulin action is decreased in liver, adipose tissue and muscle. Because of insulin resistance, obese hyperinsulinemic children may lose less weight than the sensitive ones.

**Patients and methods:** We studied 125 obese children, aging 10.2 ± 1.2 years, on a behavior modification weight loss program. Anthropometric assessment was monthly measured. Body Mass Index (BMI) and BMI Zscore were calculated. Blood samples were taken for measurement of glucose, insulin, lipid profile, leptin. Children were randomized in two groups according to fasting insulin level. G1 hold those with insulin levels <15 microU/mL and G2, ≤15 microU/mL.

**Results:** The groups had similar initial degree of obesity. Insulin levels, leptin, HOMA-IR, area under curve insulin were significantly higher in G2. After treatment, triglycerides and leptin levels significantly fell, especially in G2. HOMA-IR significantly reduced only in G2 (5.36 ± 0.25 to 3.31 ± 0.21). Z score BMI significantly reduced in G1 and G2, but weight loss was more important in G1 (4.379 ± 0.016 to 3.479 ± 0.166 and 4.54 ± 0.15 to 3.83 ± 0.15).

**Conclusion:** Although hyperinsulinemic obese children have good metabolic response to treatment, they lose less weight than non-hyperinsulinemic ones. These children may have a hypothalamic resistance to insulin action which increases appetite and energy store.

O076

**Excess childhood body mass index at age 7 years is associated with coronary heart disease in adulthood among a cohort of Danish school children****JL BAKER, LW OLSEN and TIA SØRENSEN***The Danish Epidemiology Science Center, Institute of Preventive Medicine, Copenhagen University Hospital, Denmark*

**Introduction:** Worldwide, children are becoming excessively heavy at younger ages. It has been demonstrated that coronary heart disease (CHD) risk factors exist among heavy children. However, the long-term consequences of excess childhood weight for the development of CHD in adulthood are largely unknown. Therefore we investigated if excess BMI at age 7 years is associated with an increased risk of CHD in adulthood.

**Materials and methods:** The subjects were 77 951 boys and 77 521 girls born between 1932–1975 from the Copenhagen School Health Records Register. A body mass index (BMI; kg/m<sup>2</sup>) was calculated for each child, and values were categorized into deciles based on distributions from the boys and girls, respectively. CHD status was obtained via a linkage to the Danish Hospital Register.

**Results:** The median BMI at 7 years was 15.4 kg/m<sup>2</sup> among the boys and 15.3 kg/m<sup>2</sup> among the girls. Using Cox regression, we found a higher rate of CHD occurrence among boys with a BMI between 16.4–16.9 kg/m<sup>2</sup> (80–89th percentiles) [relative risk (RR) + 1.16; 95% CI: 1.01–1.33; *P* + 0.04] or ≤17.0 kg/m<sup>2</sup> (≤90th percentile) (RR + 1.24; 95% CI: 1.08–1.43; *P* + 0.002) compared to boys with a BMI between 15.4–15.7 kg/m<sup>2</sup> (50–59th percentiles). No significant associations were detected among the girls.

**Conclusion:** These results suggest that excess BMI at 7 years among boys, but not among girls, is associated with developing CHD in adulthood. Thus there is further cause for concern about excess childhood BMI as it has negative consequences for adult health.

O077

**Children are more frequently affected by the metabolic syndrome (MS) than deterioration of glucose tolerance****C DRUET\*, V BALTAKÉ†, M DABBAS‡, C PAYEN¶, G SEBAG§, S DORGERET§, R HANKARD†, D CHEVENNE\*, M POLAK‡, M TAUBER¶, CORINNE ALBERTI\*\* and C LEVY-MARCHAL\****\*INSERM Unit 457, †Pediatric Clinic, Robert Debré Hospital, ‡Pediatric Endocrinology, Diabetic Unit, INSERM EMI 0363, Hôpital des Enfants-Malades, §Department of Pediatric Radiology, Robert Debré Hospital, Paris, ¶Pediatric Endocrinology, Hôpital des Enfants, Toulouse, \*\*Clinical Epidemiology Unit, Robert Debré Hospital, Paris, France*

**Introduction:** First cases of type 2 diabetes mellitus (T2D) in children have been reported in France, where we know that obesity increases in this age group. The objective was to evaluate glucose tolerance (WHO definition), insulin resistance (IR) (HOMA >75<sup>th</sup> perc. of the distribution for age and gender) and MS (ATP III definition) in obese children.

**Patients and methods:** 310 children were included (168 girls and 142 boys; age + 7 to 17 years; BMI + 4.9 ± 1.5 DS for age and sex); 143 (46.4%) were prepubertal, 40 (12.9%) had a family history of T2D and 222 (72.1) were Caucasians. Body fat was assessed by absorptiometry (DEXA) and distribution of adiposity on abdominal MRI section.

**Results:** There were 11 cases (3.5%) with deterioration of glucose tolerance (1 T2D, 8 IGT, 2 HFG). Other metabolic features were as follow:

	IR+	IR–
MS+	39 (12.6%)	10 (3.2%)
MS–	183 (59.0%)	78 (25.2%)

Glucose tolerance was significantly affected by puberty (*P* + 0.007), male gender (*P* + 0.0003) and family history of T2D (*P* + 0.01). MS and IR were significantly associated with higher BMI (*P* + 0.04 and *P* + 0.006), visceral fat mass (*P* + 0.03 and *P* < 0.0001) and the ratio of visceral/subcutaneous abdominal fat mass (*P* + 0.02 for each). Ethnicity had no statistical effect on any parameter.

**Conclusion:** In contrast to what observed in some countries like USA, disorders of glucose tolerance do not seem highly frequent in European obese children. By contrast IR is highly prevalent in obese children and frequently associated with MS, identifying a group of children probably at high risk of diabetogenic and atherogenic complications.

O078

**Relations of visceral and subcutaneous abdominal adipose tissue to left ventricular mass in adolescents****B GUTIN, V ROBINSON, G KAPUKU, MC HUMPHRIES, M JOHNSON and P BARBEAU***Georgia Prevention Institute, Department of Pediatrics, Medical College of Georgia, Augusta, GA, USA*

**Introduction:** Already in childhood, central adiposity is associated with unfavorable left ventricular mass indexed to height (LVMI), which is an important risk factor for cardiovascular mortality later in life. In adults, visceral adipose tissue (VAT) is more highly correlated with unfavorable indices of cardiovascular health than is subcutaneous abdominal adipose tissue (SAAT). In youths, the relative influences of VAT and SAAT on LVMI are not known.

**Subjects and methods:** Healthy black and white youths 14–18 years of age (*n* + 435) were the subjects. VAT and SAAT were derived via magnetic resonance imaging and LVMI was measured with echocardiography.

**Results:** The association of VAT and SAAT to LVMI was determined by establishing a base model of age, sex and race before introducing each adiposity measure into the model. The base model explained 7 percent of the variance in LVMI, with the blacks and the boys having higher LVMI than the whites and girls, respectively (*P* < 0.01). Both VAT and SAAT explained significant (*P* < 0.01) additional amounts of the variance in LVMI (7 and 9 percent, respectively).

**Conclusion:** Visceral and subcutaneous abdominal adiposity have similar deleterious effects on left ventricular geometry in adolescents. The relative importance of VAT may emerge later in life as it constitutes a greater relative proportion of central adiposity.

## T6: Adipocytocines and their Role in Obesity

O079

### Weight loss and the renin-angiotensin-aldosterone system

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**Introduction:** The renin-angiotensin-aldosterone system (RAAS) has been causally implicated in obesity-associated hypertension. Secretion of angiotensinogen (AGT) from adipocytes was found to contribute to blood pressure regulation in animal models.

**Patients and methods:** We studied the influence of obesity and weight reduction on the circulating and adipose tissue RAAS in menopausal women. Blood samples were analyzed for AGT, renin, aldosterone, angiotensin-converting enzyme (ACE) activity, and angiotensin II. In adipose tissue biopsies we analyzed AGT, renin, renin-receptor, ACE and AT<sub>1</sub>-receptor gene expression.

**Results:** Obese women ( $n + 19$ ) had higher circulating AGT, renin, aldosterone, and ACE compared to lean women ( $n + 19$ ), and lower AGT gene expression in adipose tissue. Seventeen women successfully participated in a weight reduction protocol over 13 weeks to reduce daily caloric intake by 600 kcal. Body weight was reduced by -5% as were: AGT levels by -27%, renin by -43%, aldosterone by -31%, ACE activity by -12%, and AGT expression by -20% in adipose tissue (all  $P < 0.05$ ). The plasma AGT decrease was highly correlated with the waist circumference decline ( $r + 0.74$ ;  $P < 0.001$ ). Weight and RAAS reduction were accompanied by a -7 mmHg reduced systolic ambulatory blood pressure.

