『高尿酸血症・痛風の治療ガイドライン（第２版）』ダイジェスト英語版

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『高尿酸血症・痛風の治療ガイドライン（第１版）』が2002年に発行され、８年が経過した。ガイドライン第１版は、わが国の高尿酸血症・痛風診療の標準化に大きく寄与し、さらにわが国における生活習慣病に関するガイドラインの先駆けとなって他の診療ガイドラインにも大きな影響を及ぼした。しかしながら、この８年間にさまざまなエビデンスが蓄積され、またガイドラインそのもののあり方も大きく進歩した。日本痛風・核酸代謝学会ではこれらの状況を鑑み、2006年からガイドライン改訂を企画し、３年あまりの年月をかけて、この度、『高尿酸血症･痛風の治療ガイドライン（第２版）』を発行することができた。作成にかかわったすべての委員の方々に心より感謝申し上げる。

ガイドライン改訂にあたっては、第１版の精神を継承し、かつ客観的に評価されるガイドライン作りを目指した。その結果、作成過程ではエビデンスに基づくガイドライン作成班が等しく遭遇している問題点、すなわち構造化抄録の作成、エビデンスレベルや推奨度の基準、合意形成の取り入れ、外部評価の方法、利益相反の扱いなどに苦慮し、

予想外の時間を要することになった。治療ガイドラインはエビデンスに基づくことが基本であるが、ガイドラインの対象疾患によってはエビデンス準拠に限界があることも指摘されている。高尿酸血症・痛風の領域もその一例といえ、今回の改訂作業においては、ガイドラインの内容と日常診療との乖離を防ぐことも目的として、コンセンサスのレベルも定量的に判定し、推奨度に反映させる試みを取り入れた。

ガイドライン第 2 版は、日本痛風・核酸代謝学会 ガイドライン改訂委員会の編集により 2010 年 1 月 1 日にメディカルレビュー社から出版された。そしてその 6 ヵ月後にガイドライン第 2 版のダイジェスト版が同じくメディカルレビュー社から出版され、期を同じくしてガイドライン第 2 版ダイジェスト英語版を日本痛風・核酸代謝学会の学会誌「痛風と核酸代謝（第 34 巻第 1 号）」に掲載することになった。本誌に掲載するダイジェスト英語版は論文として引用されることを前提にしたもので、引用文献も完備させた。本学会が世界に向けて発信する強いメッセージとなることを期待したい。なお、ダイジェスト版（和文）はガイドライン第 2 版の出版日より 1 年を経過した 2011 年 1 月に日本痛風・核酸代謝学会ホームページに掲載される予定であり、また「痛風と核酸代謝（第 35 巻第 1 号、2011 年 7 月発行予定）」にも掲載される予定である。さらに、本ガイドラインの骨子は、2011 年 1 月以降に財団法人日本医療機能評価機構のホームページ Minds（http://minds.jcqhc.or.jp/）に掲載が予定されている。

医学の進歩が診療の質を高めるためには、医学の進歩を正しく評価し、体系化する必要がある。今日的な治療ガイドラインの目的はまさにここにあると言ってよい。高尿酸血症・痛風に関する日本の医学をリードする日本痛風・核酸代謝学会が治療ガイドラインを作成したことは、医学の進歩をこの領域の診療の進歩に結び付けるものであることを今一度認識して、本ガイドラインを読破されんことを願う次第である。

2010 年 7 月

Digest of
Guideline for the management of hyperuricemia and gout
2nd edition

The Guideline Revising Committee of
Japanese Society of Gout and Nucleic Acid Metabolism

Introduction

This manuscript describes the key points in the “Guideline for the Management of Hyperuricemia and Gout, 2nd edition”, which was published in January 2010 by the Japanese Society of Gout and Nucleic Acid Metabolism.

After the publication of the 1st edition of this guideline in 2002, a series of evidences concerning management of hyperuricemia and gout has accumulated and the circumstances surrounding to clinical guidelines have also changed.

Therefore, the Japanese Society of Gout and Nucleic Acid Metabolism established a committee to revise the Guideline (Chairman: Hisashi Yamanaka, MD) in 2006. The committee actively collected the evidences related to hyperuricemia and gout and discussed the significance of this information in daily practice. Finally, the 2nd edition was published in January 2010.

In this manuscript, the key messages from each chapter are listed together with evidence level, consensus level, and strength of recommendation.

The committee members sincerely wish that this manuscript provides useful information that can aid decision making in the clinical management of hyperuricemia and gout.

The essential points and the presence/absence of evidence have been summarized in a manner such that they can be easily understood, thereby facilitating adherence to this guideline among healthcare professionals.
For routine medical practice, please utilize this revised guideline by referring to the supplementary notes on evidence level, consensus level, and advisability.

• Evidence level

Evidence level 1a : Whether meta-analysis of randomized comparative trial (RCT) has been performed, and whether the results obtained by multiple RCTs are almost consistent.

Evidence level 1b : There is at least 1 RCT.

Evidence level 2a : There are well-designed comparative studies (non-randomized), including prospective cohort studies.

Evidence level 2b : There are well-designed semi-empirical studies, including retrospective studies.

Evidence level 3 : There are well-designed non-empirical descriptive studies, including case control studies.

Evidence level 4 : Evidence based on case reports, non-controlled studies, low-quality cohort studies, and cross-sectional studies is available

Evidence level 5 : Evidence based on expert's reports/opinions/experience, etc., is available

• Consensus level

Consensus level was assessed using a 7-rank rating, wherein rank 1 indicated a full consensus; rank 4, no opinion; and rank 7, no consensus.

• Recommendation level

Advisability was assessed on the basis of the evidence level and consensus level as shown below.

1) On the epidemiology/diagnosis of gout/hyperuricemia (Chapters 1 and 2)

Recommendation level A : There is strong evidence for certainty.
(There are one or more studies on **evidence level 1**)

Recommendation level B : There is evidence for certainty.
(There are one or more studies on **evidence level 2**)

Recommendation level C : There is no evidence for certainty
(cases other than those mentioned above)

2) On the therapy for gout/hyperuricemia (Chapters 3 and 4)

Recommendation level A : Therapy is strongly recommended
(There are one or more studies on **evidence level 1**)

Recommendation level B : Therapy is recommended
(There are one or more studies on **evidence level 2**)

Recommendation level C : Therapy may be considered for certain cases
(cases other than that mentioned above)

Chapter 1 : Recent Trend and Risk of Hyperuricemia/Gout

1-1 Definition of hyperuricemia

・ Statements

1. Hyperuricemia is a major pathogenic factor for urate deposition diseases (gouty arthritis, renal disorder, etc.). It is defined as a disease condition showing a serum urate level exceeding 7.0 mg/dL, regardless of sex and age. Evidence level 2a Recommendation level B

2. In women, the risks of lifestyle-related diseases increase with increase in serum urate level, even when it is not more than 7.0 mg/dL. Examination for possible underlying diseases and lifestyle guidance should be given; however, drug therapy with urate–lowering drugs is not indicated. Evidence level 2a Recommendation level B

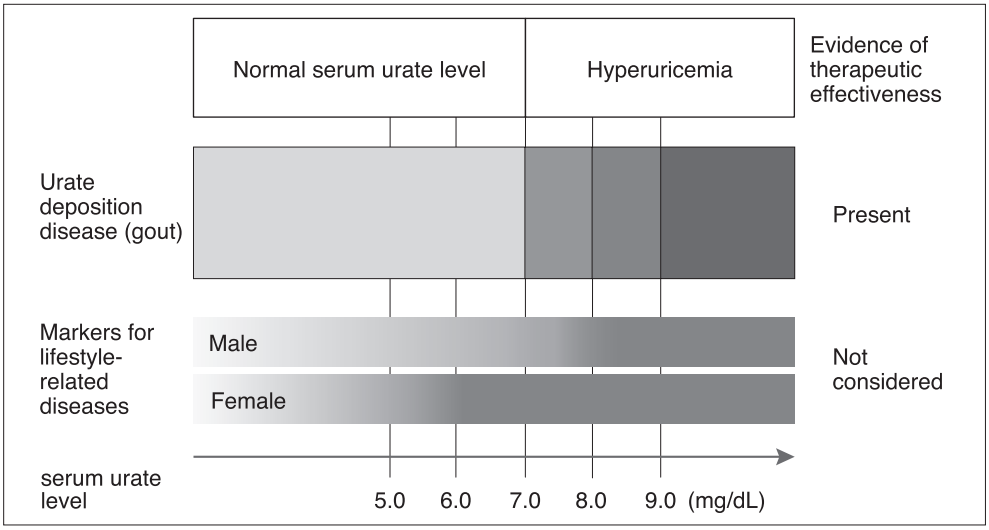
In the "Guideline for the management of hyperuricemia and gout 2nd edition", the significance of serum urate level is evaluated from two viewpoints:

1. Hyperuricemia as the cause of urate deposition diseases such as gouty arthritis and renal impairment.
2. Serum urate level as a clinically useful index (marker) of the pathology of various lifestyle-related diseases.

