28

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.

https://doi.org/10.1016/j.orcp.2016.10.029

29

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