**Conclusion:** These data suggest that a 5% reduction in body weight can lead to a meaningfully reduced RAAS in plasma and adipose tissue which may contribute to the reduced blood pressure. Furthermore, a contribution of adipose-tissue AGT expression can be assumed, as fat mass reduction not only decreases local AGT expression, but also circulating AGT.

O080

### The link of adiponectin level with postprandial lipemia/glycaemia in patients with familial obesity

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Low adiponectin level is associated with insulin resistance and obesity. Decrease in the synthesis and/or secretion of adiponectin from the adipose tissue may play a role in the development of atherosclerosis.

**Aim:** The aim of our study was to estimate the link between plasma adiponectin level and postprandial lipemia/glycaemia in patients with familial obesity.

**Material and methods:** Eighty patients from obese families were examined. The measurement of BMI, WHR and the percent of fat tissue was performed (Maltron BF-905). Serum adiponectin, TG, FFA, glucose, insulin, leptin and vWF were determined during oral lipid tolerance test (OLTT) and oral glucose tolerance test (OGTT). Polymorphisms of the obesity candidate-genes: PPAR gamma2, beta<sub>2</sub>AR, beta<sub>3</sub> AR, LPL-H, D<sub>2</sub>R were also considered as the metabolic determinants.

**Results:** In the group of 80 patients (43 women, 37 men) the mean BMI was 33.4 kg/m<sup>2</sup> (SD ± 7.3), percentage of body fat was 35.2 (SD ± 18.8). The mean adiponectin level in all subjects was 8.28 µg/ml (SD ± 4.9). The level of plasma adiponectin negatively correlated with WHR ( $P < 0.05$ ) and the waist circumference ( $P < 0.05$ ). Plasma adiponectin level was significantly higher in women than in men and in lean subjects compared to obese ones. Moreover individuals with lower adiponectins demonstrated elevated von Willebrand levels. Significant negative correlation between TG concentration and positive correlation between FFA concentration and plasma adiponectin level was noticed during OLTT. Significantly diminished adiponectin level was observed in patients with increased insulin and glucose concentration during OGTT. HOMA-IR was increased in patients with low adiponectin concentration both in women and men. No correlation was observed between adiponectin plasma level and genes' polymorphisms.

**Conclusions:** Glycemia/lipemia tolerance parameters are impaired in obese patients with decreased adiponectin level. Impaired postprandial FFA tolerance might be regarded as risk factor of insulin resistance and endothelial dysfunction.

**Acknowledgment:** This work was supported by the KBN (Ministry of Informatics and Science) grants 3P05D08424; 4P05D 01016; 4P05D 05319; 501/Pk/113/L; W<L/> 130/P/L and bilateral cooperation 'Polonium'.

O081

### The peripheral endocannabinoid system in human obesity

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**Introduction:** The cannabinoid receptor type 1 (CB<sub>1</sub>) is involved in food intake. The presence of peripheral CB<sub>1</sub>-receptors on rodent adipocytes has been demonstrated, and CB<sub>1</sub>-receptor antagonists increased expression of the adiponectin gene and activated lipogenic enzymes in rodent adipocytes. **Patients and methods:** We studied CB<sub>1</sub> gene expression and the levels of circulating endocannabinoids in lean and obese postmenopausal women ( $n + 40$ ), and during dietary weight reduction ( $n + 17$ ). All volunteers were characterized by anthropometry and clinical chemistry. RNA was isolated from subcutaneous abdominal adipose tissue. Gene expression was analyzed by TaqMan-RT-PCR. Western blots were used to demonstrate CB<sub>1</sub> in adipocyte and preadipocyte lysates.

**Results:** CB<sub>1</sub>-receptors were demonstrated on the RNA and protein level in mature isolated human adipocytes. CB<sub>1</sub> RNA and protein levels were significantly increased in mature human adipocytes compared to preadipocytes. The lean (23 kg/m<sup>2</sup>) and obese (35 kg/m<sup>2</sup>) groups were of similar age (56 vs. 58 years). CB<sub>1</sub> gene expression was similar between both groups, but circulating endocannabinoids were slightly but significantly raised in the obese group. 5% body weight reduction during 11-13 weeks did reduce body fat, insulin resistance and other obesity-associated variables, but did neither influence adipose-tissue gene expression of the CB<sub>1</sub>-receptor, nor circulating endocannabinoid levels.

**Conclusions:** No consistent data are currently available that suggest an upregulation of the peripheral endocannabinoid system in human obesity. Further studies are needed to clarify the physiological and pathophysiological role of adipocyte CB<sub>1</sub>-receptors.

O082

### Ghrelin, insulin and adipocytokines variations with diet composition under controlled carbohydrate allowance

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**Introduction:** Many different types of diets have been proposed for weight management but there are controversies about their real effects either on the short or the long term. The aim of the present study was to measure the effects of 4 diets with a fixed carbohydrate content (55% of energy) on body weight and metabolic parameters.

**Materials and methods:** Male Long-Evans were fed for 10 weeks on 4 diets differing by their protein (5, 15, 22.5 and 40% of energy) and lipid (40, 22.5, 15 and 5% of energy) contents. Body weight and food intake were measured during the experiment and a hormonal and metabolic profile was determined at the end.

**Results:** All rats gained weight during the experiment but the rats fed the HP (P40/L5) diet tended to gain less than the other groups ( $P < 0.055$ ) and were less fat ( $P < 0.005$ ). Over the whole study, control (P15/L30) rats ate about 12% more than the HP and HF (P5/L40) rats ( $P < 0.0025$ ). Plasma glucose and triglycerides decreased proportionally to the augmentation of the protein content. Adiponectin levels followed the same variations. HF rats had higher leptin and lower ghrelin ( $P < 0.002$ ) levels than HP rats. Insulin did not vary significantly.

**Conclusion:** The high protein/low fat diet was the less obesogenic diet. The first signs of insulin resistance are observed with the HF (40%) diet but the leptin, adiponectin and ghrelin systems are activated in order to limit the development of the metabolic syndrome.

**Acknowledgments:** Supported by Institut B. Delessert (Paris).

## O083

**Circulating plasma levels and monocytic expression of TNF $\alpha$  and Interleukin-6 (IL-6) are increased in obese type 2 diabetic women**P TSIOTRA\*, C TSGIOS\*, E ANASTASIOU<sup>†</sup> and SA RAPTIS\*<sup>‡</sup>\*Hellenic National Diabetes Center, <sup>†</sup>Dept. of Endocrinology, Alexandra Hospital, <sup>‡</sup>2<sup>nd</sup> Dept. of Internal Medicine, University of Athens, Athens, Greece

**Introduction:** The inflammatory cytokines TNF $\alpha$  and IL-6 are thought to be involved in the pathogenesis of insulin resistance and atherosclerosis. We examined whether TNF $\alpha$  and IL-6 mRNAs levels produced from human peripheral monocytes are altered in type 2 diabetes and whether they relate to their plasma levels.

**Patients and methods:** We studied 11 overweight women (BMI > 27) with type 2 diabetes (DM2) and 27 healthy women with normal glucose tolerance [15 with BMI > 27 (NGT-overw), and 12 with BMI < 27 (NGT-lean), all premenopausal. We measured relative TNF $\alpha$  and IL-6 mRNA levels in isolated blood monocytes, using a real-time quantitative RT-PCR, and plasma TNF $\alpha$ , IL-6 and adiponectin levels by Elisab (R&D Systems). We also measured fasting and 2 hour post-OGTT glucose and insulin (RIA).

**Results:** Monocyte TNF $\alpha$  and IL-6 mRNA levels were several-fold higher in DM2 compared to NGT-lean or NGT-overw controls (Table). Circulating TNF $\alpha$  and IL-6 levels were significantly higher in DM2 compared to NGT-lean, the former also against NGT-overw. By contrast, plasma adiponectin levels were significantly lower in the DM2 compared to both control groups. Furthermore, circulating TNF $\alpha$  and IL6, but not monocyte mRNA levels, correlated significantly with insulinemia and HOMA-IR ( $P < 0.05$ ) and negatively with adiponectin levels.

