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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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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

physical activity, caffeine and dietary supplements 24 h prior to testing.

Blood levels of UA, glucose, total cholesterol, high-density (HDL) and low-density (LDL) lipoprotein cholesterol and triglycerides were measured by enzymatic methods (Roche Diagnostics, Mannheim, Germany). Serum insulin levels were measured using a Cobas Integra 800 Autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA). Ultrasensitive C-reactive protein was measured by CRP (latex) HS Roche kit. Hyperuricemia was defined as above 7 mg/dL in men and above 6 mg/dL in women [32].

Insulin resistance was calculated by the homeostasis model of assessment-insulin resistance (HOMA-IR) approach, calculated as insulin (microunits per milliliter) x blood glucose (millimoles per liter)/22.5. Serum leptin levels were measured by enzyme-linked immunosorbent assay (Human Leptin ELISA, Mediagnost, Reutlingen, Germany). The minimum detectable concentration was 0.2 ng/mL. The intra-assay and inter-assay coefficients of variation were <10%.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (Somers, NY, USA). Values are expressed as means ± standard deviation (SD). Continuous variables were log transformed if distribution resulted skewed by the Shapiro–Wilk normality test. Comparative analyses within and between groups were performed by Mann–Whitney U test or two-tailed unpaired Student's t test after Welch's correction, when appropriate. The simple chi-square test was used for associations between categorical variables. Spearman's correlation analysis was used to identify significant associations between variables of interest. Stepwise multivariable regression analysis was used to evaluate the independent association of variations in UA with metabolic, anthropometric or biochemical parameters. β coefficients and related significance values obtained from the models are reported. Two-sided $p < 0.05$ was considered as statistically significant.

Results

A summary of anthropometric, metabolic an biochemical data is reported in Table 1. As expected, obese and lean subjects differed for measures of adiposity, glucose and lipid metabolism, inflammatory markers, as well as leptin levels. Compared to lean individuals, obese patients also had higher REE and lower RQ values. Higher UA levels and rates of hyperuricemia (40.5% vs 3.0%; $\chi^2 = 40.6$, $p < 0.0001$) were, predictably, observed in obese compared to control subjects. Correlation analyses between UA levels and variables of interest in the population as a whole and in separate groups (Table 2) showed that UA levels were higher in males and, overall, positively associated with glucolipid parameters, inflammatory markers, fat and lean body mass and other anthropometric variables relating to visceral adiposity. Both in merged and separate groups, an evident correlation was noted between serum UA and FFM. Nevertheless, correlations obtained in the entire dataset were lost after controlling for gender, age and BMI. When serum UA was plotted against components of energy homeostasis, the pattern of association relating UA to RQ and REE was significant but divergent. In fact, a negative association was documented between serum UA and RQ values, which persisted after controlling for gender, age and BMI. This association was, however, not significant in separate groups. When REE was accounted for, a positive relationship was observed between UA levels and REE (Fig. 1), which was also significant in separate groups and remained unaltered when REE was normalized by FFM (rho = 0.13, $p < 0.05$). After controlling for BMI, age and gender as individual covariates, the association between REE and UA remained significant, whereas it was abrogated when these variables were included collectively in analysis (data not shown).

Based on the above-mentioned correlations, a number of stepwise multivariable regression models were performed that included UA levels as the dependent variable and metabolic, anthropometric and body composition parameters as independent variables. With the purpose of avoiding collinearity, different models were built that comprised either BMI or FFM and %FM, either RQ or REE, in addition to sex (0 = males, 1 = females), HOMA-IR, HDL cholesterol and triglycerides as the independent variables (Table 3). In all models thus built, neither RQ nor REE entered the regression equations.

Table 1 Summary of anthropometric, metabolic and biochemical parameters in lean subjects and obese patients. Significance between groups was calculated by Mann–Whitney test for continuous variables or the chi-square for categorical variables.

