experienced gouty attacks; however, quiescence of arthritis should not mean that therapy should be considered complete.

Therapy of Hyperuricemia

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, and 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, and 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, and Recommendation level C.

The elimination of urate deposited in body tissues due to sustained hyperuricemia and avoidance of urate deposition diseases, such as gouty arthritis, renal disorder, and so on, will become narrowly defined therapeutic goals for hyperuricemia. In addition, improvement in the prognosis for patients with hyperuricemia/gout with a high risk of cardiovascular events through improvements in lifestyle and attention to complications, such as obesity, hypertension, glucose intolerance, dyslipidemia, and so on, will become the ultimate therapeutic goal.

For the prevention of gouty arthritis recurrence by the removal of urate crystals through dissolution, serum urate should be maintained at a level of not more than 6.0 mg/dL. In the United States, where there are negative opinions regarding drug therapy for asymptomatic hyperuricemia without gouty arthritis or without gouty tophi, but with the serum urate level constantly exceeding 7.0 mg/dL, the number of patients with severe gout is greater than that in Japan; therefore, the treatment of asymptomatic hyperuricemia patients with a serum urate level higher than a certain concentration should be targeted for the prevention of gouty arthritis. Results of

a cohort study of 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 in those with a lower serum urate level. Although this was a small-scale prospective clinical study, the results suggested that a decrease in renal function can be suppressed by administration of allopurinol in patients with renal failure.[8] Drug therapy aimed at renal protection with due attention to adverse drug reactions is also considered necessary for patients with serum urate higher than a certain level. Accumulated uric acid in the body will be difficult to dissolve by lifestyle adjustment only in patients with 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 6.0 mg/dL.[9,10] For patients with a history of or with existing urinary calculus, the suppression of urinary uric acid excretion with allopurinol is necessary.

For asymptomatic hyperuricemia, a serum urate level of not less than 8.0 mg/dL is considered a criterion for the introduction of drug therapy in cases with 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, the decision to initiate drug therapy should be based on current circumstances. Evidence obtained by intervention studies is currently limited, although observational studies have proven that the risk of cardiovascular disorders is heightened by high levels of uric acid in patients with such complications (Figure 2).

Therapy of Hyperuricemia Without Gouty Arthritis/Gouty Tophus (Asymptomatic Hyperuricemia)

Statements:

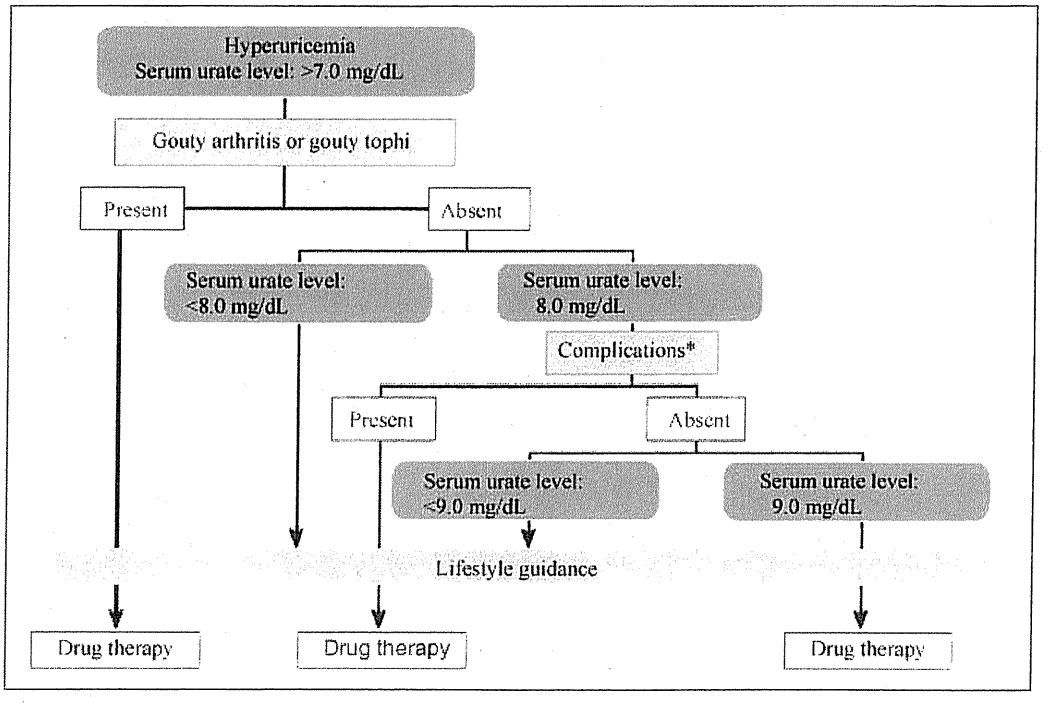
1) The serum urate level should be reduced in the asymptomatic stage of hyperuricemia to prevent the onset of gouty arthritis, gouty tophus, renal disorder, and urinary calculus, because hyperuricemia underlies these complications—Evidence level 3, Consensus level 2, and Recommendation level B.
2) Information and appropriate guidance considering 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, purines, fructose, sucrose, and calories, as well as to refrain from extreme exercises—Evidence level 3, Consensus level 1, and Advisability 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 the serum urate level reaches 8.0 mg/dL or more in cases with complications, such as urinary calculus, renal disease, hypertension, etc.—Evidence level 3, Consensus level 2, and Recommendation level B.