	BMI kg/m <sup>2</sup>	TNF $\alpha$ mRNA	IL6 mRNA	TNF $\alpha$ pg/ml	IL6 pg/ml	Adiponectin ng/ml
NGT-lean	21.8 $\pm$ 0.7	0.03 $\pm$ 0.01	23.6 $\pm$ 18.9	2.1 $\pm$ 0.2	0.8 $\pm$ 0.2	15.5 $\pm$ 2.2
NGT-obese	32.3 $\pm$ 1.4*	0.03 $\pm$ 0.009	20.0 $\pm$ 17.5	2.2 $\pm$ 0.2	1.6 $\pm$ 0.3 <sup>†</sup>	11.5 $\pm$ 1.8
DM2	36.5 $\pm$ 1.9*	0.35 $\pm$ 0.18 <sup>‡§</sup>	682.2 $\pm$ 303.2 <sup>‡§</sup>	3.6 $\pm$ 0.4 <sup>‡§</sup>	1.9 $\pm$ 0.3*	4.4 $\pm$ 1.2 <sup>‡§</sup>

\* $P < 0.007$  vs NGT-lean; <sup>†</sup> $P < 0.001$  vs NGT-obese.

**Conclusion:** Peripheral monocyte TNF $\alpha$  and IL6 mRNA production is elevated in type 2 diabetes, but unlike to the circulating levels of these cytokines, they do not appear to relate directly to the degree of insulin resistance of these patients.

## O084

**Disruption of PAI-1 circadian rhythm in obese subjects may explain a change in the time of onset of myocardial infarction**F DADOUN\*<sup>†</sup>, V ACHARD<sup>†</sup>, F PAGANELLI<sup>†</sup>, M REY<sup>§</sup>, A-M BELLAN, M-C ALESSI<sup>†</sup>, I JUHAN-VAGUE<sup>†</sup> and A DUTOUR-MÉYER<sup>†</sup>\*Departments of Endocrinology, <sup>†</sup>INSERM UMR626, <sup>‡</sup>Cardiology,<sup>§</sup>Center for Clinical Investigation, Hôpital Nord AP-HM; Sleep Laboratory, Hôpital Timone AP-H, Faculté de Médecine; Marseilles, France

**Introduction:** The time of onset of myocardial infarction (MI) exhibits a circadian pattern, with a maximal incidence around 8 am, ascribed to potential rhythmic triggers, such as coinciding increase of sympathetic activity or of anti-fibrinolytic factor PAI-1. In a retrospective study, we observed that in obese patients the maximal incidence is shifted to an earlier time of 3 am (unpublished data), and hypothesized that this shift may be related to a shift of PAI-1 circadian rhythm.

**Patients and methods:** 15 obese male subjects, with ( $n = 8$ ) or without SAS ( $n = 7$ ) matched for age/BMI, and 12 controls matched for age were subjected to blood sampling by 30 min during 25 hours, for the study of the circadian rhythm of PAI-1 antigen measured by ELISA.

**Results:** Mean 24h PAI-1 was significantly greater in obese ( $\times 4$ ) than in controls and positively correlated to BMI ( $r = 0.76$ ;  $P < 0.0001$ ) and visceral fat ( $r = 0.73$ ;  $P < 0.0001$ ), with no difference according to SAS status. PAI-1 displayed a circadian pattern with an early morning increase of similar %increment in the different groups. PAI-1 peak started significantly earlier in obese (anova for repeated measures, period 0 am–4 am:  $P = 0.016$ ), independently of SAS status. Mathematical modelization of PAI-1 peak (equation:  $y = y_0 + y_{\max} / (1 + \exp(z_1 - x)) \times (1 + \exp(2 \cdot (x - z_2)))$ );  $r = 0.89 \pm 0.08$ ) confirmed this shift (inflection point of increase: obese 2:00 am  $\pm$  1:24 vs controls 4:35 am  $\pm$  1:27;  $P = 0.003$ ), which was correlated to BMI ( $r = -0.50$ ,  $P = 0.019$ ).

**Conclusion:** Clock-time of PAI-1 circadian morning increase is significantly shifted in obesity. This may explain the shift of the time of onset of MI observed in obese patients, and suggests that PAI-1 morning peak actually participates in triggering MI.

## T1: Genetic Influences on Obesity

## O085

**Association between genetic variation in the beta-2 adrenoceptor (ADRB2) gene and the G-Protein beta-3 (GNB3) gene with a blunted in vivo lipolysis and fat oxidation in overweight subjects**JWE JOCKEN\*, EE BLAAK\*, P ARNER<sup>†</sup>, MA V BAAK\* and WHM SARIS\*\*Department of Human Biology, Nutrition and Toxicology Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands, <sup>†</sup>Department of Medicine, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden

**Introduction:** Obesity is associated with a blunted beta-adrenoceptor mediated ( $\beta$ -ADR) lipolysis and fat oxidation, which persists after weight reduction. The aim of the study was to investigate whether polymorphisms in exon 16, 27, 164 of the beta-2 adrenoceptor gene (ADRB2); and exon 10 of the G protein,  $\beta$ 3-subunit gene (GNB3) are associated with an in vivo blunted beta-adrenoceptor mediated lipolysis and fat oxidation in overweight subjects.

**Patients and methods:** 109 male ( $n = 66$ ) and female ( $n = 43$ ) overweight subjects with BMI > 27 kg/m<sup>2</sup> were included. In all subjects energy expenditure (EE), respiratory quotient (RQ), circulating fatty acids (FFA) and glycerol were determined after stepwise infusion of increasing doses of the non-selective beta-agonist isoprenaline (ISO).

**Results:** In female obese subjects the Arg16Gly genotype ( $n = 22$ ) in the ADRB2 gene was associated with a blunted increase in plasma glycerol (86  $\pm$  51 vs. 129  $\pm$  68  $\mu$ mol/l,  $P = 0.037$ ) and a blunted decrease in RQ ( $\Delta$ RQ; 0.004  $\pm$  0.038 vs. -0.017  $\pm$  0.019  $\mu$ mol/l,  $P = 0.043$ ) during  $\beta$ -ADR stimulation compared to the Gly16Gly genotype ( $n = 15$ ). Additionally, male Arg16Gly carriers ( $n = 29$ ) showed a blunted release of FFA (262  $\pm$  125 vs. 406  $\pm$  195  $\mu$ mol/l,  $P = 0.002$ ) after  $\beta$ -ADR stimulation compared to male Gly16Gly carriers ( $n = 25$ ). Furthermore, male homozygotes for the T allele in the GNB3 gene ( $n = 4$ ) showed an increase in plasma FFA and plasma glycerol after  $\beta$ -ADR stimulation compared to CC ( $n = 32$ ) and CT ( $n = 29$ ) male carriers, whereas in female subjects no association were found.

**Conclusion:** These results suggest that genetic variation in the ADRB2 gene and the GNB3 gene is associated with disturbances in 'in vivo' beta-adrenoceptor mediated lipolysis and fat oxidation during catecholamine stimulation in obese subjects.

## O086

**A paternally imprinted quantitative trait loci (QTL) for body mass (BM) in F<sub>2</sub> mice derived from two strains that differ in resting metabolic rate**KA RANCE\*<sup>†</sup>, J-M FUSTIN\*, C HAMBLY\*<sup>†</sup>, G DALGLIESH\*, L BUNGER\* and JR SPEAKMAN\*<sup>†</sup>\*Aberdeen Centre for Energy Regulation and Obesity (ACERO) School of Biological Sciences, University of Aberdeen, <sup>†</sup>(ACERO), Energy Balance and Obesity Division, Rowett Research Institute, Aberdeen, <sup>‡</sup>SAC, Sustainable Livestock Systems, Penicuik, UK

**Introduction:** We are in the midst of an obesity epidemic – but most people in the western 'obesigenic environment' do not get fat. Determining the genetic basis of obesity related traits will allow us to better understand differences in individuals' response to western lifestyles. Experiments using model animals have identified obesity related QTL, however, the widespread use of populations derived from inbred lines precludes testing of models exploring imprinting effects where parental-specific epigenetic modifications result in differential expression of parental alleles.

**Materials and methods:** We generated an F<sub>2</sub> population ( $n \approx 500$ ) of mice to investigate the genetics of obesity using mouse lines that differ in resting metabolic rate. This paper concerns QTL mapping analysis for BM at 14, 16 and 18 weeks. Data were analysed to explore both Mendelian and imprinting models. Empirical thresholds were generated and background genetic effects were included.

