ВНУТРЕННИЕ БОЛЕЗНИ
INTERNAL DISEASES

DOI: 10.29413/ABS.2021-6.1.2

Behavioral Characteristics of Gout Patients and Their Impact on the Results of Urate Lowering Therapy

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Abstract

Background. *Gout is frequently accompanied by hypertension, obesity, and/or impaired glucose tolerance, which are often complicated with heavy smoking and dietary violations, especially in male patients.*

Objective. *To determine the behavioral characteristics of gout patients that could impact the results of urate lowering therapy.*

Subjects and methods. *The relationship between behavioral characteristics and results of urate lowering therapy were investigated in 74 male gout patients of Chengdu Rheumatism Hospital. The results of treatment were evaluated using serum uric acid contents before and after treatment, VAS pain score before and after treatment. Behavioral characteristics for the last ten years (smoking status, daily volume of drinking water, etc.) were accessed by means of retrospective survey.*

Results. *In gout patients with poor treatment response, serum uric acid at the beginning of the treatment was already significantly lower (365.76 ± 163.06 μmol/L); this trend was also noted in a "slow progress" group, while patients with higher serum uric acid before treatment had notably better response to urate lowering therapy. During further analysis age negatively correlated with serum uric acid ($r = –0.328$; $p = 0.002$) and uric acid clearance ratio ($r = –0.299$; $p = 0.002$).*

In patients with uric acid clearance ratio above 40 % the prevalence of kidney diseases (stones or dysfunction) was significantly lower compared to other groups. There was no significant influence of hypertension, diabetes mellitus, fatty liver or hyperlipidaemia on uric acid clearance ratio ($p > 0.05$).

Amount of drinking water also influenced the serum uric acid clearance ratio. Bigger amount of patients in the "fast progress" group (40.0 % compared to 30.44 and 25.0 %) tended to drink more water.

Conclusion. *In most gout patients, serum uric acid levels before treatment acted as the reliable predictor of good response to urate lowering therapy. Treatment response (serum uric acid clearance ratio) correlated positively with the hyperuricemia and drinking sufficient amounts of water, negatively – with prolonged smoking (more than 10 years) and age.*

Key words: *gout, urate lowering therapy, smoking, uric acid*

For citation: Chen J., Zhou P., Tan W., Zheng W., Oshmianska **N.** Behavioral Characteristics of Gout Patients and Their Impact on the Results of Urate Lowering Therapy. *Acta biomedica scientifica*. 2021; 6(1): 13-17. doi: 10.29413/ABS.2021-6.1.2.

Поведенческие особенности пациентов с подагрой и их влияние на результаты уратоснижающей терапии

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Резюме

Обоснование. *Подагра часто сопровождается гипертонией, ожирением и/или нарушением толерантности к глюкозе, которые нередко осложняют тяжёлое курение и нарушения питания, особенно у пациентов мужского пола.*

Цель исследования: *оценить поведенческие характеристики пациентов с подагрой, которые могут повлиять на результаты урикозурической терапии.*

Материалы и методы. *Связь между поведенческими характеристиками и результатами уратоснижающей терапии была исследована у 74 пациентов с подагрой в ревматическом госпитале г. Чэнду. Результаты лечения оценивались с использованием содержания мочевой кислоты в сыворотке крови до и после лечения, по шкале болевых ощущений до и после лечения. Поведенческие характеристики за последние десять лет (статус курения, ежедневный объем питьевой воды и т. д.) были оценены с помощью ретроспективного опросника.*

Результаты. *У пациентов с подагрой, которые демонстрировали неудовлетворительный ответ на лечение, сывороточная мочевая кислота в начале лечения была значительно ниже (365,76 ± 163,06 мкмоль/л); эта тенденция была также была отмечена в группе с «медленным прогрессом», в то время как пациенты с более высоким содержанием мочевой кислоты в сыворотке крови до лечения демонстрировали заметно лучший ответ на терапию. В ходе дальнейшего анализа возраст отрицательно коррелировал с сывороточной мочевой кислотой (r = –0,328; p = 0,002) и коэффициентом клиренса мочевой кислоты (r = –0,299; p = 0,002). У пациентов с коэффициентом клиренса мочевой кислоты выше 40 % распространённость заболеваний почек (камни или дисфункция) была значительно ниже по сравнению с другими группами. Значимого влияния гипертонии, сахарного диабета, ожирения печени или гиперлипидемии на коэффициент клиренса мочевой кислоты отмечено не было (p > 0,05).*

Количество питьевой воды также влияло на клиренс мочевой кислоты в сыворотке крови. Большее количество пациентов в группе «быстрого прогресса» (40,0 % по сравнению с 30,44 и 25,0 %) имели тенденцию пить больше воды.

