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The limited storage capacity of gonadal adipose tissue directs the development of metabolic disorders in mice.

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Introduction: White adipose tissue (WAT) consists of various depots with different adipocyte functionality and immune cell composition. Knowledge about WAT depot-specific differences in expandability and immune cell influx during the development of obesity is limited, and therefore we aimed to characterize different WAT depots during the development of obesity in mice.

Methods: Gonadal (gWAT), subcutaneous (sWAT) and mesenteric WAT (mWAT) were isolated from male C57Bl/6J mice with different body weights (approximately 25-60 g), analysed, and predictive mathematical functions were developed that describe the extent of WAT depot expandability and immune cell composition as a function of body weight.

Results: Whereas mouse sWAT and mWAT remained expanding with body weight, gWAT expanded mainly during the initial phase of body weight gain, after which the expansion diminished around a body weight of 40 grams. From this point on, crown-like structure formation in gWAT, liver steatosis and insulin resistance occurred. Mouse WAT depots showed major differences in immune cell composition; gWAT mainly consisted of macrophages, whereas sWAT and mWAT contained primarily lymphocytes.

Conclusion: Marked inter-depot differences exist regarding WAT immune cell composition and expandability. The limited storage capacity of gWAT seems to direct the development of metabolic disorders in mice.

A selective glucocorticoid receptor modulator prevents diet-induced obesity and inflammation by reducing caloric intake and increasing fat oxidation

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Introduction: High-fat diet exposure results in obesity and chronic low-grade inflammation in adipose tissue. Whereas glucocorticoid receptor (GR) antagonism reduces diet-induced obesity (DIO), GR agonism reduces inflammation, the combination of which would be desired in a strategy to combat the metabolic syndrome. Selective GR modulators combine GR agonism and antagonism The aim of this study was to assess the beneficial effects of the selective GR modulator C108297 on both diet-induced weight gain and inflammation in mice, and to elucidate underlying mechanisms.
Methods and results: 10-week old C57Bl/6J mice were fed a 60% high-fat diet for 4 weeks while being treated with C108297, a full GR antagonist (RU486) or vehicle. C108297 and, to a lesser extent, RU486 reduced body weight gain and fat mass. As measured by fully automatic metabolic cages, RU486 increased energy expenditure and thermogenic markers in energy-combusting brown adipose tissue (BAT), but did not affect inflammation. In contrast, C108297 decreased caloric intake and increased lipolysis in WAT and free fatty acid levels in plasma resulting in decreased fat cell size and increased fatty acid oxidation. Furthermore, C108297 reduced pro-inflammatory M1 macrophage infiltration in WAT and reduced inflammation in the hypothalamus as measured by immunostaining for the microglia marker CD45.
Conclusion: C108297 attenuates obesity by reducing caloric intake and increasing lipolysis and fat oxidation, and in addition attenuates inflammation. These data suggest selective GR modulation as a strategy for the reduction of diet-induced obesity in addition to inflammation.

Conflict of interest and funding: J.K.B. and H.H. are employees of Corcept Therapeutics, which develops glucocorticoid receptor ligands for clinical use. Corcept Therapeutics has provided compounds and financed part of the experiments.

POSTPRANDIAL REGULATION OF SKELETAL MUSCLE LIPID METABOLISM BY ANGIOPOIETIN-LIKE PROTEIN 4 IN OVERWEIGHT SUBJECTS WITH IMPAIRED GLUCOSE METABOLISM

