Essence of the Revised Guideline for the Management of Hyperuricemia and Gout

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Abstract

Hyperuricemia and gout are common diseases that can be treated by general and family physicians, but with the wide range of diagnosis and treatment departments that treat them, these are diseases for which guidelines are demonstrably useful. Published in 2002 by the Japanese Society of Gout and Nucleic Acid Metabolism in 2002, *the Guideline for the Management of Hyperuricemia and Gout* was subsequently revised, and in January 2010 *the Revised Guideline for the Management of Hyperuricemia and Gout* was published. While maintaining the spirit of the original guideline, the revised guideline not only fulfills the prerequisites required for formulating the current guideline but also incorporates new approaches such as the quantification of consensus levels. In addition to emphasizing that hyperuricemia has the duel aspects of being a urate deposition disease and a disease associated with lifestyle diseases, as well as the fact that all hyperuricemia patients require correction of lifestyle habits related to obesity, hypertension, and metabolic syndrome, the revised guideline covers the current evidence in detail. It is the author's sincere hope that this guideline will be utilized effectively in daily medical practice in this field.

Key words Uric acid, Recommendation level, Evidence, Consensus

Introduction

Hyperuricemia and gout are common diseases that can as a general rule be treated by general and family physicians. However, there is a wide variety of diagnosis and treatment departments that treat hyperuricemia and gout. For example, if a patient is told in a health checkup that their serum urate level is high, they see an internist; if the patient has arthritis, they see an orthopedic surgeon or rheumatologist; and if the patient has urinary lithiasis, they see an urologist. Furthermore, there are also many myths surrounding hyperuricemia and gout, with not only patients but physicians holding misconceptions in many cases. For these reasons, it can be said that these are diseases for which guidelines are demonstrably useful.

Background to the Publication of *the Revised Guideline for the Management of Hyperuricemia and Gout*

In 2000 the Japanese Society of Gout and Nucleic Acid Metabolism established the Guideline for the Management of Hyperuricemia and Gout Drafting Committee, and in 2002 published *the Guideline for the Management of Hyperuricemia and Gout*,[1] which covered in detail all of the evidence gathered at that point.

Subsequently, new drugs for treating gout were developed[2] and much evidence was also generated. The European League Against Rheumatism (EULAR) also formulated guidelines regarding gout.[3,4] Such developments increased the necessity for revision of *the Guideline for the*

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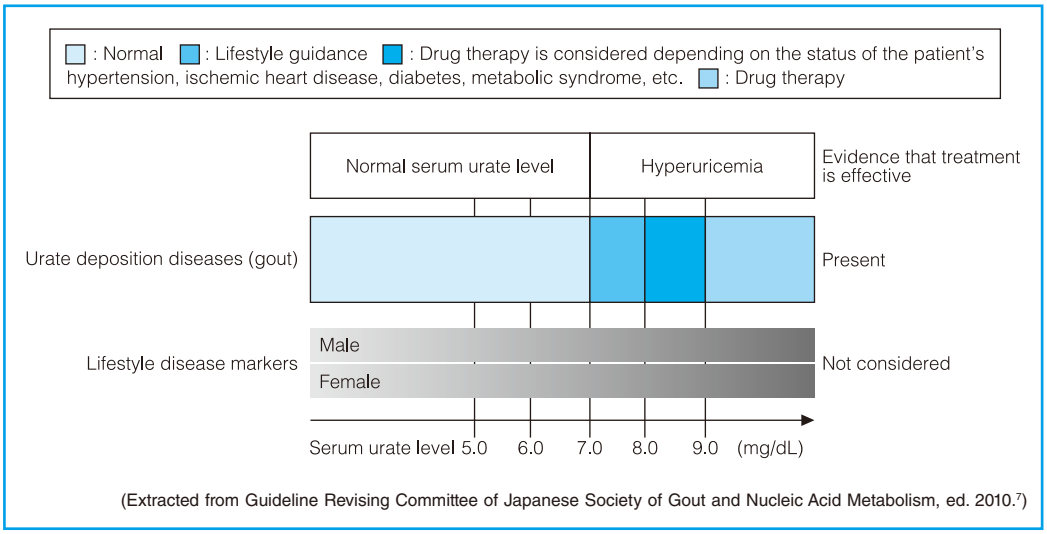

Fig. 1 Definition of hyperuricemia

Management of Hyperuricemia and Gout, and consequently the Japanese Society of Gout and Nucleic Acid Metabolism established a Guideline Revising Committee, which undertook the task of revising the guideline.

