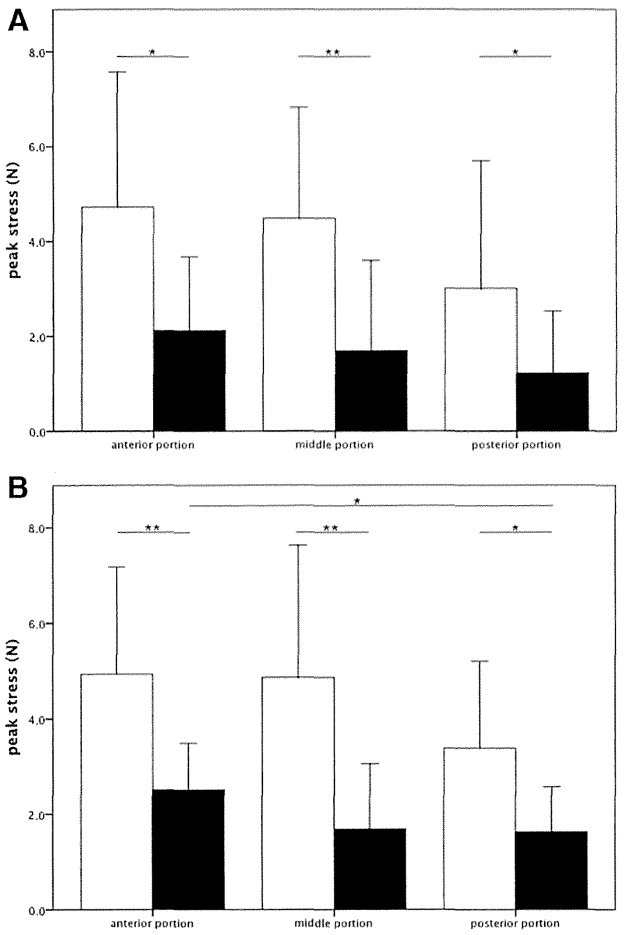

Figure 12. Peak stress of the lateral (A) and medial (B) menisci. The open box is peak stress of the central zone, while the closed box is peak stress of the peripheral zone in each region. $^{*}p < 0.05$, $^{**}p < 0.01$. Error bar, ±2 SD.

the PZ is higher than that in the CZ (Fig. 10). Large radial tie fibers were observed in the PZ (Fig. 3 arrow).[8,17] Instead, GAG content in the CZ was higher (Fig. 11). Results of the current and a previous biomechanical analysis have shown that compression strength in the CZ was high (Fig. 12), but the CZ was weak under tensile stress. On the other hand, tensile strength in the PZ was high, but the PZ was weak under compression.[8] Not only zonal differences, but also anatomic and regional differences, influence strength against tensile stress in the human meniscus.[17]

Tissues subjected to large tensile stresses contain a large amount of collagen, whereas tissues subjected primarily to compressive loading contained a large amount of proteoglycans with charged GAG chains. It is clear that the concentration of GAGs contributes to strength against compressive stress. It is expected that strength against compressive stress would be high, but the result was opposite (Fig. 12). Collagen is another factor that has a predominant influence biomechanical property. It has been reported that circumferential fibers transformed the axial load to hoop stress and that the radial tie fibers influence the tensile properties. Current results suggest that this might be the reason why peak stress was not consistent with GAG content.

In the current study, we used the menisci of 6-month-old pigs. We must consider differences associated with species and age of the animal. Clear differences have been demonstrated between different species.[7] For example, the shape and ECM contents of lapine meniscus are different from those of human meniscus.[18] The porcine meniscus resembles human meniscus in shape, vascular penetration,[19] and collagen orientation.[20] In many studies, the more mature porcine model is used for repair models.[21] The adult porcine meniscus is as an often-used animal model for meniscus repair, but the detail about locational difference in the cellular phenotype, vascular penetration and ECM remain unclear. We focused to analyze the biologic characteristic of the different locations within immature porcine meniscus in this study. Although further study is required, the data obtained in the current study using a comprehensive approach are useful for understanding the biology of the meniscus.