**Results:** Genome wide significant QTL were identified for BM at all ages on chromosomes 5, 7, 8, 9 and 18. Suggestive evidence ( $P < 0.10$ ) for QTL at one or more BM age were found on six other autosomes. The proximal end of chromosome 8, had a highly significant, paternally imprinted QTL explaining > 14% of total phenotypic variance. Candidate genes include Insulin receptor substrate 2, which although not previously identified as being imprinted does possess common features of imprinted genes including CpG islands and clustered direct repeats.

**Conclusion:** We have identified a novel paternally imprinted QTL on mouse chromosome 8. This study highlights the need to explore imprinting models when mapping QTL.

O087

**Twin study of genetic influence on physical activity**  
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**Introduction:** A reduced contribution of physical activity (PA) to daily energy expenditure contributes to the increased prevalence of obesity. If activity-induced energy expenditure (AEE) is genetically controlled, there is a genetic susceptibility to obesity. This study investigated the proportions of the variance of AEE and PA that are explained by genetic and environmental factors.

**Subjects and methods:** 12 monozygotic (MZ) and 8 same-sex dizygotic (DZ, including 2 same-sex sibling pairs with an age difference  $\geq 2.5$  years) twin pairs, aged between 18 and 39 years, participated in the study. AEE was measured for one day in a respiration chamber and for 2 weeks in daily life with doubly labeled water. PA was recorded simultaneously with a tri-axial accelerometer. Structural equation modeling was used to separate and quantify the observed variance into the sex-adjusted additive genetic ( $a^2$ ), common ( $c^2$ ) and unique ( $e^2$ ) environmental contribution.

**Results:** Variance components for AEE in daily life were  $a^2 + 0.72$  and  $e^2 + 0.28$ , and for PA  $a^2 + 0.78$  and  $e^2 + 0.22$ . Within the respiration chamber variance components for AEE were  $c^2 + 0.68$  and  $e^2 + 0.32$ , and unique environmental factors completely explained the variation in PA. The same genetic factors explained 67% of the covariance of AEE and PA in daily life, in the respiration chamber 38% of the covariance was accounted for by the same common environmental factors.

**Conclusion:** Genetic factors explained a large part of the variation in AEE and PA in daily life, while both AEE and PA were influenced by environment only within the confined area of the respiration chamber.

O088

**Association of the V103I MC4R polymorphism with BMI in two population-based surveys including 7937 participants**  
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**Introduction:** The melanocortin-4-receptor gene (MC4R) is part of the melanocortinergic pathway that controls energy homeostasis. A recent meta-analysis of 14 case-control studies reported a mild negative association of the MC4R V103I (rs2229616) polymorphism with obesity. However, evidence in a large homogenous population-based study and a significant estimate of the change in quantitative measures of obesity was lacking.

**Methods:** Probands By MALDI-TOF MS-based SNP genotyping we performed an association analysis on two population-based surveys of Caucasians with the same high quality study protocol including a total of 7937 participants.

**Results:** Linear regression results showed a significant decrease of 0.52 BMI units [95% CI + (-0.02, -1.03),  $P + 0.043$ ] for carriers of the heterozygote rs2229616G/A genotype, that was observed in 3.7% of the participants. By logistic regression we found a significantly negative association of the MC4R variant with 'above average weight' (BMI  $\leq$  median BMI) yielding an odds ratio of 0.75 [95% CI + (0.59, 0.95),  $P + 0.017$ ], obtaining similar results comparing obese (BMI  $\leq 30$  kg/m<sup>2</sup>, WHO 1997) to non-obese (BMI  $< 30$  kg/m<sup>2</sup>). These findings were detected for each gender and each survey separately and did not depend on the modelling of age-, sex- and survey effects.

**Conclusions:** Our study confirms previous findings of a meta-analysis. The relatively infrequent G/A genotype of the V103I MC4R polymorphism is negatively associated with above average weight and obesity in population-based original data of 7937 participants. Our study extends previous findings by showing for the first time a significant decrease of BMI in individuals carrying the infrequent allele of this MC4R variant.

O089

**Impact of ACE polymorphisms on obesity-related phenotypes in Greek children aged 0–6 years**

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**Introduction:** This study aimed to investigate any association between individual polymorphisms or haplotypes of the ACE gene in children aged 0–6 years, in order to reduce environmental influences related to age.

**Methods:** 2033 infants and children (984 girls, 1049 boys) from nursery schools in Greece took part in the study. All provided a buccal swab for genetic analysis. Measurements were taken for height, weight and derived body mass index (BMI), circumferences, and skinfolds.

**Results:** Significant associations were observed between the ACE I/D polymorphism and several obesity-related phenotypes. In girls aged  $> 4$  years, the I-allele was strongly associated with lower weight ( $P + 0.014$ ), BMI ( $P + 0.020$ ), triceps skinfolds ( $P + 0.014$ ), subscapular skinfolds ( $P + 0.048$ ), total skinfolds ( $P + 0.014$ ), waist circumference ( $P + 0.002$ ), hip circumference ( $P + 0.038$ ), arm circumference ( $P + 0.014$ ), and weakly associated with biceps skinfolds ( $P + 0.093$ ), and suprailliac skinfolds ( $P + 0.063$ ). In boys aged 1–2 years, the I-allele was strongly associated with higher BMI ( $P < 0.001$ ) and subscapular skinfolds ( $P + 0.023$ ), and weakly associated with weight ( $P + 0.093$ ) and total skinfolds ( $P + 0.085$ ).

**Conclusion:** These results suggest that the ACE I/D polymorphism has contrasting effects on several obesity-related phenotypes in boys and girls and are mediated at different stages of physical growth.

O090

**Long-term prospective and controlled studies demonstrate marked leptin deficiency in the post-obese state**  
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**Introduction:** Little is known about the role of leptin for long-term changes in body weight. We therefore studied leptin production in obese subjects before and after long-term stable weight reduction to the non-obese state.

**Material and methods:** The study was a prospective case-control study. Thirty-seven obese subjects were followed  $2.6 \pm 0.9$  years (mean  $\pm$  SD) until they reached a steady state weight reduction following life style modification or bariatric surgery (cases). Treatment target was the non-obese state which is  $< 30$  kg/m<sup>2</sup> in body mass index (BMI). Each case was compared with a control subject matched for age, sex and BMI at nadir of weight for the cases. Subcutaneous adipose tissue secretion of leptin, serum leptin levels and fat cell volume were determined.

**Results:** Sixteen obese subjects (43%) reached the non-obese state. This was accompanied by marked decreases in fat cell volume, leptin secretion and serum leptin concentrations ( $P < 0.0001$ ). However, the post-obese had 36% smaller fat cell volume ( $P + 0.0002$ ), 57% lower adipocyte leptin production ( $P + 0.0015$ ) and 35% lower serum leptin levels ( $P + 0.0002$ ) than control subjects, despite almost identical percentage body fat in the two groups. Fat cell volume but not percentage body fat or BMI was directly proportional to leptin secretion and serum leptin concentrations.

**Conclusions:** Low leptin production resulting in marked hypoleptinemia is a common feature of post-obese subjects and is probably due to adipose tissue hyperplasia (many small fat cells). Leptin deficiency may account for the frequent weight gain following anti-obesity therapies.

## TM: New Aspects of Body Weight Regulation

O091

**A novel deletion in the melanocortin-4 receptor (MC4R) gene results in severe early-onset obesity and type II diabetes**

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**Introduction:** Melanocortin-4 receptor (MC4R) plays a crucial role in neuroendocrine regulation of appetite and energy balance. MC4R gene mutations constitute the most common genetic cause of human morbid obesity. As part of an ongoing project, we searched for MC4R mutations.

**Patients and methods:** MC4R gene was examined by dHPLC and sequencing in 252 morbidly obese adults (BMI  $\leq 40$  kg/m<sup>2</sup>) and 146 children with severe early-onset obesity (weight for height  $\leq +70\%$  before age 10). Allele frequencies were determined in a background population of 321 healthy blood donors.

**Results:** Among children with severe-early onset obesity, we detected a novel MC4R deletion, 308delT, in a 13-year old girl, S127L mutation in a 14-year old boy and an 11-year old girl, M200V and P299H mutations in a 15- and a 10-year old boy, respectively. In a 16-year old girl we detected a deletion, -439delGC, located in a transcription factor-binding site in the promoter region. The girl with the 308delT deletion had severe early-onset obesity and early-onset Type II diabetes. This deletion is predicted to result in a grossly truncated receptor, whereas all other mutations result in reduced signaling through the receptor or intracellular retention. No pathogenic mutations were found in the adult cohort.

