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Review

Hypertension in Japan

—An overview focusing on pathogenesis and treatment aspects—

Ylva TRANAEUS *Karolinska Institute in Stockholm*

Introduction

Today hypertension is more common in Japan than in Sweden, with about 25% of the Japanese population[1] and 15% of the Swedish population being hypertensive[2]. Hypertension is closely related to cardiovascular disease, such as myocardial infarction and stroke, which is the most common cause of death in both populations. Indeed, Japan has the highest mortality rate caused by stroke among all developed countries. This project therefore, though primarily aimed at examining the causes and treatment of essential hypertension in Japan, will also address to what extent and why aspects of hypertension differ between Japan and other countries, including Sweden.

This paper is based on a review of relevant literature and on discussions with Japanese doctors specializing in this field.

Classification and definition of essential hypertension in Japan

The 1999 World Health Organization-International Society of Hypertension (WHO-ISH) guideline criteria[3], used worldwide, are substantially the same as those described in the Sixth Report of the Joint National Committee (JNC VI) guideline criteria of the United States[4]. The classification of blood pressure in the Japanese Society of Hypertension Guidelines (JSH 2000-Table 1)[5] also corresponds to the WHO-ISH classification with the exception of borderline hypertension, which was not included in JSH 2000[5].

Furthermore, in JSH 2000, patients are classified as belonging to the low-risk group, the medium-risk group or the high-risk group for developing hypertensive complications depending on the presence of major risk factors (Table 2)[5]. In Japan, these risk factors are primarily considered to be genetic poly-

Table 1 Classification of hypertension according to JSH 2000.

	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal blood pressure (BP)	<120	<80
Normal BP	<130	<85
Upper normal BP	130–139	85– 89
Mild hypertension (HT)	140–159	90– 99
Moderate HT	160–179	100–109
Severe HT	>180	>110
Isolated systolic HT	>140	<90

Table 2 Classification of severity of hypertension (HT) and the risk of developing hypertension-related complications according to the number and type of risk factors[3].

Number of risk factors or clinical disorder	Mild HT 140–159/90–99	Moderate HT 160–179/100–109	Severe HT >180/>110
No risk factor	Low risk	Moderate risk	High risk
1–2 risk factors	Moderate risk	Moderate risk	Very high risk
3 or more risk factors, organ damage or diabetes	High risk	Very high risk	Very high risk
Other cardio-vascular disorders	Very high risk	Very high risk	Very high risk

morphism, age, former history of cardiovascular events, increased salt intake, obesity, hyperlipidemia, Type II diabetes, stress, smoking, alcohol intake, inappropriate food habits, and lack of exercise[5].

In the evaluation of a patient's risk of developing complications from hypertension, a special risk stratification chart has been put forward by the WHO-ISH[3]. This categorization is internationally accepted and used worldwide, including in Japan.

Regional differences in the prevalence of hypertension

The prevalence of hypertension in Japan differs in comparison to other countries and populations. Comparison of blood pressures and its related factors between Japanese, US whites and US blacks aged 30–74 years shows that age-specific and age-adjusted mean systolic blood pressures of Japanese were generally higher than those of US whites, while mean diastolic pressures were similar in both populations in both men and women. Mean weight and BMI and their standard deviations were lower for the Japanese than the Americans. In US blacks, blood pressure was higher than in Japanese or US whites. At specific levels of BMI, Japanese systolic blood pressures were markedly higher than those of US whites in all age-sex groups, and diastolic pressures were higher in the Japanese than in US whites, slightly so at younger ages and more so at ages 60 and over for both genders[2].

Within Japan, the prevalence of hypertension differs among regions as well. Individuals in the northern part of Japan (Tohoku area) are especially prone to develop hypertension. This is believed to be related to the climate and the rural diet and life style use the some form throughout in this area. The people use salt to preserve vegetables and fish harvested and caught during summertime. They also eat a lot of salty pickles. In fact, the average intake of salt per day in this area is around 16g. This figure seems high, but it is lower than that for 1954 when it was estimated to be 30g per day[6]. The high salt intake increases the risk of developing hypertension[7]. In comparison to the north region, the incidence of hypertension is lower in the southern and western part of Japan. For example, in Okinawa in the far south, people have the highest age rates in the country with most people able to celebrate their 85th birthday. The secret of this longevity in Okinawa is thought to be due to a less salty diet and hence a low prevalence of hypertension and stroke[6]. However, even here people have westernized their diet and their life expectancy has decreased[1].

The incidence of hypertension has been shown to vary not only with geographical location but also between rural areas and cities, being more prevalent in rural than in urban areas[8]. One of the reasons for this is the high salt intake in rural areas[9]. Moreover, more aged people live in rural areas than in larger cities and hypertension is more com-

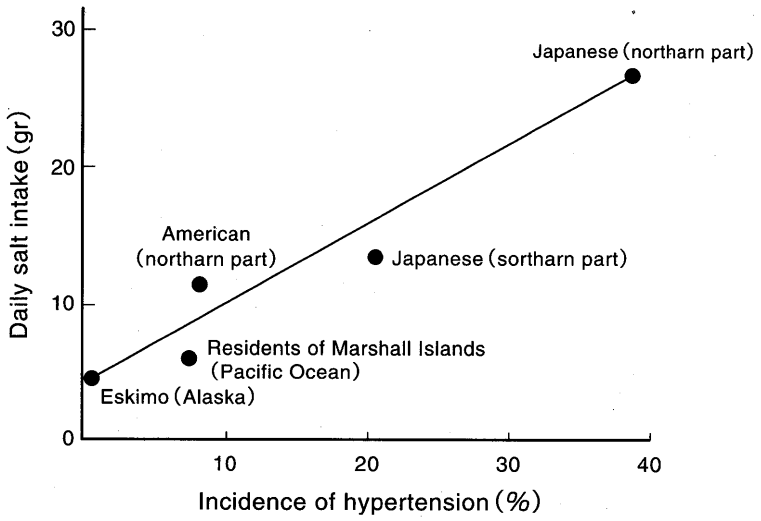

Fig. 1 Correlations between estimated salt intake and incidence of hypertension among ethnic groups[9].

mon among the elderly[8]. Belonging to a lower social class in Japan has been said to be a risk factor for developing hypertension and stroke[8], but the incidence is today very similar regardless of social class. The incidence is also rather similar between males and females[6].

The prevalence and risk factors of high blood pressure among Japanese differ depending on the country of their domicile. The prevalence of hypertension has been found to be higher for Japanese living in Hawaii and Los Angeles than in Hiroshima. This applies to both genders and almost all ages. The age- and sex-adjusted prevalence of hypertension in Hawaii, Los Angeles and Hiroshima was 42.6%, 37.2% and 29.7%, respectively[10]. This illustrates the great influence that a westernized way of living has on the development of hypertension.

Incidence and historical development of hypertension in Japan

In Japan, about 30 (out of 130) million individuals are said to be hypertensive, based on the blood pressure criterion of 140/90mmHg. In fact, the prevalence of hypertension varies between 15–35% in urban adult populations of Asia[11]. Although these are high numbers; the mean level of blood pressure is still lower in Japan today compared to 30 years ago[1]. However, for both males and females, the prevalence and incidence of hypertension in Japan have been at about the same level since the mid 1970's. The prevalence of hypertension and blood pressure levels differ from those of Caucasians, and hypertension and stroke occur at a relatively younger age in Asians (about 53% of the hypertensive patients are over 60 years of age in Japan; one-third of whom have isolated systolic hypertension)[12].