Hyperuricemia is a causative factor of urate deposition diseases, and the efficacy of therapeutic intervention has been confirmed. Hyperuricemia is a clear risk factor for gouty arthritis, the recurrence of which is suppressed by therapeutic interventions. Metabolic syndrome has attracted attention, and the results of the analysis focusing on the risks of cardiovascular diseases have demonstrated that a high serum urate level is also predictive of the onset of lifestyle-related diseases. However, the significance of urate in such pathologic conditions is unclear. Furthermore, reports indicating the improvement of these pathologic risks by therapeutic interventions are unavailable to date.

Taking these points into consideration, attention should be given to the fact that the risks of lifestyle-related diseases increase with increase in serum urate level in both males and females, even if it is less than 7.0 mg/dL (**Figure 1**). Examinations of potential diseases and lifestyle guidance are recommended at the lower serum urate level in females than in males. However, the risks increase linearly; thus, no clear threshold of serum urate level against the risk for diseases, including cardiovascular diseases, was determined. Also, urate–lowering drugs are currently not recommended for such cases.

Figure 1. Definition of Hyperuricemia



: normal ,
: lifestyle guidance,
: drug therapy should be considered depending on disease conditions in cases of hypertension/ischemic heart disease/diabetes/metabolic syndrome, etc. ,
: drug therapy

1-2 Recent trends in the prevalence of hyperuricemia/gout

• Statements

1. The prevalence of hyperuricemia has been estimated to be 30% in Japanese male adults 30 years or older. Evidence level 3 Recommendation level C

2. Hyperuricemia cases are still increasing. Evidence level 2b Recommendation level B

3. The prevalence of gout has been estimated to be higher than 1% in male adults 30 years or older. Gout cases are also currently on the rise. Evidence level 3 Recommendation level C

[1] Prevalence of hyperuricemia by sex/age

Two recent large-scale surveys conducted in Japan reported that the prevalence of hyperuricemia is 21.5% or 26.2% in adult males[1)2)]. The prevalence in males by age was highest in the 30s and 40s, and reached 30% in the 30s[1)]. A 16.3% prevalence was already reported in 10s[1)]. Since serum urate level increases post menopause, menopausal status should be taken into consideration when discussing the prevalence of hyperuricemia in females; however, no such reports are available in Japan. The menopausal age of Japanese females has been reported to be 45–55 years. A workplace survey reported that the prevalence of hyperuricemia in females was 1.3% and 3.7% in those under and over 50 years old, respectively[1)].

[2] Trend in the prevalence of hyperuricemia

Many reports support the increasing trend in the prevalence of hyperuricemia in Japan. In a workplace survey conducted from 1996 to 2004, an increasing trend was found in all age groups ranging from 20s to 60s in males[1].

[3] Recent prevalence of gout

According to the Comprehensive Survey of the People on Health and Welfare, which was conducted in 2004, 874,000 patients answered that "they were visiting hospitals due to gout." In this survey, the subjects replied to the question on why they visited hospitals[3]. The number of patients in 2004 is 2.1- and 3.4-fold greater compared to that in 1995 and 1986, respectively, showing the rapidly increasing trend. Hyperuricemia was not included in the questionnaires in this survey; therefore, it is assumed that patients with asymptomatic hyperuricemia with no gouty attacks but had already been treated with urate–lowering drugs were included in this survey.

1-3 Risk of hyperuricemia

1-3-1 Gouty arthritis/gouty tophus

・ Statements

1. The risk of gouty arthritis increases with increase in serum urate level to above 7.0 mg/dL. Evidence level 2a Recommendation level A

2. Gouty tophus is more likely to occur with longer duration and higher degree of hyperuricemia. Evidence level 3 Recommendation level C

3. Alcohol intake dose-dependently increases the risk of gout onset. Gout is more likely to occur in a population that consumes large amounts of meat/sugar-containing soft drinks/fructose or in individuals with high body mass index (BMI). Evidence level 2a Recommendation level B

4. Gout is less likely to occur in a population that consumes large amounts of coffee, runs long distances, or exercise regularly in moderate amounts. Evidence level 2a Recommendation level B

[1] Risks of onset of gouty arthritis

In 1987, Campion et al.[4] conducted a 14.9-year prospective cohort study in 2,046 healthy male subjects in the United States. As a result, a clear increase in the incidence of onset of gout was found in association with increase in serum urate level. In 2000, Lin et al.[5] conducted a 5-year prospective cohort study in 223 male subjects in Taiwan, who had asymptomatic hyperuricemia, and reported data almost analogous to that reported by Campion et al.

[2] Lifestyle and onset of gout

In 2004, Choi et al.[6] conducted a 12-year prospective cohort study in 47,150 male subjects in the United States, who had no history of gout. Among the target population, gout occurred in 730 subjects, demonstrating anew that various lifestyles affected the onset of gout, which clearly positioned gout as a lifestyle-related disease.

Particularly, it was revealed that high intakes of meat, alcohol, sugar-containing soft drinks, etc., increased the incidence of gout onset; on the contrary, high intakes of dairy products, coffee, etc., decreased it.

1-3-2 Renal disorder

• Statements

1. Serum urate level correlates with the onset or progress of chronic kidney disease (CKD). Evidence level 2b Recommendation level A

2. Hyperuricemia is a risk factor for renal failure in the general population. Evidence level 2b Recommendation level A

3. Hyperuricemia is a risk factor related to the prognosis of renal function in IgA nephropathy. Evidence level 3 Recommendation level B

4. Accumulation of lead in the body may likely be involved in cases having both CKD and gout. Evidence level 1b Recommendation level A

Multiple recent evidences have proven that hyperuricemia and renal disorder are closely correlated in both the general population and the population with CKD.

1-3-3 Urinary stones

• Statements

1. The risk factors for uric acid stones include 1) decreased urinary volume, 2) hyperuricosuria, and 3) acidic urine. Evidence level 3 Recommendation level B

2. The incidence of urinary stones is not always increased by hyperuricemia. Evidence level 3 Recommendation level B

3. The incidence of urinary stones tends to be increased by hyperuricosuria. Evidence level 3 Recommendation level B

4. Constant acidic urine condition is the greatest risk factor for urinary stones. Evidence level 3 Recommendation level B

5. Uricosuric agents can accelerate uric acid stone formation with excessive intake of dietary products rich in purine, and/or accelerate acidic urinary condition. Evidence level 3 Recommendation level B

6. Urinary stones as a complication of hyperuricemia and/or gout is composed of not only uric acid stones, but also calcium oxalate stones that are commonly observed in all kinds of urinary stones. Evidence level 3 Recommendation level B

Based on the recent report in 2005, 5.5% males and 2.2% females have uric acid stones associated with hyperuricemia and/or gout in Japan[7]. In gout patients, the incidence of uric acid stones was approximately 10–20%[8]. Decreased urinary volume or insufficient intake of fluid, increased urinary excretion of uric acid, and low urinary pH are the factors to induce uric acid stone formation[8)9)].

1-3-4 Relation between gout and metabolic syndrome

・ Statements

1. The incidence of metabolic syndrome increases with the increase in levels of serum urate. Evidence level 3 Recommendation level B

2. Patients with gout frequently experience complications of metabolic syndrome, such as visceral obesity, hypertension, dyslipidemia, and impaired glucose tolerance. The prevalence of metabolic syndrome is higher in patients with gout. Evidence level 3 Recommendation level B

3. Although not included in the diagnostic criteria, hyperuricemia is considered to be a biomarker of metabolic syndrome. Evidence level 3 Recommendation level B

4. Serum concentration of uric acid increases in association with visceral fat accumulation. Evidence level 3 Recommendation level B

5. Hyperinsulinemia accelerates reabsorption of uric acid at the proximal renal tubules, leading to an increase in serum urate level. Evidence level 2b Recommendation level B

Metabolic syndrome consists of multiple risk factors for arteriosclerosis, including visceral fat obesity, dyslipidemia (excluding hypercholesterolemia), impaired glucose tolerance, and hypertension. The incidence of metabolic syndrome increases in accordance with the levels of serum urate[10)-15)]. Conversely, serum urate levels increase with the number of metabolic syndrome components, suggesting a close relationship between these two disease entities[16)17)]. Moreover, serum urate level has been reported to be an independent predictive factor for the future development of metabolic syndrome[12)18)]. The existence of metabolic syndrome in childhood predicts increased urate levels in adulthood.

The higher prevalence of metabolic syndrome in patients with gout may in part contribute to their susceptibility to atherosclerotic diseases. Therefore, increased attention should be given to the presence of metabolic syndrome in patients with gout to reduce their risk for cardiovascular disease complications.