**Conclusion:** A novel deletion, MC4R 308delT, results in severe early-onset obesity and early-onset Type II diabetes. MC4R mutations are found in 4% of Finnish children with severe early-onset obesity, but not among subjects with adult-onset morbid obesity. Mutations in the MC4R alter receptor function by several different mechanisms.

O092

**Functional analysis of three novel mutations in MC3R gene**  
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**Introduction:** As shown by linkage studies and knock-out mice experiments, melanocortin 3 receptor (MC3R) plays a critical role in weight regulation and body composition. We have previously identified three novel mutations in the MC3R gene (A293T, I335S and X361S) in three different obese patients. In this study, signalling properties of the mutated receptors were evaluated in vitro by assessing intracellular production of cAMP after stimulation with increasing concentrations of alpha-MSH.

**Materials and methods:** The coding sequence of MC3R gene was cloned in an expression vector. Mutations were introduced into wt MC3R by site-directed mutagenesis and the constructs were transiently transfected in HEK293 cells. After agonist stimulation, intracellular cAMP concentration was evaluated using a radioimmunoassay. Wt and mutated receptors were subcloned in GFP fusion vector, transiently transfected in HEK293 cells and visualised by confocal analysis.

**Results:** In comparison with the wt receptor, the I335S mutation resulted in a complete loss of signalling. In contrast, the A293T and X361S mutations did not affect the ability to generate cAMP in response to ligand. Confocal analysis indicated that the three mutations did not impair cell surface expression of the receptor.

**Conclusions:** The results of this study show that the I335S MC3R represents a functionally inactive mutant of the MC3R and suggest that the I335S MC3R mutation might be a genetic factor predisposing the carriers to obesity. Other studies are necessary to clarify the functional role of the A293T and X361S mutations.

O093

**Oxidative stress mediated suppression of beta-adrenergic thermogenesis in older humans**

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**Introduction:** Beta-adrenergic stimulation is an important mechanism in the regulation of energy expenditure in humans. Beta-adrenergic receptor mediated thermogenesis is impaired in older compared with young adults. The physiological mechanism responsible for this impairment has not been determined, but increased oxidative stress may be involved. Accordingly, the purpose of this study was to measure the beta-adrenergic receptor mediated increase in energy expenditure above resting metabolic rate (RMR) under normal (control) conditions and during acute administration of a potent antioxidant, ascorbic acid (vitamin C), in groups of healthy young and older adult humans.

**Patients and methods:** Incremental doses of isoproterenol (6, 12 and 24 ng/kg fat free mass/min) were administered intravenously to 9 young (5 male, 4 female,  $23 \pm 2$  years (mean  $\pm$  SE)) and 15 older (11 male, 8 female,  $64 \pm 1$  years) healthy non-obese adults on two different days: control and ascorbic acid (intravenous: 0.04 g/kg fat free mass) (random order). Energy expenditure was measured via indirect calorimetry (ventilated hood).

**Results:** In the older adults the % increase in energy expenditure above RMR during beta-adrenergic stimulation was greater ( $P + 0.01$ ) with ascorbic acid compared to control ( $10.0 \pm 1.1$ ,  $12.5 \pm 1.0$  and  $19.2 \pm 1.1$  vs.  $5.9 \pm 0.8$ ,  $10.8 \pm 1.0$  and  $15.9 \pm 1.2$ ). In contrast, ascorbic acid had no effect ( $P + 0.57$ ) on beta-adrenergic stimulated thermogenesis in the young adults (control:  $7.2 \pm 1.2$ ,  $10.9 \pm 0.8$ ,  $19.0 \pm 1.5$ ; ascorbic acid:  $8.6 \pm 1.4$ ,  $12.8 \pm 1.3$ ,  $18.9 \pm 1.9$ ).

**Conclusion:** These results support the hypothesis that oxidative stress tonically suppresses beta-adrenergic thermogenesis in healthy non-obese older adults. Thus, oxidative stress may contribute to age-associated reductions in energy expenditure in humans.

O094

**Energy expenditure of genuine laughter**

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**Background:** Laughter is a uniquely human vocal signal with possible beneficial health effects. Clinical manifestations of laughter have been described, but its possible physiological benefits including energy cost have not.

**Patients and methods:** We measured energy expenditure (EE) and heart rate (HR) during laughter produced in 45 adult friend dyads (same-sex male  $n + 7$ , same-sex female  $n + 21$ , and mix-sex male-female,  $n + 17$ ) in a whole-room indirect calorimeter equipped with an acoustic recording system. Participants viewed film clips in 4 cycles either intended to evoke laughter (10 min) or unlikely to elicit laughter (5 min). Digitized audio-data were reviewed (minute-by-minute) using a computerized system, and scored for laugh rate (number/minute), duration (seconds), and type (voiced, unvoiced, mixed). Data were synchronized with HR (5 sec intervals) and EE (1 min intervals). EE of laughter was defined as EE above resting during laughter episodes.

**Results:** Laughter-EE was  $0.19 \pm 0.31$  kcal/min higher than resting EE ( $P < 0.001$ , 95% CI  $+ 0.18$  to  $0.21$  kcal/min), ranging from  $-0.60$  kcal/min to  $2.31$  kcal/min. HR during L segments increased above resting baseline by  $2.1 \pm 3.8$  beats/min, ranging from  $-7.6$  to  $26.8$  beats/min. Laughter EE was correlated with HR ( $r + 0.250$ ,  $P < 0.01$ ). Both laughter-EE and HR were positively correlated with laughter duration ( $r + 0.258$  and  $0.444$ , both  $P < 0.001$ ) and rate ( $r + 0.225$  and  $0.352$ , both  $P < 0.001$ ).

**Conclusion:** Ten to 15 min of voiced laughter could increase energy expenditure by 10 to 40 kcal/day. This may translate into an annual weight loss of 0.5 to 2 kilograms.

O095

**Insulin-stimulated modification of cardiac autonomic balance predicts weight reduction after gastric bypass**

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**Introduction:** This study was aimed at documenting the predictive role of the autonomic nervous system responsiveness in the outcome of bariatric surgery.

**Patients and methods:** Since hyperinsulinemia leads to a shift of the cardiac autonomic balance towards a sympathetic prevalence, an euglycemic, hyperinsulinemic clamp was performed in a group of 22 morbid obese subjects (age: 38 ± 2 years, BMI: 46.0 ± 1.0 kg/m<sup>2</sup>) undergoing a gastric bypass. Spectral analysis of heart rate variability was performed before and during the test and the Low-to-High Frequency ratio (L/H), a parameter of the sympathetic-parasympathetic balance, was evaluated.

**Results:** L/H measured in basal, fasting condition was significantly ( $P + 0.01$ ,  $r^2 + 0.18$ ) positively related to fasting glycemia. The insulin-induced modifications of L/H, measured during the clamp (% Δ L/H), were significantly negatively related to both age ( $P + 0.04$ ,  $r^2 + 0.22$ ) and Fat Mass ( $P + 0.03$ ,  $r^2 + 0.22$ ). Moreover, % Δ L/H showed a significant ( $P + 0.0009$ ,  $r^2 + 0.43$ ), positive relationship to the reduction of body weight, measured one year after surgery and expressed as % excess weight loss (% EWL). Pre-operative BMI was also significantly ( $P + 0.0009$ ,  $r^2 + 0.43$ ) negatively related to the 12 months % EWL. In a multiple regression analysis, % Δ L/H remained a significant ( $P + 0.003$ ), independent predictor of body weight loss, even when pre-operative BMI was taken into account.

**Conclusion:** The autonomic responsiveness influences gastric bypass-induced body weight loss by mechanisms which remain to be elucidated.

**Keywords:** obesity, body weight loss, Sympathetic Nervous System, Roux-en-Y gastric bypass.

O096

**Plasma total ghrelin levels in chronic renal failure: comparison with healthy subjects and relationship with haemodynamic parameters**

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**Introduction:** The effect of renal function on ghrelin's plasma levels is hardly known. We investigated the possible differences in plasma ghrelin levels between patients with chronic renal failure (CRF) and healthy subjects, and ghrelin's relationship to indices of left ventricular (LV) function.