In preparing the revised guideline, guideline was formulated based on the Appraisal of Guidelines for Research and Evaluation (AGREE) checklist.[5] In addition, in this revision not only evidence levels but also consensus levels were expressed quantitatively applying the Delphi method,[6] thus incorporating the completely new approach of determining advisability for both evidence and consensus.

The Revised Guideline for the Management of Hyperuricemia and Gout[7] was published in January 2010 and a digest version was posted on the website of the Japanese Society of Gout and Nucleic Acid Metabolism (http://www.tukaku.jp/) on January 1, 2011.

Essence of *the Revised Guideline for the Management of Hyperuricemia and Gout*

The revised guideline provide statements and other information about the risks of hyperuricemia, diagnosis of hyperuricemia and gout, and treatment of hyperuricemia and gout. This paper introduces those of the statements in the guideline that are regarded as being directly applicable in daily medical practice.

Recommendation level regarding epidemiology/diagnosis was categorized as follows:
Recommendation level A: Strong grounds for assertion
Recommendation level B: Grounds for assertion
Recommendation level C: No grounds for assertion.

Recommendation level regarding treatment was categorized as follows:
Recommendation level A: Implementation is strongly advised
Recommendation level B: Implementation is advised
Recommendation level C: Implementation may be considered.

Definition of hyperuricemia (Fig. 1)

(1) Hyperuricemia is the cause of urate deposition diseases (such as gouty arthritis and renal damage) and is defined as serum urate levels of more than 7.0 mg/dL. The disease affects people of both genders and all ages. **Recommendation level B**
(2) Amongst women, the risk of lifestyle diseases increases with rises in serum urate levels, even if serum urate levels are below 7.0 mg/dL. Testing for underlying diseases and lifestyle guidance are carried out, but uric acid-lowering drugs are not indicated. **Recommendation level B**

