Hypertension and the Development of Complications in Patients With Non-Insulin Dependent Diabetes Mellitus in Japan

Ryuichi Kikkawa,1 Shin-ichi Araki, Masakazu Haneda, Nobuyuki Kajiwara, Hideki Hidaka, and Yukio Shigeta

In this review, we examine the effect of hypertension on the development of diabetic nephropathy and CAD in Japanese patients with NIDDM. The different effects of hypertension on the development of these complications among Japanese and white populations with diabetes are emphasized.

ABSTRACT
Hypertension is a very frequent condition in individuals with non-insulin dependent diabetes mellitus (NIDDM) in Japan and has affected the occurrence of late diabetic complications, especially stroke and nephropathy. Despite similar characteristics of hypertension among Japanese and white patients, the effect of hypertension on the development of coronary artery disease (CAD) in these two populations is strikingly different. In white NIDDM patients, hypertension is one of the major risk factors for the development of CAD. However, CAD is an infrequent complication in NIDDM patients in Japan, even though they have hypertension, lipid abnormalities, and renal complications.

Key Words: Non-insulin dependent diabetes mellitus, hypertension, epidemiology, macroangiopathy, nephropathy

Epidemiologic studies carried out in the Japanese population during the last 10 yr have documented a high incidence and prevalence of non-insulin dependent diabetes (NIDDM) (1–3). Approximately 10% of the population aged 40 yr or more is estimated to have NIDDM (1,2).

Essential hypertension is another prevalent disease in the adult Japanese population, and it is a known risk factor for the development of stroke, coronary artery disease (CAD), and renal failure. Because diabetes mellitus, on its own, increases the risk of these complications, Japanese who suffer from both NIDDM and hypertension may be at particularly high risk for the development of cardiovascular complications.

HYPERTENSION IN THE GENERAL JAPANESE POPULATION

Blood pressure levels—both systolic and diastolic—were shown to decline between 1956 and 1980 in Japan (4); however, the prevalence of hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg) is still very high: 27.7% in men and 22.5% in women aged 30 yr and older (5). The prevalence of hypertension increased with age, reaching 54.8% in individuals aged 70 yr or more (Table 1). These rates are higher than in the U.S. white population. For example, in a random sample of the civilian U.S. population examined from 1976 to 1980, the prevalence of hypertension increased with age from 10.4% in the 34 to 45 age group to 44% in the 65 to 74 age category (6).

It is not clear what factors account for the high prevalence of essential hypertension in Japan. High salt intake has been postulated to be one of the major factors responsible for the high prevalence of hypertension in the Japanese population (7). Obesity is considered to be another major risk factor. Although the degree of obesity assessed by body mass index (BMI) appears quite modest (BMI range, 21 to 24 kg/m2) compared with that in the white U.S. population (BMI range, 23 to 27 kg/m2), the prevalence of hypertension is significantly higher in obese than nonobese Japanese individuals (8,9).

Diminished insulin sensitivity has recently been found to be associated with essential hypertension in many studies in white patients (10–12). A similar association was found in a group of Japanese subjects with essential hypertension (13). In the study of nonobese, normoglycemic, and normolipidemic patients, Hirose et al. (13) found that the presence of hypertension was associated with decreased insulin sensitivity. Although further studies are needed to confirm this observation, one may hypothesize that, similar to that in as white patients, hypertension in...
Hypertension was diagnosed if diastolic blood pressure was ≥95 mm Hg and/or systolic blood pressure was ≥160 mm Hg and/or treated with antihypertensive drugs. The survey was conducted in November 1980, and is adapted from reference 5.

Japanese individuals is associated with diminished insulin sensitivity and hyperinsulinemia. As in white patients (14), genetic susceptibility seems to be another important factor contributing to the development of hypertension in the Japanese population (15). The Na/Li countertransport activity in red blood cells is significantly increased in normotensive and hypertensive individuals with family histories of hypertension when compared with that in individuals without a family history of hypertension (16). The low level of intracellular magnesium may also be related to the predisposition of essential hypertension (17). Uneda et al. showed that the normotensive children of hypertensive parents had an increase in renal vascular resistance when compared with that in normotensive children of normotensive parents (18). The urinary excretion of dopamine was found to be reduced in normotensive individuals with a family history of hypertension when compared with that in those without a family history of hypertension (19).

Considering the above observations, one may hypothesize that the development of essential hypertension in the Japanese population is determined by factors similar to those in white patients. However, the pathomechanisms of essential hypertension are not known yet and we cannot be sure whether exactly the same genetic susceptibilities are involved in the development of essential hypertension in these populations. Among environmental factors, high salt intake and obesity appear to be the main determinants of the development of hypertension in both races.

### OCCURRENCE OF HYPERTENSION IN NIDDM

Hypertension occurs more frequently in diabetic than among nondiabetic white patients (20-22). In the random sample of the U.S. population examined from 1976 to 1978, patients with diabetes had age-adjusted prevalence of hypertension of 33% compared with 15% for nondiabetics (23). The mechanisms responsible for the excess of hypertension in NIDDM in white patients are not clear. Three possibilities may be considered (24). First, NIDDM and hypertension can occur together because they share common risk factors such as obesity and insulin resistance. Second, certain antihypertensive drugs increase insulin resistance, which in turn may increase the risk of the development of NIDDM. Third, the metabolic abnormalities of NIDDM may cause the development of renal complications, which may lead to the development of hypertension.

