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ORIGINAL ARTICLE

Association of family history of type 2 diabetes with blood pressure and resting heart rate in young normal weight Japanese women

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Abstract

Objective We suggested association of family history of type 2 diabetes (FHD) with microvascular dysfunction, which may cause blood pressure (BP) elevations. We test whether FHD may be associated with higher BP.

Research design and methods Resting BP, heart rates (in beats per minute: bpm), body composition and fasting concentrations of glucose, insulin, leptin and adiponectin were measured in 332 Japanese women aged 18–24 years. They were grouped according to BP category defined by the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline.

Results BMI averaged < 22 kg/m^2 and did not differ cross-sectionally between 73 with (FHD+) and 259 without FHD (FHD−). FHD+ had higher mean (81 ± 9 vs. 77 ± 7 mmHg, $p < 0.001$), systolic (111 ± 13 vs. 106 ± 10 mmHg, $p = 0.003$) and diastolic BP (65 ± 8 vs. 60 ± 7 mmHg, $p < 0.001$). Prevalence of elevated BP (11.0 vs. 6.2%), hypertension stage 1 (4.1 vs. 0.8%) and stage 2 (2.7 vs. 0.4%) was higher as well ($p = 0.01$). Endurance training in FHD+ abolished the differences in BP readings and BP prevalence. However, the mean resting heart rate in FHD+ athletes (61.2 bpm) was close to those in FHD+ (64.7 bpm) and FHD− nonathletes (64.6 bpm) and was higher than in FHD− athletes (56.5 bpm). Fat mass and distribution evaluated by dual-energy X-ray absorptiometry, markers of insulin resistance, and serum adipokines studied did not differ between the two groups.

Conclusions FHD was associated with higher BP and higher prevalence of elevated BP and hypertension, suggesting contribution of microvascular dysfunction in BP elevations in normal weight young Japanese women. FHD may be associated with reduced heart rate response to endurance training as well.

Keywords Family history of type 2 diabetes · Microvascular dysfunction · Blood pressure · Hypertension · Young lean offspring

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Introduction

Obesity is a major risk factor of type 2 diabetes and hypertension. It is well known that obesity-driven insulin resistance is a core defect in type 2 diabetes [1]. Further, insulin resistance is one common feature of both prediabetes and prehypertension and an antecedent of progression to hypertension and type 2 diabetes [2]. Microcirculatory abnormalities associated with vascular insulin resistance in obesity may be one of important causes of primary hypertension and insulin resistance [3–5]. Some [6–8] but not all [9] studies have reported associations of family history of type 2 diabetes (FHD) with microvascular dysfunction.

Blood pressure (BP) is mainly determined by cardiac output and systemic vascular resistance. The recent study has shown that systemic vascular resistance index calculated by whole-body impedance cardiography was directly and independently associated with blood pressure progression and incident hypertension among young adults [10]. Vascular resistance is chiefly determined by the microcirculation since they present the greatest resistance to blood flow [11]. It has been suggested that elevated BP in young people is because of high cardiac output accompanied by normal total peripheral resistance: a hyperkinetic/hyperdynamic circulation [12]. However, a recent study has shown that elevated BP in adolescence is attributable to a combination of elevated cardiac output and total peripheral resistance [13]. In addition, in the Enigma Study, a vascular phenotype, characterized by elevated peripheral vascular resistance, was dominant in females whereas a cardiac phenotype was associated with elevated BP and hypertension in males [14]. We have recently suggested that FHD might be associated with impaired microvascular function in young, normal weight Japanese women although we did not measure microvascular function directly [15]. As microvascular dysfunction may contribute to an increase in peripheral vascular resistance and BP elevations [3–5], we tested the hypothesis that FHD associated with microvascular dysfunction may be related to increased BP and a higher prevalence of hypertension in young Japanese women. As our young women are comprised of collegiate female athletes and untrained women [15–17], we investigated whether chronic exercise training may affect results in women with FHD because endurance training has been reported to increase skeletal muscle microvascular perfusion as discussed later.