Historically, Japan has not only experienced and been affected by the Great Depression in the US in 1930 and by World War II in the 1940's which resulted in poverty and malnutrition, with American aid, the Japanese economy recovered and experienced high economic growth between the 1960's and 1980's. This led to a change in the life style including excessive salt intake, even greater than what was traditional in Japan, and overnutrition. These conditions have provided a unique opportunity to observe a natural experiment of changes in risk factors. Unfortunately, the result was a high prevalence of adult diseases such as hypertension, hyperlipidemia, diabetes mellitus, stroke and ischaemic heart disease, thus bringing about changes in the pattern of diseases in Japan[9].

Before the 1960's, the Japanese in general had a tradition of high salt and alcohol intake and low animal protein and fat intake, strenuous labor-intensive work and poor housing conditions (which causes more physical stress) contributing to high blood pressure levels. However, after the 1960's blood pressure levels declined due to improvements in drug therapy and dietary improvements such as sodium reduction. In fact, the mean blood pressure level of the entire adult population was 177/65mmHg in 1961 but 160/84mmHg in 1988[5]. More active anti-hypertensive treatment came into effect during the 1970's. In 1961, 10% of patients with hypertension

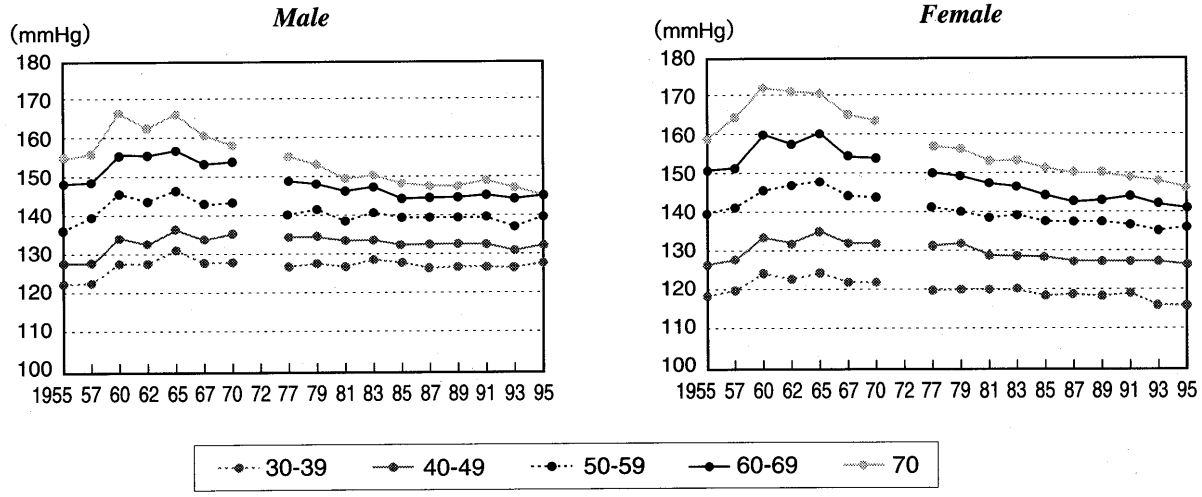

Fig. 2 Blood pressure levels for men and women between the years 1955 to 1995 in Japan[5].

were treated with some kind of medication, with the members rising to 37% in 1974 and 62% in 1988[5]. However, despite an increased public awareness of the importance of a proper life style, such as salt reduction, there was an increase in alcohol consumption and body mass index. Also, serum total cholesterol increased along with an increase intake of meat, egg, milk and dairy products. Interestingly, the decline in mean blood pressure values did not correspond to the incidence of hypertension which instead showed a small increase. In spite of this, the overall effect was a 70% decline in the mortality rate due to stroke, a common complication of hypertension in Japan, from the years 1960 to 1990[13]. Unfortunately, this decline of stroke mortality rates from 1950 to 1997 became less evident, especially for men[15], possibly because the population was becoming older.

In summary, the average blood pressure of the Japanese population has decreased, while the incidence of hypertension has increased. This difference is more prominent in the rural areas than in the larger cities.

Etiological aspects of essential hypertension

Blood pressure shows a continuous distribution for different ages and populations and is influenced by multiple genes as well as multiple environmental factors[15]. The epidemiology of essential hypertension varies greatly and the development of hypertension depends upon, as mentioned earlier, various risk factors, as discussed below.

Genetic aspects

The genetics of hypertension has recently become an active research area. Several genes have been considered as candidates for being causative genes of essential hypertension, most of which are still controversial[15]. As stated above, the kidney plays a major role in essential hypertension, via the renin-angiotensin-aldosterone system (RAA) that determines 15–20% of blood pressure variation, revealing its important role in the regulation[16]. Several gene polymorphisms in the renin-angiotensin system are known, and reseach on their involvement as risk factors of cardiovascular diseases has just begun. Recent progress in genetic studies of the renin-angiotensin system includes the detection of the angiotensinogen (AGT) gene, and the angiotensin-converting enzyme (ACE) gene, shown to be related to hypertension[15].

The AGT gene shows polymorphism at codon 235 on chromosome 1q4, denoted as M235 T[15]. M and T stand for the amino acids methionine and threonine, respectively. The T allele is considered to be associated with a risk for developing hypertension via an increase in plasma angiotensinogen concentration[15]. This allele is a salt-preserving gene. Being homozygous for this allele means that there is a lower secretion of salt through the kidneys in relation to the intake, i. e. being salt-sensitive, resulting in a permanent high salt load and subsequent hypertension. In addition, homozygocity of 235T has been found to be associated with a 10% increase in plasma angiotensinogen levels in both genders[17].

This polymorphism is said to be the original characteristic of this gene, being the only one our ancestors (the primates) had. These animals did not consume much salt, and as salt was a commodity in short supply, there was a great need to preserve the salt ingested. Today about 40% of the Caucasian population, 60% of the Oriental population and 80% of the black population are considered to be homozygous for the AGT 235T variation[6]. Why the number is so much higher in the black population can potentially be explained by the so-called "slave theory". When black people were brought from Africa to America to become slaves they were shipped on boats for a very long time with no access to salt, and only the AGT 235T sub-population, that could preserve the little salt they had in their body, survived[6]. However, why the percentage is higher in the Oriental population compared to Caucasians is still unknown. It could be explained by an equivalent to the slave theory in that the Japanese may have originated from the Asian mainland and have thereby been exposed to a similar selection phenomenon in crossing over to Japan.

The relationship between sweating, resulting in a loss of salt despite the kidney salt- saving function, and the RAA system reveals another theory explaining the diversity among the different races. This hypothesis is based on the assumption that initially, the salt load was the same for all races. However, the blacks lived in a tropical area where they lost a lot of salt through sweating. As a result their kidneys evolved to limit salt excretion more than those (Caucasians) living in colder areas.

In the former case, the RAA system would be activated. The Orientals on the other hand, evolved in a sub-tropical area, with kidneys displaying intermediate salt-excreting capacity, and thus with kidneys excreting more salt than those in colder areas and some suppression of the RAA system. Since more activated RAA system leads to a higher concentration of AGT, blacks tend to have the highest incidence of AGT 235T homozygote polymorphism, Orientals an intermediate incidence and whites a less common incidence[6].