1-3-5 Hypertension/cardiovascular diseases

- **Statements**

1. Serum urate level is an independent predictive factor for the development of hypertension. Evidence level 1b Recommendation level A
2. Recent prospective observational studies in general populations and hypertensive patients produced conflicting findings on whether serum urate level correlates with the independent risk factors for cardiovascular diseases. Evidence level 2a Recommendation level B
3. No evidences of randomized controlled trials (RCT) to examine the impacts of decreased serum urate level on cardiovascular events have been demonstrated. A few subsequent analyses of interventional studies concerning antihypertensive and lipid-lowering therapies have demonstrated that changes in serum urate levels correlate with the risk for cardiovascular events. Evidence level 2a Recommendation level B
4. A few recent prospective observational studies indicated serum urate level as a possible predictive factor for the risks of new onset and recurrence of stroke as well as prognosis of heart failure and rehospitalization. Evidence level 2a Recommendation level B

Recent prospective observational studies demonstrated that serum urate level is an independent predictive factor for the development of hypertension. Many prospective cohort studies to clarify whether high serum urate level is an independent risk factor for cardiovascular diseases have been reported; however, they offer conflicting results.

Reports showing that change in urate level, in association with treatment of lifestyle-related diseases, has impacts on cardiovascular events are limited to subanalyses, in which serum urate level was newly set as an explanatory variable after intervention studies of antihypertensive and lipid-lowering therapies.

Results of an RCT conducted to examine the impacts of therapeutic interventions to reduce serum urate level on cardiovascular events should be awaited to be able to conclude that urate level is a risk factor for cardiovascular events.

1-3-6 Malignant tumor

- **Statements**

1. Epidemiological studies have shown the association of serum urate level with death due to malignant tumor. Evidence level 2a Recommendation level B
2. Whether the risk of malignant tumor can be decreased by controlling the serum urate level is unclear. Evidence level 2a Recommendation level B

Although uric acid has been hypothesized to have anticarcinogenic effects due to its antioxidant activity, several epi-

demiological studies reported otherwise. Rather, it has been suggested that death due to malignant tumor increases with increase in serum urate level. However, since insulin resistance and hyperinsulinemia have been suggested to be associated with carcinogenesis, it is necessary to take such factors into consideration in discussing the relationship between serum urate level and malignant tumor.

1-3-7 Total death

- **Statements**

1. Serum urate level may be related to the risk of total death. Evidence level 2a Recommendation level B

2. In women, serum urate levels lower than the diagnostic value for hyperuricemia may likely be associated with increase in the relative risk of total death. Evidence level 2a Recommendation level B

3. Whether the relative risk of total death is decreased by control of serum urate level is unclear. Evidence level 2a Recommendation level B

The association of serum urate level with total death has been reported in numerous studies. However, such epidemiological studies have been observational, with no intervention to reduce serum urate level. Currently, clinical control of the factors related to both the risk of death and serum urate level, such as hypertension and dyslipidemia, is undoubtedly important.

Chapter 2 : Diagnosis of Hyperuricemia/Gout

2-1 Method for determination of urate

- **Statements**

1. The uricase-peroxidase method using an automatic analyzer is being adopted in many medical institutions. Evidence level 2b Recommendation level A

2. The variation of measurement, shown as coefficient of variation (CV), is 9.0%, taking the influence of serum components into consideration. The difference among the medical institutions is 2.7–6.8%; therefore, it can be considered a reliable analytical method. Evidence level 3 Recommendation level B

3. Although blood collection under a fasting condition is not always needed for judging hyperuricemia, multiple measurements are recommended for judging constant hyperuricemia. Evidence level 3 Recommendation level B

Analytical measurement of urate becomes reliable through improvements of methodology and routine accuracy control; the coefficients of variation (CV) are around 2.0%. Data variations are estimated to be about 9.0% when the in-

fluence of other serum components are taken into account; therefore, if serum urate level is 4.6 mg/dL, a measurement value will be obtained within the range of 4.6 ± 0.4 (4.2–5.0 mg/dL) [19]. In addition, physiological fluctuations should also be considered in judging whether the measured serum urate level is normal or abnormal. Circadian and seasonal variations were observed in serum urate levels. The circadian variation in serum urate level is about 0.5 mg/dL in healthy subjects who are taking normal diets. The serum urate level is a little high in the morning and decreases in the evening[20]. In addition, serum urate level is changed by taking alcohol and meals, performing exercise and mental activities, etc. (it is increased to 1.04- and 1.1-fold higher levels by exercise and by taking a lunch, respectively) [21]. Serum urate level increases after intake of purine, soybeans, or alcohol, while it slightly decreases after intake of animal-derived proteins[22]. Although for the screening of hyperuricemia, it is unnecessary to measure serum urate level under a fasting condition, it should be judged after multiple measurements whether a patient contracts hyperuricemia or not.

2-2 Classification of hyperuricemia

- **Statements**

1. Hyperuricemia is broadly classified into the following 3 types: "uric acid-overproduction type," "uric acid-underexcretion type," and "combined type." Evidence level 2b Recommendation level A
2. The uric acid clearance rate and creatinine clearance (Ccr) rate are determined for the classification (uric acid-overproduction type, urinary uric acid excretion > 0.51 $mg \cdot kg^{-1} \cdot hr^{-1}$; uric acid-underexcretion type: uric acid clearance < 7.3 mL/min). Evidence level 2b Recommendation level A
3. Changes in the disease type during the treatment should be carefully observed. Evidence level 2b Recommendation level A

The bodies of healthy people usually contain approximately 1,200 mg of uric acid. Approximately 700 mg of uric acid is produced per day. Approximately 500 mg/day of the produced uric acid is excreted in the urine, while approximately 200 mg/day is excreted in sweat or digestive fluids etc. (extrarenal disposal) [23][24]. The following classification of hyperuricemia is based on its causes: increased uric acid production (uric acid -overproduction type), reduced renal clearance of uric acid (uric acid-underexcretion type), and a combination of the 2 causes (combined type) [24][25].

Since a direct assay for assessment of the uric acid production needs RI injection, the uric acid production is usually estimated by measuring the amount of uric acid excreted in the urine. The presence or absence of uric acid underexcretion is determined on the basis of the data of uric acid clearance. According to a report by Nakamura et al., the incidences of uric acid-overproduction type, uric acid-underexcretion type, combined type, and the normal type, were 12%, 60%, 25%, and 3% respectively[26].

2-3 Diagnosis of gout

・ Statements

1. Gouty arthritis is an inflammatory arthritis caused by monosodium urate crystals.

2. Acute gouty arthritis (gouty attack) frequently occurs in the first metatarsophalangeal (MTP) joint and the ankle joints, etc. Evidence level 2a Recommendation level A

3. Diagnosis of gout is based on the characteristic symptoms and clinical course, past history of hyperuricemia, and identification of monosodium urate crystals in the inflamed joint. Evidence level 3 Recommendation level B

4. Hyperuricemia is not always identified during gouty attack. Evidence level 3 Recommendation level B

5. Gouty tophi consist of monosodium urate crystals and granulation tissue, and are important for the diagnosis of gout. Evidence level 2a Recommendation level A

Gout is one of the crystal-induced types of arthritis. It is caused by monosodium urate (MSU) crystals that had been deposited inside the joint as a consequence of sustained hyperuricemia. Gouty arthritis is usually monoarthritis. It commonly involves the first MTP joint, ankle, and mid tarsal joint. Redness around the involved joint usually occurs in gouty arthritis. A painful acute arthritis[27] on the first MTP joint, with recurrence, in a middle-aged man who has hyperuricemia has a strong likelihood of being diagnosed as gout. The preliminary criteria for the classification of acute gout have been published by American Rheumatism Association[28].

We have to be careful about the points listed in **Table 1** for the diagnosis of gout. Gout has to be differentiated from other diseases with acute monoarthritis (bacterial arthritis, traumatic arthritis, pseudogout, palindromic rheumatism, etc.). Disorders without arthritis, including phlegmone, hallux valgus, paronychia, bursitis, etc., may exhibit similar findings to gout.

Table 1. Points to Consider in the Diagnosis of Gouty Arthritis

1. Serum levels of urate may not be high during the acute phase of gouty arthritis.
2. Microscopic examinations of synovial fluid to identify MSU crystals should be performed as soon as joint fluid is aspirated.
3. Although gouty tophus is one of the most important findings for the diagnosis of gout, its prevalence is low.

2-4 Secondary hyperuricemia/gout

- **Statements**

1. The possibility of the secondary type should be examined at diagnosis of hyperuricemia/gout. Evidence level 2b Recommendation livel B
2. Acute uric acid nephropathy and tumor lysis syndrome are emergent diseases for which cure should be aspired. Evidence level 1b Recommendation level A

Secondary gout that is clearly caused by underlying diseases or drug administration, etc., comprises about 5% of all gout cases. It is important to be aware of the presence of underlying diseases and medications through detailed diagnostic interview and examination of medication history, as well as by physical and laboratory examinations, etc., for the diagnosis of secondary hyperuricemia/gout[29].