Methods

Among 481 female university students (170 collegiate athletes and 311 nonathletes), whose details were reported elsewhere [15–17], 332 women (129 athletes and 203 nonathletes) provided data on FHD. Seventy-three women (18 athletes and 55 nonathletes) were considered FHD positive (FHD+) as the questionnaire to their parents reported that a parent or a grandparent was on oral antidiabetic drugs. Unfortunately, information was not available on the extent of family history (i.e., how many family members have the condition) and the nature of the family history (paternal or maternal). There were no significant differences in anthropometric and biochemical measurements between 332 women studied and 149 women whose FHD data were not available (data not shown). Athletes were students of the Department of Health and Sports Sciences and were also members of the volleyball club, basketball club, or track club (middle-distance runners) of the University. They had been training regularly for 2 years or longer before the study, 5 h a day, and 6 days a week, and participated regularly in competitive events in their respective sport specialties. Nonathletes were students of the Department of Food Sciences and Nutrition of the University and were not engaged in any regular sport activity. Subjects with clinically diagnosed acute or chronic inflammatory diseases, endocrine, cardiovascular, hepatic, renal diseases, hormonal contraception, and unusual dietary habits were excluded. Nobody reported to receive any medications or have regular supplements. The study was approved by the Mukogawa Women's University Ethical Committee (No. 07–28 on 19/02/2008) to be in accordance with the Helsinki declaration. All subjects were recruited as volunteers and gave written consent after the experimental procedure had been explained.

After a 12-h overnight fast, participants underwent blood sampling, measurement of anthropometric indices, BP and body composition as previously described [16, 17]. Systolic and diastolic BP (SBP and DBP) and pulse rates were measured using an automated sphygmomanometer (BP-203RV II, Colin, Tokyo, Japan) after participants had rested at least 5 min. The measurements were repeated after 2–3 min, and the average of the measurements was used for analyses. Although heart rates were not measured, pulse rates may be equal to heart rates in young healthy women. Therefore, we used heart rates expressed in beats per minute (bpm) instead of pulse rates in the present study. Subjects were grouped according to seated brachial BP following the American Heart Association/American College of Cardiology 2017 guidelines for the classification of hypertension [18]: normal BP (SBP < 120 mmHg and DBP < 80 mmHg); elevated BP (SBP: 120–129 mmHg

and DBP: < 80 mmHg); hypertension stage 1 (HT1: SBP 130–139 mmHg or DBP 80–89 mmHg); and hypertension stage 2 (HT2: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg). Pulse pressure was the difference between SBP and DBP and mean BP (MBP) was calculated as DBP plus 1/3 PP.

Plasma glucose, serum insulin, adiponectin and leptin were measured as previously reported [16, 17]. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as the product of fasting insulin and glucose [19].

Fat mass, bone mass, and lean mass for arms, legs, trunk, and the total body were measured using whole-body dual-energy X-ray absorptiometry (DXA) (Hologic QDR-2000, software version 7.20D, Waltham, MA) as previously reported [17]. The leg region included the entire hip, thigh and leg. General adiposity was assessed by fat mass index (FMI) calculated as body fat mass in kg divided by height in meters squared. Abdominal fat accumulation was assessed by the ratio of trunk fat to leg (gluteofemoral) fat [20]. Since lean mass in arms and legs represents skeletal muscle mass, a sum of the two was used as appendicular skeletal muscle mass. Height-adjusted skeletal muscle mass was assessed by skeletal muscle mass index (SMI), calculated as skeletal muscle mass in kilograms divided by squared height in meters.

The data were presented as mean ± SD. Due to deviation from normal distribution, HOMA-IR was logarithmically transformed for analyses. Differences between two groups in means and percentages were compared by *t*-test and Chi-square test, respectively. A two-tailed value of $p < 0.05$ was considered significant. The statistics were performed with SPSS system 17.0 (SPSS Inc, Chicago, IL).

Results

Mean BMI, fasting glucose and HOMA-IR were < 22 kg/m^2, < 90 mg/dL and < 1.5, respectively, and did not differ between 73 FHD+ and 259 FHD− (Table 1). Among 332 participants, only 8 (2.4%) had hypertension (5 in HT1 and 3 in HT2) and 24 (7.2%) had elevated BP whereas the remaining 300 (90.4%) had normal BP. As previously reported [16], DBP (59 ± 7 vs. 61 ± 8 mmHg, $p = 0.001$) and resting heart rate (57 ± 8 vs. 65 ± 10 bpm, $p < 0.001$) were slightly but significantly lower in 174 athletes compared to 311 nonathletes although SBP was the same (both 106 ± 10 mmHg, $p = 0.83$). As expected, athletes had lower fat mass and higher muscle mass.

FHD+ compared to FHD− women had higher MBP, SBP and DBP (Table 1). FHD+ had higher resting heart rates as well. However, pulse pressure, FMI and trunk/leg fat ratio did not differ whereas FHD+ had lower BMI and SMI, which may be due to lower percentage of athletes in FHD+.