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Association of Serum–Free Fatty Acid Level With Reduced Reflection Pressure Wave Magnitude and Central Blood Pressure

The Nagahama Study

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Abstract—Central blood pressure (BP) has been suggested to be a better predictor of cardiovascular disease risk than brachial BP. Given that central BP and arterial waveform are both influenced by insulin resistance, major initiators of insulin resistance, such as serum–free fatty acid (FFA), are suspected of potentially being involved in central hemodynamics. To confirm that insulin signaling is an important modulator of central hemodynamics, we investigated this hypothesis in a large-scale general population. Brachial BP and radial arterial waveform were measured simultaneously in 9393 middle-aged to elderly individuals. The augmentation index was calculated from the radial waveform as the ratio of the height of the late systolic peak to that of the first peak. Central systolic BP was defined as the absolute pressure of the late systolic peak of the waveform. Differences in central and brachial pulse pressure (PP) were considered to represent PP amplification. PP amplification differed significantly among serum FFA level quartiles (Q1, 7.8±5.3; Q2, 8.6±5.0; Q3, 9.3±5.7; Q4, 10.3±6.1 mm Hg; $P<0.001$), and the maximum difference in combination with diabetes mellitus status was 4.9 mm Hg. Multivariate analysis adjusted for major covariates indicated that higher serum FFA was an independent determinant for higher PP amplification ($\beta=0.145$, $P<0.001$) and lower augmentation index ($\beta=-0.122$, $P<0.001$) and central systolic BP ($\beta=-0.044$, $P<0.001$), whereas the association between FFA and PP amplification significantly decreased ($\beta=0.022$, $P<0.001$) after further adjustment for augmentation index. Serum FFA is an overlooked factor favorably influencing central hemodynamics. A low-magnitude reflection pressure wave might be involved in this paradoxical relationship. (*Hypertension*. **2014;64:1212-1218.)** • **Online Data Supplement**

Key Words: aortic blood pressure ■ free fatty acid ■ insulin resistance ■ pulse wave analysis

Hypertension is a leading cause of cardiovascular disease, with brachial blood pressure (BP) being a standard measure in the assessment of arterial pressure load. However, central BP estimated from the radial arterial waveform has recently been suggested to be more closely associated with cardiovascular outcomes than brachial BP.[1–3] In addition to these epidemiological findings, clinical studies from several groups[4–6] and our own[7] have suggested that antihypertensive drugs might exert different effects on arterial waveform and central BP, possibly resulting in different cardiovascular outcomes. The Conduit Artery Function Evaluation substudy[4] of the Anglo-Scandinavian Cardiac Outcomes Trial demonstrated that calcium channel blockers were superior to β-blockers for reducing cardiovascular events. This effect was presumably because of the central systolic BP (SBP) being lower in the calcium channel blocker treatment arm, whereas no class-specific effects were observed regarding brachial SBP. The apparent influence of central BP on cardiac outcomes highlights the importance of identifying factors that might affect central BP levels.

Several factors have been reported to influence central BP levels by altering the arterial pressure waveform,[8] a composite waveform of the forward pressure wave generated by cardiac ejection and the backward pressure wave reflected at peripheral sites. Arterial stiffness causes the early return of reflection pressure waves from peripheral sites and thus increases overlaps between forward and reflection pressure waves at the aorta, which increase central SBP. Other factors also influence arterial waveform, such as tall stature greatly decreasing the overlap of the 2 waveforms by delaying the arrival of the

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reflection pressure wave and increased heart rate (HR) reducing the overlap by shortening the cardiac ejection period.

