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Original article

Antacids' side effect hyperuricaemia could be alleviated by long-term aerobic exercise via accelerating ATP turnover rate

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ABSTRACT

Hyperuricemia is the term for an abnormally high serum uric acid level. Many factors contribute to hyperuricemia, however no definite correlation between proton pump inhibitors (PPIs) and hyperuricemia has been reported before. Physical exercise also decreases serum uric acid levels. However, the detailed biochemical-regulatory mechanisms remain unknown. Here we found that adenylate deaminase activities are much higher in hyperuricemia patients than in the healthy people. Therefore, the patients have higher levels of adenosine metabolites hypoxanthine and uric acid. Acid-inhibitory drugs (antacids) significantly increased serum uric acid level and may lead to gout in the hyperuricemia patient. Long-term aerobic exercise significantly increased serum phosphorus and decreased serum ATP and its metabolites, and therefore decreased serum uric acid. Antacids slow down the ATP turnover rate and result in serum uric acid elevation subsequently. While the long-term aerobic exercise decreases serum uric acid levels by accelerating ATP turnover rate. The results imply that long-term aerobic exercise may be a useful strategy to prevent and treat hyperuricaemia.

1. Introduction

Gout is a condition characterized by the deposition of monosodium urate crystals in the joints or soft tissue. The four phases of gout include asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. The peak incidence occurs in patients 30–50 years old, and the condition is much more common in men than in women. Although gouty arthritis characteristically occurs in patients with hyperuricemia, it is incorrect to equate hyperuricemia with clinical gout [1]. Asymptomatic hyperuricemia is the term for an abnormally high serum urate level, without gouty arthritis or nephrolithiasis. Hyperuricemia is defined as a serum urate concentration greater than 7 mg *per* dL (416 μmol *per* L by the uricase method), the approximate level at which urate is supersaturated in plasma [1]. Many factors contribute to hyperuricemia, including genetics, insulin resistance, hypertension, renal insufficiency, obesity, diet, use of diuretics and some drugs (like salicylates), and consumption of alcoholic beverages [2]. However, no definite correlation between acid-inhibitory drugs (antacids) and hyperuricemia has been reported before [3]. Antacids, like Ranitidine, are very commonly used in treatment of peptic ulcer disease and gastroesophageal reflux disease. If they may cause hyperuricemia, such side effect is worth of highly attentions. Here we first report antacids' side effect – Hyperuricemia, which may lead to gout in the patient with a basic high uric acid level. Antacids famotidine and omeprazole also have this side effect. This hyperuricaemia is not related with the sex steroids, but the decreased serum phosphorus level (by retarding ATP turnover presumably).

There is an interesting example about the putative role of physical exercise on hyperuricemia alleviation. In October 2015, one patient had a 12-day travel (mostly mountain-climbing). Three days after the travel (15 days without any antacid), his serum uric acid level decreased from 540 μmol/L to 500 μmol/L. So we assume that the sport may help reducing serum uric acid. Physical exercise influences serum uric acid levels that moderate exercise may counteract the cardiovascular pathological mechanisms (by decreasing plasma renin activity and ambulatory heart rates) involved in the hyperuricemia and the associated hypertension [4,5]. However, the detailed metabolic regulation mechanisms remain unknown. Here we investigated the relationships among antacids, exercise, uric acid and ATP metabolism in ten hyperlipidemia patients and three healthy volunteers. Through the analysis to ATP metabolites, we presume that long-term aerobic exercise decreases serum uric acid levels by accelerating ATP turnover rate (indicated by the increase in serum phosphorus and decrease in serum adenosine).

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Table 1
ATP metabolism and gout flare attacks after one-time ranitidine administration.