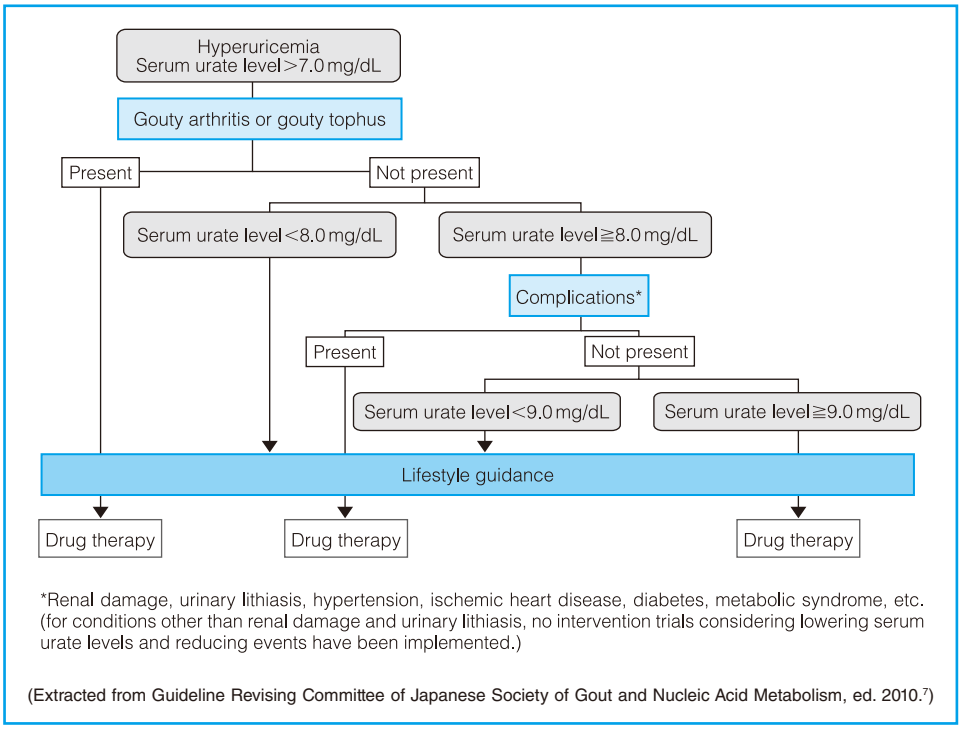

Fig. 2 Hyperuricemia treatment guidelines

The revised guideline is divided into the risks of urate deposition diseases and lifestyle disease markers. For urate deposition diseases, serum urate levels are a risk that is clearly related to disease onset, and treatment of serum urate levels reduces this risk. In contrast, for lifestyle disease markers a correlation between serum urate levels and disease onset has been shown to exist,[8] but no direct relationship has been proven and treatment has not been proven to control disease onset. Accordingly, there is also the possibility that these are simply markers, and expectations are held for future investigation.

Diagnosis of gout

(1) Gouty arthritis is arthritis caused by uric acid crystal deposits inside the joints.
(2) Acute gouty arthritis (gouty attack) appears more commonly in first metatarsophalangeal joint (MTP) and ankle joint. **Recommendation level A**
(3) For diagnosis, identification of characteristic symptoms, previous hyperuricemia, and uric acid crystals in joint fluid is important. **Recommendation level B**
(4) During a gouty attack, serum urate levels are not necessarily high. **Recommendation level B**
(5) In gouty tophus, the uric acid crystals appear granular; a fact that can applied in diagnosis. **Recommendation level A**

In the case that acute arthritis develops in the lower leg(s) of a male patient who has previously been diagnosed with hyperuricemia, there is a high possibility of gout, but differential diagnosis is necessary. Although hyperuricemia is well-known, it must be noted that during the period in which gouty arthritis is developing, serum urate levels are maintained lower than usual in many cases.

Treatment of gouty arthritis/gouty tophus

(1) In the precursory stage of a gouty attack, one tablet (0.5 mg) of colchicine is administered to prevent onset of the attack. In the case that gouty attacks occur frequently, administration of one tablet per day of colchicine ("colchicines cover") is effective. **Recommen-**

dation level B
(2) In the advanced stage of a gouty attack, non-steroid anti-inflammatory drugs (NSAID) are effective, but are administered for short periods only in comparatively large doses in order to soothe the inflammation (NSAID pulse therapy). Care must be taken with regard to the occurrence of side-effects. **Recommendation level B**
(3) In cases where NSAID cannot be used, NSAID administration is ineffective, or the patient experiences multiple occurrences of arthritis, adrenocortical steroids are administered orally. **Recommendation level A**
(4) Since fluctuating serum urate levels at the time of a gouty attack are known to exacerbate onset of the attack in many cases, as a general rule uric acid-lowering drugs are not administered during the attack. **Recommendation level B**
(5) Although extraction is also considered as a treatment for gouty tophus, drug therapy is also required in cases where surgery is performed. **Recommendation level B**

Colchicine is only effective in the precursory stage of a gouty attack; its effectiveness is markedly reduced after arthritis develops. The main treatment method for gouty arthritis is NSAID. Since fluctuating serum urate levels at the time of a gouty attack are known to exacerbate onset of the attack in many cases, administration of uric acid-lowering drugs must not commence administered during the attack. However, this rule does not apply in cases where the patient is already taking uric acid-lowering drugs on a regular basis.

