GUIDELINES FOR THE TREATMENT OF DIABETIC NEPHROPATHY*

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Abstract: Diabetic nephropathy is the most devastating complication of diabetes and is now the leading cause of end-stage renal failure in many developed countries. How to halt the steady increase in the number of diabetic patients with end-stage renal failure is a pressing issue in Japan. The most important point for the management of diabetic nephropathy is detecting it as early as possible by regular screening for urinary protein or albumin. Microalbuminuria is a reasonably reliable marker for diabetic nephropathy in the early stage, and the blood glucose and blood pressure levels of microalbuminuric patients should be strictly controlled. Once it progresses to overt proteinuria, glycemic control does not appear to be as effective as in the microalbuminuric stage. Blood pressure control seems to be the main therapeutic approach in those proteinuric patients. ACE inhibitors are the antihypertensive agents of first choice in type 1 diabetics. When the disease has progressed to the stage of chronic renal failure, a low-protein diet should be prescribed to prevent the progression of diabetic nephropathy. In conclusion, early detection of diabetic nephropathy and treatment appropriate to each stage is the best strategy for the management of diabetic nephropathy.

Key words: Diabetic nephropathy; Microalbuminuria; Glycemic control; Blood pressure control; Low-protein diet

Introduction

The number of patients who develop end-stage renal failure and are placed on dialysis therapy as a result of diabetic nephropathy has been steadily increasing. In 1998 it finally exceeded 10,000 patients in Japan, and having replaced glomerulonephritis, it now occupies first place and represents an alarming state of affairs.

According to a survey study of the Ministry of Health and Welfare of Japan there are approximately 30,000 to 50,000 patients with diabetic nephropathy in the stage of renal failure one step before the end-stage (plasma creatinine 2 mg/dl or more), and it has been estimated on the basis of the results of other surveys that there may be as many as 800,000 to 1,000,000 patients with diabetic nephropathy who manifest proteinuria, and it seems that the number of patients who may

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progress to serious stage will probably continue to grow in the future.

How to deal with this continually increasing kidney disease is a major medical problem, and it could hardly be claimed that an adequate system had been put in place to eradicate diabetic nephropathy in our country. In the meantime, the most important measure to deal with this problem would seem to be to have all medical practitioners engaged in the care of nephropathic patients sufficiently understand the gravity of the situation facing us and provide care to their patients with a thorough knowledge of just what appropriate treatment is.

Below I will explain the treatment guidelines based on a rough classification of the stages of nephropathy.

**Treatment of Incipient Nephropathy**

The stage of nephropathy in which microalbuminuria is observed is referred to as “incipient nephropathy” (stage 2). The most important point is to make every effort to diagnose nephropathy in the incipient stage, and that means regular quantitative urinary albumin testing of all diabetics.

It is not necessary to repeat urine albumin testing monthly in diabetics who have never manifested microalbuminuria (stage 1), once or twice a year is sufficient. More frequent testing is required, however, in incipient nephropathy patients who have already been found to have microalbuminuria, because an increase in urinary albumin excretion is often the sole clinical sign in this stage, and changes in its excretion serve as an indicator for evaluating the pros and cons of treatment. The possibility that measurement of urinary type IV collagen excretion might be useful in the diagnosis of incipient nephropathy and in judging the appropriateness of treatment has also been pointed out.1)

As regards methods of treating incipient nephropathy, it has been reported that tight glycemic control is effective in preventing progression to overt nephro-
pathy manifested by albuminuria and it is now the basic modality of treatment (Fig. 1). HbA1C values less than 7% or less than 6.5% has been proposed as the target for glycemic control, but some are also of the opinion that the lower the HbA1C level, the better. In any event, it is wise to make an effort to evaluate the success of glycemic control on an individual basis while using shifts in urinary albumin values for reference.

Based on the view that angiotensin-converting enzyme (ACE) inhibitors, which are antihypertensive agents, possess renal protective activity, it has been reported that they might be effective in the treatment of incipient nephropathy, and opinions recommending their fairly aggressive use are seen in European countries. Since their use in hypertensive patients is covered by the Japanese national health insurance, it is all right to try them. Nevertheless, since their efficacy has never been compared with other antihypertensive agents, it would be difficult to recommend using them alone. However, there are numerous opinions supporting their efficacy in the management of hypertension, and it seems that aggressive antihypertensive therapy should be carried out in incipient nephropathy patients who have hypertension. There is a strong opinion that the target blood pressure values of the antihypertensive therapy should be less than 130/85 mmHg.

### Treatment of Overt Nephropathy

Since it is questionable whether glycemic control is effective in overt nephropathy manifested by proteinuria (stage 3), a treatment policy that emphasizes blood pressure control might be a better approach. The fact that the majority of the nephropathy patients in stage 3 have hypertension also supports the importance of blood pressure control.