Table 1 Anthropometric and cardiometabolic characteristics of young Japanese women with (FHD+) and without (FHD−) a family history of type 2 diabetes

	FHD+ ($n = 57$)	FHD− ($n = 259$)	*p* values
Age (years)	20.3 ± 1.1	20.0 ± 1.2	0.079
Height (cm)	160.4 ± 6.0	161.4 ± 6.3	0.243
Weight (kg)	52.5 ± 8.5	54.9 ± 7.4	0.021
Body mass index (kg/m^2)	20.3 ± 2.6	21.0 ± 2.1	0.023
Fat mass index (kg/m^2)	5.21 ± 1.88	5.51 ± 1.58	0.161
Trunk/leg fat ratio	1.23 ± 0.24	1.22 ± 0.24	0.689
SMI (kg/m^2)	6.12 ± 0.75	6.39 ± 0.83	0.014
Fasting glucose (mg/dL)	84 ± 7	85 ± 7	0.497
Fasting insulin (μU/mL)	5.5 ± 3.0	6.2 ± 4.5	0.216
HOMA-IR	1.1 ± 0.7	1.3 ± 1.0	0.182
Leptin (ng/mL)	7.1 ± 3.5	7.9 ± 3.8	0.094
Adiponectin (mg/L)	11.8 ± 4.7	11.5 ± 4.2	0.523
Systolic BP (mmHg)	111 ± 13	106 ± 10	0.003
Diastolic BP (mmHg)	65 ± 8	60 ± 7	0.000
Mean BP (mmHg)	81 ± 9	77 ± 7	0.000
Pulse pressure (mmHg)	46 ± 8	46 ± 7	0.445
Resting heart rate (bpm)	63.8 ± 10.3	61.2 ± 9.9	0.046
Athletes (*n*, %)	18, 24.7	111, 42.9	0.003

Mean ± SD or *n*, %

bpm beats per minute, *SMI* skeletal muscle mass index, *HOMA-IR* homeostasis model assessment-insulin resistance, *BP* blood pressure

Table 2 Comparison between young Japanese female nonathlete with (FHD+) and without (FHD−) a family history of type 2 diabetes

	FHD+ ($n = 55$)	FHD− ($n = 148$)	*p* values
Age (years)	20.5 ± 1.0	20.3 ± 1.2	0.289
Height (cm)	159.5 ± 5.5	158.7 ± 4.9	0.281
Weight (kg)	51.1 ± 8.6	51.7 ± 6.3	0.633
Body mass index (kg/m^2)	20.0 ± 2.9	20.5 ± 2.1	0.203
Fat mass index (kg/m^2)	5.40 ± 2.02	5.89 ± 1.58	0.069
Trunk/leg fat ratio	1.25 ± 0.25	1.25 ± 0.25	0.873
SMI (kg/m^2)	5.85 ± 0.61	5.84 ± 0.55	0.987
Fasting glucose (mg/dL)	83 ± 7	84 ± 7	0.458
Fasting insulin (μU/mL)	5.4 ± 3.1	6.2 ± 3.7	0.188
HOMA-IR	1.1 ± 0.8	1.3 ± 0.9	0.257
Leptin (ng/mL)	7.3 ± 3.8	9.0 ± 4.0	0.007
Adiponectin (mg/L)	12.0 ± 5.1	11.3 ± 4.0	0.355
Systolic BP (mmHg)	111 ± 13	106 ± 9	0.007
Diastolic BP (mmHg)	67 ± 8	61 ± 7	0.000
Mean BP (mmHg)	82 ± 9	77 ± 7	0.000
Pulse pressure (mmHg)	45 ± 8	45 ± 7	0.743
Resting heart rate (bpm)	64.7 ± 11.0	64.6 ± 9.8	0.990

Mean ± SD. Abbreviations are the same as in Table 1

Table 3 Comparison between young Japanese female athletes with (FHD+) and without (FHD−) a family history of type 2 diabetes