**Patients and methods:** Fasting plasma total ghrelin levels were measured by radioimmunoassay in 122 CRF patients (57 on, 65 not on haemodialysis) and 57 control subjects. Indices of LV function [LV chamber dimensions and wall thicknesses, E/A ratio, deceleration time (DT) of the peak early velocity, isovolumic relaxation time (IVRT) and myocardial performance index of the LV (MPI)] were evaluated using echocardiography. Blood pressure was also measured.

**Results:** Plasma total ghrelin levels (mean values ± 1 SD) were higher in patients with CRF compared to controls (1367.6 ± 455.6 pmol/l vs 591.6 ± 330.3 pmol/l respectively,  $P < 0.0001$ ), but were not different between patients on or not on haemodialysis. In a multivariate linear regression model, after adjustment for sex, body mass index, systolic blood pressure and low density lipoprotein cholesterol, presence of kidney dysfunction explained 41% of the variability of ghrelin values. The etiology of renal failure (diabetic nephropathy or nephropathy from other causes) had no influence on ghrelin levels in the renal patients. Ghrelin levels were not associated with indices of LV systolic function or blood pressure in these patients.

**Conclusion:** Fasting plasma ghrelin concentrations are higher in CRF patients, regardless of their need for haemodialysis, compared to controls. The etiology of renal failure does not affect its plasma levels. In addition, ghrelin levels are not associated with haemodynamic parameters in patients with CRF.

**T5: Surgical and Other Treatment Modalities**

O097

**Implantable gastric stimulation for obesity: a mechanism involving gastric distention**

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Implantable gastric stimulation (IGS) has been applied to treat obesity. Clinical studies have revealed an increase in satiety, whereas canine experiments suggested gastric distention with IGS.

**Aim:** The aim of this study was to investigate the correlation between electrical stimulation-induced gastric distention and food intake in dogs.

**Method:** Fourteen dogs were surgically implanted with a gastric cannula and electrodes in the stomach or intestine. Electrical stimulation was performed via the gastric/intestinal electrodes. In experiment 1, unlimited solid food was given to the dog for 1 hour with or without stimulation. In experiment 2, a polyethylene bag was positioned in the proximal stomach via the gastric cannula and the gastric volume was measured using an electronic barostat for 30 min at baseline and 30 min with stimulation.

**Results:** (1) Food intake was positively correlated with body weight ( $r + 0.62$ ,  $P + 0.02$ ) as well as the baseline fasting gastric volume ( $r + 0.59$ ,  $P + 0.02$ ). (2) Electrical stimulation reduced food intake by about 50% (240.8 g ± 42.5 g vs. 445.0 g ± 33.7 g,  $P < 0.005$ ) and increased fasting gastric volume by 350% (263.4 ± 25.5 vs. 74.4 ± 4.3 ml,  $P < 0.0001$ ). (3) The amount of food intake during stimulation was negatively correlated with gastric volume during stimulation ( $r + -0.58$ ,  $P + 0.02$ ).

**Conclusions:** Electrical stimulation reduces food intake and induces gastric distention. The correlation between reduced food intake and increased gastric volume with stimulation suggests the involvement of gastric distention with IGS for the treatment of obesity.

O098

**Progressive rise in Glucagon-Like Peptide-1 and Peptide YY after Roux-en-Y gastric bypass suggests gut adaptation and may account for increased satiety and stable weight loss**

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**Introduction:** Bariatric surgery is the most effective treatment for morbid obesity. We investigated prospective entero-hypothalamic axis changes after Roux-en-Y gastric bypass (RYGB), examining the meal-stimulated responses of peptide YY (PYY), enteroglucagon, glucagon-like peptide 1 (GLP-1), insulin and ghrelin. GLP-1 promotes insulin release, PYY is a satiety factor and enteroglucagon is associated with gut adaptation.

**Methods:** Six patients were investigated pre-operatively and at 1.3 and 6 months following RYGB. Blood was collected while fasting and at intervals for 180 minutes after a 420kcal mixed meal, and plasma levels of gut hormones were determined. Visual analogue scores (VAS) were used to assess satiety and nausea.

**Results:** Satiety increased significantly post-operatively ( $P < 0.05$ ).

	Pre-op	1 month post-op	3 months post-op	6 months post-op	P value
BMI kg/m <sup>2</sup> (SEM)	48.3 ± 1.4	41.9 ± 1.4	39.5 ± 1.8	36.4 ± 1.5	$P < 0.05$
Fasting leptin ng/ml (SEM)	44.7 ± 8.1	29.4 ± 7.7	19.8 ± 4.0	14.0 ± 2.9	$P < 0.05$
HOMA-IR (SEM)	5.8 ± 2.2	3.9 ± 1.0	2.0 ± 0.5	1.4 ± 0.2	$P < 0.05$
15 min GLP-1 pmol/L (SEM)	36.6 ± 7.2	76.7 ± 13.7	91.0 ± 13.4	151 ± 23.9	$P < 0.01$
30 min Enteroglucagon pmol/L	90.6 ± 13.5	166.7 ± 58.7	193.0 ± 24.7	189.9 ± 31.3	$P < 0.05$
90 min PYY pmol/L (SEM)	23.3 ± 2.9	31.1 ± 5.2	36.7 ± 6.7	41.2 ± 7.5	$P < 0.001$
Fasting ghrelin pmol/L (SEM)	232 ± 72	287 ± 82	239 ± 46	331 ± 95	NS

**Conclusions:** Non-surgical weight reduction results in lower leptin and insulin which enhances appetite and weight regain. RYGB results in substantial weight loss and similar changes in fasting leptin but without an increase in hunger. Our studies suggest that gut adaptation after RYGB and an increase in the release of gut hormones overcomes the normal counter-regulation, leading to enhanced satiety and a lower, stable weight plateau.

## O099

**Safety and efficacy of botulinum toxin therapy in obese patients: a pilot study**

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**Introduction:** Botulin toxin (BTX) is an effective tool in the treatment of a number of neurological conditions and has widespread applications in gastroenterology for treatment of motility disorders. BTX has recently been proposed as a potential obesity treatment, based on a single case-report (Rollnik, 2003). Aim of the present pilot study was to evaluate short-term efficacy and safety of BTX in obese patients.

**Patients and methods:** Eight subjects (4 M, 4 F; median age 46 yrs, range 35–57) with severe obesity (median BMI 47.1 kg/m<sup>2</sup>, range 38.2–56.7) and previous multiple dietary treatment failures were studied in an open-label fashion following written informed consent. In a single endoscopic session, 500 UI of BTX-A were injected in the gastric antral region.

**Results:** No clinically significant side-effects were observed. No changes in fasting serum gastrin were observed following BTX injection. In all patients, despite not being on a specific diet, a reduction of body weight was observed at one month (median baseline weight 124.4 kg vs 121.8 kg at one month,  $P < 0.05$ ). Two treatment-unrelated dropouts were observed. At four months, three out of six patients had a further weight loss. Treatment effect was apparently independent of changes in hunger or satiety (measured by visual analogue scale), or to changes in fasting and postprandial plasma ghrelin and in serum leptin, thus suggesting a different pharmacological mechanism.

**Conclusion:** BTX-A treatment via antral injection at the dose of 500 UI appears to be safe and well tolerated by obese patients, while short-term efficacy varied widely. Therefore, placebo-controlled, dose-ranging studies are warranted to ascertain its potential role in obesity management.

## O100

**TANTALUS™ – a new surgical approach for treating morbid obesity**

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**Introduction:** TANTALUS™ is a new device for gastric electrical stimulation aimed at inducing early satiety through enhancement of antral contractility by delivery of Gastric Contractility Modulation (GCM) signals during meals. The objective of this study was to assess the effect of the TANTALUS™ system on body weight change in morbidly obese patients.

**Patients and methods:** In this prospective, non-randomized, open-label trial 12 subjects (age 36.1 ± 9.8 years, BMI 43.2 ± 2.7 kg/m<sup>2</sup>, body weight 128.8 ± 18.1 kg, mean ± SEM) underwent implantation of the TANTALUS™ system (Metacure Inc., USA) and were followed postoperatively for a period of 20 weeks, 16 weeks of GCM therapy. The subjects received the TANTALUS™ implantable pulse generator and three pairs of bipolar leads implanted by laparoscopic technique. Two bipolar leads were placed in the antrum for eating detection and GCM signal delivery and a third pair of leads was placed in the fundus for eating detection.

