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Original article

Dietary acid load, metabolic acidosis and insulin resistance – Lessons from cross-sectional and overfeeding studies in humans

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SUMMARY

Background & aim: Western diets rich in animal protein and poor in fruit and vegetables increase the body acid load, a predictor of type 2 diabetes risk. The relationships between dietary acid load, mild metabolic acidosis and insulin resistance remain unclear. The objective of this study was to assess the association between dietary acid load, body acid/base markers and peripheral insulin resistance at baseline and following a short-term overfeeding intervention in healthy individuals.

Methods: In a cross-sectional study of 104 men and women, insulin sensitivity was measured by hyperinsulinemic-euglycemic clamp. Plasma lactate, a marker of metabolic acidosis, was assessed and acid load scores (potential renal acid load, PRAL and net endogenous acid production, NEAP) derived from diet diaries. The cohort was grouped into lean and overweight/obese and the latter further classified as insulin-sensitive (Ob_{sen}) and insulin-resistant (Ob_{res}) based on hyperinsulinemic-euglycemic clamp glucose infusion rate (GIR, top tertile vs. bottom 2 tertiles). A subset of 40 individuals participated in an overfeeding intervention (+1250 kcal/day) for 28 days and studies repeated.

Results: Ob_{sen} and Ob_{res} were matched for adiposity (BMI and fat mass, both $P = 1$). Fasting plasma lactate was higher in Ob_{res} (0.78 [0.63–1.14] mmol/L) compared with both lean (0.71 [0.44–0.90] mmol/L, $P = 0.02$) and Ob_{sen} (0.67 [0.56–0.79] mmol/L, $P = 0.04$) and not different between lean and Ob_{sen} ($P = 0.9$). Overfeeding was characterized by an increase in dietary acid load scores PRAL ($P = 0.003$) and NEAP ($P = 0.05$), a reduction in GIR necessary to maintain euglycemia ($P = 0.03$) and an increase in fasting plasma lactate ($P = 0.02$). The change in lactate was inversely associated with the change in GIR ($r = -0.36$, $P = 0.03$).

Conclusions: Mild metabolic acidosis, measured by plasma lactate, aligns with insulin resistance independent of obesity and is induced by short-term increases in energy and dietary acid load in healthy humans. Further studies are required to determine whether buffering mild metabolic acidosis improves insulin resistance and reduces diabetes risk.

Abbreviation: ARIC, Atherosclerosis Risk in Communities; CT, Computed tomography; DXA, Dual-energy X-ray absorptiometry; FFM, Fat free mass; GIR, Glucose infusion rate; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; NEAP, Net endogenous acid potential; Ob_{res}, Overweight/obese insulin-resistant; Ob_{sen}, Overweight/obese insulin-sensitive; PRAL, Potential renal acid load; RNAE, Renal net acid excretion; SFAT, Subcutaneous fat; TEI, Total energy intake; VFAT, Visceral fat.

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1. Introduction

Insulin resistance is closely associated with obesity and precedes the development of type 2 diabetes. In lean healthy adults, induction of mild metabolic acidosis by ammonium-chloride administration over three days decreased insulin sensitivity [1]. Conversely, correction of metabolic acidosis in chronic renal failure patients, following four weeks bicarbonate treatment, increased insulin sensitivity [2].

A diet with a persistently high acid load can cause blood pH to decrease towards the lower end of the normal physiological range [3]. This disequilibrium in acid/base balance, if not compensated for by homeostatic mechanisms or dietary modification can lead to the development of chronic mild metabolic acidosis [4,5]. The Western diet is characteristically high in animal proteins that when metabolized generate sulfate, a major contributor to dietary acid load [6]. This is typically accompanied by inadequate consumption of fruit and vegetables, rich in mineral cations and bicarbonate precursors that have an alkalizing effect when digested [6,7].

The acidogenic potential of foods can be calculated using potential renal net acid load (PRAL) [8,9] and net endogenous acid production (NEAP) scores [4]. PRAL takes into account the nutrient ionic balance and intestinal absorption rates of protein, phosphorous, potassium, magnesium and calcium as well as the metabolism of protein in the production of sulfate [9,10]. A positive PRAL score indicates an acid forming potential, while a negative score indicates an alkaline forming potential [9]. NEAP is based on the dietary intake of protein and potassium as the main determinants of endogenous acid production [4]. For example, the NEAP score of a Western diet was ~48 mEq/d [9] and a strict to moderately strict vegan diet was ~15 mEq/d [11]. A high score is therefore indicative of the consumption of animal proteins in quantities not sufficiently compensated for by intake of fruit and vegetables.