	FHD+ ($n=18$)	FHD− ($n=111$)	p values
Age (years)	19.7 ± 1.2	19.6 ± 1.2	0.741
Height (cm)	163.3 ± 6.4	165.1 ± 6.1	0.248
Weight (kg)	56.7 ± 6.5	59.1 ± 6.6	0.150
Body mass index (kg/m^2)	21.2 ± 1.5	21.7 ± 2.0	0.344
Fat mass index (kg/m^2)	4.63 ± 1.25	5.02 ± 1.46	0.289
Trunk/leg fat ratio	1.16 ± 0.18	1.18 ± 0.22	0.749
SMI (kg/m^2)	6.96 ± 0.44	7.11 ± 0.56	0.282
Fasting glucose (mg/dL)	88 ± 8	86 ± 7	0.416
Fasting insulin (μU/mL)	5.9 ± 2.5	6.3 ± 5.4	0.752
HOMA-IR	1.2 ± 0.6	1.4 ± 1.3	0.505
Leptin (ng/mL)	6.5 ± 2.3	6.5 ± 3.0	0.943
Adiponectin (mg/L)	11.3 ± 3.4	11.7 ± 4.5	0.745
Systolic BP (mmHg)	110 ± 11	107 ± 10	0.145
Diastolic BP (mmHg)	62 ± 7	58 ± 7	0.058
Mean BP (mmHg)	78 ± 7	77 ± 7	0.353
Pulse pressure (mmHg)	49 ± 9	48 ± 8	0.853
Resting heart rate (bpm)	61.2 ± 7.1	56.5 ± 7.9	0.020

Mean ± SD. Abbreviations are the same as in Table 1

Table 4 Blood pressure status of young Japanese women with (FHD+) and without (FHD−) a family history of type 2 diabetes

	FHD+	FHD−	p values
A: total	($n=73$)	($n=259$)	
Normal blood pressure	60, 82.2	240, 92.7	0.034
Elevated blood pressure	8, 11.0	12, 4.6	
Hypertension stage 1	3, 4.1	6, 2.3	
Hypertension stage 2	2, 2.7	1, 0.4	
B: nonathletes	($n=55$)	($n=148$)	
Normal blood pressure	44, 80.0	135, 91.2	0.031
Elevated blood pressure	7, 12.7	8, 5.4	
Hypertension stage 1	2, 3.6	5, 3.4	
Hypertension stage 2	2, 3.6	0, 0.0	
C: athletes	($n=18$)	($n=111$)	
Normal blood pressure	16, 88.9	105, 94.6	0.47
Elevated blood pressure	1, 5.6	4, 3.6	
Hypertension stage 1	1, 5.6	1, 0.9	
Hypertension stage 2	0, 0.0	1, 0.9	

Data are n, %

Fasting PG and insulin, HOMA-IR, serum leptin and adiponectin did not differ between the two groups.

Higher MBP, SBP and DBP were evident in nonathletic FHD+ whereas resting heart rates were comparable (Table 2). In contrast to nonathletes, differences in BP were not significant in athletes although SBP and DBP were higher in athletic FHD+ (Table 3). However, mean resting heart rate was lower in FHD− compared with FHD+ athletes. Pulse pressure, anthropometric indices, fasting glucose and insulin, HOMA-IR and adipokines did not differ between FHD+ and FHD− of the two groups, except for lower serum leptin in nonathletic FHD+. DBP ($p=0.01$) and resting heart rate ($p<0.001$) were lower in athletes with FHD compared to nonathletes with FHD although SBP was comparable ($p=0.40$).

In total, the prevalence of elevated BP, HT1 and HT2 was higher in FHD+ compared to FHD− women (Table 4A). Differences in the prevalence of the four BP groups between FHD+ and FHD− were evident in nonathletes (Table 4B) whereas they did not reach statistical significance in athletes (Table 4C). The higher prevalence of women with SBP/DBP ≥ 120/80 mmHg between FHD+ vs. FHD− was evident in the total population (17.8 vs. 7.3%, $p=0.007$) and nonathletes (20.0 vs. 8.8%, $p=0.02$) but the difference was not significant in athletes (11.1 vs. 5.4%, $p=0.35$).

In correlation analyses, FHD+ was associated with both SBP ($r=0.19$, $p<0.001$) and resting heart rate ($r=0.11$, $p=0.04$) whereas training (athletes) was associated with resting heart rate ($r=0.36$, $p<0.001$) but not with SBP ($r=0.001$, $p=0.97$).

Discussion

Our study demonstrates that young normal weight Japanese women with FHD, which has been shown to be associated with microvascular dysfunction [15], had higher BP and a higher prevalence of elevated BP and hypertension in spite of comparable fat mass and distribution, markers of insulin resistance, serum adipokines studied. Further, there was no difference in SBP, MBP and BP prevalence between FHD+ athletes and FHD− athletes. Resting heart rate was higher in FHD+ athletes than in FHD− athletes, whose resting heart rate averaged 56.5 bpm.