Two other variations of the AGT gene lead to better coping with a high intake of salt; a heterogenecity for T and M and a homozygocy for M. In a study of Japanese workers at an occupational site in Shimane Prefecture, 4% were homozygous for M, 32% were heterozygous for M and T and 64% were homozygous for T[18]. Being homozygous for T has also been noted to be related to having an increased body mass index (BMI) which also correlates with a higher risk of developing hypertension[19]. It is estimated that the odds ratio for developing hypertension is 1.6 times higher in subjects with homozygocy for the 235T allele[14]. This is further supported by a Nordic study, where it was found that in a randomly selected group of those with Danish heritance, 54% were shown to have elevated blood pressure, and 41% of these individuals were homozygous for the 235T allele polymorphism[19].

In the same study a gender difference in regard to this gene was also noted. Women, but not men, homozygous for 235T versus non-carriers had an odds ratio of 1.5 for elevated blood pressure, including isolated elevated systolic blood pressure and of mild pressure elevation[19]. Furthermore, in a study comparing females of different populations, there was evidence of early expression of the AGT 235T gene predisposing for pregnancy hypertension in the ages between 20 and 34 years in Japanese women, but not in Caucasian women[20]. Moreover, the expression of this gene is more common among young women than young men, while the prevalence is the same between the genders after 55 years of age. This might be explained by the fact that in the past, this gene expression was also more common among older women than men, but this incidence has declined as women have began hormone replacement therapy (HRT) with estrogen. This hypothesis is supported by the possibility of female hormones influencing the expression of the AGT 235T gene, i. e. estrogen being a protector against hypertension[21]. This is also in line with the finding of HRT being uncommon in Japanese (< 1% of Japanese women use HRT) and the prevalence of the homozygous AGT 235T allele being more common among the elderly in Japan than among Caucasians[22].

The second candidate gene for an increased risk of developing hypertension is ACE I/D polymorphism. Insertion-deletion polymorphism is well documented as a genetic risk factor for ischemic heart disease. However, there is also some evidence for an association between the ACE gene and hypertension[15]. The ACE locus is on chromosome 17q23. In a study performed in England, a genetic variation in this gene accounted for 16% of the inter-individual variance in mean arterial pressures, and 32% in a subset of subjects with a positive family history of hypertension[23]. In contrast to the AGT 235T allele being more commonly related to hypertension in women, ACE D polymorphism has been found to significantly increase the risk of hypertension in males. In a Japanese male homozygous for the D genotype, the relative risk for hypertension is 1.75 times higher than in a male with a homozygous ACE I genotype[15]. In a Japanese study, the frequency of homozygous D in hypertensive men (17.1%) was significantly higher than that of mildly normotensive men (11.8%). However, as opposed to the AGT 235T gene being more prominent among Japanese, the ACE D gene is more common in Caucasians. In fact, the frequency of a homozygous D genotype in Caucasians (26%) is twice that in Japanese (13%)[22]. Black people have been found to have a higher incidence of a homozygous AGT 235T allele, and they also have a higher frequency of the D allele than both the Caucasians and Japanese[22].

In conclusion, the ACE D allele and AGT 235 T polymorphism may be involved in the occurrence of hypertension, with the ACE D allele being more common in women and Caucasians and the AGT 235T allele more common in males and Japanese[17].

Salt intake

Essential or primary hypertension was originally defined as a high blood pressure of unknown etiology. However, it has been sug-

gested that essential hypertension should be defined as having an impaired capacity to excrete salt through the kidneys in response to the salt load, i. e. to be regarded as a renal disorder[5]. This theory emerged from an experiment in which kidneys from a hypertensive rat were transplanted to a normotensive rat with the recipient becoming hypertensive. It was also shown that a hypertensive rat would become normotensive if given kidneys from a normotensive rat[16]. Support for the hypothesis that a lowered capacity of salt excretion predisposes to the development of hypertension, i. e. being related to a kidney disorder, may also be inferred from clinical evidence that elevated blood pressure in patients on hemodialysis who show persistent volume expansion, all improve after receiving a kidney transplant from a normotensive donor[16].

A potential explanation for the above is that the kidney possesses an intrinsic mechanism of "pressure-natriuresis", in which an increase in perfusion (i. e. increased systemic blood pressure) promotes natriuresis. This would lead to the assumption that individuals with a high NaCl intake whould have a higher systemic blood pressure in order to achieve a steady state of sodium concentration. In normal subjects, however, dietary sodium intake has little effect on systemic blood pressure, making the slope of the pressure-natriuresis curve very steep (Fig. 3)[16].

The pressure-natriuresis curve indicates that hypertensive subjects can be classified as salt-sensitive or non-salt-sensitive based on their responses to dietary sodium loading. Salt-sensitive hypertension is characterized by the inability of the kidney to excrete unnecessary amounts of sodium in the body. This may be caused by either a decreased ultrafiltration coefficient or increased tubular reabsorption[16]. When dietary sodium intake is increased in salt-sensitive individuals, the body fluid volume and hence the systemic blood pressure increase, leading to an elevated glomerular capillary pressure and therefore an increase in the glomerular filtration rate (GFR). With such an increase in GFR, more sodium is loaded to the tubules to maintain sodium balance. Thus, in salt-sensitive hypertension, glomerular hypertension is a common feature regardless of the cause of hypertension[16].

The prevalence of salt sensitivity in different populations has been investigated for whites and blacks, but no study of significance has been published regarding the Japanese. However, 29% of normotensive and 26% of hypertensive whites are salt sensitive, while 36% of normotensive and as much as 73% of hypertensive blacks are shown to be salt sensitive[24]. From these data one could estimate the prevalence for salt sensitivity in Japan to be between the values for whites and blacks, as the incidence of hypertension and mean blood pressure level are between the other two populations[25]. Furthermore, it has been revealed that normotensive salt-sensitive individuals have a higher risk of developing hypertension in the future[24]. Thus, the Japanese can be expected to be more susceptible to developing hypertension than Caucasians.

One study on the Japanese compared, mus-

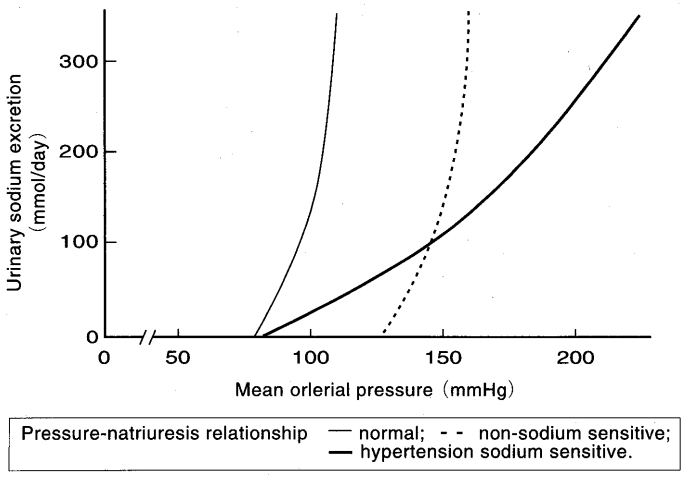

Fig. 3 Relationship between blood pressure and natriuresis.

cle sympathetic nerve activity, plasma concentration and urinary excretion of catecholamines, and ambulatory blood pressures during low (4g NaCl) and high (16g NaCl) salt diets. Muscle sympathetic nerve activity, plasma concentration and urinary excretion of norepinephrine in salt-resistant subjects were significantly reduced by salt intake, whereas the plasma concentration of epinephrine was unchanged and urinary excretion of epinephrine was reduced. In contrast, urinary excretion of epinephrine in salt-sensitive subjects was significantly elevated during high salt intake, whereas muscle sympathetic nerve activity and urinary excretion of norepinephrine remained unchanged despite a significant increase of ambulatory blood pressure. Moreover, of the salt-sensitive subjects examined, 73% had a positive family history of hypertension. These data indicate that normal inhibition of sympathetic activity during high salt intake does not occur in salt-sensitive young adults, and this may be linked with a hereditary predisposition to hypertension[26].