Заключение. *У большинства пациентов с подагрой уровни мочевой кислоты в сыворотке крови до лечения являлись надёжным предиктором удовлетворительного ответа на уратоснижающую терапию. Ответ на лечение (коэффициент клиренса мочевой кислоты в сыворотке крови) положительно коррелировал с гиперурикемией и употреблением достаточного количества воды, отрицательно – с длительным курением (более 10 лет) и возрастом.*

Ключевые слова: *подагра, уратоснижающая терапия, курение, мочевая кислота*

Для цитирования: Чэн Д., Жу П., Тан В., Джен У., Ошмянская Н.Ю. Поведенческие особенности пациентов с подагрой и их влияние на результаты уратоснижающей терапии. *Acta biomedica scientifica.* 2021; 6(1): 13-17. doi: 10.29413/ABS.2021-6.1.2.

INTRODUCTION

Gout is one of the most common rheumatic diseases in the world, which affects about 1.14 % of the general population in China, and from 1.4 to 2.5 % in other countries with recent epidemiologic data suggesting that its incidence is increasing [1, 2]. Clinical manifestations of gout include osteoarthritis and associated inflammation as much as system disorders linked to impaired purine metabolism, which often lead to restricted mobility and significantly lower the patients' quality of life.

There is a direct link between the increase of serum uric acid (UA) levels and the deposition of the large number of monosodium urate crystals around the joints [1]. Serum UA levels ≥ 420 μmol/L for men and ≥ 360 μmol/L for women are still widely used as main diagnostic criteria.

The treatment of gout includes controlling the disease by urate lowering therapy (xanthine oxidase inhibitor, allopurinol, etc.) [3, 4]. Additional surgical intervention is needed in cases of gouty arthritis if there is cosmetic deformation or functional disorder of joint.

Multiple studies have assessed the potential effect of smoking on serum UA, either focusing on both serum UA and smoking in the development of gout, or by assessing the effect of smoking and/or serum urate as a secondary variable. There is considerable observational evidence to suggest that cigarette smoking lowers serum UA, however the results have not been consistent, with many reports providing evidence for the opposite effect, or no significant association of smoking and serum UA [12].

In recent years, studies have shown that obesity, oxidative stress, lifestyle and other general factors may also affect the body's uric acid levels, causing resistance to treatment [4]. Recent epidemiologic studies have shed some light on the prognosis of hyperuricemia, but the large scale research is still needed to access the relationship between the urate lowering therapy, behavioral characteristics of gout patients, cardiovascular risk and other comorbidities.

MATERIALS AND METHODS

Medical records of 74 male patients with gout were included to the study. All patients were admitted to Chengdu Rheumatism Hospital in 2019–2020. Patients satisfied the preliminary criteria of gout and were prescribed with urate lowering therapy. The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Chengdu Rheumatism Hospital. All participants provided written informed consents.

Data collection. In all patients anthropometrical parameters were measured, including waist circumference, body height and weight, body mass index (BMI). In addition, blood pressure at systolic and diastolic phases, blood levels of triglycerides, fasting serum glucose, and creatinine were measured.

Serum UA was measured on the first day and after the end of treatment by standard ELISA method. The progress of UA clearance was calculated as (serum UA after treatment) / (serum UA before treatment) and mean values was 32–33 % independent of age. In order to look further into the reasons of better or worse UA clearance we divided subjects into 4 groups:

Group 1 – no progress, UA clearance ratio was negative;

Group 2 – very slow progress, UA clearance ratio – below 30 %;

Group 3 – slow progress, UA clearance ratio – 30–40 %;

Group 4 – fast progress, UA clearance ratio – above 40 %.

Presence of fatty liver was detected by B-ultrasonography, in some cases with additional MRI or liver biopsy. The diagnosis of renal dysfunction was based on serum creatinine and glomerular filtration rate (GFR); kidney stones was detected by X-ray and B-ultrasonography.

Statistical analysis was conducted using IBM IPSS statistics software (version 23, IBM Co., Armonk, NY, USA).