Hyperuricemia without clinical symptoms, such as gouty attack (acute gouty arthritis), gouty tophus, renal disorder, etc., is called "asymptomatic hyperuricemia."[11] 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.

There is a major difference in the management of asymptomatic hyperuricemia outlined in this Japanese guideline and that in Europe. In the



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

FIGURE 2 Guidelines for therapy of hyperuricemia.

Japanese guideline, it is stated that asymptomatic hyperuricemia under certain conditions should be treated if lifestyle modification fails; on the other hand, in the United States and Europe, it is the general consensus that asymptomatic hyperuricemia should not be treated with drugs. Even if there is no large-scale comparative study to explore the beneficial effect of earlier intervention for asymptomatic hyperuricemia, it is noteworthy that the incidence of refractory gout and/or gouty tophi is much lower in Japan compared with that in Europe and the United States. Further study should be conducted to see whether this active management of asymptomatic hyperuricemia proposed in the Japanese guideline is beneficial for patients with hyperuricemia.

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 anti-inflammatory drugs (NSAIDs) or NSAID pulse therapy, but not by urate-lowering drugs—Evidence level 2b, Consensus level 1, and Advisability level A.
2) The serum urate level should be reduced gradually to 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, and Recommendation level B.
3) Medication with urate-lowering drugs should be started at a low dose (benzbromarone: 12.5 mg, allopurinol: 50 mg) about 2 weeks after remission of gouty arthritis—Evidence level 2b, Consensus level 2, and Recommendation level B.
4) Concomitant administration of low-dose colchicine is recommended at an early stage after the start of administration of urate-lowering drugs for the prevention of gouty arthritis—Evidence level 1b, Consensus level 2, and Recommendation level B.
5) When gouty arthritis occurs after the administration of urate-lowering drugs at an appropriate dose, the 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, and Recommendation level B.

Gouty attack is exacerbated by the change in serum urate level during gouty arthritis. Gouty arthritis often results from a drastic reduction in the serum urate level after the initiation of urate-lowering drugs.[12] Moreover,

hyperuricaciduria is caused by a drastic increase in uric acid excretion induced by uricosuric drugs, causing uric acid calculus and renal disorder. Accordingly, attention should be given to the means of administration of urate-lowering drugs.

After NSAID pulse therapy, remission of the attack should be awaited before the 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; drug administration should be started at a low dose, and then the dose should be gradually increased. 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). 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 the start of administration.[5] 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. Thus, drug therapy over a period of 3–6 months is used to decrease the serum urate level gradually to not more than 6.0 mg/dL.

In addition, when gouty arthritis results from the 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 the serum urate level does not reach the intended range, the dose of urate-lowering drugs should be increased gradually 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. Thereafter, the dose of urate-lowering drugs should be continued so that the serum urate level is maintained at not more than 6.0 mg/dL.[9,10]

Therapy in Patients with Complications/Concurrent Diseases

Statements for the management of patients with renal disorder, urinary stones, hypertension/cardiovascular diseases, dyslipidemia, and metabolic syndrome are also listed in this guideline; however, because of the space limitations of this proceeding, these statements are not shown.

Lifestyle Intervention for Patients with Hyperuricemia/Gout

Statements:

1) Hyperuricemia and gout are lifestyle-related diseases. Education and proper guidance aimed at modifying the patients' lifestyle play a crucial role in improving the clinical course of the disease with or without drug therapy—Evidence level 2a, Consensus level 1, and 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 the serum urate level—Evidence level 2a, Consensus level 1, and Recommendation level B.
3) Nutrition therapy for hyperuricemia/gout includes appropriate consumption of calories and water and reduced consumption of dietary purines and fructose—Evidence level 2a, Consensus level 1, and 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, and Recommendation level C.

Lifestyle modification has an important role in improving the clinical course of hyperuricemia/gout based on the viewpoint that the diseases are typical lifestyle-related diseases.[13–16] The purposes of intervention are to motivate patients to self-correct their lifestyle by good contact with physicians and to help them resolve their lifestyle issues.

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