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Introduction: Angiopoietin-like protein 4 (ANGPTL4) decreases plasma triglyceride clearance via inhibition of lipoprotein lipase (LPL), and may thereby contribute to impairments in lipid metabolism in humans. In this study, modulation of circulating ANGPTL4 after high-fat meals with varying dietary fat quality was studied in overweight subjects. Secondly, we examined whether ANGPTL4 acts as a myokine after a high-saturated fat (SFA) meal.
Methods: The effects of a mixed-meal either high in SFA, mono- (MUFA) or polyunsaturated (PUFA) fat on plasma ANGPTL4 levels were studied in ten obese insulin resistant men (BMI 33.8 ± 3.8 kg/m^2). Skeletal muscle fatty acid handling and ANGPTL4 fluxes across muscle (forearm balance technique) were examined in 73 middle-aged overweight subjects (BMI 30.4 ± 0.4 kg/m^2) with impaired glucose metabolism before and during a 4-hour high-SFA mixed-meal test.
Results: Plasma ANGPTL4 concentrations were decreased after intake of the SFA meal (5.2 ± 0.2 vs. 4.0 ± 0.2 ng/ml; P<0.01; n=73). This decrease was evident after the SFA and MUFA meal but not after a PUFA meal in the late postprandial phase (P=0.04, n=10). Under fasting conditions, no release of ANGPTL4 from forearm skeletal muscle was observed (-0.1 ± 0.1 ng·100 ml tissue^{-1}·min^{-1} *vs*. zero; P=0.46; n=73), while after a high-SFA meal ANGPTL4 was released (-0.2 ± 0.1 ng·100 ml tissue^{-1}·min^{-1} *vs*. zero; P=0.05; n=73). At NASO2015, data on the relationship between ANGPTL4 and *in vivo* muscle LPL activity will be available.
Conclusion: A SFA and MUFA but not a PUFA meal decreased plasma ANGPTL4 concentrations, indicating a differential regulation with dietary fat quality in overweight subjects. For the first time, we showed a significant ANGPTL4 release across forearm muscle after a high-SFA meal.

Gut microbiota composition strongly correlates to peripheral insulin sensitivity in obese men but not in women

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Introduction: Gut microbiota composition and functionality may play an important role in the development of obesity-related comorbidities. However, only few studies have investigated the relation between microbiota composition and tissue-specific insulin sensitivity. Furthermore, manipulation of microbiota composition might be involved in observed benefits of polyphenol-supplementation on lipid metabolism.

Methods: Fecal microbiota composition (qPCR), insulin sensitivity (hyperinsulinemic-euglycemic clamp), body composition (DEXA), substrate oxidation (indirect calorimetry), systemic lipids and inflammatory markers were determined in 38 overweight/obese subjects before and after 12-wk-supplementation with Epigallocatechin-gallate+Resveratrol (E+R) or Placebo.

Results: At week 0, The Bacteroidetes/Firmicutes-ratio (B/F-ratio) was higher in men than in women (P=0.001). B/F-ratio was significantly related to peripheral insulin sensitivity in men but not in women, whilst no relationship with hepatic insulin sensitivity was found. The relationship between B/F-ratio and peripheral insulin sensitivity in men was not mediated by dietary fiber and saturated fat intake, body composition, fat oxidation and low-grade inflammation.

After E+R-supplementation, abundance of Bacteroidetes significantly decreased in men but not in women. However, this observed reduction was not associated with observed changes in lipid metabolism.

Conclusion: The metabolic impact of microbiota composition seems different in men versus women, implying that women might be less responsive to gut microbiota-induced metabolic aberrations than men. Benefits of polyphenol-supplementation on lipid metabolism are independent of alterations in bacterial phyla composition.

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The effects of 12 weeks combined polyphenol supplementation on peripheral and hepatic insulin sensitivity, substrate metabolism and mitochondrial oxidative capacity in overweight men and women

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Introduction: Obesity and related cardiometabolic disorders are characterized by insulin resistance and reduced mitochondrial capacity. Recent evidence suggests that dietary polyphenols might improve these deteriorations. Indeed, we have shown that 3-day Epigallocatechin-gallate+Resveratrol supplementation (E+R) increased energy expenditure (EE)[1]. Moreover, metabolic flexibility tended to improve after a high-fat mixed meal (HFMM, 2.6MJ, 61E% fat) in men. These findings may translate into long-term benefits on insulin sensitivity and lipid metabolism.