Volunteer or Hyperuricaemia patient	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6	Patient7	Patient8	Patient9	Patient10	Volunt1	Volunt2	Volunt3
Gender	male	male	male	male	female	female	male	female	male	male	male	male	female
Age	34	45	42	62	52	65	53	58	48	39	31	45	63
Gout flare history	never	attacked	never	attacked	attacked	attacked	never	attacked	never	attacked	never	never	never
Uric acid basic level (μmol/L)	540 ± 17^{b}	510 ± 15^{c}	492 ± 14^{c}	545 ± 16^{b}	547 ± 17^{b}	566 ± 18^{b}	506 ± 18^{c}	518 ± 18^{c}	563 ± 19^{b}	611 ± 21^{a}	285 ± 10^{e}	301 ± 11^{e}	336 ± 11^{d}
Uric acid after ranitidine admin.	658 ± 19^{a}	647 ± 19^{a}	618 ± 16^{a}	667 ± 20^{a}	639 ± 19^{a}	682 ± 20^{a}	640 ± 20^{a}	644 ± 20^{a}	687 ± 21^{a}	694 ± 24^{a}	367 ± 11^{c}	384 ± 12^{c}	430 ± 13^{b}
Gout flare after ranitidine admin.	No	No	No	attacked	No	attacked	No	No	No	attacked	No	No	No
Serum ATP level (mmol/L)	1.8 ± 0.1^{a}	1.2 ± 0.1^{b}	1.1 ± 0.1^{b}	0.91 ± 0.09^{c}	1.4 ± 0.1^{b}	1.2 ± 0.1^{b}	1.1 ± 0.1^{b}	1.7 ± 0.1^{a}	1.0 ± 0.1^{b}	1.4 ± 0.1^{b}	0.92 ± 0.09^{e}	1.3 ± 0.1^{b}	1.1 ± 0.1^{b}
Serum ATP after ranitidine admin.	2.2 ± 0.1^{a}	1.5 ± 0.1^{b}	1.4 ± 0.1^{b}	1.1 ± 0.1^{c}	1.6 ± 0.1^{b}	1.5 ± 0.1^{b}	1.5 ± 0.1^{b}	2.1 ± 0.1^{a}	1.4 ± 0.1^{b}	1.7 ± 0.1^{b}	1.3 ± 0.1^{b}	1.5 ± 0.1^{b}	1.4 ± 0.1^{b}
Serum adenosine level (mmol/L)	18 ± 1.6^{a}	15 ± 1.4^{a}	16 ± 1.6^{a}	12 ± 1.4^{b}	13 ± 1.4^{b}	17 ± 1.6^{a}	15 ± 1.7^{a}	19 ± 1.8^{a}	11 ± 1.2^{b}	15 ± 1.5^{a}	8.3 ± 1.0^{c}	15 ± 1.5^{a}	12 ± 1.4^{b}
Serum adenosine after ranitidine ad.	20 ± 1.8^{a}	17 ± 1.8^{a}	19 ± 1.8^{a}	15 ± 1.6^{a}	15 ± 1.6^{a}	19 ± 1.8^{a}	17 ± 1.7^{a}	21 ± 1.9^{a}	13 ± 1.4^{b}	18 ± 1.7^{a}	11 ± 1.3^{b}	17 ± 1.5^{a}	15 ± 1.4^{a}
Serum HYPO level (mmol/L)	17 ± 1.6^{a}	13 ± 1.4^{a}	15 ± 1.4^{a}	11 ± 1.3^{b}	15 ± 1.4^{a}	14 ± 1.4^{a}	15 ± 1.4^{a}	18 ± 1.8^{a}	11 ± 1.3^{b}	16 ± 1.4^{a}	8.1 ± 1.0^{c}	6.4 ± 0.8^{c}	7.5 ± 0.9^{c}
Serum HYPO after ranitidine admin.	20 ± 1.8^{a}	16 ± 1.6^{b}	17 ± 1.6^{b}	14 ± 1.5^{b}	17 ± 1.6^{b}	17 ± 1.5^{b}	17 ± 1.6^{b}	21 ± 1.9^{a}	13 ± 1.4^{b}	17 ± 1.6^{b}	10 ± 1.1^{c}	8.9 ± 0.9^{c}	9.3 ± 1.0^{c}
Basic ADA activity (U/L)	20 ± 1.8^{a}	16 ± 1.6^{a}	18 ± 1.7^{a}	18 ± 1.7^{a}	14 ± 1.3^{b}	17 ± 1.6^{a}	18 ± 1.7^{a}	13 ± 1.4^{b}	16 ± 1.6^{a}	14 ± 1.3^{b}	5.2 ± 0.6^{d}	8.3 ± 0.8^{c}	9.2 ± 1.0^{c}
ADA activity after ranitidine admin.	19 ± 1.8^{a}	17 ± 1.6^{a}	18 ± 1.7^{a}	16 ± 1.6^{a}	15 ± 1.4^{a}	16 ± 1.6^{a}	18 ± 1.7^{a}	14 ± 1.4^{b}	17 ± 1.6^{a}	13 ± 1.4^{b}	3.9 ± 0.4^{c}	7.2 ± 0.7^{b}	9.3 ± 0.8^{b}

HYPO, hypoxanthine; ADA, adenylatedeaminase. The experiment was repeated twice. The data are shown as the mean ± standard deviation. Different lowercase letters within a row indicate significant differences at 0.05 ($P < 0.05$) levels.