**Results:** Automatic eating detection by the device was demonstrated in all patients. Body weight decreased ( $P < 0.05$ ) from 128.9 ± 5.2 to 119.8 ± 5.9 kg, corresponding to an excessive weight loss (EWL) of 17.6%. In parallel, blood pressure decreased ( $P < 0.05$ ) from 148 ± 6/93 ± 3 to 122 ± 4/81 ± 2 mmHg. Two distinct patterns of weight loss were identified: In 9 patients there was a marked EWL of 23.3%, whereas 3 patients did not respond to therapy (EWL -0.8%).

**Conclusion:** The application of electrical signals (GCM) to the stomach during food intake may enhance a natural mechanism of satiety leading to weight loss. Thus, TANTALUS™ is a promising minimal invasive treatment for obesity.

## O101

**Effect of dietary protein and carbohydrate type on appetite and energy intake and plasma ghrelin and cholecystokinin**

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**Background:** Dietary protein is thought to be more satiating than carbohydrate. However, the role of satiety hormones and type of protein or carbohydrate in this relationship is unclear. This study aimed to compare the acute post prandial effect of dietary proteins (whey vs. casein) with high and low glycemic index (GI) carbohydrates on subjective and objective indicators of appetite.

**Design:** Obese men ( $n + 19$ , BMI 32.2 ± 0.9 kg/m<sup>2</sup>) consumed four liquid 'breakfast' preloads (1 MJ; >80% energy from whey, calcium, lactose or glucose) in a cross over design. Subjective appetite ratings, plasma glucose, insulin, amino acids, cholecystokinin (CCK), ghrelin and gastric emptying were measured for 3 h post prandially, followed by assessment of ad libitum energy intake at a buffet lunch.

**Results:** Energy intake, appetite ratings and ghrelin were greater 3 h after the high GI preload compared to the protein (no effect of protein type) and low GI preloads ( $P < 0.01$ ). Both protein treatments produced an additional second peak in CCK 90 min after the preloads ( $P < 0.01$ ) which coincided with 15 ± 3% lower gastric emptying ( $P < 0.01$ ). Whey and casein preloads produced similar total and branched chain amino acid profiles.

**Conclusion:** The glycemic index, but not the type of protein, in liquid preloads affects acute satiety, ad libitum energy intake and post prandial ghrelin. Prolonged CCK secretion and delayed gastric emptying may contribute to the higher satiating capacity of dietary proteins compared to carbohydrates.

## O102

**Stimulation of thermogenesis by combination of bio-active food ingredients**

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**Introduction:** A combination of tyrosine, capsaicin, catechines and caffeine stimulates the sympathetic nervous system and may, together with calcium, promote satiety, lipolysis and thermogenesis. The present objective was to investigate the acute and sub-chronic effect of a supplement containing these 5 food ingredients taken 3 times/d on thermogenesis, faecal fat excretion and fat loss.

**Methods:** 93 overweight-obese subjects (BMI: 31.3 ± 2.6 kg/m<sup>2</sup>, mean ± SD) underwent an initial 4-weeks hypocaloric meal replacement diet (3.4 MJ/d). Those who lost >4% ( $n + 80$ ) were instructed to a hypocaloric diet (-1.3 MJ/d), and were randomized to receive either placebo ( $n + 23$ ) or bio-active supplement ( $n + 57$ ) in a double-blind, 8-weeks intervention. The thermogenic effect of the compound was assessed by indirect calorimetry on the first and last day of intervention, together with blood pressure, heart rate, body weight and composition.

**Results:** The initial weight loss was 6.8 ± 1.9 kg. At the first exposure the thermogenic effect of the bio-active supplement exceeded that of placebo by 87 kJ/4 h (95% CI: 51; 124,  $P + 0.005$ ), and after 8 weeks this effect was sustained [86 kJ/4 h (48; 123),  $P + 0.03$ ]. Body fat mass decreased more in the supplement group, by 0.9 kg (0.5; 1.3), compared with placebo ( $P < 0.05$ ). The bio-active supplement had no effect on faecal fat excretion, blood pressure or heart rate.

**Conclusion:** The bio-active supplement increased 4-h thermogenesis by 90 kJ more than placebo, and the effect was maintained after 8-weeks and accompanied by a slight reduction in fat mass. These bio-active food components may be of value in supporting weight maintenance after a weight reduction.

## T2: Predictors and Determinants of the Metabolic Syndrome

### O103

**Prolonged treatment of genetically obese mice with conjugated linoleic acid (CLA) improves glucose tolerance and lowers plasma insulin concentration: possible involvement of PPAR activation**  
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**Introduction:** Studies in rodents and some in humans have shown that conjugated linoleic acid (CLA) reduces body fat content. However, some studies have found that CLA promotes insulin resistance. The role of peroxisomal proliferator-activated receptors (PPAR) regulation in these effects is unclear. We have conducted experiments with CLA in genetically obese mice, and investigated the effects of CLA isomers in PPARgamma and PPARalpha reporter gene assays.

**Methods:** CLA (15 or 25 g/kg diet, containing equal amounts of *trans-10,cis-12* and *cis-9,t-11* isomers, or enriched to 90% with the isomers) or high oleic sunflower oil (which had no effects compared to chow) was included in the diet of female *lep<sup>ob</sup>/lep<sup>ob</sup>* mice for 3 or 11 weeks. Reporter gene assays were conducted in Cos-7 cells.

**Results:** CLA or CLA enriched with its *trans-10,cis-12* isomer reduced body weight gain and white fat pad weight. After two weeks, CLA or its *trans-10,cis-12* isomer raised fasting blood glucose and plasma insulin concentrations, and exacerbated glucose tolerance. After 10 weeks, however, CLA lowered glucose and insulin concentrations, and markedly reduced the plasma adiponectin concentration. CLA (50microM) enriched with *trans-10,cis-12* CLA, but not with *cis-9,trans-11* CLA, stimulated PPARgamma-mediated reporter gene activity; both isomers (10–100 microM) stimulated PPARalpha.

**Conclusion:** CLA initially decreased but subsequently increased insulin sensitivity in *lep<sup>ob</sup>/lep<sup>ob</sup>* mice. Activation of both PPARgamma and PPARalpha may contribute to the improvement in insulin sensitivity. In the short term, another mechanism, activated primarily by *trans-10,cis-12*-CLA, which probably leads to reduced adipocyte number and consequently reduced plasma adiponectin concentration, may decrease insulin sensitivity.

### O104

**The metabolic syndrome- can it be predicted during pregnancy?**

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**Background:** Birth weight of a child may predict health later in life – not just for the offspring, but also for the mother. The aim of the study was to examine the relationship between pregnancy and later metabolic syndrome (MS) in women.

**Methods:** A population based cohort of 482 mothers who delivered children in 1984–1985 were followed up 17 years later. Anthropometric measurements and questionnaires, blood samples covering metabolic factors and data from the Swedish medical birth register were collected. The WHO classification of MS was used.

**Results:** BMI was  $21 \pm 2.5$  kg/m<sup>2</sup> before first pregnancy and at follow-up  $24.5 \pm 4.2$ . The women had gained an average of  $7.2 \pm 7.2$  kg over these 17 years. However, BMI before first pregnancy could not predict this weight gain. At follow-up 7.3% of the women were classified as having MS. BMI before pregnancy did not differ between the MS/non-MS groups, but the MS group 1. gained more weight during the first pregnancy ( $16.1 \pm 1.5$  vs  $13.9 \pm 4.1$ ,  $P < 0.01$ ), 2. delivered heavier babies ( $3630 \pm 630$  g vs  $3410 \pm 500$  g,  $P < 0.05$ ), 3. continued to gain more weight after pregnancy and gain an average of 10 kg more and 4. ended with a significant higher BMI at follow-up.

**Conclusion:** Future MS women did not enter pregnancy with a higher weight but gained more during pregnancy and continued to gain weight. Pregnancy could thus be seen as a predictive 'stress test' for later weight gain and metabolic complications.

### O105

**Physical activity energy expenditure predicts the metabolic syndrome independently of aerobic fitness in middle-aged healthy Caucasians: the MRC ely study**

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**Introduction:** The prospective associations between objectively measured physical activity energy expenditure (PAEE), and the metabolic syndrome, independent of aerobic fitness ( $VO_{2max}$ ), is unknown. To examine these associations over a period of 5.6 years, in a population-based cohort of middle-aged men and women ( $n + 605$ ), who were free of the metabolic syndrome at baseline.