We have recently found that FHD was associated with microvascular dysfunction [15] and decreased early phase glucose-induced insulin secretion (insulinogenic index) [21] in young normal weight Japanese women. These and the present finding of association of FHD with a higher prevalence of elevated BP and hypertension may be compatible with a prospective study showing that parental history of type 2 diabetes and lower insulin secretion are associated with incident hypertension [22], because microvascular endothelial dysfunction may contribute not only to primary (essential) hypertension [3–5] but to insulin resistance and reduced insulin secretion [23, 24].

The Bogalusa Heart Study demonstrated that parental diabetes is an independent predictor of longitudinal changes among the offspring for adiposity, insulin, glucose,

HOMA-IR, SBP and DBP [25]. Using differential prevalence of the risk variables during childhood, adolescence, and young adulthood, these offspring of diabetic parents display excess body fat beginning in childhood advancing to disorders of dysglycemia during adolescence and finally to dyslipidemia and hypertension (> 140/90 mm Hg) by young adulthood [25]. We have recently shown that young normal weight Japanese FHD+ and FHD− women did not differ in BMI at age 12 and 15 years [21]. In the absence of excess weight gain and dysglycemia (Table 1), FHD was associated with higher BP and higher prevalence of elevated BP and hypertension in the present study, suggesting obesity-independent mechanisms linking FHD and high BP.

In addition to obesity, low birth weight is an important driver of microvascular dysfunction [24]. We found, in young normal weight Japanese women, that FHD was associated with (1) reduced birth weight [21], (2) decreased glucose-induced insulin secretion and increased glucose excursion after an oral glucose load [21], (3) microvascular dysfunction (impaired microvascular insulin sensitivity) [15] and (4) higher BP and higher prevalence of elevated BP and hypertension in the present study. Taken together, subtle microvascular dysfunction associated with FHD may contribute to elevations not only in BP but also in glycemia associated with reduced insulin secretion in normal weight Japanese women although we did not measure microvascular function directly.

Higher BP and higher prevalence of elevated BP and hypertension were not found in FHD+ athletes in the present study, suggesting that endurance training improved impaired microvascular insulin sensitivity in FHD+ offspring as previously reported [26–28]. Exercise has been reported to increase human skeletal muscle insulin sensitivity via coordinated increases in microvascular perfusion and molecular signaling in muscle [29, 30].

It is well known that athletes have a low resting heart rate. Reduced intrinsic heart rate and an increase in cardiac parasympathetic activity may contribute to a low resting heart rate associated with exercise training [31, 32] although the mechanisms are under debate. In addition, the heart rate response to exercise has been shown to be heritable although less is known about the genetic basis of long-term heart rate responses to exercise [33]. In the present study, a difference (decrease) in the mean resting heart rate in nonathletes vs. athletes was evident in FHD− (64.6 vs. 56.5 bpm) whereas it was smaller in FHD+ (64.7 vs. 61.2 bpm). These observations suggest that FHD may be associated with reduced heart rate response to endurance training in normal weight Japanese women.

Insulin sensitivity was decreased in white children with FHD whereas insulin secretion did not differ between children with and without FHD [34]. In contrast, it is insulin secretion that was decreased in young Japanese adults with FHD whereas insulin sensitivity did not differ or rather increased in FHD youth [35, 36]. In young Japanese women, FHD was related to decreased insulin secretion but was not related to insulin resistance/sensitivity [21].

The strengths of the present study include a homogeneous study population with scarce confounding factors as previously reported [34] and accurate and reliable measures of DXA-derived body composition. Several limitations of this study warrant consideration. It is well known that family history of hypertension is a risk factor for hypertension [35]. However, we did not assess this information. The cross-sectional design of the present study complicates the drawing of causal inferences. A single measurement of BP, heart rate and biochemical variables may be susceptible to short-term variation, which would bias the results toward the null. Athletes studied were small in number. The recruitment procedure may also have some potential impact on the results. As the participation was voluntary, women who pay more attention to health may be more likely to participate. We used crude measures of insulin sensitivity/insulin resistance and insulin secretion, which may be less accurate. Statistical power was not calculated. As we studied young Japanese women only, results may not be generalized to other genders, age populations, races, or ethnicities.

In conclusion, the present study demonstrates that young Japanese women with FHD have higher BP and higher prevalence of elevated BP and hypertension. Although we can only speculate about the mechanisms underlying these differences and recognize that they should be further investigated, we believe that young Japanese women with FHD should be encouraged to modify their lifestyles to increase their insulin sensitivity by exercise and thereby avoid further development of metabolic and subsequent cardiovascular diseases. Reduced heart rate response to endurance training in women with FHD needs further studies.

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Declarations

Conflict of interest None of the authors has any potential conflicts of interest to declare associated with this research.

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