RESULTS

General characteristics of patients. A total of 74 male patients with gout were included in this study. The mean age of patients was 49.55 ± 15.54 years, the mean weight was 72.76 ± 10.87 kg, the mean BMI was 25.97 ± 3.43 kg/m^2. BMI data indicated that majority of patients were overweight according to criteria of obesity by the World Health Organization. The mean serum UA level assessed at the first day of treatment was 495.62 ± 127.81 μmol/L, mean serum UA after treatment was 334.89 ± 112.78. Fatty liver was described in almost half of patients (45.94 %), total of 37.84 % of patients had hypertension and 8.11 % had diabetes mellitus (DM).

TREATMENT CONTROL

All patients were asked to access the level of pain in joints according to VAS pain score before the treatment start and after the last day of treatment. There was a weak link between reported values before treatment and serum UA ($r = 0.161$; $p = 0.05$), however, after treatment the majority of patients reported significant improvement in pain which was not linked to serum UA.

Therefore, it has been decided to use UA blood levels on the first day and after the end of the treatment as a control points for this paper. Average blood UA before treatment was 493.09 ± 96,95 μmol/L, and after treatment – 334.89 ± 90.93 μmol/L; only in 13.51 % of all patients the levels of serum UA after treatment was higher of equal to the levels before treatment (Fig. 1).

After that, study groups were analyzed according to the clearance ratio of serum UA. In the "no progress" group mean serum UA at the beginning of the treatment was already significantly lower compared to other groups (365.76 ± 163.06 μmol/L); this trend was also noted in a "slow progress" group, while those patients who had higher serum UA before treatment was notably higher UA clearance ratio in response to urate lowering therapy. During further analysis age negatively correlated with serum UA ($r = –0.328$, $p = 0.002$) and UA clearance ratio ($r = –0.299$, $p = 0.002$).

In patients with UA clearance ratio above 40 % the prevalence of kidney diseases (stones or dysfunction) was significantly lower compared to other groups. There was no significant influence of hypertension, DM, fatty liver or hyperlipidaemia on UA clearance ratio ($p > 0.05$). For more details, see Table 1.

Further analysis leads to removing the first group from the statistical analysis, because of the ununiformity of the response due to different outer factors. In the remaining three groups, behavioral characteristics were analyzed. In the "slow progress" group mean serum UA was 485.5 ± 115.87 μmol/L before treatment, and 392.45 ± 92.86 μmol/L after treatment; in the "average progress" group it was equal to 533.36 ± 102.28 μmol/L before treatment, and 341.31 ± 62.06 μmol/L after treatment; and in the "fast progress" group – equal to 532.71 ± 106.61 μmol/L before treatment, and 239.95 ± 72.75 μmol/L after treatment.

Groups were not statistically different in BMI or age. The habit of smoking was reported less often in "fast progress" group but differences were not statistically significant. However, after stratifying patients according to the length

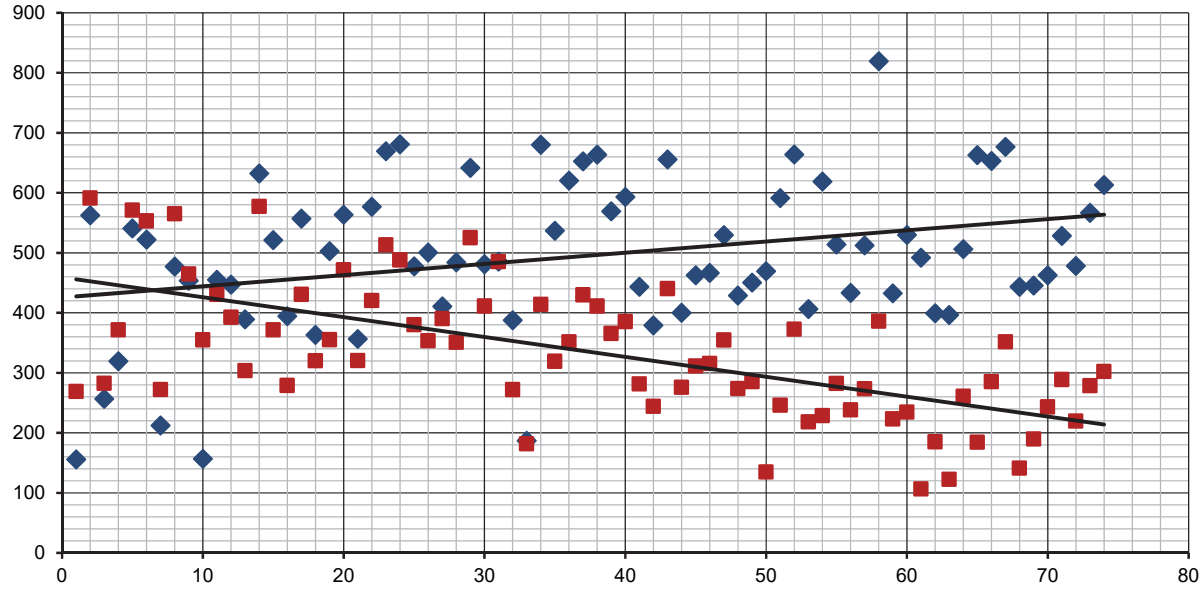

Fig. 1. Serum UA levels in study patients before (blue) and after (red) urate lowering treatment (μmol/L)