Today, the average salt intake for Caucasians is about 7–8g/day and for Japanese about 12–13g/day[27]. In Japan, this figure decreased from 13.7g/day in 1975 to 11.7g/day in 1987, but has since increased for unknown reasons the most recent figure being 13.0g/day[5]. This increase might be explained by the recent increased intake of fast foods that contain more salt than home-cooked food[1].

The physiological requirement for salt is estimated to be only 0.5g to 3g/day[5]. Thus, such a marked salt load in addition to a hereditary predisposition to hypertension, i. e. having an AGT 235T polymorphism, which in turn means being salt-sensitive (as is the case for half of the Japanese population), suggests a very risk of developing hypertension.

Obesity

Body mass index is strongly and positively correlated with blood pressure[28]. Moreover, both age and obesity are factors found to have a linearly increased odds ratio for developing hypertension[29]. It has also been shown that hyperinsulinemia and leptin released from adipose tissue play an important role in the development of hypertension in obese patients[30]. Insulin and leptin increase sympathic tone, which results in sodium retention and hyper-responsiveness of blood vessels. As leptin also has a direct vasodilative and diuretic action, its effect on blood pressure is bi-directional[30].

On a global scale, the body weight of all populations together with the incidence of Type II diabetes is increasing. The acceptance of a western life style and western food has increased the consumption of protein and fat. Thus, the frequency of obese children in Japan increased from 5% to more than 10%, over a period of two decades from 1974 to 1995, as shown in a study of more than 200,000 children (aged 6–14) in Japan[31]. For the Japanese population in general, only 2% of males and 3% of females have a body mass index (BMI) over 30 (the value considered to indicate obesity in the west), while the figures for Europe are 15% and 22%, respectively, and 10% and 12% in Sweden[32]. The figures for

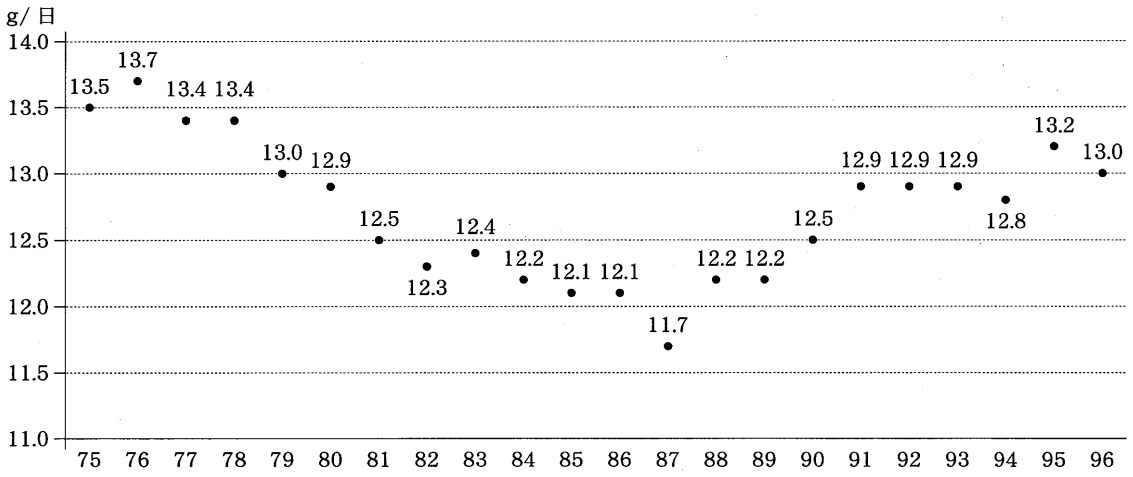

Fig. 4 Daily intake of salt (g) in Japan during the last two decades.

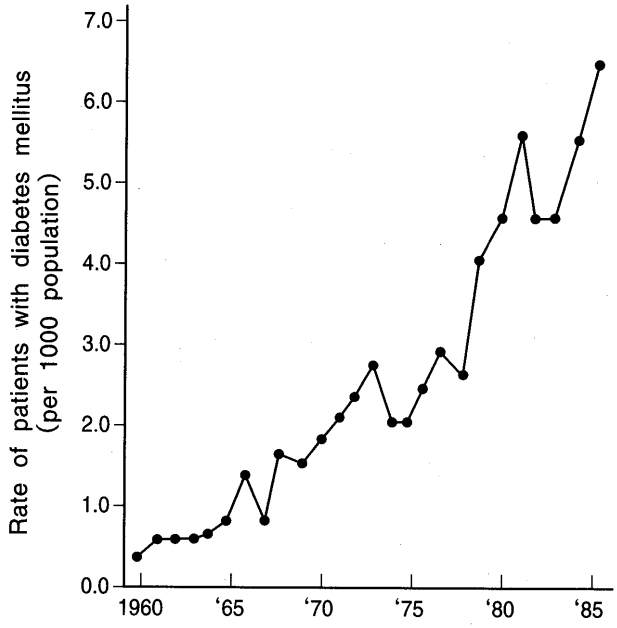

Fig. 5 Trends in the number of patients with diabetes mellitus in Japan (1960–1985)[9].

Japan might not seem alarming, but it must be remembered that the Japanese are of slight built and affected more by a low increase in BMI than Caucasians[8]. In fact, the risk of hypertension in Japan is said to increase at a BMI of 23–25[8].

Even though the Japanese might not be as obese as the westerners they have a higher incidence of Type II diabetes. The marked increase in Type II diabetes in Japan has been explained by a decreased reserve of insulin to be secreted[1]. This together with insulin also promotes hypertension as well[1]. This problem seems to affect both men and women.

One interesting example of the relationship between being overweight and hypertensive in Japan is the case of the sumo wrestlers. These athletes have less visceral than subcutaneous fat, probably due to their strenuous exercise, and they do not develop Type II diabetes or hypertension until they stop training[1].

Finally, it is of interest to examine the historical development of these matters in Japan. In the past, the Japanese were thin, had low cholesterol levels and many were non-salt sensitive. However, they are now becoming more obese, having insulin resistance, impaired glucose tolerance, hyperlipidemia and increased salt sensitivity[1].

The problem of obesity has also increased in Sweden which, like Japan, has taken on a more Americanized way of life. In fact, in Sweden the prevalence of obesity (defined as an BMI > 30) has increased by 50% during 1981–1998[33].