Chapter 3 : Therapy of Hyperuricemia/Gout

3-1 Therapy of gouty arthritis/gouty tophus

- **Statements**

1. One tablet of colchicine (0.5 mg) is used in the aura phase of gouty attack to stop further development of arthritis.. In case of frequent occurrence of gouty attack, daily medication with one tablet of colchicine, "colchicine cover," is effective. Evidence level 3 Consensus level 1 Recommendation level B
2. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the acute phase of gouty attack. NSAIDs are administered at a relatively high dose for a limited period to alleviate inflammation (NSAID pulse therapy). Thereby, the occurrence of adverse drug reactions should be noted. Evidence level 3 Consensus level 1 Recommendation level B
3. Corticosteroids are orally administered when NSAIDs cannot be administered or their administration is ineffective, or when polyarthritis occurs. Evidence level 1a Consensus level 1 Recommendation level A
4. Since gouty attack is exacerbated when serum urate level is changed at the time of attack, in principle, medication with uric acid–lowering drugs should not be initiated. Evidence level 3 Consensus level 1 Recommendation level B
5. Surgical resection is considered necessary in the treatment of some cases of gouty tophus, but drug therapy is also necessary in such cases. Evidence level 3 Consensus level 1 Recommendation level B

Gouty attack is acute arthritis caused by urate crystals. Alleviating patients' pain and improvement of their quality of life(QOL) by appropriate therapy are the objectives of gouty attack treatment. In addition, introduction to long-term therapy of hyperuricemia, which causes gout, is important for patients who have experienced gouty attack;

however, quiescence of arthritis should not mean that therapy should be considered complete.

[1] Therapy of gouty arthritis

Three treatment options are available for gouty arthritis: colchicine, NSAID (**Table 2**), and corticosteroids. All these remedies have proven clinical efficacy. Oral administration of 1 tablet of colchicine in the aura phase of gouty attack, followed by administration of NSAID at a relatively high dose for a short term only in the acute phase for the purpose of sedation of inflammation, has been adopted as a general remedy. However, corticosteroids are also adequately effective drugs, with the advantage of variable administration routes depending on patient condition, such as oral administration, intramuscular injection, intra-articular injection, etc.

[2] Therapy of gouty tophus

Gouty tophus can be reduced or eliminated, and its recurrence can be prevented, by retaining serum urate at a level of not more than 6.0 mg/dL[30)31)]. Surgical resection of tophus is considered when gouty tophus is accompanied by infection due to self-destruction (51%), when gouty tophus causes mechanical stimulation (27%), when it is necessary to diagnostically differentiate gouty tophus from malignant tumor due to the formation of a large mass (18%) or to suppress pain due to nerve compression (4%), however, concomitant drug therapy is still necessary even after the surgery[32)33)].

Table 2. List of NSAIDs Approved for the Indication of Gouty Arthritis

General name	Commercial name	Dosage form	Recommended administration method for treating gouty attack
Indomethacin	Inteban®SP (generic drug), etc.	25 mg or 37.5 mg, Sustained-release capsule	25 mg b.i.d; depending on disease conditions, 37.5 mg b.i.d.
Naproxen	Naixan®	100 mg tablet	Initially 400–600 mg, then 200 mg t.i.d. or 300 mg per treatment every 3 hours up to 3 times
Oxaprozin	Alvo®, etc.	100 mg or 200 mg tablet	Usual dose: 400 mg; maximum dose: 600 mg
Pranoprofen	Niflan® Pranoprofen tablets (Towa) (generic drug) Pranoprofen capsule (Nichi-Iko) (generic drug), etc.	75 mg tablet	150–225 mg t.i.d., then 75 mg t.i.d. from the next day

Precautions

- As general precautions, affected sites should be relaxed and kept cool wherever possible during gouty attack, and abstinence from alcohol should be instructed. Urate–lowering drugs should not be administered during gouty attack as they can exacerbate the condition. However, when patients have been treated with urate–lowering drugs, in principle such medication should not be discontinued and concomitant medication with colchicine, NSAID, or corticosteroids, etc., should be administered.
- Aspirin slightly increases serum urate level at a low dose, but decreases it at a high dose. When serum urate level is lowered during gouty attack, the symptom is exacerbated or protracted. Because administration of aspirin at a dose exerting analgesic effects reduces serum urate level, aspirin should be avoided during gouty attack.
- After arthrocentesis for gouty attack, purulent arthritis due to bacterial infection and steroid-induced arthritis due to crystallization of injected corticosteroid is likely to occur, and close attention should be paid to these developments.
- NSAID should be discontinued on remission of gouty arthritis.

3-2 Therapy of hyperuricemia

3-2-1 Therapeutic goal

• Statements

1. The most important aim of treatment of hyperuricemia is to improve lifestyle changes that are related to the onset of hyperuricemia, in which prognosis-related complications, such as obesity, hypertension, glucose intolerance, and dyslipidemia, are prone to occur. Evidence level 2a Consensus level 1 Recommendation level A

2. Urate–lowering therapy is indicated in patients with recurrent gouty arthritis or gouty tophi; thereby, it is desirable to maintain serum urate at a level of not more than 6.0 mg/dL. Evidence level 2a Consensus level 1 Recommendation level A

3. Urate–lowering therapy may be indicated for asymptomatic hyperuricemia showing a serum urate level of not less than 8.0 mg/dL as a guide; however, it should be applied with caution. Evidence level 3 Consensus level 2 Recommendation level C

Elimination of urate deposited in body tissues due to sustained hyperuricemia and avoidance of urate deposition diseases, such as gouty arthritis, renal disorder, etc., will become narrowly defined therapeutic goals for hyperuricemia. In addition, improvement in life prognosis of hyperuricemia/gout with high risks of cardiovascular events through

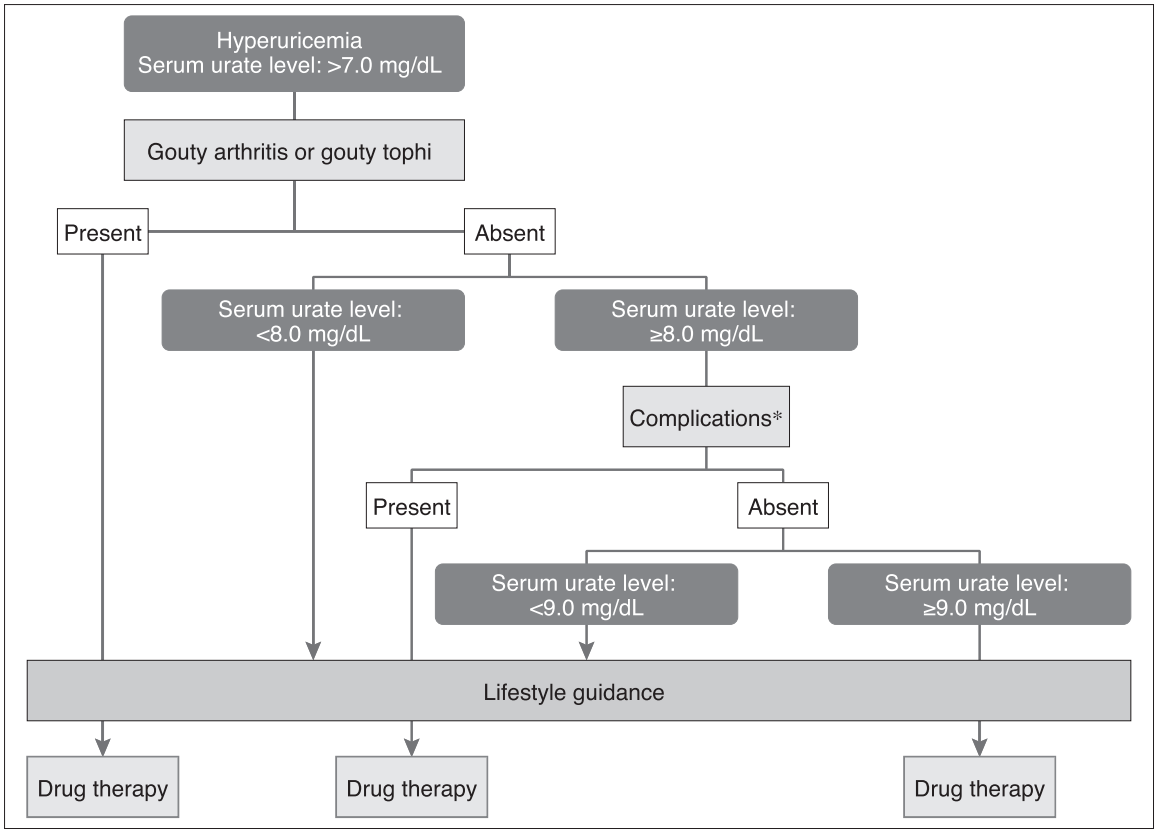
improvement in lifestyle and giving attention to the complications, such as obesity, hypertension, glucose intolerance, dyslipidemia, etc., will become the ultimate therapeutic goal.