Table 1

The prevalence of accompanying diseases and conditions in gout patients according to UA clearance ratio

	Group 1 (no progress), *n* = 10	Group 2 (< 30 %), *n* = 23	Group 3 (30–40 %), *n* = 16	Group 4 (> 40 %), *n* = 25
UA base levels before treatment, μmol/L	**365.76 ± 163.06**	**485.5 ± 115.87**	**533.36 ± 102.28**	**532.71 ± 106.61**
BMI	26.47	26.01	25.89	25.79
Hypertension, %	40	52.17	31.25	28.0
Diabetes mellitus, %	0	8.69	6.25	12.0
Fatty liver, %	40	43.49	50	48.0
Hyperlipidaemia, %	10	39.13	25	16.0
Hepatic dysfunction	10	4.35	18.75	8.0
Renal dysfunction	**20**	**34.78**	**37.5**	**20.0**
Kidney stone	**20**	**17.39**	**31.25**	**8.0**

of smoking, it was found than smoking more than 10 years was reported significantly less often in "fast progress" group.

Amount of drinking water also influenced the serum UA clearance ratio. Bigger amount of patients in the "fast progress" group (40.0 % compared to 30.44 and 25.0 %) tended to drink more water.

DISCUSSION

Poor response to urate lowering therapy in gout patients became a real concern of many researchers. According to the one of recent studies by Mu et al. [3], which was conducted on 370 patients, patients with poor response to ULT had younger age and higher proportion of obesity, as well as higher baseline UA. Review by Graham et al. [5] dated 2018, also stated that higher pre-treatment serum UA, younger age of patients, higher BMI and/or total cholesterol was associated with a decreased probability of achieving treatment success.

However, in those studies poor response was determined only by serum UA above 6 mg/dL after the end of treatment, which rules out the cases where the initial serum UA was not very high, or when it was high and lowered gradually in response to treatment, but has not reached the average values yet.

In our study, we used the rate of serum UA clearance to access the effectiveness of urate lowering therapy (Fig. 2). Higher baseline UA was associated with better response to treatment and higher UA clearance, but it is interesting to note that in group 3 and group 4 baseline serum UA was almost the same (533.36 ± 102.28 μmol/L compared to 532.71 ± 106.61 μmol/L) whereas the serum UA levels after treatment were significantly different (341.31 ± 62.06 μmol/L compared to 239.95 ± 72.75 μmol/L).

Many patients with gout have additional renal impairment and others, because of hypertension or concomitant disease states, are taking loop or thiazide diuretics [5]. The influence of renal impairment and diuretics on the response to ULT are therefore of considerable clinical interest.

Renal impairment increases the concentrations of serum UA because the renal clearance of urate is reduced [6], as well as the renal clearance of oxypurinol or other medicine, which is cleared by the kidney. However, pharmacokinetic modeling indicates a substantial increase in the dose of allopurinol that is required for an adequate response in patients who are taking concomitant thiazide or loop diuretics [7]. In addition to that, it is important to note that pre-treatment concentration of serum UA as well as the serum urate concentration during treatment is higher in patients taking diuretics [8].

It is advised, that in patients who are prescribed with concomitant diuretics the amount of ULT should be, on average, increased in order to achieve response. But as clinical trials showed, percentage of responders to ULT is not influenced statistically in patients with mild or moderate renal impairment [9].

In our study patients with UA clearance ratio above 40 % had significantly lower prevalence of renal impairment (stones or dysfunction) compared to other groups, which indicates the independent role of kidneys in adequate ULT response as there was no significant influence of hypertension, DM, fatty liver or hyperlipidaemia on UA clearance ratio ($p > 0.05$). However, the larger study needed to fully access the efficacy of ULT, taking into account concomitant diuretic therapy and its impact on serum urate concentrations during treatment.