Stress

The Japanese people have very high work ethics and work hard and long hours. The roots of this attitude probably can be traced back to the time of Confucius, a Chinese philosopher. According to his philosophy one must maintain a high ethical standard in one's life. This includes a respect for parents and the elderly or superiors, and a studious attitude towards work. It also emphasizes the importance of a continuous contribution to society. The average Japanese has a strong incentive to work hard and fulfill family responsibilities, even though it may not be powerful among the young. It is this sense of commitment that stimulates the sympathetic nerve drive, leading to hypertension[6]. While the impact of overtime work and responsibilities can have an effect on mental health, job control, skill use and worksite support, as well as qualitative job demands, have great effects on psychological distress and are shown to cause increased alcohol consumption in cross-sectional as well as prospective studies[34]. Nevertheless, long working hours have been shown to be associated with a higher risk of myocardial infarction, diabetes mellitus and hypertension. There is evidence

that the job demands-control model, as well as the use of new technologies at work, is associated with higher blood pressure and serum lipids among the Japanese working populations[34].

Japanese workers tend to suppress expression of feelings, which results in apparently higher psychological distress and lower job satisfaction among Japanese workers as compared to workers in the US[35]. In addition, in one study, the relation of anger expression to blood pressure levels and hypertension was investigated in rural and urban Japanese communities. The study findings suggest that Japanese males who do not express their anger, especially when they have low coping behaviour, may have an increased risk of high blood pressure[36]. This is most probably very common in the Japanese society where one is taught to hold one's temper and behave in a controlled manner.

Smoking

Smoking is a big problem in Japan. While the total number of male smokers is decreasing, the number of female smokers and also of young smokers are increasing. It is estimated that about 70–80% of the young in Japan smoke sometime during their adolescence[6].

For many years, the effect of smoking on blood pressure increase has been discussed. Nicotine can raise blood pressure for about 30 minutes after smoking. However, the blood pressure subsequents decreases and it has not been shown whether smoking causes a sustained, chronic raise in blood pressure. It has even been shown that smoking can lower blood pressure[37], but this might be explained by the fact that smokers often have a lower body weight than nonsmokers.

Smoking is a clear risk factor for cardiovascular disease and Type II diabetes[38], and can cause increased blood pressure via these disorders. In fact, smokers have been shown to have a 3–4 times increased risk of developing Type II diabetes[1].

Alcohol intake

Many Japanese people drink alcohol, this even though many of them lack metabolizing dehydrogenases, which makes them less tolerant to alcohol.

There are two types of alcohol-metabolizing enzymes, aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ALD). The former has been widely utilized for epidemiological studies regarding the ethnic differences of alcohol drinking behavior. A majority of these studies have revealed that a substantial difference exists among different ethnic groups. Homozygotes of allele ALDH2, which represents alcohol tolerance, is predominantly distributed in the Caucasian group. On the other hand, the homozygous ALDH1, which carries alcohol intolerance, is much more predominant in the Oriental population; the frequency is estimated to be around 40%. Alcohol tolerance of heterozygous ALDH1/ALDH2 is positioned just between the two homozygotes[6].

Together with the fact that the Japanese have a smaller body weight than Caucasians, this genetic variation might explain why Japanese individuals show a higher increase in blood pressure while drinking compared to westerners. In fact, alcohol consumption of 56 g alcohol per day doubles the odds ratio for developing hypertension, compared to those who do not drink alcohol[29]. Chronic overconsumption of alcohol has a positive correlation with developing hypertension[39]. Conversely however, a small or moderate alcohol intake has been shown to lower blood pressure because of its anti-atherosclerotic effect[1].

Type of food

The traditional Japanese diet is a good example of how a hypertensive patient should eat. It is low in cholesterol and saturated fatty acids. During a four-year study of elderly Japanese men and women, a negatively correlation was found with the amount of boiled rice intake for men and Japanese tea intake for women[40]. These changes are reflected in findings in a study where serum lipid levels and blood pressures were measured for two Japanese populations, one in Japan and one in Brazil. This study showed that the Japanese in Japan had a lower incidence of hyperlipidemia and hypertension than the Japanese in Brazil. Also, the Japanese in Brazil more frequently had hyperinsulinemia[41]. Moreover, the Japanese in Japan had a higher level of unsaturated fatty acids in their blood, which lowered the blood pressure. This has been thought to be an effect of the well-balanced Japanese diet which is low in meat and fat but high in fish[6]. Fish is rich in taurine and low in calories, which has a beneficial effect on blood

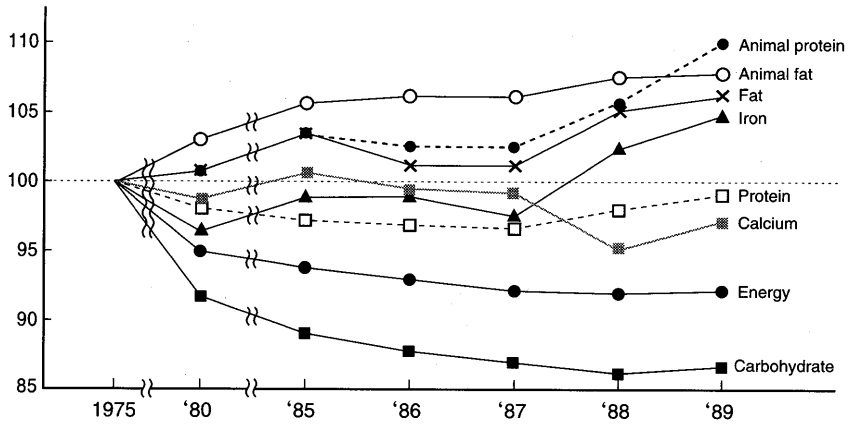

Fig. 6 People's intake of nutrients (1975=100)[9].

pressure[42]. However, the intake of this balanced and healthy diet, has decreased as the Japanese become accustomed to western food, including more or less unhealthy fast food. Not surprisingly, recent studies have shown an increased intake of cholesterol in Japan, which is today on the same level or almost even higher than in the US. In fact, the mean level in the US today is decreasing whereas the opposite is occurring in Japan. This has resulted in an increased incidence of cardiovascular disorders in Japan, especially among the young[1].

Physical activity

Physical activity has been shown to exert beneficial effects on patients with risk factors for hypertension or an inherited tendency toward of developing hypertension. Aerobic exercise, such as walking, running, bicycling and swimming, has been shown to have the best effects[5]. In a study evaluating the results of exercise on cardiovascular diseases, all physically active groups showed a significantly higher HDL cholesterol value, lower subcutaneous fat thickness in the triceps, scapula and iliac, and lower smoking rates. However, the BMI did not differ significantly between the groups. The sum of the risk factor scores for hypertension ; abnormal glucose tolerance, hypertriglyceridemia, hypercholesterolemia and low HDL cholesterol level was highest in the sedentary group[43].

Today, the young in Japan are said to exercise more not so much for the sake of health, but because of the modern trend of looking fit. However, rather than exercising, many eat less and smoke more to keep their weight. This is especially common among younger women. The lower blood pressure of these people is because they are underweight. In rural areas, people also do not exercise much because they are relying on cars more and more instead of walking[1]. The older population in Japan also has a low rate of exercising, resulting in an increasing number of Type II diabetics. The underlying pathophysiological mechanism is that exercise lowers insulin resistance and increases insulin sensitivity because during exercise the muscle is able to take up glucose without the presence of insulin[44].