For prevention of recurrence of gouty arthritis by removal of urate crystals through dissolution, the serum urate level should be maintained at a level of not more than 6.0 mg/dL. The number of patients with severe gout is greater in the United States (where there are negative opinions against drug therapy for asymptomatic hyperuricemia without gouty arthritis or without gouty tophi, but with serum urate level constantly exceeding 7.0 mg/dL) than in Japan; therefore, treatment of such asymptomatic hyperuricemia patients with a serum urate level higher than a certain concentration should be aimed for the prevention of the onset of gouty arthritis[34)35)]. The cohort study in healthy male subjects showed that the incidence of future gouty arthritis is significantly higher in those with a serum urate level exceeding 8.0 mg/dL, particularly 9.0 mg/dL, than those with a lower serum urate level[36)37)]. Although this is a small-scale prospective clinical study, the results suggest that decrease in renal function can be suppressed by administration of allopurinol in patients with renal failure[38)]. Drug therapy aimed at renal protection with due attention to adverse drug reactions is also considered necessary for the therapy of patients showing a serum urate level higher than a certain level. For urinary calculus, hyperuricaciduria and aciduria are more greatly involved than high serum urate level[39)], and recurrence of not only uric acid calculus but also calcium calculus can be prevented by reduction of urinary uric acid excretion and urine alkalinization[40)].

Unhealthy lifestyle, such as overeating, preference for high-purine/high-fat/high-protein diets, habitual alcohol drinking, lack of physical activity, etc., not only causes hyperuricemia but is also strongly involved in obesity, hypertension, glucose intolerance and dyslipidemia, and eventually complications such as metabolic syndrome, etc[41)]. Therefore, dietary guidance is important for the treatment of hyperuricemia. Accumulated uric acid in the body will be difficult to dissolve only by lifestyle adjustment in patients showing recurrent gouty arthritis or gouty tophi. Therefore, in such cases, it is desirable to use drug therapy to maintain the serum urate at a level of not more than at 6.0 mg/dL. For patients with a history of, or with existing, urinary calculus, suppression of urinary uric acid excretion by the use of allopurinol is necessary.

For asymptomatic hyperuricemia, a serum urate level of not less than 8.0 mg/dL is considered as a criterion for introduction of drug therapy in cases of complications such as hypertension, ischemic heart disease, diabetes mellitus, and metabolic syndrome, which are considered risk factors for renal disorders, including urinary calculus, and cardiovascular disorders. However, drug therapy should be considered depending on current circumstances (**Figure 2**). Evidence obtained by intervention studies is currently limited, although observational studies have proven that the risk of cardiovascular disorders is heightened by uric acid in patients with such complications.

Figure 2. Guidelines for Therapy of Hyperuricemia



* : Renal disorder, urinary calculus, hypertension, ischemic heart disease, diabetes, metabolic syndrome, etc. (No intervention studies were performed on considering decreased events by lowering the serum uric acid level, except for renal disease and urinary calculus.)

3-2-2 Types and selection of urate–lowering drugs

• Statements

1. Three types of uricosuric drugs are available in Japan, while allopurinol is the solely available uric acid production–inhibitory drug.

2. Uricosuric drugs and uric acid production–inhibitory drug (allopurinol) are selected for treating patients categorized as uric acid underexcretory and uric acid overproductive types, respectively, as basic therapeutic principles. Evidence level 3 Consensus level 2 Recommendation level C

3. Allopurinol is selected for treating renal dysfunction of a moderate degree or greater [creatinine clearance (Ccr), estimated glomerular filtration rate (eGFR): not more than 30 mL/min/1.73 m^2; serum creatinine level: not less than 2.0 mg/dL]. Evidence level 3 Consensus level 2 Recommendation level C

4. When allopurinol is administered in patients with renal failure, its dose should be adjusted depending on the degree of renal function. Evidence level 3 Consensus level 1 Recommendation level B

5. Allopurinol should be selected in cases with history or complication of urinary calculus. Evidence level 3 Consensus level 2 Recommendation level C

6. When uricosuric drugs are used, attention should be given to occurrence of urinary calculus, and urinary alkalinizing–drugs should be concomitantly used. Evidence level 3 Consensus level 1 Recommendation level B

7. Since benzbromarone and bucolome increase blood concentration of warfarin potassium, attention should be given to their concomitant use. Evidence level 4 Consensus level 1 Recommendation level A

Urate–lowering drugs are classified into uricosuric drugs and urate production– inhibitory drugs based on the differences of their action mechanism. Although 3 types of uricosuric drugs are available in Japan, allopurinol is the only available urate production–inhibitory drug (**Table 3**).

For selection of urate–lowering drugs, satisfactory results can be obtained using any drug type for any case, except for renal dysfunction[42]. The incidence of urinary calculus is high in patients with greater urinary excretion of uric acid[43]. Moreover, administration of uricosuric drugs in such patients also tends to induce urinary calculus. Therefore, uricosuric drugs are inappropriate for patients showing high uric acid excretion. Administration of allopurinol is desirable in such cases, and uricosuric drugs should not be used in cases of complication of urinary calculus. Blood concentration of oxypurinol, which is a metabolite from allopurinol, is prone to increase in patients of uric acid underexcretory type, and the risks of adverse drug reactions related to accumulation of oxypurinol may likely be heightened. For these reasons, application of uricosuric drugs to uric acid underexcretory patients, and uric acid production–suppressive drug (allopurinol) to uric acid overproductive patients, are the basic therapeutic principles mainly aimed at avoiding adverse drug reactions[44] (**Table 4**).

Urinary calculus as a complication of use of uricosuric drugs can be prevented by concomitant medication with urine-alkalinizing drugs[45]. Since the safety of the use of benzbromarone in patients with renal dysfunction has not been adequately confirmed, allopurinol should be selected in cases of complications of renal dysfunction of a moderate to severe degree (Ccr, eGFR: not more than 30 mL/min/1.73 m^2; serum creatinine level: not less than 2.0 mg/dL)[34]. However, dose adjustment corresponding to the degree of renal function is recommended to avoid serious adverse drug reactions[46]. The use of drugs deviating from the basic principle is unavoidable in cases with adverse drug reactions by the recommended regimen.

Table 3. Types, Doses, and Adverse Drug Reactions of Uric Acid–Lowering Drugs

	General name	Commercial name	Recommended daily dose and administration method	Drugs requiring precaution for coadministration*	Significant adverse drug reactions*
Uricosuric drugs	Probenecid	Benecid®	500–2,000 mg, by dividing into 2–4 doses	Salicylate preparations, indomethacin, naproxen, zidovudine, oral diabetic drugs, pantothenic acid, cephalosporin antibiotics, penicillin antibiotics, aciclovir, valaciclovir hydrochloride, zalcitabine, gatifloxacin hydrate, diaphenylsulfone, methotrexate, oral anticoagulants, sulfonamides, ganciclovir, and nogitecan hydrochloride	Hemolytic anemia, aplastic anemia, anaphylactoid reaction, hepatonecrosis, and nephrotic syndrome
	Bucolome	Paramidin®	300–900 mg, by dividing into 1–3 doses	Coumarin anticoagulants	Muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome) and toxic epidermal necrosis (Lyell syndrome)
	Benzbromarone	Urinorm® Narcaricin® (generic drug) Benzmarone® (generic drug) Muirrodine® (generic drug), etc.	25–100 mg, by dividing into 1–2 doses	Coumarin anticoagulants, antitubercular drugs, and salicylate preparations	Serious hepatopathy
Uric acid production-suppressive drugs	Allopurinol	Zyloric® Adenock® (generic drug) Alositol® (generic drug) Salobel® (generic drug) Riball® (generic drug), etc.	100–300 mg, by diving into 1–3 doses	Mercaptopurine (6-MP), azathioprine, vidarabine, coumarin anticoagulants, chlorpropamide, cyclophosphamide, cyclosporin, phenytoin, xanthine-related drugs, didanosine, pentostatin, captopril, hydrochlorothiazide, and ampicillin	Muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), serious anthema such as exfoliative dermatitis, shock, anaphylactoid symptoms, aplastic anemia, pancytopenia, agranulocytosis, thrombopenia, serious liver dysfunction such as fulminant hepatitis, jaundice, renal failure, exacerbation of renal failure, renal disorder including interstitial nephritis, interstitial pneumonia, and rhabdomyolysis

* : It is based on package insert

Table 4. Selection of Urate–Lowering Drugs

Application of uricosuric drugs	Application of uric acid production–inhibitory drugs (allopurinol)
• Uric acid underexcretory type • Allopurinol cannot be used due to adverse drug reactions	• Uric acid overproductive type • Past or existing urinary calculus • Renal dysfunction of moderate or greater degree (Ccr: eGFR: ≤30 mL/min/1.73 m^2; serum creatinine level: ≥2.0 mg/dL) • Uricosuric drugs cannot be used due to adverse drug reactions

Ccr : creatinine clearance, eGFR : estimated glomerular filtration rate

3-2-3 Therapy of hyperuricemia without gouty arthritis/gouty tophus (asymptomatic hyperuricemia)

• Statements

1. Serum urate level should be reduced in the asymptomatic stage of hyperuricemia to prevent the onset of gouty arthritis, gouty tophus, renal disorder, and urinary calculus because hyperuricemia is the condition underlying these complications. Evidence level 3 Consensus level 2 Recommendation level B

2. Information and appropriate guidance regarding lifestyle improvement with the aim of reducing serum urate levels, should be provided; concrete instructions should be given to patients to avoid excessive consumption of alcoholic drinks, purine, fructose, sucrose, and calories, as well as to refrain from extreme exercises. Evidence level 3 Consensus level 1 Recommendation level A

3. In cases of asymptomatic hyperuricemia with a serum urate level of not less than 9.0 mg/dL, drug therapy should be considered despite improvement in lifestyle. Further, drug therapy should be considered when serum urate level reaches 8.0 mg/dL or more in cases of complications such as urinary calculus, renal disease, hypertension, etc. Evidence level 3 Consensus level 2 Recommendation level B

Hyperuricemia without clinical symptoms, such as gouty attack (acute gouty arthritis), gouty tophus, renal disorder, etc., is called “asymptomatic hyperuricemia.” It is desirable to reduce the serum urate level at this disease stage to prevent the onset of gouty arthritis, gouty tophus, renal disorder, and urinary calculus, which are caused by hyperuricemia as an underlying disease.