Parameters	Obese subjects	Lean subjects	p
Males/Females	52/69	34/65	0.2
Age (years)	35.1 ± 9.1	35.3 ± 7.9	0.8
BMI (Kg/m^2)	43.1 ± 7.1	22.5 ± 2.5	<0.001
WC (cm)	121.0 ± 26.5	85.0 ± 14.8	<0.001
FM (%)	45.0 ± 6.7	24.9 ± 6.4	<0.001
FFM (kg)	66.7 ± 17.7	47.6 ± 8.5	<0.001
RQ (VO_2/VCO_2)	0.84 ± 0.08	0.90 ± 0.12	<0.001
REE (Kcal/24 h)	2054 ± 432	1577 ± 255	<0.001
pREE (Kcal/24 h)	2119 ± 471	1469 ± 203	<0.001
REE/pREE	0.98 ± 0.10	1.08 ± 0.13	<0.001
UA (mg/dL)	6.49 ± 1.51	4.32 ± 1.19	<0.001
CHO (mg/dL)	201 ± 35	199 ± 37	0.6
HDL CHO (mg/dL)	47 ± 16	64 ± 16	<0.001
LDL CHO (mg/dL)	135 ± 33	132 ± 84	0.6
TG (mg/dL)	155 ± 79	94 ± 43	<0.001
Insulin (mIU/mL)	14.2 ± 7.3	9.7 ± 8.8	<0.001
Glucose (mg/dL)	84.6 ± 13.6	86.0 ± 14.5	0.4
HOMA-IR	3.05 ± 1.78	1.94 ± 1.42	<0.001
CRP (mg/dL)	0.93 ± 0.96	0.19 ± 0.32	<0.001
Fibrinogen (mg/dL)	407.7 ± 66.9	305.5 ± 67.8	<0.001
Leptin (mg/mL)	33.92 ± 15.18	8.95 ± 7.83	<0.001

For abbreviations: BMI, body mass index; WC, waist circumference; TBW, total body water; FM, fat mass; FFM, free fat mass; RQ, Respiratory Quotient; REE, resting energy expenditure; pREE, predicted resting energy expenditure; UA, uric acid; CHO, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; HOMA-IR, homeostatic model of insulin resistance; CRP, C-reactive protein.

Table 2 Spearman's correlation analysis between serum UA levels and variables of interest in merged groups (whole), obese patients and lean subjects. For significance: a, $p < 0.05$; b, $p < 0.01$; c, $p < 0.001$; d, $p < 0.0001$.

Parameters	Whole population	Obese subjects	Lean controls
Age (years)	−0.07	−0.15	0.04
BMI (Kg/m^2)	**0.64**^{d}	**0.25**^{b}	**0.38**^{d}
WC (cm)	**0.74**^{d}	**0.44**^{d}	**0,57**^{d}
FM (%)	**0.43**^{d}	**−0.34**^{d}	−0.12
FFM (kg)	**0.73**^{d}	**0.50**^{d}	**0.60**^{d}
RQ (VO_2/VCO_2)	**−0.32**^{d}	−0.02	−0.11
REE (Kcal/24 h)	**0.66**^{d}	**0.46**^{d}	**0.47**^{d}
CHO (mg/dL)	0.11	0.14	0.11
HDL CHO (mg/dL)	**−0.54**^{d}	**−0.29**^{c}	**−0.34**^{d}
LDL CHO (mg/dL)	**0.24**^{d}	0.14	**0.23**^{a}
TG (mg/dL)	**0.43**^{d}	**0.27**^{b}	0.16
Insulin (mIU/mL)	**0.44**^{d}	**0.38**^{d}	0.04
Glucose (mg/dL)	0.05	0.05	**0.36**^{d}
HOMA-IR	**0.44**^{d}	**0.36**^{d}	0.11
CRP	**0.47**^{d}	0.02	0.06
Fibrinogen (mg/dL)	**0.34**^{d}	−0.03	−0.11
Leptin (mg/mL)	**0.36**^{d}	**0.23**^{a}	**0.39**^{d}

For abbreviations: BMI, body mass index; TBW, total body water; FM, fat mass; FFM, free fat mass; RQ, Respiratory Quotient; REE, resting energy expenditure; CHO, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; HOMA-IR, homeostatic model of insulin resistance; CRP, C-reactive protein. Bold values indicate significance.

Discussion

The results of our study show that serum UA not only reflects metabolic phenotype but also acts as a surrogate index of the resting energy state in lean and obese subjects. We observed that UA levels were inversely associated with values of RQ and increased with increasing values of REE. In multivariate analysis, neither RQ nor REE acted as independent predictors of UA levels, suggesting that stronger metabolic determinants rule overall UA levels in the circulation.