Methods: In this double-blind RCT, 42 healthy overweight subjects (age 38±2y, BMI 29.7±0.5kg/m2, HOMAIR 2.05±0.2) received either E+R (300+80mg/d, respectively) or placebo (PLA) for 12 weeks. Before and after intervention, peripheral and hepatic insulin sensitivity was assessed by 2-step-hyperinsulinemic-euglycemic clamp. Fasting and postprandial (HFMM) lipid handling was measured using indirect calorimetry, blood sampling, microdialysis and adipose tissue and skeletal muscle biopsies.

Results: Insulin-stimulated glucose rate of disappearance, respectively suppression of endogenous production, were not affected by the intervention ($P>0.70$). In contrast to PLA, postprandial TAG-concentrations did not increase after E+R-supplementation compared with week 0 ($p<0.01$). Moreover, E+R increased fasting ($p=0.06$) and postprandial fat oxidation ($p=0.03$) without changes in EE. This was accompanied by increased oxidative capacity in permeabilized muscle fibers ($p<0.05$). Finally, E+R tended to decrease visceral fat mass, while whole-body mass and composition, assessed by 12-wk E+R-supplementation improved lipid handling and oxidative capacity, but this did not translate into increased insulin sensitivity in healthy obese men and women.

1. Most, J., et al., *Short-term supplementation with a specific combination of dietary polyphenols increases energy expenditure and alters substrate metabolism in overweight subjects.* Int J Obes (Lond), 2014. **38**(5): p. 698-706.

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Effects of Gut Microbiota Manipulation by Antibiotics on Host Metabolism in Obese Humans

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Introduction Recent studies indicate that gut microbiota manipulation can affect metabolic health. Because human data are scarce, we investigated the effects of gut microbiota knock-down by antibiotics on insulin sensitivity and parameters of metabolism in the human host.

Methods 57 obese male subjects (BMI 31.2±2.6kg/m^2, age 59±7y, HOMA-IR 4.5±0.2) with impaired glucose homeostasis, were randomized to amoxicillin (AMOX; broad-spectrum), vancomycin (VANCO; aimed at gram positive bacteria) or placebo for 7 days, 1500mg/d. Hepatic and peripheral insulin sensitivity (hyperinsulinemic-euglycemic clamp using [6,6-$^2H_2$]-glucose), energy expenditure, substrate oxidation, gut permeability, systemic inflammatory markers, plasma leptin and GLP-1 concentrations were measured. Adipose tissue and skeletal muscle biopsies were collected for microarrays and metabolic fluxes. Feces was collected for analysis of microbiota composition and energy excretion.

Results Both AMOX and VANCO had no significant effect on insulin-mediated suppression of hepatic endogenous glucose production (EGP) and insulin-stimulated glucose disposal (Rd) compared to PLA. However, insulin-stimulated non-oxidative glucose disposal (glycogen storage) significantly decreased after AMOX compared to PLA (-3.2±1.5 vs. 2.6±1.6 µmol/kg/min, p=0.017). Antibiotic treatment did not affect energy intake and expenditure, substrate oxidation, gut permeability, plasma LPS-binding protein, IL-6, IL-8, TNF-α, leptin and GLP-1 concentrations.

Conclusion The present study demonstrates for the first time that robust knock-down of intestinal bacteria by antibiotics has no significant effects on insulin sensitivity, host energy metabolism and systemic inflammation, but decreases insulin-stimulated glycogen storage in obese humans.

1. Conflict of interest: none

2. Funding: TIFN

The relationship of macronutrients, food groups and diet quality with non-alcoholic fatty liver in a general Dutch population

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Introduction: Non-alcoholic fatty liver disease (NAFLD), the accumulation of triglycerides within hepatocytes, is considered the hepatic manifestation of the metabolic syndrome. Diet is known to affect liver fat accumulation in humans. The objective was to assess the relationship between dietary intake and fatty liver as scored by the validated Fatty Liver Index (FLI), in a large cross-sectional study among a general Dutch adult population.

Methods: A total of 1283 participants of the NQ-plus study, aged 20-70y, were included. At baseline, anthropometrics, blood sampling, and dietary assessment with validated FFQ were performed. FLI was calculated from BMI, waist circumference, triglycerides and gamma-glutamyltransferase. Associations were adjusted for energy intake, alcohol intake, age, sex, education, smoking and prevalence of hypertension and diabetes. Additionally, the Dutch Healthy Diet index (DHD)-score was assessed.