Treatment of hyperuricemia (Fig. 2)

(1) What is most important in the treatment of hyperuricemia is the improvement of lifestyle habits that are related to the development of hyperuricemia and which also easily lead to the development of prognosis-related complications such as obesity, hypertension, and lipid metabolism abnormalities. **Recommendation level A**
(2) Drug therapy is indicated in cases where gouty arthritis occurs repeatedly or gouty tophus is diagnosed, and maintenance of serum urate levels of 6.0 mg/dL or lower is desirable. **Recommendation level A**
(3) Drug therapy for asymptomatic hyperuricemia is implemented when serum urate levels are 8.0 mg/dL or higher as a general indicator, but should be undertaken with caution. **Recommendation level C**

Lifestyle guidance is necessary for all hyperuricemia patients. In addition, administration of uric acid-lowering drugs is begun and continued as necessary. In such cases, serum urate levels are strictly controlled to remain at 6.0 mg/dL or lower.

There is scant evidence regarding treatment for asymptomatic hyperuricemia and consensus is also insufficient. First of all, patients undergo lifestyle guidance, and then if serum urate levels remain high, drug therapy is considered.

Treatment of hyperuricemia/gout with concomitant renal damage

(1) In cases of hyperuricemia/gout complicated by concomitant renal damage or urinary lithiasis, allopurinol is administered to lower uric acid levels. In addition, in cases complicated by renal damage, administration of allopurinol and benzbromarone in small dosages is effective. **Recommendation level B**
(2) As renal function declines, it is necessary to reduce the allopurinol dosage used. **Recommendation level B**
(3) Treatment of hyperuricemia using allopurinol is helpful in maintaining renal function in chronic kidney disease (CKD) patients. **Recommendation level B**
(4) Losartan potassium is helpful in controlling hypertension/hyperuricemia in renal transplant patients undergoing cyclosporine therapy. **Recommendation level A**
(5) Uricosuric drugs are highly useful in controlling post-renal transplant hyperuricemia following a renal transplant. **Recommendation level B**
(6) Hyperphosphatemia treatment with sevelamer hydrochloride—used with maintenance hemodialysis patients—also prevents/reduces hyperuricemia. **Recommendation level B**

Since the effectiveness of uricosuric drugs declines in cases where the patient has moderate to high renal damage, allopurinol is the drug of

first choice, but care is necessary as allopurinol is a renal excretory and can cause serious side-effects. Hyperuricemia treatment using allopurinol is gaining attention due to its usefulness in maintaining renal function in CKD patients.

Treatment of hyperuricemia/gout with concomitant urinary lithiasis

(1) Guidance concerning water intake aims to ensure that patients drink 2,000 mL/day of water or more. **Recommendation level B**
(2) Allopurinol is the drug of first choice for the treatment of hyperuricemia complicated by concomitant urinary lithiasis. **Recommendation level B**
(3) Because uricosuric drugs stimulate the formation of urate stones, as a general rule they are not used in the treatment of hyperuricemia cases complicated by concomitant urinary lithiasis. **Recommendation level B**
(4) Using mainly citric acid formulations, the aim of urine alkalinization is to maintain urine ph between 6.0 and 7.0. Diet therapy, such as purine intake limitations, also needs to be implemented concurrently. **Recommendation level B**
(5) Allopurinol and urine alkalinization drugs are effective in preventing the reoccurrence of calcium oxalate stones associated with hyperuricosuria. **Recommendation level A**
(6) The main treatment for urate stones is extracorporeal shock wave lithotripsy (ESWL), but stone dissolution therapy using urine alkalinization drugs or allopurinol is also an option. **Recommendation level B**

Amongst hyperuricemia/gout patients, there is a high frequency of urinary lithiasis complications, and attention should be paid to urinary tract management. Drinking water is especially important and has the effect of preventing increases in serum urate levels due to dehydration.