Guidance for improving lifestyle is important in decreasing the serum urate level. Particular attention should be given to alcohol and purine consumption and obesity. Excessive consumption of alcoholic drinks, purine, and calories should be avoided[47)48)]. Since fructose and sucrose increase the serum urate level, excessive consumption of beverages and fruits containing these sugars in abundance should be avoided[49)]. To prevent urinary calculus, patients should be instructed to consume adequate amounts of water such that their urinary output can be maintained at not less than 2,000 mL/day. In addition, since heavy, anaerobic exercise may increase serum urate level, patients should

be instructed to refrain from such exercises. In cases of asymptomatic hyperuricemia showing a serum urate level of not less than 9.0 mg/dL, drug therapy should be considered despite improvement in lifestyle. In addition, in the presence of complications such as urinary calculus, renal diseases, hypertension, etc., drug therapy should be considered when serum urate level is 8.0 mg/dL or more. It is important to maintain serum urate level within the normal range whenever possible, while paying attention to the administration of serum urate–increasing drugs (diuretics, salicylic acid, pyrazinamide, etc.).

3-2-4 Treatments at gouty attack (gouty arthritis) and interval stage of gout

- **Statements**

1. At the onset of gouty arthritis in untreated cases, gouty attack should be remitted by high doses of nonsteroidal antiinflammatory drugs (NSAIDs) or NSAID pulse therapy, but not by administration of urate–lowering drugs. Evidence level 2b Consensus level 1 Recommendation level A

2. Serum urate level should be gradually reduced to a level of not more than 6.0 mg/dL over 3–6 months of drug therapy for hyperuricemia; thereafter, medication should be continued at the dose necessary to maintain serum urate at such a level. Evidence level 2b Consensus level 2 Recommendation level B

3. Medication with urate-lowering drugs should be started at a low dose (benzbromarone: 12.5 mg, allopurinol: 50 mg) from about 2 weeks after remission of gouty arthritis. Evidence level 2b Consensus level 2 Recommendation level B

4. Concomitant administration of low-dose colchicines is recommended in an early stage after the start of administration of urate-lowering drugs for prevention of gouty arthritis. Evidence level 1b Consensus level 2 Recommendation level B

5. When gouty arthritis occurred after administration of urate-lowering drugs at an appropriate dose, concomitant use of NSAID pulse therapy according to the therapy of gouty arthritis, without discontinuation of urate-lowering drugs, is recommended. Evidence level 2b Consensus level 2 Recommendation level B

Gouty attack is exacerbated by the change in serum urate level during the gouty arthritis. Gouty arthritis often occurs from a drastic reduction in serum urate level with initiation of urate–lowering drugs[43)50)]. Moreover, hyperuricaciduria is caused by a drastic increase in uric acid excretion induced by uricosuric drugs, causing uric acid calculus and renal disorder[43)]. Accordingly, attention should be given to the means of administration of urate–lowering drugs.

After NSAID pulse therapy, remission of attack should be awaited before administration of urate–lowering drugs at the occurrence of gouty arthritis. From about 2 weeks after remission, urate–lowering drugs suited for the disease type should be selected[44)]; drug administration should be started at a low dose, and then the dose should be gradually increased. Thereby, it is desirable to start with benzbromarone at 12.5 mg (25 mg tablet divided in half) or allopurinol at 50 mg (allopurinol 50 mg tablet, or 100 mg tablet divided in half) [51)]. In addition, the onset of gouty arthritis can be prevented by concomitant administration of urate–lowering drugs with low-dose colchicine in the early stages

after start of administration[52]. A serum urate level of not more than 6.0 mg/dL, which is lower than the dissolution limit of uric acid in the body fluid (6.4 mg/dL), is set as a therapeutic goal[53]. Thus, drug therapy over a period of 3–6 months is used to gradually decrease the serum urate level to not more than 6.0 mg/dL.

In addition, when gouty arthritis occurred from administration of urate–lowering drugs, drug administration should be continued at the same dose with the concomitant use of NSAID pulse therapy according to the therapy of gouty arthritis. When serum urate level did not reach the intended range, the dose of urate–lowering drugs should be gradually increased in the same manner from about 2 weeks after remission of gouty arthritis to keep the serum urate at a level of not more than 6.0 mg/dL[53]. Thereafter, the dose of urate–lowering drugs should be continued so that serum urate level is maintained at not more than 6.0 mg/dL.

To prevent uric acid calculus, potassium citrate + sodium citrate hydrate (urine-alkalinizing drugs) should be concomitantly administered (3–6 g/day, by dividing into 3–4 portions) to maintain urine pH at 6.0 to 7.0[43)45)]; moreover, water intake should be enforced rigorously at regular times, keeping daily urinary output level at not less than 2,000 mL. Periodic blood examination is important to check changes in serum urate level and to discover adverse drug reactions at an early time. It is desirable to perform blood examination every month during the period of 6 months after the start of administration.

3-3 Therapy in patients with complications/concurrent diseases

3-3-1 Renal disorder

- **Statements**

1. Allopurinol should be used as a urate–lowering drug in cases of complications such as renal disorder or urinary calculus. Concomitant use of low-dose allopurinol and benzbromarone is also effective in cases with renal disorder. Evidence level 3 Consensus level 2 Recommendation level B
2. The dose of allopurinol should be reduced depending on the decrease in renal function. Evidence level 3 Consensus level 1 Recommendation level B
3. Treatment of hyperuricemia with allopurinol is useful for retaining renal function in patients with chronic kidney disease (CKD). Evidence level 1b Consensus level 2 Recommendation level B
4. Losartan potassium is useful for controlling hypertension/hyperuricemia in patients who had renal transplantation and are under treatment with cyclosporine. Evidence level 1b Consensus level 2 Recommendation level A
5. Uricosuric drugs are highly useful for controlling hyperuricemia after renal transplantation. Evidence level 3 Consensus level 2 Recommendation level B
6. Treatment of hyperphosphatemia with sevelamer hydrochloride may result in a countermeasure against hyperuricemia in maintenance hemodialysis patients. Evidence level 1b Consensus level 2 Recommendation level B

Allopurinol, a xanthine oxidase inhibitor, is selected mainly for cases with renal disorder and urinary calculus. Moreover, it has been reported that concomitant use of low-dose benzbromarone (25–50 mg/day), which is relatively effective even in cases of decreased renal function, and allopurinol (50–100 mg/day) is also effective in cases with renal disorder showing Ccr ≤30 mL/min, through which the dose of allopurinol can be reduced[54)55)].

Losartan potassium is useful for controlling hypertension/hyperuricemia in patients who had renal transplantation and are under treatment with cyclosporine. Moreover, it has been reported that uricosuric drugs, rather than allopurinol, are more useful for controlling hyperuricemia after renal transplantation.

Since sevelamer hydrochloride exerts serum urate–reducing effects, treatment of hyperphosphatemia with this drug may also result in a countermeasure for hyperuricemia in patients undergoing maintenance hemodialysis.

3-3-2 Urinary stones

• Statements

1. Daily consumption of fluid should be at a level that produces at least 2,000 mL of urine. Evidence level 2b Consensus level 2 Recommendation level B

2. The primary treatment of choice for hyperuricemia with urinary stones is allopurinol. Evidence level 3 Consensus level 1 Recommendation level B

3. In principle, uricosuric agents are contraindicated in patients with urinary stones, because these agents increase the excretion of uric acid, which can stimulate urinary stone formation. Evidence level 3 Consensus level 2 Recommendation level B

4. Urine alkalization is achieved by administration of citrate compounds. The appropriate urinary pH is between 6.0 and 7.0. Concomitant dietary guidance, such as restriction of dietary products rich in purine, is mandatory. Evidence level 3 Consensus level 2 Recommendation level B

5. Allopurinol and alkalizing medications are useful in preventing recurrence of calcium oxalate stones in patients with hyperuricosuria. Evidence level 1b Consensus level 1 Recommendation level A

6. Extracorporeal shock wave lithotripsy is the first-line therapy for treating uric acid stones. In particular, uric acid stones can be dissolved by medical agents such as orally administered alkalizing medications with concomitant use of allopurinol. Evidence level 2b Consensus level 1 Recommendation level B

[1] Prevention of recurrent urinary stone formation

The most important objective is to prevent uric acid stone formation. Major risk factors for uric acid stone formation include 1) decreased urinary volume or insufficient intake of fluid, 2) increased urinary excretion of uric acid, and 3) a low urinary pH[8)9)]. Excessive intake of dietary products rich in purines further increases the risk of uric acid stone formation. Therefore, these risk factors should be reduced to prevent uric acid stone formation. Adequate fluid consumption can reduce the saturation of uric acid in urine. Daily fluid consumption should be at a level (approximately

2,000–2,500 mL) that produces at least 2,000 mL of urine[56]. In principle, uricosuric agents are contraindicated in patients with urinary stones. If patients previously had a stone episode and uricosuric agents are the only medication used to improve hyperuricemia, these drugs should be administered carefully under favorable urinary pH and volume. Urine alkalization is an essential factor for the control of urinary stone formation in patients with hyperuricemia and/or gout. Citrate compounds are commonly used to achieve urine alkalization. The appropriate urinary pH is between 6.0 and 7.0. Dietary guidance such as restriction of consumption of dietary products rich in purine is very effective.