Results: In this population (age: 53.6 ± 11.2y; BMI: 25.9 ± 4.0 kg/m^2; FLI 35.6 ± 27.8), the prevalence of fatty liver as indicated by an FLI>60, was 22.0%. Compared to persons with a normal FLI score of <30, protein intake was positively associated with high FLI score >60 (OR: 1.26 per 1 en%, 95%CI 1.16-1.37). This was especially clear for protein intake from animal sources (OR 1.28, 95%CI 1.19 – 1.38). Furthermore, the DHD-index, was significantly lower in the high FLI group (FLI<30: 63.4 ± 10.8 vs. FLI 30-60: 62.1 ± 10.1 vs. FLI>60: 59.3 ± 11.1; p<.0001).

Conclusion: Subjects in the highest FLI-category were more likely to be male, have a higher BMI and a larger waist circumference. Furthermore, these subjects consumed more protein, especially from animal origin. Additionally, people in the highest FLI group had a lower DHD-score reflecting a lower adherence to the Dutch healthy eating guidelines. Results are in line with previous studies on protein intake and diabetes risk.

1. Conflict of interest: none

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Sedentary time in 'metabolically healthy' versus 'metabolically unhealthy' obese and non-obese individuals

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Background Although both obesity and the metabolic syndrome (MetS) frequently occur together in the same individual, they can also develop independently from each other. The (patho)physiology of "metabolically healthy obese" (i.e. obese without MetS) and "metabolically unhealthy non-obese" phenotypes (i.e. non-obese with MetS) is not fully understood, but sedentary behaviour may play a role. We therefore investigated sedentary behaviour patterns across 4 groups of subjects: I) metabolically healthy obese (MHO), II) metabolically unhealthy obese (MUO), III) metabolically healthy non-obese (MHNO) and IV) metabolically unhealthy non-obese (MUNO).
Methods Data were available from 2,494 men and women, aged 40-75 years who participated in The Maastricht Study from 2010 to 2013. Participants were classified into the 4 groups according to obesity (body mass index [BMI] ≥30 kg/m^2) and MetS (Adult Treatment Panel III definition). Physical activity and sedentary behaviour were objectively measured for 7 days with the ActivPAL™ physical activity monitor. General Linear Models were used to assess cross-sectional differences in sedentary time across the 4 groups.
Results In our study population, 562 individuals were obese. 19.4% of the obese individuals and 72.7% of the non-obese individuals was metabolically healthy. On average, people spent 60.2% of total waking time sedentary. After adjustment for age, sex, educational level, smoking status and alcohol use, significant differences in sedentary time were found between MHO and MUO (60.3% versus 64.4%, P<0.001) and between MHNO and MUNO (58.2% versus 61.8%, P<0.001). Further adjustments for type 2 diabetes, history of cardiovascular diseases and higher intensity physical activity did not alter the results.
Conclusions Total time spent sedentary was lower in the subgroups without MetS (MHNO and MHO) compared to both subgroups with MetS (MUNO and MUO), independent of level of physical activity. Therefore, sedentary time may partly explain the presence of MetS in obese as well as non-obese individuals.

What about optimal gestational weight development for the obese?

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Introduction: Starting a pregnancy as obese increases health risks for fetus, the later child, delivery, the pregnant woman and the later mother. Independently a not optimal gestational weight development increases these risks even further. To come to an optimal gestational weight development competitive risks must be balanced. This is challenging, especially for the obese. In recent years many new studies appeared. Here an update of the literature and a proposal for a guideline is presented.

Methods: Review of the literature.