Curiously, type 2 diabetes mellitus and insulin resistance have been favorably associated with central hemodynamics. Several groups[9,10] and our own[11] have shown that individuals with type 2 diabetes mellitus had relatively low central SBP, despite the well-established pathogenicity of diabetes mellitus for arterial stiffness and cardiovascular diseases. Although the mechanisms behind this paradoxical relationship are unclear, a possible explanation is reduced magnitude of the reflection pressure wave[12] because of a stiffer aortic artery and consequently larger penetration of pulsatile energy into the microcirculation.[13,14] Insulin-mediated vasoconstriction under insulin-resistant conditions[15] might also be involved in the increased transmission of pulsatile energy.

Free fatty acid (FFA) is a major initiator of insulin resistance.[15,16] FFA blocks insulin signaling via phosphorylation of insulin receptor substrate 1, which inhibits translocation of glucose transporter to the cell membrane and reduces glucose uptake.[15] Further, FFA has been shown to reduce endothelium-dependent vasodilation by decreasing endothelial nitric oxide production.[14] Given these molecular bases of FFA in initiation of insulin resistance, we hypothesized that serum FFA levels might also be associated with central hemodynamics. Proving our hypothesis would further support the involvement of insulin signaling in central hemodynamic control and would help to further understand the basis of paradoxical relationship between insulin resistance and better central hemodynamic profile.

Here, we investigated our hypothesis using a data set from the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study), a large-scale population-based cohort study in Japan.

Methods

Study Subjects

Study subjects were 9393 apparently healthy middle-aged to elderly citizens who had participated in the Nagahama Study. This study cohort was recruited from 2008 to 2010 from the general population of Nagahama City, a largely suburban city of 125 000 inhabitants in central Japan. Community residents aged 30 to 74 years, living independently and with no physical impairment or dysfunction, were recruited. Of 9804 total subjects, those meeting any of the following conditions were excluded from this study: history of symptomatic cardiovascular diseases (n=266), taking insulin therapy (n=22), unsuccessful assessment of clinical parameters required for this study (n=80), and pregnant women (n=43).

Of the 9393 subjects remaining after exclusion, individuals with available fasting blood specimens (>11 hours) were used as the study panel (n=4322), whereas those with peripheral blood samples drawn within 10 hours of their last meal were used as the replication panel (n=5071).

All study procedures were approved by the ethics committee of Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board. Written informed consent was obtained from all participants.

BP Measurement

Radial arterial waveform, brachial BP, and HR were measured simultaneously (HEM-9000AI; Omron Healthcare, Kyoto, Japan) after 5 minutes resting in the sitting position. Briefly, brachial BP was measured at the right upper arm using a cuff-oscillometric device, and the radial arterial waveform was simultaneously obtained from the left wrist using a multielement tonometry sensor. The augmentation index (AIx) was calculated from the radial arterial waveform as the ratio of the height of the late systolic peak (SBP2) to the first systolic peak. The absolute pressure of SBP2 obtained by calibrating the first systolic peak with brachial SBP was considered to represent the central SBP. Pulse pressure (PP) amplification was calculated by subtracting central PP from brachial PP and expressed in absolute values (mm Hg). Measurements were taken twice, and the mean value of these measurements was used in analysis. The validity of SBP2 in estimating central SBP has been demonstrated by invasive simultaneous measurement of the ascending aorta and radial artery pressure.[17,18] We also previously reported that radial SBP2 was closely related to the central SBP calculated by the widely used generalized transfer function.[19] Mean BP was calculated using the following formula: Mean BP=diastolic BP +(SBP−diastolic BP)/3.

Clinical Parameters

Basic clinical parameters were measured at the baseline examination of the Nagahama cohort study. Serum FFA levels were quantified using an enzymatic assay (NEFA-HR; Wako Pure Chemical Industries, Ltd., Osaka, Japan). Intra- and interassay coefficients of variation in FFA measurements were 1.42% and 1.79%, respectively. Homeostasis model assessment of insulin resistance was calculated as an index of insulin resistance using the following formula: [insulin (IU/l)×glucose (mg/dL)]/405.