[2] Treatment of existing uric acid stones

For fragmentation and removal of urinary stones, extracorporeal shock wave lithotripsy, percutaneous nephrolithotripsy, and transurethral ureterolithotripsy are the first-line treatments. When active interventions cannot be selected, uric acid stones can be dissolved by medical agents such as alkalizing medications administered orally under adequate fluid consumption[57)58)]. Thereby, allopurinol is concomitantly used in many cases.

3-3-3 Hypertension/cardiovascular diseases

・ Statements

1. In hyperuricemia complicated by hypertension, lifestyle modification to avoid the onset of hyperuricemia is necessary to prevent multiple organ involvement. Evidence level 2a Consensus level 1 Recommendation level B

2. Antihypertensive drugs are selected based on achieving the desired blood pressure levels with less adverse effects on uric acid metabolism whenever possible. Evidence level 2b Consensus level 1 Recommendation level B

3. When serum urate level is not less than 8.0 mg/dL, even after lifestyle modification and administration of antihypertensive drugs that are desirable for uric acid metabolism, uric acid–lowering drugs are taken into consideration. Serum urate levels should be retained below 6.0 mg/dL during drug therapy. Evidence level 3 Consensus level 2 Recommendation level C

4. Uric acid–lowering drugs should be selected based on classification of uric acid metabolism, and their dosing should be decided cautiously based on the degree of renal and hepatic disorders. In addition, concomitant use of urinary-alkalinizing drugs is also considered based on urine pH. Evidence level 3 Consensus level 2 Recommendation level C

The aim for patients with hyperuricemia complicated by hypertension, which is often associated with obesity and glucose and lipid metabolic disorders, is to avoid multiple organ involvement.

First, treatment should be aimed at correcting the serum urate level by starting lifestyle guidance. Since it has been reported that hyperuricemia is significantly related to cardiovascular events after control of blood pressure in many cases of patients with hyperuricemia complicated by hypertension[59)-64)], blood pressure control should be prioritized in drug therapy. The antihypertensive goal should be compliant with the “Guideline for the Management of Hypertension (2009)” published by the Japanese Society of Hypertension (**Figure 3**) [65)]. It is desirable to control blood

pressure by preferentially using antihypertensive drugs with no adverse effects on uric acid metabolism whenever possible.

The impacts of individual antihypertensive drugs on serum urate level are listed in **Table 5**. Losartan potassium, an angiotensin II receptor blocker (ARB), reduces serum urate level by about 0.7 mg/dL on average by inhibition of the actions of urate transporter-1 (URAT1) that is present in the renal tubule[66)-69)]. Other ARB drugs have no clear impacts on serum urate level at their clinical doses. The combination preparations of ARB with thiazide diuretics (hydrochlorothiazide) are designed by adjusting the type/dose of ARB and the dose of hydrochlorothiazide after considering the increase in serum urate level due to the later drug.

[1] Urate–lowering drugs

When serum urate remains at a level not less than 8.0 mg/dL even after the aforementioned improvement in lifestyle and administration of antihypertensive drugs with no adverse effects on uric acid metabolism, starting the administration of urate–lowering drugs should be considered (**Figure 4**). Patients with hypertension and cardiovascular diseases are prone to be complicated by CKD, and a relationship characterized by a vicious cycle has been suggested for individual diseases (cardio-renal linkage). Therefore, it is recommended that the dose of allopurinol is decreased based on the degree of renal dysfunction.

[2] Urine alkalinization

Since patients with hyperuricemia complicated by hypertension show a low pH value in many cases, urine pH should be determined and concomitant use of urine-alkalinizing drugs should be considered.

Figure 3. Antihypertensive Goal [65)]

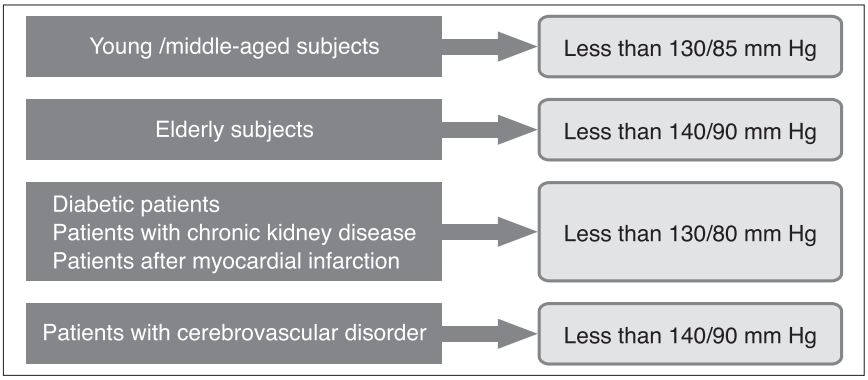
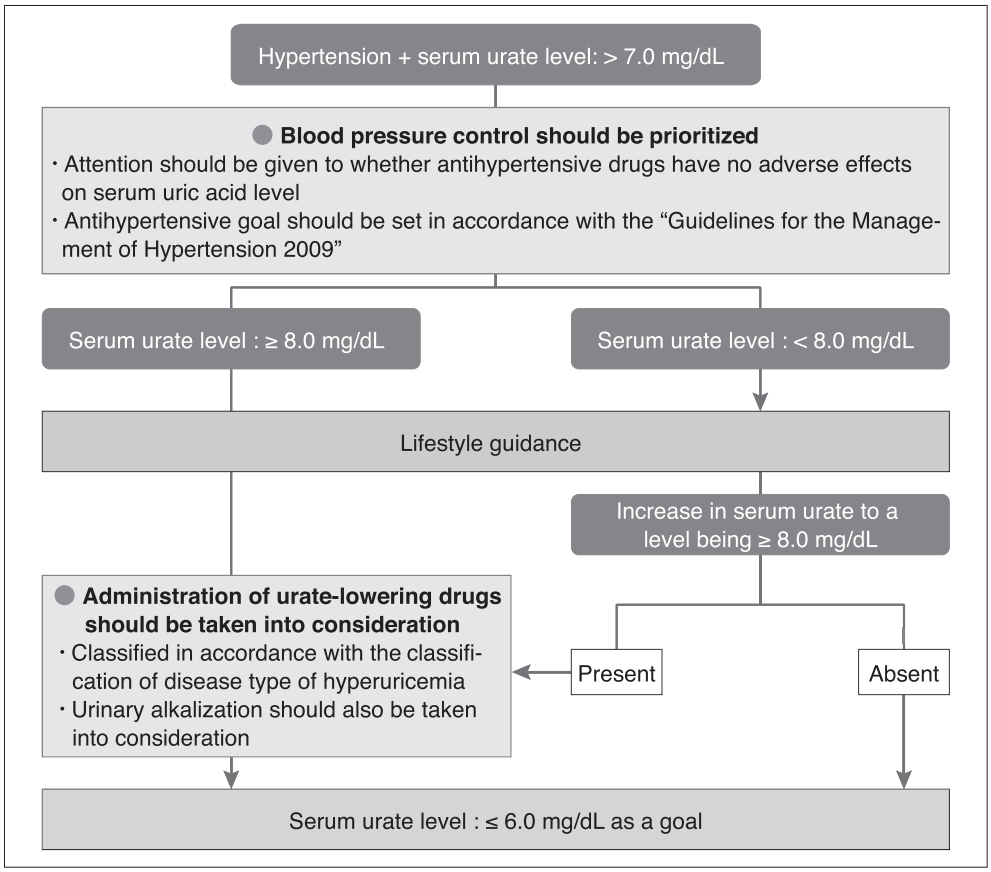


Table 5. Impacts of Antihypertensive Drugs on Serum Urate Level

	Impact on serum urate level
lLosartan potassium	Decreased
Other ARB	Unchanged
ACE inhibitors	Decreased or unchanged
Calcium antagonists	Decreased or unchanged
α-Methyldopa	Unchanged
α_1-Blockers	Decreased or unchanged
β-Blockers	Increased
α, β-Blockers	Increased
Loop diuretics	Increased
Thiazide antihypertensive diuretics	Increased
ARB-thiazide antihypertensive diuretics combination	Increased or unchanged

