In this article, some of our findings of epidemiologic and clinical studies on the actual state of insulin resistance in hypertension occurring in Japanese were described. In epidemiologic studies, a high prevalence of concomitant hypertension and impaired glucose tolerance was observed, and a significant positive correlation was found between blood pressure and blood glucose levels, even at a low degree, in two towns, the agricultural districts of Hokkaido. In clinical studies, insulin sensitivity, which was measured as $M$-values by the euglycemic hyperinsulinemic glucose clamp method, was significantly lower in essential hypertensives than in normotensive subjects. Moreover, this suppression of insulin sensitivity was also observed in young normotensive subjects with an apparent family history of hypertension, preceding the manifestation of hypertension. At the same time, obesity and aging were definitely correlated to the decrease in insulin sensitivity. On the assumed criterion that the normal range of $M$-values is mean $\pm 1$ SD of non-obese, non-diabetic young normotensive subjects, the prevalence of individuals with lowered $M$-value, which means existence of insulin resistance, was calculated as $45.4\%$ in essential hypertensives and as $16.3\%$ in normotensive subjects in this study. Increases in plasma norepinephrine levels and plasma renin activity, and decreases in urinary excretion of sodium and fractional excretion of sodium were observed during hyperinsulinemia produced by glucose clamp test. These responses to hyperinsulinemia were not different from those in normotensive subjects and, therefore, not specific to essential hypertensives. From these results, it was concluded that insulin resistance definitely exists among Japanese essential hypertensives, and that it plays an important role in the pathophysiology of essential hypertension. (Hypertens Res 1996; 19 Suppl. I:S1-S8)

Key Words: insulin sensitivity, insulin resistance, hyperinsulinemia, essential hypertension, impaired glucose tolerance

Hypertension is frequently complicated with obesity, diabetes and dyslipidemia (1-5). The co-existence of these abnormalities has been known to markedly accelerate the progression of arteriosclerotic cardiovascular diseases (6-8). Insulin resistance and/or hyperinsulinemia have attracted great attention over the past several years, because they may play an important role in the co-existence of these complications as common background factors (9-12).

The close association between hypertension and diabetes mellitus was already noted in the early 20th century. Although the high prevalence of concomitant hypertension and diabetes has been partially recognized, and some reports demonstrated particularly frequent occurrence of hypertension in patients with diabetes mellitus (13), we knew almost nothing precise about the interrelation between hypertension and diabetes or the outcome of their co-existence until a very recent date.

With regard to insulin resistance, insulin antagonism and elevation of plasma insulin levels were noted first in patients with myocardial infarction (14). Welborn described the presence of hyperinsulinemia in hypertensives in 1966 (15); however, his finding was not definitely confirmed until 20 years later. Since then, studies have tremendously accelerated in this field (16-21).

As a result of accumulation of epidemiologic and clinical data, insulin resistance and hyperinsulinemia are now considered to have particularly important roles in linking hypertension, glucose intolerance, dyslipidemia and obesity to accelerated arteriosclerotic cardiovascular diseases (6, 10, 12, 22). New concepts or new syndromes concerning insulin resistance/hyperinsulinemia have been proposed (23); Syndrome X (24), Deadly Quartet (25), and the Syndrome of Insulin Resistance (26) have been most widely accepted of these. However, there are still some unsolved questions about their etiologic involvement in individual diseases, in addition to differences among some ethnic groups (27-30). In this background, we have performed epidemiologic and clinical studies to reveal the state of insulin resistance in Japanese patients with essential hypertension and pathophysiological significances of insulin resistance/hyperinsulinemia in these patients. Our major findings are described below, with the hope of aiding understanding the actual state of insulin resistance in Japanese hypertension.

Epidemiologic Studies

We have conducted longitudinal epidemiologic stud-
ies of cardiovascular diseases in two towns (towns T and S), the agricultural districts in Hokkaido, since 1977. We randomly selected 1996 residents aged 40–64 at the start of this follow-up study as subjects (475 men and 521 women in town T; 469 men and 531 women in town S) (31).