**Methods:** PAEE was measured objectively by individually calibrated heart rate against energy expenditure.  $VO_{2max}$  was predicted from a sub-maximal exercise stress test. Fat mass and fat-free mass were assessed by bio-impedance. A metabolic syndrome score was computed by summing the standardized values for obesity, hypertension, hyperglycemia, insulin resistance, hypertriglyceridemia, and the inverse level of high-density lipoprotein cholesterol, and expressed as a continuously distributed outcome. Generalized linear models were used to examine the independent prospective associations between PAEE and  $VO_{2max}$  and the metabolic syndrome score after adjusting for sex, baseline age, smoking, SES, follow-up time, and baseline phenotypes.

**Results:** PAEE predicted the metabolic syndrome, independent of baseline metabolic syndrome, body fat,  $VO_{2max}$  and other confounding factors (standardised  $\beta + -0.00085$ ,  $P + 0.046$ ). This association was similar when excluding the adiposity component from the metabolic syndrome (standardised  $\beta + -0.004$ ,  $P + 0.036$ ).  $VO_{2max}$  was not an independent predictor of the metabolic syndrome after adjusting for physical activity (standardised  $\beta + 0.00011$ ,  $P + 0.93$ ).

**Conclusions:** PAEE predicts the development of the metabolic syndrome independent of aerobic fitness, obesity and other confounding factors. This finding underscores the importance of physical activity for metabolic disease prevention without any improvement in aerobic fitness.

### O106

**Association between C-reactive protein and serum antioxidant concentrations**

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**Introduction:** C-reactive Protein (CRP) is a systemic inflammatory marker, which is associated with risk of cardiovascular disease (CVD). Antioxidants have the potential to reduce inflammatory response, however results to date have been conflicting. The aim of this study, using data from the 1998 Scottish Health Survey, was to examine the relationship between CRP and serum concentrations of key antioxidants: vitamin C, E, retinol and carotenoids ( $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin, luteine and lycopene). 776 blood samples were taken from adults aged 16–74 years and of those 726 carotenoid and vitamin E, and 667 vitamin C samples were valid (308 males and 359 females). General linear model, logistic and multiple linear regressions were used to examine relationships.

**Results:** After adjustment for body mass index, age, smoking, physical activity and alcohol consumption,  $\alpha$ -carotene ( $P < 0.05$ ),  $\beta$ -cryptoxanthin ( $P < 0.005$ ), luteine ( $P < 0.02$ ), total  $\beta$ -carotene ( $P < 0.005$ ) in both sexes and retinal ( $P < 0.001$ ), total lycopene ( $P < 0.02$ ) and vitamin C ( $P < 0.001$ ) in men were negatively associated with CRP level. The odds ratio (OR) for higher CRP ( $\leq 3$  mg/l) in third tertile vs. the first tertile for  $\alpha$ -tocopherol, retinol, vitamin C, total  $\beta$ -carotene,  $\alpha$ -carotene, luteine and  $\beta$ -cryptoxanthin were 0.56 (0.34–0.92), 0.43 (0.26–0.70), 0.41 (0.24–0.69), 0.24 (0.14–0.42), 0.30 (0.17–0.50), 0.34 (0.20–0.56) and 0.37 (0.22–0.62) respectively. The most important determinants of CRP for women were  $\beta$ -carotene and luteine, and for men were luteine, vitamin C and retinol when all variables were included in the regression model.

**Conclusion:** These results suggest that higher plasma antioxidants concentrations may favour reductions in CRP. Increasing blood antioxidants concentrations could be most beneficial for those with elevated CRP.

O107

**Markers of inflammation and risk of developing type 2 diabetes mellitus. Results from the MONICA/KORA case-cohort study 1984–2002**

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**Introduction:** Prospective data examining the association between inflammatory markers other than C-reactive protein (CRP) and type 2 diabetes mellitus (T2D) is limited and sex differences have rarely been analysed. Therefore, the aim of the present study was to investigate prospectively associations between several markers of inflammation [interleukin-18 (IL-18), interleukin-6 (IL-6), CRP] and incident T2D in a population-based sample of men and women.

**Subjects and methods:** A case-cohort study was conducted in 7936 middle-aged subjects based on data from three MONICA/KORA Augsburg surveys carried out between 1984 and 1995. All incident cases which occurred until December 31<sup>st</sup>, 2002 were included. Markers of inflammation were measured in stored samples of 527 subjects with incident T2D and in 1698 non-case subjects.

**Results:** Men and women with elevated baseline levels of IL-18 and IL-6 had a significantly increased risk of developing T2D after multivariable adjustment including BMI. Hazard ratios (HRs) and 95% confidence intervals (CIs) comparing tertile extremes of IL-18 were 1.47 (1.05–2.05) for men and 1.93 (1.26–3.00) for women. Respective HRs and 95% CIs for IL-6 were 1.55 (1.09–2.21) and 2.03 (1.25–3.30). Elevated levels of CRP were associated with T2D in both sexes in age and survey adjusted analyses, however, after multivariable adjustment CRP was predictive of T2D in women only [HR (95% CI) for the upper vs. lower tertile: 2.75 (1.52–4.97)].

**Conclusion:** Low grade systemic inflammation is associated with an increased risk of T2D, but the strength of the association may be different in men and women.

O108

**Hypertriglyceridemic waist is a predictor of incident ischemic vascular disease in middle-aged subjects: the SUVIMAX study**

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**Introduction:** Cross-sectional studies suggest that elevated plasma triglycerides (TG) and waist circumference (WC), termed 'hypertriglyceridemic waist' (HTGW) is a marker of risk for ischemic vascular disease (IVD). We examined the prospective association between HTGW and IVD risk in a French cohort.

**Material and methods:** Subjects were participants of the SU.VI.MAX study, an intervention trial testing the impact of antioxidant supplementation on chronic diseases. Baseline plasma lipids, BMI, WC and other IVD risk factors were collected in 1995–1996 in 8227 men and women (mean age, 49.2 ± 6.3 years), free of IVD, and followed-up for 7.5 years. Cut-offs were WC ≤ 94/80 cm in men/women and TG ≤ 2 mmol/l. Cox model was used to assess the relative risk (RR) (95% CI) of IVD according to HTGW.

**Results:** In this population, 65% of the subjects had a low WC/low TG, 27% a high WC/low TG, 3% a low WC/high TG, and 5% a HTGW. During follow-up, 145 subjects developed IVD. After adjustment for age and sex, using low WC/low TG as the reference category, the risk of IVD was: 1.47 (1.00–2.17) for high WC/low TG, 2.28 (1.19–4.36) for low WC/high TG and 3.61 (95% CI: 2.29–5.67) for the HTGW group. Adjusting for blood pressure, active smoking, fasting blood glucose and physical activity did not modify the association between HTGW and IVD.

**Conclusion:** Hypertriglyceridemic waist is a simple clinical phenotype that may be useful to screen subjects at risk of IVD.

**PL5: The Mediterranean Diet in Modern Societies and its Role Against the Development of Obesity and Related Risk Factors**

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**Introduction:** It has been documented that Mediterranean diet reduces mortality and improves longevity. However, concerns have been expressed, on the basis of both ecological evidence and analytic data, that the Mediterranean diet may be associated with overweight and obesity.

**Participants and methods:** We have used cross-sectional data from 23 597 apparently healthy men and women recruited over a five year period (1994–1999) from around Greece in the context of the EPIC-Greece project. Height, weight as well as waist and hip measurements were recorded. Usual dietary intake over the years preceding enrollment was assessed through a validated, semi-quantitative, interviewer administered food frequency questionnaire which included approximately 150 foods and beverages commonly consumed in Greece. The quantities per day of total energy intakes (in kcal) were computed for each study participant. Standard portion sizes were used for the estimation of consumed quantities. A gradient of adherence to the traditional Greek Mediterranean diet was constructed based on 9 nutritional components. Information on important covariates, including socioeconomic status, lifestyle variables, tobacco smoking and physical activity were also recorded. The data were modeled through multiple regression equations with body mass index or, alternatively, waist to hip ratio as dependent variables and the Mediterranean diet score and socio-demographic and life style factors as predicted variables.

**Results:** There was no association between Mediterranean diet score on the one hand and BMI and waist to hip ratio on the other when all potential confounders, including energy intake, are controlled for. When energy intake was not controlled for, a marginally positive, but clinically unimportant, association between Mediterranean diet and overweight indicators emerged.

**Conclusion:** It is concluded that Mediterranean diet does not substantially affect body mass index and the high prevalence of overweight in Mediterranean countries is probably accounted for by high prevalence of inactivity in conjunction with relative excess energy intake.