In a study on insulin resistance and hypertension in Japan, a significant positive correlation between the two was found. Also, the insulin sensitivity is significantly lower in essential hypertensives than in normotensive subjects[45]. The existence of insulin resistance was calculated to be 45.5% in essential hypertensives and 16.3% in normotensive subjects in this Japanese study. This suppression of insulin sensitivity has also been observed to be more common in young normotensive subjects with an apparent family history of hypertension. At the same time, obesity and aging have been found to be definitely correlated with the decrease in insulin sensitivity[45]. 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 the glucose clamp test and could in fact explain the relationship between Type II diabetes and hypertension[45].

Moreover, in a group of physically active Japanese, the serum concentration of taurine was increased by 26%. The change in serum taurine levels is negatively correlated with a

change in plasma norepinephrine, but positively correlated with a change in diastolic blood pressure[46].

Finally, the fact that the prevailing life style in Japan has become westernized inevitably has had a negative impact and affects not only the nutritional state and eating patterns of the youth, but also the whole life style. The above-mentioned effects may be summarized as follows : 1) a lack of physical activities, 2) an increasing number of working mothers, 3) irregular timing of food intake, 4) an increasing intake of energy in the form of fat, 5) increasing consumption of salt-rich processed foods ready for consumption, 6) an increased intake of alcohol and of nicotine in the form of cigarettes, and 7) a lack of integrated management systems such as health education programs against atherogenic risk factors. These changes have resulted in an increasing number of young people being exposed to atherogenic risk factors[47].

In conclusion, the habit of using a lot of salt in cooking together with eating more westernized types of food and exercising less are the three most important risk factors for hypertension in Japan today[1]. In addition, and also related to a more westernized life style, increases in body weight, smoking and alcohol consumption among the Japanese seem to be major factors explaining the increasing frequency of hypertension[6].

Treatment : general aspects

Many epidemiological studies have shown that hypertension, irrespective of etiology, is a major risk factor for cardiovascular diseases and that it is closely related to cardiovascular mortality[13]. An epidemiological study conducted on a group in the general population of a small town outside Tokyo in Japan, demonstrated that mildly hypertensive individuals with a blood pressure of 140–159/90–99 mmHg had a significantly higher incidence of cerebral infarction than did subjects with lower blood pressure, and that increasing blood pressure was positively related to the incidence of stroke[13]. This correlation was more prominent for cerebral hemorrhage than for cerebral infarction[13]. Moreover, besides stroke, hypertension is also a risk factor for ischemic heart disease and renal disease[13].

The incidence of stroke due to hypertension

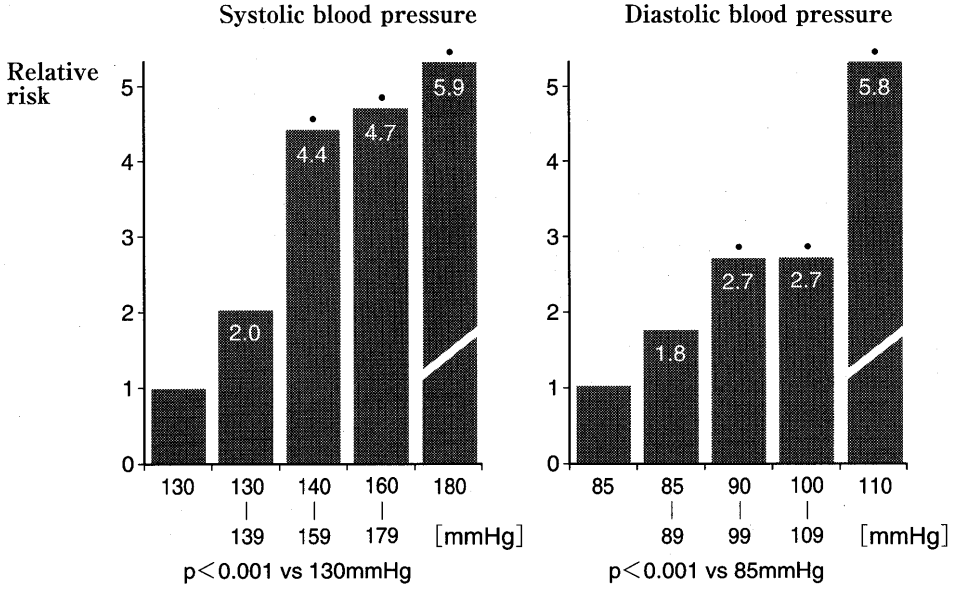

Fig. 7 Relationship of blood pressure and relative risk of cardiovascular mortality in Japan today[5].

Table 3 Beneficial effect of hypertensive treatment on stroke reduction[5].

	Medication	Placebo	Relative reduction rate (%), p for all <0.001
Stroke	525	835	38
Myocardial Infarction	934	1,104	16
Death	1,435	1,634	13
	n=23,487	n=23,806	

in Japan is higher, but the incidence of cardiovascular disorders is lower than in the US[13]. The main goal of the treatment of hypertension in Japan is therefore to minimize the occurrence of such cardiovascular disorders. As stated previously, when starting to actively treat hypertension during the 1970's, the incidence of stroke in Japan decreased. However, from the mid 1980's and on, this trend ceased and a plateau phase was observed. In fact, an increase in thrombotic stroke has been observed due to increased incidence of atherosclerosis arising from higher cholesterol intake, although the incidence of hemorrhagic stroke decreased due to the hypertensive treatment introduced[1].

Thus, treatment must be intensified and increased[5]. In fact, one study has shown that the rate of stroke is 3–5 times higher than the rate of cardiovascular disorders in Japan[5]. In 1997, 39.4 out of 100,000 Japanese developed a cardiovascular complication while 111.0 suffer from a stroke-related complication due to hypertension[5]. However, treating hypertension lowers the rate of stroke. The relative reduction rate was 38% for stroke compared to 16% for cardiovascular disorders after medical treatment compared to an untreated control group[5].

Also, another complication of hypertension is renal failure, not infrequently leading to the need for dialysis. In fact, as many as 200.000 patients are on dialysis in Japan today. This figure is increasing at the rate of 8 % per year, which means that over 30.000 patients are put on dialysis per year. This has had a financial impact on the total cost of health care in Japan. The total Japanese medical budget is about 30 • 10^12 yen per year. Today, dialysis requires 1/30 of this budget[1]. The increase in the number of dialysis patients is also due to a rapid increase in the number of Type II diabetes in Japan, of which a majority have hypertension. In fact, during the last 10 years, the incidence of Type II diabetes has tripled to at least 6–7 million individuals out of the population of 130 million. This shows the true significance and importance of the need to stop this trend and start intensive preventive treatment against hypertension and diabetes, not only to save lives but also to support the Japanese medical economy[1].