As shown in Fig. 1, the results obtained in the first-year of this epidemiology study disclosed that the incidence of hypertension and that of borderline hypertension progressively increased in the worsening state of glucose tolerance; normal glucose tolerance (NGT) group, impaired glucose tolerance (IGT) group, and diabetes mellitus (DM) group (32). The incidence of hypertension in the DM group was about 2 times higher than that in NGT group. The incidence of diabetes mellitus and that of impaired glucose tolerance were significantly higher in HT and BHT groups than in the normotensive (NT) group. The early morning 75 g oral glucose tolerance test (75 g OGTT) could be examined in 725 subjects, excluding those definitely diagnosed as having hypertension and/or diabetes to avoid the effect of drug treatment. The plasma glucose levels were significantly higher in the BHT group at all measurement points of 0, 60, and 120 min, as compared with each in the NT group, and the 120-min plasma insulin (IRI) level and the sum of plasma IRI levels at all measurement points were also significantly higher in the BHT group. Moreover, both systolic and diastolic blood pressure, measured simultaneously with the 75 g OGTT, showed significant positive correlations with blood glucose levels and plasma IRI levels during fasting and at 60 and 120 min after glucose loading and with the sum of plasma IRI levels, although the correlation coefficients were never high, below 3.0 (33). These results were quite compatible with those reported from other laboratories, in which a significant correlation of blood pressure was described with blood glucose (34, 35) and plasma IRI levels (36–39) as well as with insulin sensitivity or insulin resistance (40–42). On the other hand, it still arouses controversy as to whether the blood glucose level and/or IRI level can be used as a predictor for the progression of hypertension (43–46). Therefore, we also performed multiple logistic analysis of the data obtained from our 10-years follow-up studies. We divided subjects into a hypertension-progressing group when they altered from NT to BHT or from NT/BHT to HT, and into a diabetes-progressing group when they altered from NGT to IGT or from NGT/IGT to DM. In this analysis, fasting plasma glucose level and systolic blood pressure were found to be significant independent predictors for the progression of hypertension and of glucose intolerance, respectively (33).

Next, we assessed the distribution of 120-min plasma IRI levels, which had the greatest difference between NT and BHT groups and the highest correlation coefficient between plasma IRI levels and blood pressure in the previous studies. Normal distribution curves, calculated from frequency distributions of 120-min plasma IRI levels, were compared between the non-obese, non-diabetic normotensive control group, the BHT/HT group, and the IGT group, as shown in Fig. 2. Defining a normal range of 120-min IRI levels as mean ± 1 SD, and hyperinsulinemia as levels above this range, hyperinsulinemia was observed in 11.5% of the normal control group, 31.8% of the BHT/HT group, and 43.6% of the IGT group.

Thus, our epidemiologic studies disclose that hypertension frequently occurs in subjects with impaired glucose tolerance, and hypertensives are frequently complicated with impaired glucose tolerance, in Japanese as in other ethnic groups. Moreover, it has been confirmed that blood glucose and plasma IRI levels are correlated with blood pressure and respectively play roles in the progression of hypertension and of glucose metabolic disorder.

Clinical Studies

Clinical studies were performed on hospitalized nor-
motensives (NT) and essential hypertensives (EHT), who had been given a diet containing 120 mEq sodium and 75 mEq potassium per day without any drug medication, and the following examinations were performed when their blood pressure was stabilized during hospitalization for 2 weeks.

In the 75 g OGTT taken in the early morning, no significant difference was found in plasma glucose levels between age- and body mass index (BMI)-matched NT and EHT groups, whereas plasma IRI levels at 60, 90, and 120 min and the sum of plasma IRI levels were significantly higher in the EHT group than in the NT group. There were no differences in fasting plasma glucose or plasma IRI levels between the two groups.

Next, insulin sensitivity of NT and EHT was evaluated as M value determined by using the 2-h euglycemic hyperinsulinemic glucose clamp (GC) method (47), which is the most common standard of measuring insulin sensitivity. As shown in Fig. 3, M values were apparently lower ($p < 0.01$) in the EHT group, as compared with age- and BMI-matched NT groups (32, 48).

To determine whether such a decrease in insulin sensitivity preceded the onset of hypertension, we compared the insulin sensitivity between young normotensives with a definite family history of hypertension and those without such a history. M values, measured by the GC method, were found to be markedly lower in the family history-positive group [FH(+)]] than in the family history-negative group [FH(-)] ($p < 0.05$), although there were no significant differences in fasting plasma glucose or plasma IRI levels between the two groups (Fig. 4). These results also agree with those reported by other investigators (49-53), suggesting that insulin resistance precedes the onset of hypertension in essential hypertensive patients.