ARB : angiotensin II receptor blockers, ACE : angiotensin-converting enzyme

Figure 4. Therapeutic Strategy for Hyperuricemia Patients Complicated with Hypertension



3-3-4 Dyslipidemia

• Statements

1. Along with treatment of hyperuricemia, dyslipidemia, a causative factor of atherosclerotic diseases, is also treated, aiming at alleviation of atherosclerotic diseases. Evidence level 1b Consensus level 1 Recommendation level A

2. Diagnosis should be made according to the diagnostic standards proposed by the "Guidelines for Prevention of Atherosclerotic Diseases (2007)." Namely, hyper-LDL-cholesterolemia (LDL-cholesterol 140 mg/dL), hypo-HDL-cholesterolemia (HDL-cholesterol <40 mg/dL), or hypertriglyceridemia (triglyceride 150 mg/dL) is diagnosed as dyslipidemia. Evidence level 1b Consensus level 1 Recommendation level A

3. Treatment of dyslipidemia complicated by hyperuricemia/gout should be carried out according to the "Guidelines for Prevention of Atherosclerotic Diseases (version 2007)." Evidence level 1b Consensus level 1 Recommendation level A

4. Among drugs for treating dyslipidemia, some may have impacts on serum urate level; therefore, this should be taken into consideration. Particularly, fenofibrate is a drug that is effective for hypertriglyceridemia complicated by hyperuricemia, particularly that of the uric acid excretion–decreased type. Evidence level 3 Consensus level 1 Recommendation level A

Although uric acid is strongly suspected of being an independent risk factor for atherosclerotic diseases, this has not been clearly proven; therefore, dyslipidemia noted in patients with hyperuricemia/gout should be treated according to the "Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (2007)" [70] regardless of urate level. Hypertriglyceridemia, hypo-HDL-cholesterolemia, and high lipoprotein (a) [Lp(a)] [71)72)] level associated with coronary arterial diseases are found in many cases of patients with hyperuricemia/gout[73)74)]. Thus, the importance of the treatment of dyslipidemia in patients with hyperuricemia/gout complicated by such pathologic conditions has been suggested.

3-3-5 Metabolic syndrome

・ Statements

1. The ultimate goals of the therapy for metabolic syndrome are the prevention of the onset of the syndrome and inhibition of the progress of its clinical outcomes, namely, atherosclerotic diseases or type 2 diabetes mellitus. Evidence level no judgment Consensus level 1 Recommendation level A

2. Dietary therapy or exercise therapy as well as improvements in lifestyle, such as discontinuation of smoking, are the primary therapies. Evidence level 1b Consensus level 1 Recommendation level A

3. The various pathologic conditions, including hyperuricemia, associated with metabolic syndrome are alleviated by dietary therapy or exercise therapy; in particular, greater improvement may be observed if the body weight is reduced by stringently following both therapies. Evidence level 1b Consensus level 1 Recommendation level A

4. If the improvement is poor or if adequate improvement cannot be achieved by only improvements in lifestyle, drug therapy for individual complications can be employed. Such a drug therapy should be adopted while taking into consideration its impact on uric acid metabolism. Evidence level 4 Consensus level 1 Recommendation level C

Although serum urate level is not included in the diagnostic criteria for metabolic syndrome, the results of many studies have shown that hyperuricemia and gout are often observed in patients with metabolic syndrome[75)-81)]. Therefore, in cases of hyperuricemia/gout, the presence or absence of metabolic syndrome should be examined, and the onset and progress of atherosclerotic diseases and type 2 diabetes mellitus should be prevented by management of the serum urate level as well as obesity, blood pressure, serum lipid level, blood glucose level, etc.

Lifestyle modification is the basis of the therapy for metabolic syndrome, and various pathologic conditions associated with this syndrome were found to be alleviated by dietary therapy or exercise therapy. Weight reduction therapy also reduces the accumulation of visceral fat and alleviates insulin resistance and high serum urate levels[82)]. Concomitant with weight reduction, uric acid clearance also increased[83)].

For patients who have undergone general therapy for hyperuricemia and have developed complications of metabolic syndrome, drug therapy involves administration of urate-lowering drugs according to the type of abnormal urate metabolism, presence or absence of urinary calculus, and renal disorders. Since the incidence of complications of urinary calculus is high in cases of metabolic syndrome[84)], calculus formation should be prevented by maintaining sufficient fluid intake or by administering urinary alkalinizers etc.

3-3-6 Secondary hyperuricemia/gout

• Statements

1. The treatment method should be adjusted depending on the progression and regression of the underlying diseases. Evidence level 2b Consensus level 1 Recommendation level B

2. Acute uric acid nephropathy and tumor lysis syndrome are emergency (usually oncologic), for which appropriate treatment can avoid fatal outcomes. Evidence level 1b Consensus level 1 Recommendation level A

3. The therapy for combined-type secondary hyperuricemia should be administered in accordance with that for primary hyperuricemia by considering the characteristics of the uric acid-overproduction type and the uric acid-underexcretion type hyperuricemia. Evidence level 3 Consensus level 2 Recommendation level C

4. Benzbromarone, a uricosuric drug, is the first-choice drug for the treatment of uric acid-underexcretion type of hyperuricemia. However, since patients with decreased renal function require concomitant use or monotherapy with allopurinol (an inhibitor of uric acid production), the dose of allopurinol should be reduced depending on the renal function. Evidence level 3 Consensus level 2 Recommendation level C

Treatment of the underlying diseases and discontinuation/dose reduction of the causative drugs are the most important steps in the management of secondary hyperuricemia/gout. Therefore, the identification of underlying diseases/pathologic conditions by diagnostic interviews, physical examinations, general laboratory findings, etc. is important. However, the improvement of this condition is limited by the nature of the causative disease/drugs in each case.

Therapeutic options similar to those for primary hyperuricemia should be selected for the treatment of patients with secondary hyperuricemia of the uric acid-overproduction type. One of the therapeutic options is the administration of allopurinol. Although benzbromarone is used as the first-choice drug for treating secondary hyperuricemia of the uric acid-underexcretion type, patients showing progression of renal dysfunction should also receive allopurinol in the same way as in primary cases. Significant decrease in the diastolic blood pressure and serum urate levels were detected after administration of losartan potassium to patients, complicated by hypertension[85], who were treated with cyclosporine after undergoing renal transplantation.

Chapter 4 : Lifestyle Intervention for Patients with Hyperuricemia/Gout

4-1 Lifestyle intervention

・ Statements

1. Hyperuricemia and gout are lifestyle-related diseases. Education and proper guidance aimed at modifying the patient's lifestyle play a crucial role in improving the clinical course of the disease with or without drug therapy. Evidence level 2a Consensus level 1 Recommendation level B

2. Lifestyle modification consists of three parts: nutrition therapy, restriction of alcohol consumption, and recommendation for physical training. Modest weight loss has been shown to reduce serum urate level. Evidence level 2 Consensus level 1 Recommendation level B

3. Nutrition therapy for hyperuricemia/gout includes appropriate consumption of calories and water and reduced consumption of dietary purine and fructose. Evidence level 2a Consensus level 1 Recommendation level B

4. Patients with metabolic syndrome should be advised to perform physical activity to improve their clinical impairments. Evidence level 3 Consensus level 2 Recommendation level C

Lifestyle modification has an important role in improving the clinical course of hyperuricemia/gout based on the viewpoint that they are typical lifestyle-related diseases. The purpose of intervention is to motivate the patients to self-correct their lifestyle by good contact with physicians, and to help them resolve their lifestyle issues.

[1] Nutrition therapy

It is impossible to take low-purine diets every day. However, patients should be advised to refrain from high-purine diets as far as possible. The total amount of urine intake should not exceed 400 mg a day.

The key point of diet therapy for hyperuricemia/gout is the switch from a purine-restricted diet to a calorie-restricted diet. Especially for hyperuricemia/gout patients with a high tendency to gain weight, restriction of energy intake should be strictly implemented following treatment of diabetes. A high-carbohydrate diet is unfavorable for increasing insulin resistance. Active intake of dairy products is recommended because they decrease the serum urate level and reduce the risk of gout[86)87)]. Excessive consumption of sucrose and fructose should be avoided[88)89)].

[2] Restriction of alcohol consumption

Since alcohol metabolism increases serum urate level irrespective of the body's purine content, excessive consumption of all types of alcoholic beverages should be strictly avoided. Beer, in particular, is a high-energy drink, and owing to its ethanol equivalent besides its high purine content, weight gain should be closely monitored. To maintain its effects on serum urate level at a minimum, daily consumption of alcohol should not exceed approximately 180 mL of sake, 500 mL of beer, or 60 mL of whisky.

[3] Recommendation of physical training

Excessive exercise and anaerobic activities should be avoided, because they may result in an increase in serum urate level. To achieve the appropriate body weight (BMI < 25), modest physical training should be limited to3 times a week. Aerobic exercise, on the other hand, has no effect on serum urate level, and it improves various pathological conditions of metabolic syndrome.

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