Assessment of Arterial Stiffness

Arterial stiffness was assessed by pulse wave velocity (PWV) measured between the brachia and ankle (baPWV). Briefly, cuffs were applied to both brachia and ankles, and BP was measured simultaneously in the supine position using a cuff-oscillometric device (Vasera-1500; Fukuda Denshi, Tokyo, Japan). Pulse volume waveforms were also recorded simultaneously using a plethysmographic sensor connected to the cuffs. The baPWV was calculated from the time interval between the wave fronts of the brachial and ankle waveforms and the path length from the brachia to ankle (0.597×height+14.4014).[20] The colinearity of baPWV with a carotid-to-femoral PWV, a standard measure of arterial stiffness, has been previously reported.[21]

Statistical Analysis

Quartile of PP amplification and serum FFA level was calculated for each sex and then combined to avoid potential sex differences. Differences in numeric parameters among subgroups were assessed by analysis of variance, whereas the frequency of differences among subgroups was evaluated using a χ^2 test. Factors independently associated with PP amplification and AIx were assessed by multiple linear regression analysis. Statistical analysis was performed using JMP 9.0.3 software (SAS Institute, Cary, NC, USA). $P<0.05$ indicated statistical significance.

Results

Clinical characteristics of study subjects are summarized in Table 1. Plasma levels of triglycerides, insulin, and FFA were slightly higher in the replication panel than in the study panel ($P<0.001$), whereas no marked differences were observed for other parameters.

Table 2 shows the differences in metabolic parameters among quartiles of PP amplification. Subjects with larger PP amplification were markedly younger and taller and had faster HR than those with less amplification. Although several clinical parameters significantly differed among quartiles in crude analysis, parameters for insulin resistance, including FFA levels, remained significant even after adjustment for major covariates.

As a whole, women had significantly higher FFA levels than men (Figure 1). Older age ($r=0.087$, $P<0.001$), lower body mass index ($r=-0.084$, $P<0.001$), increased high-density lipoprotein

Table 1. Clinical Characteristics of Study Subjects

Factors	Study Panel (4322)	Replication Panel (5071)
Age, y	53±13	53±13
Sex (men, %)	31.6	32.9
Body height, cm	160.1±8.4	159.9±8.5
Body weight, kg	57.0±10.9	57.3±10.9
Body mass index, kg/m^2	22.1±3.2	22.4±3.3
Waist circumference, cm*	79.8±9.8	80.4±9.3
Medication, %		
Hypertension	15.6	16.1
Hyperglycemia	2.4	2.4
Dyslipidemia	11.5	10.9
Brachial SBP, mm Hg	123±18	124±18
Central SBP, mm Hg	114±19	114±18
DBP, mm Hg	76±11	76±11
PP amplification, mm Hg	9±6	10±6
Radial AIx, %	81.6±13.4	79.8±13.4
Heart rate, bpm	69±10	70±10
baPWV, cm/s	1261±231	1262±227
Type 2 diabetes mellitus	4.0	3.6
Glucose, mg/dL	90±14	90±16
HbA1c, %	5.5±0.5	5.4±0.5
Insulin, μU/mL	5.0±3.1	5.7±6.1
Total cholesterol, mg/dL	207±34	207±35
HDL cholesterol, mg/dL	66±17	65±17
LDL cholesterol, mg/dL	123±31	123±31
Triglyceride, mg/dL	91±58	103±68
FFA, mEq/L	0.69±0.24	0.78±0.31

Values are mean±standard deviation. The study panel consisted of individuals whose fasting blood specimens (>11 h) were available, and the replication panel consisted of individuals whose peripheral blood samples were drawn within 10 h of their last meal. AIx indicates augmentation index; baPWV, brachial-to-ankle pulse wave velocity; DBP, diastolic blood pressure; FFA, free fatty acid; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PP, pulse pressure; and SBP, systolic blood pressure.

*Data available for 4320 (study panel) and 5069 (replication panel) subjects. Type 2 diabetes mellitus was defined as one or more of fasting plasma glucose ≥126 mg/dL, occasional plasma glucose ≥200 mg/dL, HbA1c ≥6.5%, or taking oral antihyperglycemic drugs.