Results: Today's evidence about optimal gestational weight development for obese women is mostly based on large observational studies, because only few good quality experimental studies on restricting gestational weight gain exist. In 2009 the American Institute of Medicine/National Research Council sharpened their BMI class specific gestational weight development advises from 1990. For all obese women a gestational weight gain of 5-9 kg is advised, which results in a net weight loss of about 5 kg after delivery. However this advise is controversial. Many investigators plead for a more stringent advise for the obese and also plead for obesity class specific advises. Even a small weight loss during pregnancy, especially for the morbidly obese pregnant women, is now suggested.

Conclusion: Although the exact optimal gestational weight development for obese women is unknown and high quality trials are necessary, today's evidence suggest more stringent advises than given by the 2009 American Institute of Medicine/National Research Council report, especially for the morbidly obese.

1. Conflict of interest: none.

2. Funding: none.

A systematic review and meta-analysis on the effects of exercise training *versus* hypocaloric diet: distinct effects on body weight and visceral adipose tissue

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Introduction: Exercise training ("training") and hypocaloric diet ("diet") are frequently prescribed for weight loss in obesity. Whilst changes in body weight are commonly used to evaluate lifestyle interventions, visceral adiposity (VAT) is a stronger predictor for morbidity and mortality than body weight. Currently, it is not known whether training or diet has superior effects on VAT. The aim of this study is to compare the impact of training *versus* diet on VAT in overweight/obese humans and to examine the correlation between changes in body weight and VAT.

Methods: Pubmed, Cochrane, Web of Science and Embase were systematically searched for eligible studies that evaluated the effects of training or diet (duration $\geq$4 weeks) on radiographic quantified VAT in overweight/obese humans.

Results: 117 Studies (n=4,815) were included. Training and diet caused VAT loss: standard mean difference (SMD): -0.47; 95%CI -0.56/-0.39 and SMD -0.63; 95%CI-0.71/-0.55, respectively, (both P<0.0001). When comparing diet *versus* training, diet caused a larger weight loss (SMD 0.308; 95%CI 0.02/0.596; P=0.04). In contrast, a trend was observed towards a larger VAT decrease in training (SMD -0.59; 95%CI -1.248/0.071; P=0.08). Changes in weight and VAT showed a strong correlation after diet (R^2=0.737, P<0.001), and a modest correlation after training (R^2=0.451, P<0.001). In the absence of weight loss (Y-axis intercept), training is related to 6.1% decrease in VAT, whilst diet showed virtually no change (1.1%).

Conclusion: Both training and diet reduce VAT. Despite a larger effect of diet on weight loss, training tends to have superior effects in reducing VAT. Finally, weight loss does not necessarily reflect changes in VAT and, therefore, examining weight loss may lead to spurious conclusions when evaluating benefits of lifestyle-interventions.

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A high whey protein–, leucine-, and vitamin D–enriched supplement preserves muscle mass during intentional weight loss in obese older adults: a double-blind randomized controlled trial

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Introduction: Intentional weight loss in obese older adults is a risk factor for muscle loss and sarcopenia. The objective was to examine the effect of a high whey protein–, leucine-, and vitamin D–enriched supplement on muscle mass preservation during intentional weight loss in obese older adults.

Methods: We included 80 obese older adults in a double-blind randomized controlled trial. During a 13-wk weight loss program, all subjects followed a hypocaloric diet (2600 kcal/d) and performed resistance training 3/wk. Subjects were randomly allocated to a high whey protein–, leucine-, and vitamin D–enriched supplement including a mix of other macro- and micronutrients (150 kcal, 21 g protein; 103/wk, intervention group) or an isocaloric control. Primary outcome was change in appendicular muscle mass. Secondary outcomes were body composition, handgrip strength, and physical performance. Data were analyzed by using ANCOVA and mixed linear models with sex and baseline value as covariates.

Results: At baseline mean (±SD) age was 63±5.6 y and mean BMI 33±4.4 kg/m². During the trial protein intake was 1.11±0.28 g/kg BW/d in the intervention group compared to 0.85±0.24 in the control group ($p<0.001$). Both intervention and control group decreased in body weight (-3.4±3.6 kg and -2.8±2.8 kg; both $p<0.001$) and fat mass (-3.2±3.1 kg and -2.5±2.4 kg; both $p<0.001$) with no differences between groups. The 13 week change in appendicular muscle mass, however, was different in the intervention group compared to the control group (+0.4±1.2 kg vs -0.5±2.1 kg; beta 0.95 kg (95%CI 0.09;1.81), $p=0.03$). Muscle strength and function improved over time without significant differences between groups.