The report Health Japan 21, published by the Health Service Bureau of the Japanese Ministry of Health and Welfare, estimated that an average 2 mmHg reduction of systolic blood pressure in the whole population would reduce stroke incidence by 20,000 people and stroke death by 10,000 people and decrease the number of subjects disabled or experiencing decreased activities of daily living by 3,500 people. Moreover, if a decrease in deaths from ischemic heart disease is taken into account, the rate of deaths from all cardiovascular diseases would be decreased by 20,000 people. Thus, nationwide anti-hypertensive

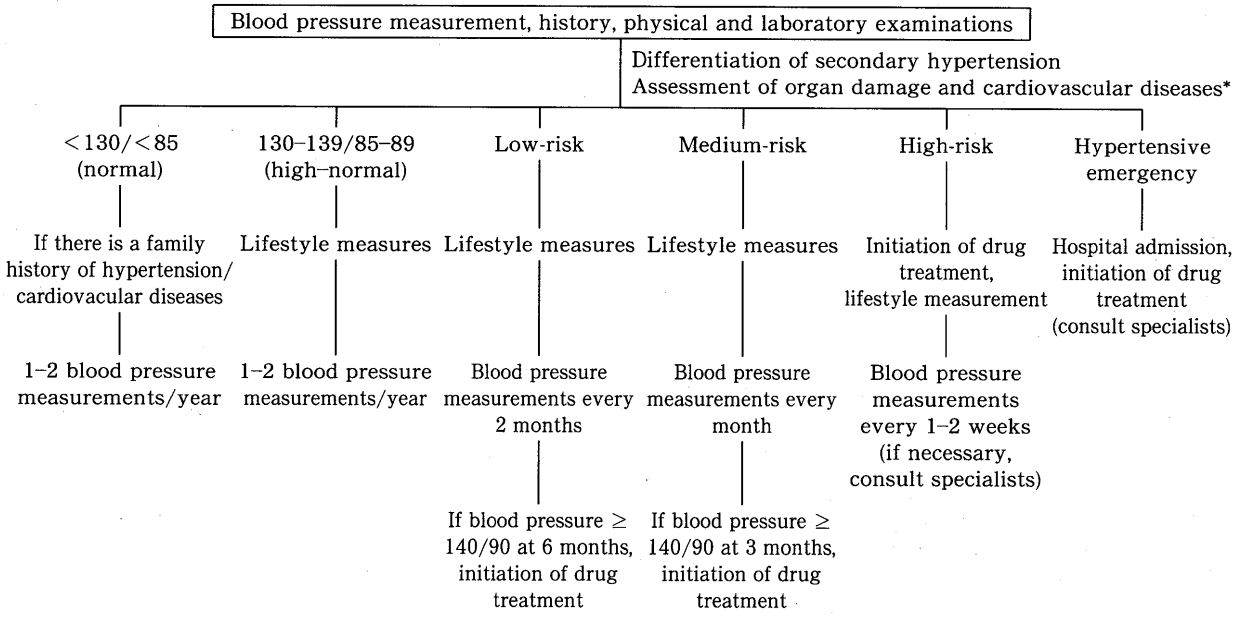

Fig. 8 Management strategy for hypertension treatment in Japan.

measures are extremely important for the prevention of cardiovascular diseases[5].

One study has noted that the average blood pressure level among the patients treated by Japanese physicians specializing in hypertension was somewhat higher than that recommended by WHO-ISH Guidelines (1999)[3]. In fact, only 35% of the total Japanese population had satisfactory blood pressure goals[48]. Multicenter trials conducted in Japan have presented an average blood pressure level of patients aged 50 years and over who are receiving antihypertensive treatment of 143/81mmHg, indicating that about half of the patients did not achieve the target blood pressure level, of less than 140/90mmHg. Therefore, the present state of hypertensive treatment in Japan is hardly satisfactory. Hypertension is one of the life style-related diseases, and the importance of reducing dietary salt intake and weight control is obvious[5]. Patient education to control life style-related risk factors, particularly regarding food and salt intake, should be emphasized together with intensified, more aggressive medical treatment.

When and how to start treatment has been controversial. Therefore, Japanese guidelines for different types of patients have been established. Hypertensive patients across a wide range of ages should be treated, although the benefits of treatment for those over the age of 85 years seems to be less than expected. The initiation of antihypertensive treatment should be based upon blood pressure levels and the existence of risk factors. Young patients or patients with diabetes should start treatment at a blood pressure of 130/80 mmHg[49], while older patients should start at 140–160/90mmHg[5]. These levels are based on the fact that vascular damage to important organs is commonly observed among elderly hypertensive patients and strict and excessive lowering of blood pressure tends to reduce organ perfusion.

In both Japan and Sweden, the treatment of hypertension commonly starts with life style interventions. These interventions consists of reduction of salt intake, a balanced diet, weight reduction, moderate intake of alcohol, exercise and smoking cessation. If these interventions are followed and show no or too small an effect, medical treatment should be started. Most often it has been shown that the life style modifications listed above do not result in a major decrease in blood pressure, but rather lowers the risk factors.

Life style modifications according to JSH 2000:

1. Reduce salt intake to about 7 g/day.
2. Have a diet low in cholesterol and saturated fatty acids and rich in vegetables. This is similar to the DASH (Dietary Approaches to Stop Hypertension) recommendations (which also include fruits and low fat diary products)[50]. Eating apples is said to be beneficial as they are rich in potassium, and hence cause a natural diuresis (increases the sodium secretion in the kidney through a mechanism of increased sodium sensitivity, decreased renin secretion, decreased, sympathetic nerve activity, and direct dilation of arteries)[51]. Also, it has been shown that an increased calcium intake through, for example low-fat dairy products may, provide a benefit of lowering blood pressure independently of other minerals such as sodium or potassium[52].

   Compliance with this diet lowers the systolic pressure by 11.4mmHg and diastolic pressure by 5.5mmHg[5]. The best results have been shown in patients with AGT gene polymorphism[53].
3. Maintain an ideal weight which is BMI 22 for the Japanese. A BMI of 18–23 is normal and 23–25 is considered overweight and over 25 as obesity[33]. Overweight (estimated as more than 20% of the ideal weight) Japanese should reduce their weight by 4kg in order to improve their blood pressure[54].
4. Keep intake of alcohol to less than 20–30 g/day (which corresponds to about 180ml of Japanese sake) for males and 10–20g/day for females.
5. Do aerobic exercise of 50% of your maximal oxygen consumption for 30–45 minutes at least 3 times a week. It has been shown that 30–45 minutes of fast walking/power walking every day for 10 weeks can lower blood pressure. Fifty percent of the hypertensive population which participated in this study showed a mean decrease in systolic blood pressure of 20mmHg and diastolic blood pressure of 10mmHg[55].
6. Stop smoking[56].
7. Avoid psychological and environmental stress[5].

The most important of these interventions is physical activity, because it leads to so many good effects and reduces the incidence of many other risk factors[1].

Health care education is also important to inform the public about hypertension. Everyone should be informed of blood pressure measurement, the effects of obesity, smoking and excessive alcohol consumption on the development of hypertension, and this should be started in high school. Also, the severity of hypertension must be taught[57].

Unfortunately, these life style modifications show a rather limited effect, mostly because of low compliance. Three important factors for increasing compliance are the good communication between the doctor and the patient, good communication between the doctor and the nurse who usually measures the blood pressure, and an increased health promotion campaign to disseminate information to the public. Unfortunately, Japan, lacks effective campaigns[1], which are needed to teach people about the seriousness of cardiovascular risk factors and to give them appropriate instructions about the management of hypertension. Early detection of hypertension is important and its management should be stringently implemented. It is especially important to instruct younger people, who should have access to information in their communities and workplaces as well as from their local governments[5].

Community-based hypertension control programs for stroke prevention have been evaluated in one study, showing a larger decline in stroke incidence in the intervention community (69%) than in the reference community (49%). In the past, effective community programs stimulated the formation of the 1982 National Act on Health and Medical Care in which every municipal government was required to conduct health screenings and education for residents aged 40 and over to prevent cardiovascular disease[8]. Increased antihypertensive treatment, improvement of life style and environmental factors, increased and intensified screening and medical check-up of high-risk patients, and increased compliance of patients resulted in a marked decrease (30%) of mortality in cardiovascular diseases during 1965–1985[1].