Of course, it must be remembered to make an effort to consider the effect of glycemic control on other organ dysfunctions, not just nephropathy, and to strive for as favorable glycemic control as possible.

I wonder if the United Kingdom Prospective Diabetes Study (UKPDS) can be said to have demonstrated that blood pressure control is highly useful in preventing the various complications that occur in diabetics. Unfortunately, no significant

### Table 1 Efficacy of Blood Pressure Control in Preventing the Progression of Nephropathy

<table>
<thead>
<tr>
<th>Blood pressure* (mmHg)</th>
<th>Protein-positive patients (%)</th>
<th>Renal failure (Total duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 3</td>
<td>Year 6</td>
</tr>
<tr>
<td>Ordinary treatment group</td>
<td>154/87</td>
<td>18/317</td>
</tr>
<tr>
<td>p value</td>
<td>0.0001</td>
<td>0.073</td>
</tr>
<tr>
<td>Tight blood pressure control group</td>
<td>144/82</td>
<td>20/618</td>
</tr>
</tbody>
</table>

Cited from UKPDS 38 (Reference 4)

* Mean blood pressure value during the observation period
differences were obtained in regard to preventive effect against nephropathy, but that may have been because the number of events was too small, the blood pressure reduction was inadequate, etc.

The mean blood pressure in the tight blood pressure control group in the UKPDS was 144/82 mmHg, and far higher than the systolic blood pressure of less than 130/85 recommended by the American Diabetes Association and the WHO (Table 1). It seems that fairly tight blood pressure control is sought to prevent the progression of overt nephropathy to renal failure. Actually, the extremely strict view that less than 125/75 mmHg is desirable has also been expressed.

Low-protein diet therapy, along with blood pressure control, is cited as a modality of treatment considered to be effective in overt nephropathy. About 1.2 g/kg body weight a day is prescribed in the usual diabetic diet, and the results of several studies have shown that the deterioration of renal function is delayed when protein is restricted to 0.7 g/kg body weight a day or less. However, implementing this level of low-protein diet therapy seems rather difficult, and the Ministry of Health and Welfare's Diabetes Research Group has proposed a slightly milder guideline of 0.8 g/kg body weight a day.

The problem with this treatment is that from the standpoint of evidence-based medicine, which has recently become a topic of considerable discussion, since no results of treatment have been obtained in a multicenter cooperative study, evidence is lacking. In other words, it is viewed with suspicion because it has not been confirmed to be a treatment that yields the same results regardless of the institution where it is conducted. Since this matter should be resolved, a multicenter cooperative study is currently being carried out in Japan, and it is hoped that favorable results will be obtained.

It is also recommended that in addition to making the necessary checks for the differential diagnosis in diabetics who manifest proteinuria, a nephrologist be consulted once.

**Treatment of Renal-failure-stage Nephropathy**

Treatment of renal failure nephropathy (stage 4) that has reached the point of manifesting an abnormally high serum creatinine, generally 2 mg/dl or more, is often difficult. However, since it is at least possible to slow its progression, as great an effort as possible should be made. An effort to develop a close working relationship with a dialysis specialist is also called desirable so that dialysis treatment can be started under the best possible circumstances.

First, it is essential to maintain continuity of blood pressure control. Adverse effects such as hyperkalemia, however, are a problem with ACE inhibitors, and sufficient caution is necessary when using them. Regardless of which antihypertensive agent is used, blood pressure control can rarely be achieved with just one drug, and the physician is often compelled to use a combination of antihypertensive agents, including calcium antagonists, antihypertensive diuretics, etc.

Next, a low-protein diet is considered essential, and there is a report that it is at least definitely effective in lessening the accumulation of nitrogen metabolites in the body and is also useful in maintaining preserved renal function. Protein restric-
tion to about 0.6 g/kg body weight a day is generally considered necessary, and the cooperation of a registered dietitian is indispensable.

There are reports that administration of an erythropoietin preparation for renal anemia is not only useful in maintaining QOL but in maintaining preserved renal function. Please refer to the references in regard to the criteria for placing patients on dialysis.7)

**Conclusion**

The incidence of diabetic nephropathy has been steadily increasing in recent years, and I have explained the modalities of treatment according to the stage of the disease. In regard to incipient nephropathy, I have stated that early diagnosis is necessary and that glycemic control forms the basis of treatment. I have explained in regard to the current approach to the treatment of the overt nephropathy, that blood pressure control is necessary and that in recent years tighter blood pressure control has been called for.

I mentioned the management of the stage of renal failure, which is the stage before end-stage renal failure. Trying nephropathy therapy according to the stage of the disease in this way is indicated in all nephropathic patients, and I hope the number of patients who progress to serious renal dysfunction will decline.

**REFERENCES**


