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Abrogated glucocorticoid signalling in osteoblasts prevents diet-induced obesity, insulin resistance and bone loss

Sarah Kim[1,*], Holger Henneicke[1], Sylvia J. Gasparini[1], Lee Thai[1], Markus J. Seibel[1,2], Hong Zhou[1]

[1] *Bone Research Program, ANZAC Research Institute, University of Sydney, Concord, NSW, Australia*
[2] *Department of Endocrinology and Metabolism, Concord Repatriation General Hospital, Concord, NSW, Australia*

Overconsumption of energy-dense diets has become a major public health challenge due its causal association with obesity, diabetes and poor skeletal health. However, most animal studies that examine diet-induced obesity and diabetes have focused solely on very high-energy high-fat feeding and thus, we aimed to determine whether these adverse health outcomes are due to the high-energy density or high-fat component of diets. We have previously shown that disruption of glucocorticoid signalling in bone protects mice from the adverse metabolic side effects of exogenous glucocorticoids hence, we also aimed to investigate whether abrogating glucocorticoid signalling in bone can protect from diet-induced metabolic disturbances.

To compare the effects of high-energy versus high-fat, two high-energy diets (both 16.3 kJ/g) were designed: standard-fat (SFD^{high}; 14% total-energy as fat) and high-fat (HFD^{high}; 43% total-energy as fat). A standard chow was used as control (13.8 kJ/g, 14% total-energy as fat). Seven-week-old male wild-type (WT) mice and their transgenic littermates that have glucocorticoid signalling selectively disrupted in osteoblasts ($n = 6$—15/group) were fed *ad libitum* for 18 weeks. At endpoint, body composition, glucose handling and bone mass were measured.

High-energy feeding, regardless of dietary fat content resulted in significantly increased fat mass in WT mice compared to WT chow-fed mice (SFD^{high}: +88%, HFD^{high}: +73%) and exhibited fasting hyperglycaemia and reduced insulin sensitivity. WT HFD^{high}-fed mice also demonstrated pronounced glucose intolerance. Both high-energy diets induced significant tibial cortical volume loss to a similar extent (SFD^{high}: −11%, HFD^{high}: −14%). Surprisingly, transgenic mice that have abrogated osteoblast glucocorticoid signalling were protected from excessive fat accrual, insulin resistance, glucose intolerance and bone loss, despite consuming the same amount as their WT littermates on either high-energy diet.

Our data indicates that high-energy density rather than high-dietary fat content is a major driver of metabolic dysfunction. These effects appear to be mediated by glucocorticoid signalling in osteoblasts.

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Circulating bile acids are associated with insulin resistance and visceral and liver fat in human subjects

Ramy H. Bishay[1,2,3,*], Katherine T. Tonks[1,2,4], Jacob George[6,5], Dorit Samocha-Bonet[4], Donald J. Chisholm[1,2,4], David E. James[7], Jerry R. Greenfield[1,2,4]

[1] *St Vincent's Hospital, Sydney, Darlinghurst, NSW, Australia*
[2] *St Vincent's Clinical School, University of New South Wales Medical School, Sydney, NSW, Australia*
[3] *St Vincent's and Mater Hospital, University of Notre Dame, Sydney, NSW, Australia*
[4] *Diabetes and Metabolism Research Program, Garvan Institute of Medical Research, Sydney, NSW, Australia*
[5] *Storr Liver Centre, Westmead Millennium Institute, Westmead Hospital, University of Sydney, Sydney, NSW, Australia*
[6] *Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, NSW, Australia*
[7] *School of Life and Environmental Sciences, Charles Perkins Centre, Sydney Medical School, University of Sydney, Sydney, NSW, Australia*

Introduction: Bile acids (BA) are purported to have a potential role in insulin resistance and obesity, although the exact mechanism remains elusive. We hypothesised that BA concentration is increased in obesity and/or insulin resistance.

Methods: Seventy-one adult volunteers formed four groups based on BMI, homeostatic model assessment of insulin resistance (HOMA-IR) and a 75-g OGTT: lean insulin-sensitive ($BMI \leq 25$ kg/m^2, HOMA-IR < 2.0, $n = 19$), overweight/obese

insulin-sensitive non-diabetic (Ob_{sen}, BMI > 25 kg/m^2, HOMA-IR < 1.5, $n = 11$), overweight/obese insulin-resistant (Ob_{res}, BMI > 25 kg/m^2, HOMA-IR > 3.0, $n = 20$) and type 2 diabetes mellitus (T2DM, $n = 21$). We measured insulin sensitivity by hyperinsulinaemic-euglycaemic clamp, body composition/central abdominal fat by dual energy X-ray absorptiometry, visceral fat area by computed tomography and fasting insulin, adiponectin and BA.