(r=0.190, P<0.001) and total cholesterol levels (r=0.085, P<0.001), and higher brachial SBP (r=0.057, P<0.001) had a significant but weak association with serum FFA levels (Tables S1 and S2 in the online-only Data Supplement). PP amplification markedly increased with FFA quartile (Figure 2), although both brachial and central SBP also showed linear association with FFA levels (Figure S1). In combined analysis with diabetes mellitus status (Figure 2C), differences in PP amplification between the highest (diabetic individuals with highest FFA quartile) and lowest (nondiabetic controls with lowest FFA quartile) subgroups reached ≈4.9 mm Hg. In contrast, AIx exhibited an inverse association with FFA quartile (Figure 2D), whereas baPWV was positively associated with FFA quartile (Figure 2E).

Table 3 summarizes the results of multiple regression analysis for central hemodynamic parameters. Results indicated that serum FFA level was an independent positive determinant for PP amplification (Model 1). Given that FFA was also strongly and inversely associated with AIx, we further adjusted AIx in the regression analysis (Model 2). Although the association between serum FFA and PP amplification remained significant, the regression coefficient of FFA substantially decreased. Lower AIx might, therefore, be involved in the relationship between elevated serum FFA levels and elevated PP amplification. Further, FFA overtook the positive association between plasma insulin level and AIx (Models 3 and 4). Results of these regression analyses indicated that serum FFA levels rather than plasma insulin concentration is a key factor in reducing AIx in subjects with insulin resistance. Waist circumference was not identified as an independent determinant when included instead of body weight in regression Model 4 (P=0.466). The association of FFA with AIx might be independent of adiposity. Serum FFA level also showed an inverse and independent association with central SBP after adjustment for brachial SBP (Model 5).

FFA was a positive determinant for arterial tone when assessed via baPWV (Model 6). However, the associations of FFA with AIx (Model 4), as well as central pressure (Model 1, 2, and 5), were independent of baPWV, suggesting that changes in reflection magnitude rather than transit time of the reflection pressure wave might be involved in the paradoxical relationship between higher FFA and better central hemodynamic profiles.

These findings were supported in the analysis using the replication panel, irrespective of potential differences in fasting status, and no marked sex differences were found in any regression model (Table S3). When MBP was adjusted in the regression models instead of SBP, no marked changes were observed in the regression coefficients of FFA as follows: Model 2 (PP amplification), β=0.030, P<0.001; Model 4 (AIx), β=−0.115, P<0.001; Model 5 (cSBP), β=−0.016, P<0.001; and Model 6 (baPWV), β=0.073, P<0.001. Further, the association of FFA with central hemodynamic parameter was independent of glycemic control levels assessed by hemoglobin A1c: hemoglobin A1c–adjusted regression coefficients of FFA; Model 2, β=0.022, P<0.001; Model 4, β=−0.123, P<0.001; Model 5, β=−0.044, P<0.001; and Model 6, β=0.069, P<0.001.

Discussion

In the present study, we clarified that elevated serum FFA levels were strongly associated with increased PP amplification and decreased AIx, which represents relatively low central BP, in a large-scale general population sample. To our knowledge, this is the first report of a favorable association of FFA with central BP and arterial waveform, which suggests the importance of insulin signaling as a modulator of central hemodynamics. Reduced magnitude of the reflection pressure wave might be involved in this paradoxical relationship.