As factors of accelerating insulin resistance, obesity (54-57) and aging (58-60) have been frequently indicated. As for obesity, abdominal obesity or intra-abdominal fat accumulation have particular attention (61-63). In fact, it was observed in our studies that M values are more closely correlated with ratios of intra-abdominal fat area to total area (VF%) calculated on CT scan, rather than with BMI.

As for aging, a negative correlation between M values and ages was observed in the NT group ($n = 49, r = 0.34, p < 0.05$). However, no certain correlation was found between M values and ages in EHT group, because these values were already suppressed in young EHT (Fig. 5).

Thus, it seems to be most rational if the M value observed in young, non-obese, non-diabetic normotensives is considered as normal insulin sensitivity. The mean ± 1 SD of normal M values was, therefore, calculated to be 224.98 ± 77.17 mg/m². When a M value below the mean −1SD was employed to indicate decreased insulin sensitivity, 16.3% of normotensives and 45.4% of essential hypertensives were determined to be included in this category (Fig. 3).
Mechanism(s) of Blood Pressure Elevation in Hyperinsulinemia

As mentioned above, a decrease in insulin sensitivity, or insulin resistance in other words, is confirmed to exist in essential hypertensives. However, it has not yet been fully clarified how insulin resistance or its corresponding hyperinsulinemia involves the pathogenesis of essential hypertension (64, 65). One possible mechanism is hyperinsulinemia, which may stimulate the sympathetic nervous system (66-68) and/or the renin-angiotensin system (69, 70) and lead to an increase in blood pressure. Another candidate is hyperinsulinemia, which may elevate blood pressure through enhancement of renal sodium reabsorption (71-74) or through its effect on transmembrane ion exchange (75, 76). From this point of view, the involvement of hyperinsulinemia in salt sensitivity in essential hypertensives has attracted attention in recent years (77, 78).

Our studies have addressed as for changes in various parameters under a hyperinsulinemic condition for two hours during the GC test. Plasma norepinephrine levels, plasma renin activity, and plasma aldosterone concentration all increased, without significant differences between young (younger than 45 years) and older (45 years or older) subjects or between NT and EHT groups. Although the activity of the sympathetic nervous system was enhanced by hyperinsulinemia, and the renin-angiotensin system was also activated, probably due to the activation of the sympathetic nervous system, the degree of such activation did not differ between NT and EHT groups or between young and older subjects. As shown in Fig. 6, urinary excretion of sodium (UNaV) and fractional excretion of sodium (FENa), measured by a renal clearance method, were decreased by hyperinsulinemia, and the degrees of these decreases did not differ between older NT, young EHT, and older EHT. However, both UNaV and FENa increased in young NT, differing from the three other groups. This difference could be explained by the following findings: the renal plasma flow (RPF) increased in young NT under the condition of hyperinsulinemia, but remained almost unchanged or decreased in the three other groups, indicating that the increase in RPF may cancel insulin-induced increase in renal sodium reabsorption in young NT.

If insulin resistance is involved not only in peripheral glucose metabolism, but also in renal sodium handling and the sympathetic nervous system, it must be difficult to elevate blood pressure in the presence of hyperinsulinemia. However, the renal sodium handling or the sympathetic nervous system actually showed no suppressed response to insulin. Thus, it was inferred that hyperinsulinemia induced by insulin resistance in peripheral glucose metabolism also enhances water-sodium retention and the activity of sympathetic nervous system, involving the pathogenesis of essential hypertension.

Anti-Hypertensive Drugs and Insulin Sensitivity

Recently, various effects of anti-hypertensive drugs on insulin resistance and hyperinsulinemia have
been discussed, because of essential hypertensives tend to be glucose intolerant, hyperinsulinemic, and dyslipidemic, and all of these abnormalities might augment risk of arteriosclerotic cardiovascular diseases. In this situation, it has been reported that insulin sensitivity is aggravated by thiazide diuretics and adrenergic beta-blockers, and improved by alpha 1-blockers and angiotensin converting enzyme (ACE) inhibitors (83, 84). The effects of calcium channel blockers on insulin resistance and hyperinsulinemia have remained unclear.