Conclusion: A high whey protein, leucine and vitamin D enriched supplement compared to isocaloric control preserves appendicular muscle mass in obese older adults during a hypocaloric diet and resistance exercise program and might therefore reduce the risk for sarcopenia.

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Rate of weight loss does not affect long-term weight regain

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Introduction: Dietary guidelines recommend 'slow'- over 'rapid'-weight loss for the management of obesity. This is based on the belief that slow weight loss is preferential for long-term weight management. However, this notion has not been confirmed by scientific studies in which weight loss in the slow- and rapid-weight loss group was similar. Therefore, the objective of this study was to investigate the effect of rate of weight loss, with similar total weight loss, on long-term weight regain in overweight and obese individuals.
Methods: Fifty-seven participants (BMI: 28 - 35 kg/m2) were randomized to a low-calorie-diet (LCD; 1250 kcal/d) for 12 weeks or a very-low-calorie-diet (VLCD; 500 kcal/d) for 5 weeks. Both groups subsequently underwent a 4-week weight-stable period followed by a 9-month follow-up. Weight and body composition (BodPod) were determined at study start and after each period.
Results: Diet-induced weight loss was similar in both groups (LCD: -9.1% and VLCD: -10.0%, p=0.26). Interestingly, regain of lost weight after follow-up was not significantly different between groups (LCD: +58.6% and VLCD: +54.7%, p=0.78). Fat-free mass (FFM) loss induced by the diet was higher in the VLCD-group compared to the LCD- group ($p<0.05$) and was associated with weight regain during follow-up (whole group: r=0.325, p=0.018). However, the difference in mean FFM loss between the groups was too small to translate into differences in mean weight regain.
Conclusion: The present study showed that, with similar total weight loss of approximately 10% of initial weight, the rate of weight loss did not affect long-term weight regain. Dietary recommendations concerning the rapidity of weight loss should be critically reviewed in light of recent scientific evidence.

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DEPOT DIFFERENCES IN ADIPOSE TISSUE OXYGEN TENSION IN OVERWEIGHT AND OBESE WOMAN

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Background: Upper and lower-body fat depots exhibit opposing associations with obesity-related cardiometabolic diseases. Recent data indicate that adipose tissue (AT) oxygen tension (AT PO_2) is related to AT dysfunction. We compared *in vivo* ATPO_2 in abdominal and femoral subcutaneous (sc) AT in overweight/obese women, and examined depot-specific effects of oxygen tension on metabolism and inflammation.

Methods: 8 overweight/obese (BMI 34.2±1.9 kg/m^2) post-menopausal women with impaired glucose metabolism were included. AT PO_2 was assessed in abdominal and femoral sc AT using microdialysis-based optochemical measurements. Furthermore, AT blood flow (ATBF) (^{133}Xe wash-out), insulin sensitivity (hyperinsulinemic-euglycemic clamp) and body composition (DEXA) were measured. AT biopsies were collected for gene/protein expression analysis and cell culture experiments to determine effects of AT PO_2 (5 vs. 10 vs. 21% O_2) on adipogenic differentiation, adipokine expression and secretion, mitochondrial oxygen consumption and glucose uptake.

Results: AT PO_2 was significantly higher in abdominal compared to femoral sc AT (62.7±6.6 *vs.* 50.0±4.5 mmHg, p=0.017), despite lower ATBF in abdominal than femoral AT (1.8±0.3 *vs.* 2.8±0.5 ml/100g tissue/min, p=0.028). Cell culture experiments and gene/protein expression analyses are currently ongoing.

Conclusion: This study demonstrated for the first time that AT PO_2 was significantly higher in abdominal than femoral subcutaneous AT of overweight/obese women, despite slightly lower ATBF, and may be an important contributor to metabolic disease risk.

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