Smoking is associated with some of the known risk factors for gout, especially obesity and alcohol intake, but consensus has yet to be reached as to the effect of smoking on serum UA or gout risk in smokers. Study by Wang and Krishnan [10] published in 2014 showed that after adjustment for age and BMI, cigarette smoking was associated not with higher, but with lower risk of gout. Later, Teng et al. [11] in a prospective cohort study (63 247 participants) obtained the same results.

In our study, we did not find any association between smoking status and response to ULT. However, after analyzing the duration of smoking, we found that in patients who reported smoking more than 10 years, UA clearance ratio was significantly lower.

Those findings might be partially explained by the fact that prolonged smoking may reduce serum UA independently to treatment [12]. Indeed, we found that serum UA levels before treatment were significantly lower in patients who reported smoking more than 10 years.

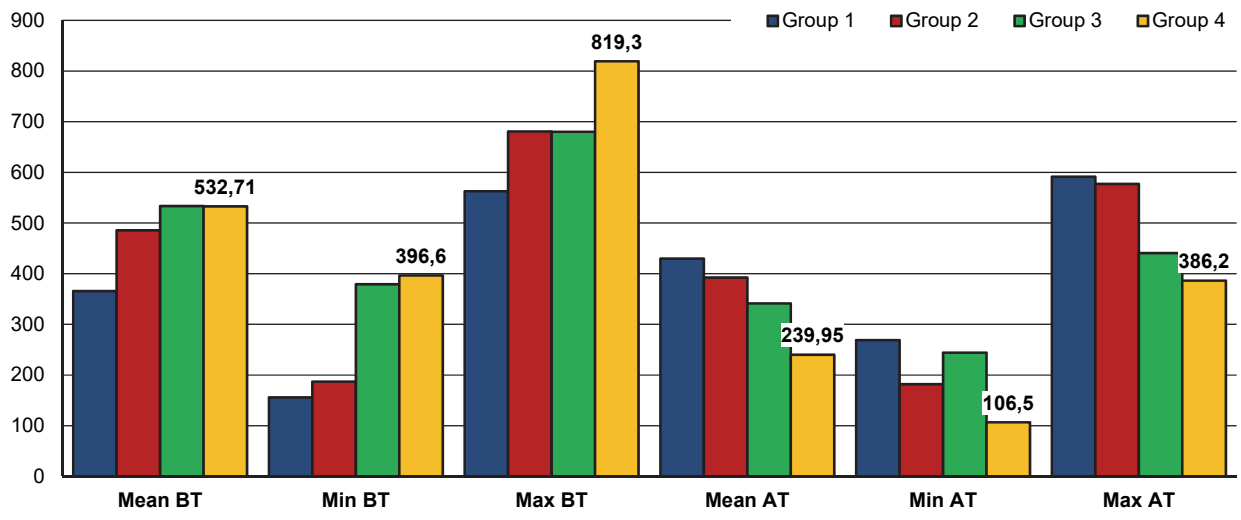

Fig. 2. Mean, minimum and maximum values of serum UA in gout patients before treatment (BT) and after treatment (AT), μmol/L, distributed according to UA clearance ratio; group 1 – no progress ($n = 10$); group 2 – UA clearance ratio < 30 % ($n = 23$); group 3 – UA clearance ratio 30–40 % ($n = 16$); group 4 – UA clearance ratio > 40 % ($n = 25$)

As mentioned above, the initial levels of UA before treatment may be a predictor of the response to ULT. Therefore, prolonged smoking, gradually reducing the level of serum UA, can thus affect the effectiveness of treatment.

Drinking sufficient amounts of water also may influence the effectiveness of treatment [13]. In our study, drinking habit also influenced the serum UA clearance ratio. Bigger amount of patients in the "fast progress" group (40.0 % compared to 30.44 and 25.0 %) tended to drink more water.

It is important to note that this link is explained not only by the serum UA increase due to dehydration, but via more complex mechanisms as well, such as oxidative stress and endothelial dysfunction.

Regardless the efficacy of ULT, previous observations identify gout patients with comorbidities as likely to be prescribed with the greater volume of pharmacological treatment. Based on the notion that hiperuricemia alone is insufficient to account for the impact of gout on the development of metabolic syndrome, liver diseases and other comorbidities, studying the behavioral characteristics of patients before treatment could make the prescription of drugs more precise, abiding recent inclination toward the individual-based personalized medicine practices.

Conflict of interest

None of the authors have any conflict of interest regarding this manuscript.

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Received: 07.08.2020. Accepted: 27.10.2020. Published: 26.02.2021.
Статья получена: 07.08.2020. Статья принята: 27.10.2020. Статья опубликована: 26.02.2021.