The association between the development of NIDDM and essential hypertension in Japanese population has not been well studied. In our study in Alto, we have found that the prevalence of hypertension was significantly higher in diabetics than in nondiabetics but only in women (8). In another study in which we examined NIDDM patients who regularly visited our university hospital, the prevalence of hypertension was 30.4% (86 of 283 cases; 171 males and 112 females), with the average age being 58.0 yr. This statistic appears much higher than the 15.3% (196 of 1,279) prevalence rate for hypertension in subjects ages 40 to 64 yr who were examined between 1980 and 1983 in the village adjacent to our hospital. However, comparing the prevalence of hypertension in our hospital population according to age (Table 2) with the prevalence of hypertension in the national sample (Table 1), we did not find any difference.

Hypertension rates among the diabetic population appear to vary widely between countries (25,26). In a multinational study by the World Health Organization (WHO) using standardized examination procedures, a 1.5- to 2-fold difference in the prevalence of hypertension was observed among the diabetic populations of 13 countries. These results, however, did not show that prevalence of hypertension in Japanese diabetics was higher than that in white diabetics.

### HYPERTENSION AND MACROVASCULAR COMPLICATIONS IN NIDDM

Hypertension is the major risk factor for the development of stroke in the general Japanese population.

### TABLE 1. Prevalence of hypertension in the Japanese general population

<table>
<thead>
<tr>
<th>Prevalence (%) by Age Group (yr)</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N = 4,795)</td>
<td>9.5</td>
<td>21.4</td>
<td>32.4</td>
<td>44.6</td>
<td>54.8</td>
</tr>
<tr>
<td>Female (N = 6,102)</td>
<td>3.1</td>
<td>14.7</td>
<td>27.1</td>
<td>41.9</td>
<td>54.8</td>
</tr>
</tbody>
</table>

* Hypertension was diagnosed if diastolic blood pressure was ≥95 mm Hg and/or systolic blood pressure was ≥160 mm Hg and/or treated with antihypertensive drugs. The survey was conducted in November 1980, and is adapted from reference 5.

### TABLE 2. Prevalence of hypertension in the Japanese NIDDM patients

<table>
<thead>
<tr>
<th>Prevalence (%) by Age Group (yr)</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N = 171)</td>
<td>6.7</td>
<td>14.3</td>
<td>23.5</td>
<td>43.5</td>
<td>42.3</td>
</tr>
<tr>
<td>Female (N = 112)</td>
<td>0</td>
<td>14.3</td>
<td>34.4</td>
<td>37.5</td>
<td>42.3</td>
</tr>
</tbody>
</table>

* Hypertension was diagnosed if diastolic blood pressure was ≥95 mm Hg and/or systolic blood pressure was ≥160 mm Hg and/or treated with antihypertensive drugs. R. Kikkawa et al., unpublished data.
Antihypertensive treatment is an effective way of reducing morbidity and mortality due to stroke (27). Contrary to that in white populations, the association between hypertension and the development of CAD is not apparent in Japan (27,28), although some reports have suggested such a relationship (29).

The role of hypertension in the development of macrovascular complications among Japanese patients with NIDDM has been examined only in few studies. Osonoi et al. report that hypertension, although partially associated with proteinuria, was the major correlate of CAD detected by electrocardiogram (ECG) abnormalities in 70 NIDDM patients (30). A similar study by Kawai et al. also showed an association between hypertension and the presence of ECG abnormalities in NIDDM patients (31). It remains to be clarified, however, whether the ECG changes that correlate with hypertension in Japanese NIDDM patients are due to atherosclerotic lesions in coronary arteries. In an autopsy study, it was found that Japanese diabetics had more frequent evidence of CAD and cerebrovascular disease than did nondiabetics (32). Mihara et al. showed that, in NIDDM subjects, the coexistence of hypertension and hyperlipidemia appears to increase the mortality due to CAD and cerebrovascular disease (33).

Despite this evidence that Japanese NIDDM patients might have an increased risk of macrovascular complications in comparison with nondiabetics, very rarely do they die as a result of CAD. The WHO's multinational study of vascular disease in diabetics demonstrated marked variation in mortality among the nine centers participating in that study (34). As shown in Figure 1, the age-adjusted all-cause mortality rate in NIDDM subjects was lowest in Tokyo. This low mortality in the Tokyo sample appears to be due to the near absence of deaths due to CAD. It is important to note here that the NIDDM patients in the Tokyo sample had hypertension and lipid abnormalities as frequently as did NIDDM patients in the centers that had a high CAD mortality rate (25,26,35).