UA is a recognized marker of metabolic derangement widely used for its ability to predict the risk of cardiometabolic morbidity [33,34]. Dietary excess, fat accumulation, insulin resistance and metabolic syndrome are all known causes of increased UA, which enhance the risk of gout and kidney disease. Different studies recently demonstrated an interesting association between serum UA and insulin resistance mediated by adiposity [35,36], providing the new concept that UA could reflect different components of metabolic syndrome. A previous study in NHANES participants showed a 1.3−1.5 times greater risk of gout in overweight individuals after adjustment for serum UA, while the prevalence ratio was 1.8 for class I

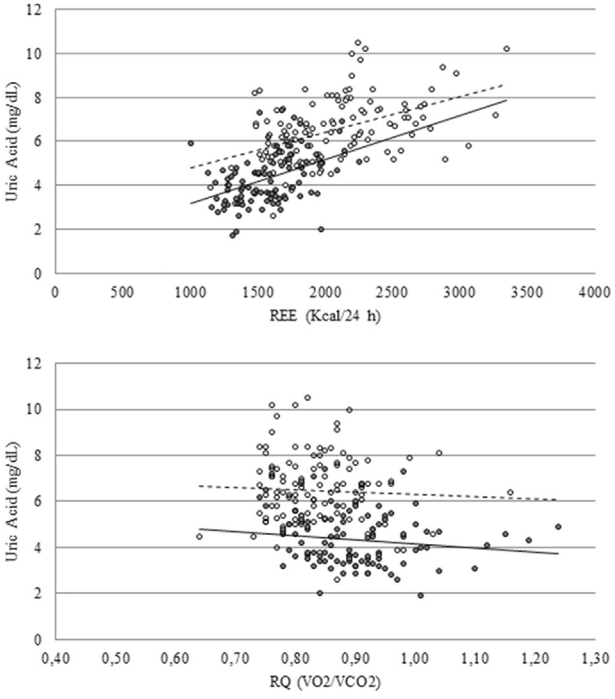

Figure 1 Bivariate correlation analysis between serum UA levels and RQ (upper panel) or REE (lower panel) in merged datasets from obese subjects and lean controls. Open circles and dashed line: obese subjects; closed circles and broken line: lean controls.

Table 3 Regression coefficients derived from the stepwise multivariable regression of UA levels. Beta standardized coefficients are shown for models built depending on non-collinear independent variables. For significance:*, $p < 0.05$,**; $p < 0.001$;***, $p < 0.0001$.

Variables	Beta standardized coefficient			
	Model 1	Model 2	Model 3	Model 4
Sex	−0.370***	−0.321***	−0.379***	−0.321***
BMI (kg/m^2)	0.604***	–	0.591***	–
FM (%)	–	0.399***	–	0.363***
FFM (kg)	–	0.340***	–	0.296**
REE (Kcal/24 h)	–	–	0.056	0.065
RQ (VO_2/VCO_2)	0.110	0.099	–	–
HOMA-IR	0.046	0.038	0.065	0.047
HDL (mg/dL)	−0.021	−0.056	−0.023	−0.020
TG (mg/dL)	0.092	0.105	0.101	0.113*

For abbreviations: BMI, body mass index; HDL, high density lipoprotein; HOMA-IR, homeostatic model of insulin resistance; FM, fat mass; FFM, free fat mass; RQ, Respiratory Quotient; REE, resting energy expenditure; TG, triglycerides.

obesity and 2.2−2.4 for class II or III obesity [37]. Epidemiologic studies have thus extensively described the ability of serum UA to act as a surrogate measure of cardiometabolic disorders, e.g. hypertension, coronary artery disease, cerebrovascular disease, and kidney disease, with this link being not entirely explained by overt hyperuricemia but also by absolute UA levels at the high-normal range [38]. Such relationship is here confirmed, as UA levels clustered with adiposity-related variables and the cardiometabolic markers presently investigated. One novel finding was the divergent association observed between UA levels and components of energy homeostasis. In keeping with the finding that RQ values were lower in obese than lean subjects, which likely originates from the effects of fat mass on the rate of FA oxidation [39], we documented that RQ values were linearly and inversely associated with UA levels. This relationship was not influenced by hyperuricaemia, i.e. subjects with hyperuricaemia did not show lower RQ levels that those without. Nevertheless, the association between RQ and UA lost significance in analysis on separate groups, likely due to the narrow regression of RQ values. RQ, which represents the moles of carbon evolved per mole of oxygen consumed, reflects macronutrients metabolism [39]. In humans, RQ values of 0.7, 0.8 and 1.0 conventionally indicate oxidation of lipids, proteins and carbohydrates, respectively [40]. As such, the inverse association seen between UA and RQ in our cohort could reflect a predominant lipid oxidation occurring in the obese group. There is evidence that UA production and lipid metabolism are related in gout [41]. Moreover, adipose tissue sampled from obese patients shows active FA synthesis [42] and de novo purine synthesis [43] through activation of the pentose phosphate pathway, which promotes UA synthesis and excretion [44]. On the other hand, lipolysis is upregulated in obese-derived adipose tissue [45], and a high content of FA may flow into the liver directly through the portal vein in subjects with visceral fat accumulation, thereby accelerating TG synthesis and promoting hypertriglyceridemia [46]. According to this view, we too observed that UA associated with plasma TG and abdominal adiposity. Hence, it can be hypothesized that UA could signal the rate of FA oxidation, e.g. the switch from glycolysis to lipolysis.