Insulin resistance and diabetic status have been shown to be favorably associated with AIx and central BP in observational studies in patients with diabetes mellitus[22,23] and general populations,[9,13] as well as in an experimental study using a euglycemic insulin clamp technique.[24] We also reported that not only increased insulin resistance but also reduced insulin sensitivity assessed by an oral glucose tolerance test were factors that

Table 2. Differences in Metabolic Parameters Among the Quartile of PP Amplification (Study Panel)

		Q1	Q2	Q3	Q4	*P*	
Range, mm Hg	Men	<6.5	6.5–9.9	10.0–14.4	≥14.5	Crude	Adjusted
	Women	<4.5	4.5–7.4	7.5–10.9	≥11.0		
No. of subjects		982	1143	1101	1096		
Age, y		57±11	56±12	53±13	47±14	<0.001	
Body height, cm		158.5±7.9	159.0±8.0	160.4±8.1	162.6±8.8	<0.001	
Body weight, kg		55.6±9.7	56.7±10.2	57.0±10.6	58.7±12.4	<0.001	
Brachial SBP, mm Hg		125±19	122±17	122±18	123±19	0.006	
Heart rate, bpm		64±8	67±9	70±10	74±11	<0.001	
Glucose, mg/dL		90±13	90±11	91±16	91±14	0.026	<0.001
Insulin, μU/mL		4.6±2.8	5.0±2.9	5.0±2.9	5.5±3.5	<0.001	<0.001
HOMA-IR		1.04±0.70	1.13±0.74	1.16±0.77	1.26±1.00	<0.001	<0.001
HbA1c, %		5.5±0.4	5.5±0.4	5.5±0.6	5.3±0.6	0.294	0.006
Total cholesterol, mg/dL		210±33	208±33	207±34	202±36	<0.001	0.362
HDL cholesterol, mg/dL		66±17	65±16	66±17	66±17	0.149	0.070
LDL cholesterol, mg/dL		126±30	125±30	123±31	119±32	<0.001	0.022
Triglyceride, mg/dL		91±51	93±57	90±53	90±69	0.618	0.337
FFA, mEq/L		0.63±0.23	0.68±0.23	0.71±0.24	0.74±0.25	<0.001	<0.001

Values are mean±standard deviation. Study subjects were divided into quartile by PP amplification within sex and then combined to avoid potential sex differences. Statistical significance was assessed by analysis of variance (crude model). *P* values adjusted for age, sex, body height, body weight, and use of antihyperglycemic or lipid level–lowering drugs were obtained by linear regression analyses (adjusted model). FFA indicates free fatty acid; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; and SBP, systolic blood pressure.

modulate the arterial waveform and reduce central BP.[12] In the present study, however, serum FFA was a more prominent determinant of AIx than insulin. FFA initiates insulin resistance via upstream inhibition of insulin signaling in target cells, whereas increased plasma insulin levels or hyperinsulinemia are secondary responses to compensate for reduced glucose uptake under conditions of insulin resistance. The phase difference in the roles of FFA and insulin may explain the stronger association of FFA with AIx.

In stiffer arteries, the stiffness gradient from aorta to resistant artery was progressively dissipated. Decreased stiffness gradient reduces partial reflection of the forward pressure wave and increases transmission of the pulsatile energy into peripheral microcirculation, which reduces the magnitude of reflection.[14] Chirinos et al[13] recently observed selective stiffening of the aorta, but not more distal arteries, in patients with type 2 diabetes mellitus and suggested that this selective stiffening was the underlying mechanism for the paradoxical observation of a lower reflection magnitude in subjects with type 2 diabetes mellitus. Odaira et al[25] also reported that the contribution of the wave reflection to central hemodynamics might be reduced in subjects with relatively stiff arteries. Because baPWV and AIx were inversely associated with FFA quartile, that is, faster baPWV and lower AIx in higher FFA quartiles, our findings support the pulsatile energy hypothesis.