Treatment of hyperuricemia/gout with concomitant hypertension

(1) For hyperuricemia patients with hypertension complications, first of all lifestyle guidance is carried out with the aim of "avoiding risks to organs overall" by simultaneously improving lifestyle habits related to the onset of hyperuricemia. **Recommendation level B**
(2) Drug therapy prioritizes blood pressure management, and it is desirable to give priority as far as possible to the use of antihypertensive drugs that do not negatively impact uric acid metabolism. **Recommendation level B**
(3) Even when lifestyle guidance and antihypertensive drugs preferable for uric acid metabolism are used, commencing administration of uric acid-lowering drugs is considered in cases where serum urate levels are 8.0 mg/dL or higher. It is desirable to maintain serum urate levels during treatment to 6.0 mg/dL or lower. **Recommendation level C**
(4) Selection of uric acid-lowering drugs is made based on disease pattern classification, and therapeutic agents and dosages are carefully decided based on the degree of renal damage and presence/absence of hepatic damage. In addition, urine pH is measured and concomitant use of urine alkalinization drugs is also considered. **Recommendation level C**

Hypertension is a highly frequent complication for patients with hyperuricemia/gout, and appropriate management from an early stage is necessary due to the effect on long-term prognosis. Although some antihypertensive drugs raise serum urate levels, losartan potassium, captopril, and enalapril are effective in treating hyperuricemia/gout complicated by hypertension because of their combined hypotensive and uricosuric effects.

Treatment of hyperuricemia/gout with concomitant hyperlipidemia

(1) In addition to treating hyperuricemia, therapy also aims to treat hyperlipidemia—which is a factor in arteriosclerotic disease—and alleviate the arteriosclerotic disease. **Recommendation level A**
(2) Diagnosis is made in accordance with the diagnostic criteria stipulated in *the Arteriosclerotic Disease Prevention Guidelines* (2007). That is, a diagnosis of hyperlipidemia is made when the patient has LDL-hypercholesterolemia (LDL-cholesterol≧140 mg/dL), HDL-hypocholesterolaemia (HDL-cholesterol <40 mg/dL), or hypertriglyceridemia (triglycerides≧150 mg/dL). **Recommendation level A**
(3) Treatment of hyperlipidemia complicating

hyperuricemia/gout is carried out in accordance with *the Arteriosclerotic Disease Prevention Guidelines* (2007). **Recommendation level A**
(4) Some drugs used to treat hyperlipidemia also have an effect on serum urate levels, and so these are considered. In particular, fenofibrate is an effective medicinal agent in cases complicated by hypertriglyceridemia and hyperuricemia, especially hyperuricemia causing a decreased uricosuric effect. **Recommendation level A**

Hyperlipidemia is a highly frequent complication for patients with hyperuricemia/gout, and appropriate management from an early stage is necessary due to the effect on long-term prognosis. Because fenofibrate has a uricosuric effect, it is useful in the treatment of patients with hyperuricemia/gout complicated by hyperlipidemia.

Lifestyle guidance for patients with hyperuricemia/gout

(1) Hyperuricemia and gout are representative lifestyle diseases. Lifestyle guidance is a non-drug therapy aimed at correcting lifestyle habits and plays an important role in treatment regardless of whether or not drug therapy is implemented. **Recommendation level B**
(2) Lifestyle guidance for hyperuricemia/gout patients centers on diet therapy, limitation of alcohol intake, and encouragement of exercise, and reducing obesity is expected to have the effect of lowering serum urate levels. **Recommendation level B**
(3) In diet therapy, patients are advised about correct energy intake, limitations on excessive purine and fructose intake, and drinking sufficient water. **Recommendation level B**
(4) Physical activity (exercise) can be encouraged to improve various pathological conditions of metabolic syndrome. **Recommendation level C**

In diet therapy for hyperuricemia/gout patients, if we consider obesity and metabolic syndrome, which complicate hyperuricemia/gout with a high frequency, rather than focusing on purine limitation, quantitative limitation is more important than qualitative limitation. First of all, patients receive guidance on how to reduce total energy intake amounts. If a patient's weight decreases, their serum urate levels will decrease. Moreover, in cases where lifestyle guidance is only minimally successful and drug therapy is implemented, correct lifestyle habits should be continued.

Conclusion

The Revised Guideline for the Management of Hyperuricemia and Gout—which, in addition to continuing the spirit of the original guideline, fulfills the prerequisites required for formulating the current guideline as well as incorporates new approaches such as quantifying consensus levels—was released in January 2010. It is the author's sincere hope that this guideline will be utilized effectively in daily medical practice in this field.

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