There is no obvious explanation for the infrequent occurrence of CAD in NIDDM patients in Japan. On the other hand, the low risk of CAD in the presence of NIDDM and hypertension in Japanese individuals seems to indicate that these conditions (NIDDM and hypertension) play a restricted role in the development of atherosclerotic lesions in coronary arteries. It is possible that these conditions cannot initiate atherosclerotic lesions, but they can influence the progression of these lesions to clinically manifested CAD once the lesions have been initiated by other factors, as seems to happen frequently in white patient populations (36).

HYPERTENSION AND RENAL COMPLICATIONS IN NIDDM

The WHO's multinational study of vascular disease in diabetics demonstrated a marked variation both

![Figure 1. Age-adjusted all-cause mortality rates in subjects with NIDDM in 10 centers participating in the WHO Multinational Study of Vascular Disease in Diabetics (Adapted from reference 34 with permission from the authors and the publisher). At the beginning of the study, NIDDM subjects were ages 35 to 55 and they were monitored on average for 7 yr. In samples from Arizona and Oklahoma, only American Indians were included.](image-url)
in the prevalence of proteinuria at the beginning of the study and in the mortality due to renal failure during the 7-yr follow-up. Among the nine diabetic populations studied, the prevalence of proteinuria and mortality from renal failure was one of the highest in the Tokyo sample (34,35). At present, there are no apparent explanations for these findings.

Using patients with NIDDM in our hospital, we studied the relationship between hypertension and diabetic nephropathy. As shown in Table 3, the prevalence of overt proteinuria in patients with hypertension was 39.5%, whereas in normotensive patients, it was 14.2%. This difference was highly statistically significant, even after adjustment for confounding factors such as age and BMI. The presence of microalbuminuria (albumin excretion rate > 15 μg/min in 24-h urine), on the other hand, was more prevalent in normotensive than hypertensive patients, but these differences were not significant. One possible interpretation for this finding is that, in the presence of hypertension, patients with microalbuminuria progress more rapidly to overt proteinuria.

A longitudinal observation of a small group of NIDDM patients supports the importance of hypertension in the progression from both the normoalbuminuric to microalbuminuric stage and the microalbuminuric to proteinuric stage (37,38). This progression was frequently observed in patients whose mean blood pressure was over 95 mm Hg compared with below 95 mm Hg (7 of 13 versus 4 of 21; \( P < 0.05 \)). Interestingly, the progression from normoalbuminuria to microalbuminuria (32.4% in 5 yr) and from microalbuminuria to overt proteinuria (33.3% in 5 yr) appears much faster than progressions reported in white patients with NIDDM (39). In white patients, only 10.9% of normoalbuminuric subjects progressed to microalbuminuria during 5 yr of follow-up. These findings are in agreement with a previous report that indicated that Japanese diabetics die of renal complication more frequently than do white diabetics (40).

The above observations suggest that renal complications are more frequent in Japanese than in white NIDDM subjects. Furthermore, hypertension might play a more important role in the development of microalbuminuria and its progression to advanced nephropathy in the former than in the latter NIDDM population. This hypothesis should be examined further in follow-up studies. Similar populations of Japanese and white NIDDM subjects should be monitored, and the onset and progression of diabetic nephropathy should be determined by standardized protocols.

It has been reported that a family history of hypertension, and therefore genetic predisposition to hypertension, may be causally related to the diabetic nephropathy in insulin-dependent diabetes mellitus patients (41). In the analysis of the data from the Table 3, we could not demonstrate an association between a family history of hypertension and the risk of nephropathy (data not shown). These negative findings are in agreement with these from another study of white NIDDM patients that failed to show an association between markers of susceptibility to hypertension and diabetic nephropathy (42). Other genetic factors, however, may be involved in the development of diabetic nephropathy in NIDDM patients (43,44).

### TABLE 3. Clinical characteristics of normotensive and hypertensive NIDDM patients

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative ((N = 197))</td>
<td>Positive ((N = 86))</td>
</tr>
<tr>
<td>Male/Female</td>
<td>121/76</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.9 ± 12.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5 ± 3.1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125.0 ± 14.1</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>71.7 ± 7.8</td>
</tr>
<tr>
<td>Duration of Diabetes (yr)</td>
<td>10.6 ± 7.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1 ± 1.4</td>
</tr>
<tr>
<td>Family History of Hypertension (%)(b)</td>
<td>27.9</td>
</tr>
<tr>
<td>Overt proteinuria (%)(c)</td>
<td>14.2</td>
</tr>
<tr>
<td>Microalbuminuria (%)(d)</td>
<td>23.4</td>
</tr>
</tbody>
</table>

\(a\) Values are mean ± SD; \( P \) value was determined by \( t \)-test or \( \chi^2 \)-test. NS, not significant; BP, blood pressure; HbA1c, hemoglobin A1c. \( b \) Family history of hypertension was positive if hypertension was present in first- and second-degree relatives.\( c \) Overt proteinuria was diagnosed if dipstick-positive proteinuria was persistently present.\( d \) Microalbuminuria was diagnosed if albumin excretion rate was 15 μg/min or more in 24-h urine collection in patients without overt proteinuria (average of two or more urine collections).

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