In our studies in EHT, it has been demonstrated that the calcium channel blocker manidipine (20 mg/d, 2 weeks) significantly increased M values ($p<0.05$), and increased UNaV and FENa during hyperinsulinemia produced by GC tests (85). Both the ACE inhibitor delapril (120 mg/d, 2 weeks) and the angiotensin II type 1 receptor (AT-1 receptor) antagonist TCV-116 (8 mg/d, 2 weeks) also significantly decreased blood pressure and increased insulin sensitivity (Fig. 7).

We further investigated the effects and its mechanism of ACE inhibitors and AT-1 receptor antagonists on insulin resistance employing fructose-fed rats (FFRs), which are known as an animal model of hypertension associated with insulin resistance (86, 87). Male Sprague-Dowley rats were fed on fructose-rich chow for 4 weeks, and treated with delapril (10 mg/kg/d), TCV-116 (1.0 mg/kg/d) or delapril with bradykinin receptor blocker Hoe 140 (0.5 mg/kg/d) for the latter 2 weeks. Insulin sensitivity was measured by the steady state plasma glucose
(SSPG) method (86) in the conscious state. Blood pressure significantly increased while insulin sensitivity decreased, i.e., SSPG values increased. Delapril and TCV-116 reduced the elevated blood pressure by the same degree, and improved the decreased insulin sensitivity. No marked differences in blood pressure or SSPG were found between the delapril-treated group and the delapril + Hoe 140-treated group (88, 89). These results suggested that insulin sensitivity is improved by ACE inhibitors mainly through inhibition of the angiotensin II action, while the enhancement of the effect of bradykinin (90) probably play no practical role in the improvement of insulin resistance.

**Conclusion**

The actual state of impaired glucose tolerance and insulin resistance in Japanese hypertensives and the pathophysiological significance of insulin resistance/hyperinsulinemia have been described, mainly based on the results obtained in our laboratory.

In our epidemiologic studies, co-existence of hypertension and glucose metabolic disorder was frequently observed, and blood pressure was correlated with blood glucose levels and/or plasma IRI levels. In our clinical studies, insulin sensitivity ($M$ value) was determined to decrease in essential hypertensives, and this decrease was also observed in young normotensives who have a definite family history of hypertension. Insulin sensitivity is known to decrease under obesity, particularly visceral obesity, and also with age. Provided that $M$ values observed in young non-obese, non-diabetic normotensive subjects are normal, insulin sensitivity was determined to decrease in 45.4% of patients with essential hypertension, whose $M$ values were below the mean $-1SD$ of the normal $M$ values, and this decrease was also observed in 16.3% of non-obese, non-diabetic normotensive subjects.

With regard to the mechanism in which hyperinsulinemia accelerates hypertension, UNaV and FENa were decreased by hyperinsulinemia induced during GC test, while PNE and PRA were increased. These responses did not differ significantly between NT and EHT, suggesting the importance of the existence of selective insulin resistance to peripheral glucose metabolism in the pathophysiology of essential hypertension. However, UNaV or FENa was not decreased by hyperinsulinemia in young non-obese, non-diabetic normotensive subjects. It was suggested in these subjects that the normal vasodilative response of renal arteries to hyperinsulinemia might be kept, and the increase of RPF might cancel insulin-induced augmentation of renal sodium reabsorption. This vasodilative response should be considered to be suppressed, particularly in essential hypertensives.

To evaluate the effects of anti-hypertensive drugs on insulin sensitivity, the effects of a calcium channel blocker (manidipine), an angiotensin converting enzyme (ACE) inhibitor (delapril), and an angiotensin II receptor antagonist (TCV-116) were examined. As a result, a hypotensive effect was simultaneously observed with the improvement of insulin sensitivity after administration of these drugs.

Thus, the existence of insulin resistance in association with hypertension was clearly indicated, and the compensatory hyperinsulinemia contributes to at least a part of the pathogenesis or pathophysiology of essential hypertension.

The results obtained in our epidemiologic and clinical studies have been described to understand the actual state of insulin resistance in Japanese hypertension.

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