Another result worth of mention was the positive association between serum UA and REE values. This association occurred both in single and merged group analysis. At the multivariable regression analysis, REE was excluded from the regression equations, suggesting that anthropometric variables maintain greater control of UA levels. It remains difficult to conceptualize on these results based on the general lack of similar data in the literature. Literature search only revealed one abstract reporting on a similar positive correlation between serum UA and REE in obese women [47]. It has long been shown that resting energy expenditure varies among people independent of body size and composition, and that skeletal muscle metabolism is the main determinant of metabolic rate. Therefore, differences in resting muscle metabolism can produce differences in metabolic rates among individuals [48]. While it could be hypothesized that the positive association linking UA and REE reflects differences in lean mass between obese and control subjects, since both FFM and UA are increased in obesity [18], the correlation was unchanged when REE was adjusted for FFM, suggesting that FFM does not directly influence the association between UA and REE. It should be stated, however, that we measured body composition by BIA, which is per se less informative than DXA due to the potential effect of fluid overload. Literature data suggests that UA, as a marker of cell metabolism, can increase in conditions associated with high REE such as hyperthyroidism [49], HIV-related infection [50], and hypoxia resulting from chronic obstructive pulmonary disease or sleep apnea [51]. As we did not assess sleep apnea in our obese patients, this issue remains open.

Under condition of adipose tissue accumulation, like in obesity, adipocyte differentiation promotes intracellular accumulation of triglycerides and secretion of UA [19], suggesting that the intracellular activation of the pentose phosphate pathway relating to synthesis of FA is accompanied with the enhanced activity of the xanthine oxidoreductase and consequent production of UA [19]. Purines, endogenous modulators of energy metabolism and signal transduction, play important roles in the physiology of platelets, muscles and neurotransmission [52]. De novo purine biosynthesis is a high-energy event that leads to the conversion of phosphoribosyl pyrophosphate (PRPP) to inosine monophosphate (IMP) through a process requiring 10 enzymatic activities and 6 ATP molecules, while only one ATP molecule is required for the purine salvage pathway [25]. Thus, UA production could provide an indirect estimate of ATP degradation. Because any increase in energy expenditure for a given amount of substrate requires either increased ATP hydrolysis or decreased ATP synthesis [53], UA could be involved in signaling ATP availability, hence the energy state to other organs or apparatuses. As independent factor, UA has been already shown to mediate its effects by inducing oxidative stress, inflammation, endothelial dysfunction and activation of the renin angiotensin aldosterone system, which play a role in the pathogenesis of cardiovascular disease [54].

Our study has some important limitations that should be mentioned. Firstly, we did not determine UA excretion in urine, which would allow us to compare the excretion rate and circulating UA levels so as to avoid the effect of UA retention in obese vs lean individuals. Secondly, we did not measure ATP levels, which could allow us to discuss the role of UA as an indirect measure of ATP degradation. Thirdly, the cross-sectionality of the study does not allow to define causality of the association between UA and components of energy metabolism. Finally, we could assess a “one-to-one” matching of participants based on the retrospective nature of our study. Notwithstanding these limitations, this study has important strengths, including the accurate analysis of REE, the inclusion of premenopausal women and the evaluation of multiple anthropometric and biochemical parameters.

In summary, UA could be one of those factors that signal the systemic oxidative phosphorylation and are able to fine tune the energy state required for cell differentiation and metabolic requirements. Further studies are warranted to clarify if the relationship between UA and REE reflects a functional link or acts as an adaptive physiological response to abnormal substrates oxidation.

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