Antihypertensive treatment

Many studies have been performed and published dealing with medical treatment of hypertension. The treatment aims to protect the three main organs, the heart, the brain and the kidney. In the treatment focused on the heart (to prevent myocardial infarction) and brain (to prevent hemorrhagic lesions), a J-shaped correlation of lowered risk of these complications in relation to a lowered diastolic blood pressure has been claimed by some researchers. The risk is shown to increase when DBP is lowered below 85mmHg. This indicates that a lowered DBP can decrease the incidence of these complications of hypertension, only to a certain level[58]. However, this J-shaped relation has not been found in all studies. Another study found a linear correlation between a lowered DBP and decreased risk of thrombotic stroke and renal failure[45], indicating the benefits of blood pressure reduction to even lower levels.

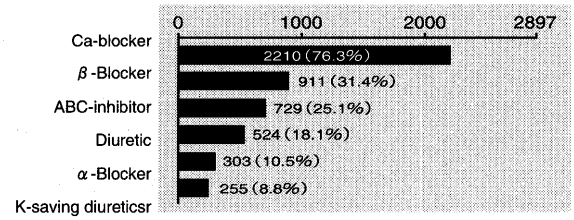

Fig. 9 Use of different types of medicines for hypertension treatment in Japan[48].

Antihypertensive drugs currently used in Japan can be classified by their mechanisms of action into the following six drug classes: Ca-antagonists, which cause vasodilation by inhibiting the inflow of Ca^{2+} from the extracellular space into the cells of the vascular smooth muscle; ACE inhibitors, which inhibit the production of AII; AII receptor antagonists, which inhibit the action of AII at the receptor level; diuretics, which promote the excretion of sodium and water from the kidneys; anti-adrenergic drugs, which centrally or peripherally inhibit the sympathetic nervous system; and vasodilators, which dilate blood vessels by directly acting on peripheral blood vessels[5].

In Japan, some 10–20 years ago it was common to use diuretics and β-Blockers, while during the last decade it has become more popular to use calcium-channel antagonists and ACE inhibitors. In fact, in Japan about 80% of the doctors prescribing medicines for hypertension prescribe calcium-channel blockers as a first choice[59]. This might be due to the beneficial effect of this blocker on spasm angina,

that is common in Japan[1]. It has been shown that in patients over 60 years of age with isolated systolic hypertension, treatment with Ca-channel anatagonists reduced the rate of ischemic heart disease by 31% and stroke by 42%[5]. An ACE inhibitor or AII receptor blocker is prescribed as the first choice by about 20% of Japanese docters.

The target blood pressure should be achieved in 2 months or longer. When the blood pressure cannot be lowered to less than 140/90mmHg by a low dosage of the first choice drug, the dose of the same drug can be increased (provided that it has been well tolerated), up to a double dose, but not more. If the target blood pressure levels are still not achieved, a combination of other drugs with an additive or synergistic effect should be used. The combination drug often chosen is an ACE inhibitor. Other types of combination therapies are calcium-channel blocker (dihydropyridine) + β-Blocker, ACE inhibitor + diuretics, β-Blocker + α-blocker and finally diuretics + β-Blocker[5]. In contrast, the drugs chosen for Caucasian patients are ACE inhibitor + β-Blocker and for black patients, diuretic + calcium-channel antagonists. These patterns can be understood from the different effects of the drugs; the latter show beneficial effects on salt sensitivity, stress-induced vasoconstriction and slower natriuresis, which is common among both blacks and the Japanese[60].

Today, β-Blockers are not used as much in Japan as in the western countries because the "lack" of cardiovascular diseases (which is a β-Blocker major indication) and also a fear of side effects, such as depression, hypotension and dyslipidemia[5].

Japanese recommendations (+) and contraindications (−) for hypertension drugs:

* Calcium-channel blocker:
  + Elderly, patients with angina pectoris or stroke, diabetics.
  − AV-block, arrhythmias.

* ACE inhibitor:
  + Diabetics, patients with heart failure, MI, LVH, mild renal dysfunction, or stroke, elderly.
  − Pregnancy, hyperkalemia, bilateral renal artery stenosis.

* AII receptor blocker:
  +/− Same as for ACE inhibitor.

* Diuretic:
  + Elderly, heart failure.
  − Gout, hyperuricemia.

* β-Blocker:
  + Patients with AMI, angina, tachycardia.
  − Asthma, AV-block.

* α-Blocker:
  + Patients with lipid abnormality, hypertrophy of prostate, diabetics.
  − Orthostatic hypotension.

The choice of treatment must be selected individually and it is important to consider the whole patient and also to treat his/her risk factors. Also, special patient groups must be treated in special ways as determined by their risk factors, such as elderly people, diabetics, patients with cardiovascular disease, patients with asthma and patients with impaired renal function.

Since Japan is an Asian country with a long history of traditional medicine, one would expect this to have some place in the treatment of hypertension, but it has been more or less neglected[6,1]. However, some articles show that there is some use of acupuncture and Japanese acupressure (Shiatsu) in the treatment. The results were in fact very promising showing scientifically robust, long-lasting, and explicable effects[61].

An increase in the number of family members with hypertension has been associated with an increasing prevalence of hypertension and blood pressure in the probands, independent of conventional risk factors for hypertension. Family members of hypertensive subjects may need primary prevention efforts related to hypertension[62]. These individuals with a family history of hypertension and an increased risk of being salt-sensitive could in the future be screened for salt sensitivity.

Another possibility for future treatment of hypertension might be gene therapy. This is particularly interesting as the major genes predisposing for hypertension, ACE and ATG gene, have been found in the Japanese population. This might become a good alternative to the current therapy which is expensive, is short-lasting (24h or less), and has many side effects, and is not highly specific. Gene ther-

apy, on the other hand, offers the possibility of producing long-lasting effects with high specificity from the genetic design[63]. However, more research is needed before this alternative can be introduced into clinical practice.

Conclusion

Japan is a country with many affected by hypertension. In fact, it is so common (more than 25% of the population) that it can be called an endemic disease. Hypertension is more common in Japan than in western countries including Sweden. Moreover, the Japanese patients also have a higher mean value of blood pressure. This might be explained by the epidemiologic differences between the two populations in the development of the disorder. The two populations differ markedly with regard to their life styles. In Japan there is a higher salt intake, lower rate of exercise, higher rate of stress, lower tolerance to alcohol and higher incidence of smoking and Type II diabetes. The Swedes are, on the other hand, in general, more obese. This might not only explain the different patterns in the development of hypertension, but also the type of complications most prominent in the two populations related to hypertension. In Japan, stroke is more common, while in Sweden myocardial infarction is more prevalent. Due to these factors, different treatments have naturally evolved in the two countries. However, while both countries have the same basic principles for treatment, such as life style interventions, both stating the importance of physical activity, the pharmacotherapy follows somewhat different patterns. In Japan, the first choice in anti-hypertensive treatment is Ca-channel antagonists due to their positive effect on stroke prevention, whereas in Sweden, β-Blocker is the first choice due to its beneficial effect in preventing myocardial infarction.

Finally, one could summarize hypertension as being a life style induced disease with some genetic traits, which are more common in Japan than in Sweden. Due to its increased incidence and known effects on many organ systems, it is important to increase and intensify both prevention and treatment, and also to conduct research to improve our knowledge of this disorder.

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