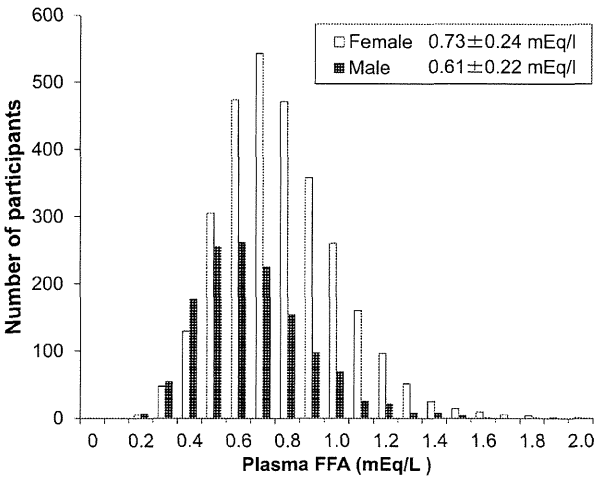

Figure 1. Histogram of serum-free fatty acid (FFA) level (study panel). Serum FFA level was significantly higher in women than in men (analysis of variance, $P<0.001$).

FFA plays a key role in the initiation of insulin resistance by inhibiting glucose uptake of target cells.[15] Given the importance of endothelium-derived nitric oxide in vascular relaxation shown in an animal model of hypertension,[26] the decreased nitric oxide production at the endothelium and subsequent endothelial dysfunction are concomitant mechanisms for the development of insulin resistance via FFA.[15] As our study participants were an apparently healthy general population without severe insulin resistance, reduced endothelial nitric oxide production might be a principal factor in the increased aortic tone and, consequently, larger pulsatile energy in subjects with higher FFA. Insulin increases aortic tone by activating the sympathetic nervous system under the condition of insulin resistance. However, given the weak relationship between serum FFA and insulin levels, the involvement of insulin-mediated sympathetic activation might be independent of the effect of FFA. This is supported by the results of our regression analysis that show the insulin-independent association of FFA with baPWV.

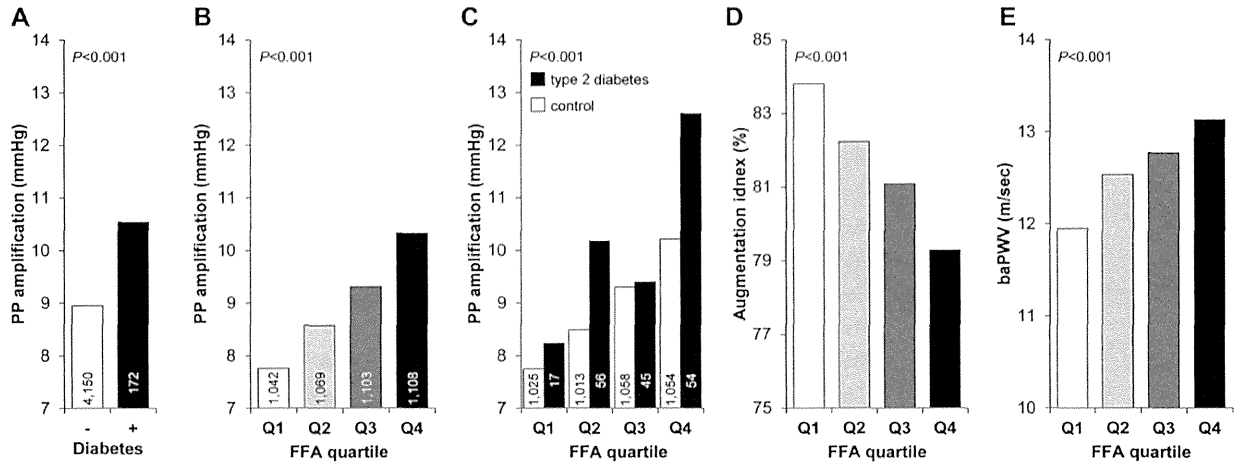

Figure 2. Association of free fatty acid (FFA) quartile with central hemodynamic parameters (study panel). Number of study participants in each subgroup are shown in the column. Statistical significance was assessed by analysis of variance. **A**, **B**, and **C**, pulse pressure (PP) amplification; **D**, augmentation index; **E**, brachia-to-ankle pulse wave velocity (baPWV).