2. Patients and methods

2.1. Patients and healthy volunteers

Ten patients of moderate hyperlipidemia (with or without the gout flare history) were enrolled with agreements. Their ages range from 34 to 65 and their basic uric acid level range from 492 to 611 μmol/L (Table 1). For more conclusive, three healthy volunteers were also enrolled with agreements (Table 1). All participants showed normal hydration statuses. All participants provided their written informed consent to participate in this study. The consent procedure was approved by the Ethics Committee of the Shanxi Public Health Clinical Center in accordance with the Helsinki Declaration, revised 2008. And the experiments were also approved by the Ethics Committee.

2.2. Drug dosage and exercise frequency

Most people in the patient group have mild to moderate acid reflux diseases. Therefore, the antacids were prescripted. Drug dosage and frequency: Oral administration of ranitidine (one capsule of 150 mg), famotidine (one tablet of 20 mg) or omeprazole (one tablet of 20 mg) at the bedtime (12 h before blood test) or in the morning (2 h before blood test). To rule out the effects of dietary choice, the patients were asked to keep low-purine diet (such as avoidance of red meat, seafood, organ meat and tea drinking) and alcohol prohibition during the ranitidine administration (or the control test without ranitidine administration).

To study the relationship among ranitidine, uric acid and sex steroids (Fig. 1A), patient 1, patient 2 and patient 3 were engaged. Ranitidine (one capsule of 150 mg) was given every day for totally 5 days, then every day for totally 10 days, then every 3 days for totally 15 days and then every 3 days for totally 30 days. Then the ranitidine administration was stopped for 15–30 days.

One-time exercise means 1600 m jogging with a speed of 35–60 s *per* 100 m (total duration of 16–28 min). Intensity and frequency of the long-term physical exercise: 45 days, every day (one hour after supper), 1600 m jogging with a speed of 35–60 s *per* 100 m (total duration of 12–21 h). Within a month before the physical exercise, the participants were prohibited to any antacid administration. To rule out the effects of dietary choice, the patients and the volunteers were asked to keep low-purine diet and alcohol prohibition during the long-term exercise.

2.3. Serum biochemical determination

Serum uric acid, lipid, estradiol, testosterone, phosphorus, calcium were measured in the fifth hospital of Chengdu (Chengdu, Sichuan, China) at 9:00–10:00 a.m.. Uric acid was detected by the direct phosphotungstic acid method [6]. Serum lipids were detected by the enzymatic assays (triglyceride was measured by the glycerol oxidase method) [7]. Estradiol and testosterone were detected by the magnetic particles-based chemiluminescence immunoassay [8]. Serum phosphorus and calcium were detected by the atomic absorption spectrophotometry method [9].

For the pharmacokinetic studies of ranitidine, famotidine and omeprazole on uric acid, serum phosphorus and calcium (Fig. 1B), the patient 1 was engaged. Serum uric acid, phosphorus and calcium levels were detected at 0–48 h after the one-time administration. This experiment was repeated twice.

Blood serum ATP, adenosine and hypoxanthine levels were determined by the high-pressure liquid chromatography (HPLC) [10]. Aliquots of 20 μl were applied to a reversed-phase HPLC (Agilent Technologies, Santa Clara, CA, USA) using a C18 column. The elution was carried out by applying a linear gradient from the solvent A (5 mM tetrabutyl-ammonium chloride, 60 mM KH_2PO_4, pH 6.0) to the solvent B (30% methanol to the solvent A) over a 40 min period (flow rate of 1.5 mL/min). Standard samples of adenosine, hypoxanthine (HYPO) and uric acid were obtained from Sigma Chemical Comp. (Sigma-Aldrich, St Louis, MO, USA).