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Serum uric acid potentially links metabolic health to measures of fuel use in lean and obese individuals

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KEYWORDS
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Abstract *Background and aims:* Uric acid (UA) is a byproduct of the high-energy purine metabolism and is conventionally regarded as a marker of cardio-metabolic impairment. Its potential relationship with energy homeostasis is unknown to date.
Methods and results: In a cross-sectional study on 121 otherwise healthy obese and 99 sex- and-age-matched lean subjects, UA levels were analyzed in relation to metabolic health, inflammatory markers, respiratory quotient (RQ) and resting energy expenditure (REE) as assessed by indirect calorimetry, fat mass (%FM) and fat-free mass (FFM) as determined by bioimpedance analysis.

As expected, obese and lean subjects differed in BMI, glucolipid homeostasis, leptin and insulin levels, inflammatory markers, %FM and FFM ($p < 0.001$ for all). Likewise, UA levels ($p < 0.001$) and rates of hyperuricaemia (40.5% vs 3.0%, $p < 0.0001$) were also higher in obese than lean controls. Further, indirect calorimetry confirmed that obesity increased REE and decreased RQ significantly ($p < 0.001$). Beyond the expected metabolic correlates, in individual and merged groups UA levels were associated negatively with RQ and positively with REE ($p < 0.0001$ for both). In multivariable regression analysis, significant independent predictors of UA were BMI and sex. When BMI was replaced by measures of body composition, %FM and FFM emerged as significant predictors of serum UA ($p < 0.0001$).
Conclusions: A potential link relates serum UA to measures of resting energy expenditure and their determinants.

Introduction

Most mammals excrete uric acid (UA), a byproduct of purine degradation [1], upon conversion to soluble allantoin by the liver enzyme urate oxidase (uricase) [2]. In humans, the lack of uricase causes UA accumulation [3] and promotes hyperuricemia, under the influence of inappropriate dietary and life-style factors [4]. Upon urate super-saturation, crystalline monosodium urate becomes susceptible to precipitation leading to potentially serious complications, such as gout and kidney disease [5]. Non-crystalline soluble component of UA possesses a unique amphipathic action [6] and exerts pro-oxidant effects in vascular cells mediated by lipid oxidation, which can lead to endothelial dysfunction and cardiovascular disease [7]. On the other hand, soluble UA acts as a powerful antioxidant that scavenges oxygen

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singlets and oxygen radicals, peroxynitrite, and chelates transition metals, thus protecting the cell membrane and DNA from oxidative damage [8].

Physiologically, UA levels are higher in men than women, increase with age and menopause, and change under the influence of antiuricosuric drugs (i.e. thiazide diuretics) or medications able to reduce UA levels (i.e. losartan and long-acting Ca channel blockers) [9–13]. Obesity is a condition associated with a typical metabolic phenotype [14] and promotes UA accumulation increasingly referred to as a proxy of the so-called metabolic syndrome [15], due to its robust association with obesity, visceral adipose tissue (VAT) accumulation, insulin resistance, systemic inflammation and muscle mass [16–18]. Obesity-associated hyperuricaemia is prompted by a number of mechanisms, including the following: overexpression of xanthine oxidoreductase in adipose tissue, which results in enhanced purine catabolism and increased production of UA [19]; hyperinsulinaemia and insulin resistance, which decrease renal UA excretion [20]; 3) VAT accumulation, which promotes fatty acid (FA) output in the portal vein [21] and, as a result of the excessive metabolic outflow, promotes de novo synthesis of purine from NADPH in the pentose phosphate pathway and increased UA production [16,22]; increased consumption of purine-rich food, especially meat and to a lesser extent fish, alcoholic drinks and soft drinks rich in fructose [23]. Blood UA reflects the balance between purine dietary uptake, production and catabolism of purines, and production and excretion of UA. Although purine turnover is relatively constant at 300–400 mg/day, dietary factors accelerate purine nucleotide depletion and rates of de novo purine synthesis, thus potentiating UA production [24]. De novo purine biosynthesis is a high-energy process that leads to the conversion of phosphoribosyl pyrophosphate (PRPP) to inosine monophosphate (IMP) through 10 enzymatic activities and consumption of 6 ATP molecules, whereas only one ATP molecule is required for the purine salvage pathway consumption [25,26]. Thus, production and excretion of UA in humans reflects energy utilization and could act as a surrogate measure of fuel utilization and energy homeostasis. On this basis, we sought to explore if UA could reflect energy storage by investigating the relationship between circulating UA and the components of energy metabolism, e.g. respiratory quotient (RQ) and resting energy expenditure (REE), in a cross-sectional analysis in lean and obese adult individuals.

Methods

Patients

This study consecutively enrolled 121 obese patients (52 males; age 18–58 yr; body mass index (BMI), 43.1 ± 7.1 kg/m^2) referred to our Institution for work-up and rehabilitation of obesity and its comorbidities, and 99 matched lean subjects (34 males; age 19–53 yr; BMI, 22.5 ± 2.5 kg/m^2). All women were premenopausal, as assessed by personal history of regular menses. Exclusion criteria for both groups included medications interfering with UA levels and hypertriglyceridemia. Patients were also excluded if suffering from autoimmune diseases, neoplasms, polycythemia, hemolysis, diabetes mellitus, liver or kidney diseases. All participants reported alcohol consumption <125 ml daily. The investigation was approved by the ad hoc Ethical Research Committee of Istituto Auxologico Italiano, functioning according to the 3rd edition of the Guidelines on the Practice of Ethical Committees in Medical Research. Written consent was obtained from all patients and controls, after full explanation of the purpose and nature of the study.

Body measurements

All subjects underwent body measurements wearing light underwear, in fasting conditions after voiding. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using standard methods. BMI was expressed as body mass (kg)/height (m)^2. Obesity was defined for any BMI over 30 kg/m^2.

The respiratory quotient (RQ; VO_2/VCO_2) and resting energy expenditure (REE; kcal/24 h) were determined in a thermoregulated room (22–24 °C) by computed open-circuit indirect calorimetry, measuring resting oxygen uptake and resting carbone dioxide production by a ventilated canopy (Sensormedics, Milan, Italy) at 1-min intervals for 30 min and expressed as a 24-h value, as previously reported [27]. The test consists of making each patient lie down relaxed on a comfortable armchair, with the head under a transparent hood connected to a pump, which applies an adjustable ventilation through it. Exhaled gas dilutes with the fresh air ventilated under the hood and a sample of this mixture is conveyed to the analyzers, through a capillary tube and analyzed. Ambient and diluted fractions of O2 and CO2 are measured for a known ventilation rate, and O2 consumption (VO2) and CO2 production (VCO2) are determined. Energy expenditure was calculated according to the Weir equation [28]: EE = 5.68 VO2 + 1.59 VCO2 − 2.17 N_u. As short-term urinary collections to assess total nitrogen excretion (N_u) may not be representative of the protein oxidized during the measurement itself, they were not be obtained in this study, and assumed to be 13 g/24 h [29]. The predicted REE (pREE) was calculated by the Harris-Benedict formula and allowed to test for metabolic efficiency, calculated as the ratio between measured/predicted REE values, as previously reported [30].

Percent fat body mass (FM) and lean body mass (FFM) were determined by bioelectrical impedance analysis (BIA) (model BIA 101/S Akern, Florence, Italy). Patients with fluid overload according to vectorial analysis were excluded to minimize errors in estimating FM and FFM in severe obesity [31].

Assays

Blood samples were drawn under fasting conditions (8–12 h). Each participant was required to avoid strenuous

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