In healthy individuals, PRAL and NEAP have been shown to provide a reliable estimation of the diet-dependent component of daily renal net acid excretion (RNAE) [4,8,10,12]. A high RNAE as well as other markers of mild metabolic acidosis, including decreased urinary pH [8,13], a high anion gap (calculated as the difference between measured anions and cations in serum) [14–16] and increased serum lactate (a small component of the anion gap) have consistently been associated with insulin resistance [17,18] and type 2 diabetes risk [18,19].

Thus, dietary acid load may be an important factor in the development of insulin resistance and type 2 diabetes [6,16]. The aim of the present study was to assess the association between dietary acid load, body acid/base markers and peripheral insulin sensitivity before and after a short-term overfeeding intervention. We hypothesized that a higher dietary acid load would be associated with mild metabolic acidosis, as indicated by elevated plasma lactate, and insulin resistance, as measured by hyperinsulinemic-euglycemic clamp.

2. Materials and methods

The study was conducted in the Clinical Research Facility at the Garvan Institute of Medical Research, Sydney. Study protocols were approved by St Vincent's Hospital Human Research Ethics Committee, Sydney and participants provided written informed consent.

2.1. Participants

2.1.1. Cross-sectional lean and overweight/obese insulin-sensitive and insulin-resistant cohort

Participants (n = 104, 47 men) were recruited, by advertisements in local newspapers, between 2007 and 2013 as part of two separate studies. Subjects were excluded if they had a personal history of diabetes, cardiovascular disease, renal or liver disease, an active inflammatory disease or if they were treated with medications known to affect glucose homeostasis. They were sedentary (engaged in exercise for less than 60 min per week), non-smoking and with stable body weight in the preceding 3 months (±5% body weight change).

2.1.2. Short-term overfeeding intervention

A subset of 40 individuals (50% males, aged 37 ± 2 years, BMI 25.6 ± 0.6 kg/m^2) underwent a short-term overfeeding intervention, as previously described [20–22]. Participants were studied at three time points: baseline, day 3 and day 28 of overfeeding. The study was registered at ClinicalTrials.gov (NCT00562393).

2.2. Diets

Baseline diet was not supervised and individuals were self-selecting their foods. Prior to the baseline study, individuals recruited to the overfeeding intervention received a 3 day standardized diet, calculated based on estimated energy requirements with a target nutritional composition of 30% fat, 15% protein and 55% carbohydrate. Participants were then overfed for 28 days with a target of 1250 kcal/day above baseline energy requirements, based on 45% fat, 15% protein and 40% carbohydrate, as previously described [21]. Briefly, during overfeeding participants were asked to supplement their daily diet with three energy dense snacks (~240 kcal; e.g. mixed nuts, cheesecake, potato crisps) and a liquid oil-based supplement added to a dairy dessert (Benecalorie, ~525 kcal), which were all provided [21]. Participants were asked to fill in food diaries before the commencement of the study and during overfeeding. Diet diaries were based on daily weighed food records and analyzed using FoodWorks 7 (Xyris, Australia).

2.3. Estimation of dietary acid load

Dietary acid load was estimated using PRAL [9] and NEAP [4] scores:

$$PRAL\left(\frac{mEq}{day}\right) = 0.49 \times Protein\left(\frac{g}{day}\right) + 0.037 \times Phosphorous\left(\frac{mg}{day}\right) - 0.021 \times Potassium\left(\frac{mg}{day}\right) - 0.026 \times Magnesium\left(\frac{mg}{day}\right) - 0.013 \times Calcium\left(\frac{mg}{day}\right)$$

$$NEAP\left(\frac{mEq}{day}\right) = 54.5 \times Protein\left(\frac{g}{day}\right) \div Potassium\left(\frac{mEq}{day}\right) - 10.2$$

The PRAL and NEAP scores were calculated based on the reported nutrients intakes. Additionally, the nutrient levels were corrected for total energy intake using the residual method of Willett [23] and adjusted PRAL and NEAP scores determined.

2.4. Hyperinsulinemic-euglycemic clamp studies

Peripheral body insulin sensitivity was assessed using a 2 h hyperinsulinemic-euglycemic clamp with insulin infusion rate of either 60 or 80 mU/m^2/min. Variable glucose infusion rate (GIR) was applied to achieve a blood glucose target of 5 mmol/L. The same procedure was repeated post 28 days of overfeeding [20,21].

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