Results: Neither total BA ($r = 0.012$, $p = 0.91$) nor cholic acid (CA, the predominant primary BA) ($r = 0.04$, $p = 0.70$) correlated with percent total body fat. However, there were significant associations between BA and CA levels and waist circumference ($r = 0.39$, $p = 0.0008$; $r = 0.34$, $p = 0.0035$), central abdominal ($r = 0.33$, $p = 0.0057$; $r = 0.28$, $p = 0.01$) and visceral fat ($r = 0.26$, $p = 0.026$; $r = 0.24$, $p = 0.045$), respectively. CA, but not total BA, correlated with liver density (an inverse marker of hepatic fat, $r = -0.25$, $p = 0.03$). Total BA inversely correlated with insulin sensitivity (glucose infusion rates corrected for fat-free mass [GIR/FFM], $r = -0.35$, $p = 0.003$) and adiponectin levels ($r = -0.24$, $p = 0.04$). In group comparisons, GIR/FFM was significantly lower, and visceral and liver fat significantly higher, in Ob_{res} compared to lean and Ob_{sen} subjects, despite similar total adiposity in Ob_{res} and Ob_{sen} (data not shown). Consistent with correlation analyses, total BA concentration tended to be higher in Ob_{res} (1.35 + 1.1 mmol/L) versus Ob_{sen} (0.67 + 0.28 mmol/L) ($p = 0.057$), but were similar between Ob_{sen} and lean (1.00 + 0.69 mmol/L).

Conclusion: Our data suggest that BA concentrations aligned closely with insulin resistance, central abdominal, visceral and liver fat in human subjects. Whether BA play an aetiolgoical role in insulin resistance is yet to be elucidated.

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Gestational diabetes mellitus among young adult women with PCOS: Association with BMI trajectories over 13 years

Nadira Sultana Kakoly*, Arul Earnest, Lisa J. Moran, Deborah Lexton, Helena J. Teede, Anju Joham

Monash University, Clayton, VIC, Australia

Objective: Meta-analyses indicate a 3X increased risk of gestational diabetes (GDM) among women with polycystic ovary syndrome (PCOS), however relationships between longitudinal trajectories of body mass index (BMI) and GDM risk in PCOS remain unclear. We aimed to identify BMI trajectory groups, compare GDM prevalence across trajectory groups and assess BMI trajectories impact on GDM risk.

Methods: This is a secondary analysis from the (Australian longitudinal Study on Women's Health) ALSWH with 8200 women aged 18—36 across five surveys (13 years). The main outcome measure was GDM prevalence. We used latent-class growth modelling to identify distinct BMI trajectories and logistic regression to assess GDM risk.

Results: 575 women (7.0%, 95% CI 6.5—7.6%) reported PCOS. Among women with ≥1 live pregnancy, 15.1% developed GDM vs. 6.0% controls ($p < 0.001$). Three distinct BMI trajectories were identified over the 13 year follow-up: low-stable (LSG) (63.4% women), moderately-rising (MRG) (29.2%) and high-rising (HRG) (7.5%). These were defined as: LSG-average trajectory remaining within healthy range; MRG-curvilinear trajectory commencing in healthy and terminating in overweight range and HRG-curvilinear trajectory starting and terminating in obese range. Women with PCOS were more likely to belong to MRG and HRG groups (OR 1.8, 95% CI 1.5—2.2 and OR 4.2, 95% CI 3.2—5.4). The GDM prevalence in PCOS differed significantly across trajectory groups (9.4% vs. 20.0% vs. 21.0%, $p = 0.02$). After adjusting for BMI trajectories, age and demographic factors, women with PCOS were twice as likely to develop GDM compared to controls (OR 2.3, 95% CI 1.6—3.2).

Conclusion: Women with PCOS have higher rates of weight gain, yet PCOS remains an independent predictor of GDM irrespective of BMI trajectories over reproductive years. This aligns with the non-BMI dependent inherent insulin resistance in PCOS highlighting need for aggressive universal GDM screening in PCOS, independent of BMI and weight gain.

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