We also investigated associations between plasma lipid parameters and PP amplification, but no remarkable relationships were observed after adjustment for basic covariates. These results further emphasize the importance of serum FFA, but not lipid profile, as a factor involved in central hemodynamics. A previous study in Australia[27] reported that obesity, particularly visceral adiposity, was significantly associated with smaller AIx. As serum FFA is mostly released from enlarged and stressed adipose tissue,[28] FFA might be a confounding factor in the inverse association between visceral adiposity and smaller AIx. No association between waist circumference and AIx was observed in the present study, which supports our hypothesis.

The maximum difference in PP amplification among all FFA quartiles was ≈2.5 mm Hg. This BP difference was somewhat larger than that observed in our previous reports of the association of smoking intensity[29] and insulin sensitivity.[12] The combination of FFA quartile and type 2 diabetes mellitus status further increased the maximum PP difference to 4.9 mm Hg. A previous clinical study, the Conduit Artery Function Evaluation (CAFE) study,[8] clearly indicated that even a 3-mm Hg difference between brachial and central SBP was associated with improved cardiovascular outcomes. Further, several studies have shown that an increase in central SBP of only 1 mm Hg has a substantial effect on large arterial remodeling[30] and silent cerebral damage.[31] Our findings therefore emphasize the importance of measuring serum FFA levels as a potential factor that modulates central hemodynamics and of measuring central BP in epidemiological and clinical settings.

Several limitations to the present study warrant mention. First, we did not directly measure transit time and magnitude of reflection pressure wave. As transit time largely correlate with baPWV, we deduced from results of the regression analysis that reduced magnitude rather than delayed arrival of reflection pressure wave might be involved in the paradoxical relationship between FFA and better central hemodynamic

Table 3. Multiple Linear Regression Analysis for Central Hemodynamic Parameters

Study Panel	Independent Variables	PP Amplification		AIx		Central SBP	baPWV
		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Study panel (n=4322)	Type 2 diabetes mellitus	0.027 (0.039)	0.015 (0.007)	−0.014 (0.233)	−0.012 (0.315)	−0.008 (0.039)	0.061 (<0.001)
	Insulin (log-transformed)	0.003 (0.855)	0.019 (0.004)	0.023 (0.100)	0.016 (0.241)	−0.001 (0.855)	0.071 (<0.001)
	AIx, %		−1.004 (<0.001)				
	FFA, mEq/L	0.146 (<0.001)	0.022 (<0.001)		−0.123 (<0.001)	−0.044 (<0.001)	0.069 (<0.001)
Replication panel (n=5071)	Type 2 diabetes mellitus	0.038 (0.001)	0.020 (<0.001)	−0.016 (0.130)	−0.018 (0.082)	−0.012 (0.001)	0.055 (<0.001)
	Insulin (log-transformed)	0.028 (0.043)	0.037 (<0.001)	0.049 (<0.001)	0.009 (0.497)	−0.009 (0.043)	0.082 (<0.001)
	AIx (%)		−1.003 (<0.001)				
	FFA (mEq/L)	0.138 (<0.001)	0.023 (<0.001)		−0.115 (<0.001)	−0.045 (<0.001)	0.051 (<0.001)

Values are standardized regression coefficients (β). *P* values are shown in parenthesis. Adjusted factors were as follows: age, sex, body height, body weight, taking medication for hypertension or dyslipidemia, SBP, heart rate, total cholesterol, and baPWV. In regression Model 6, heart rate and baPWV were not adjusted. AIx indicates augmentation index; baPWV, brachial-to-ankle pulse wave velocity; FFA, free fatty acid; PP, pulse pressure; and SBP, systolic blood pressure.

profiles. More detailed waveform analysis would be needed to obtain conclusive evidence. Second, as this was a cross-sectional study, a longitudinal study is required to confirm the prognostic significance of central SBP differences arising from differences in serum FFA levels. Third, no information on the class of antihypertensive drugs was available for the Nagahama cohort sample, though β-blockers and vasodilators have substantial class effects on central BP that are well documented.[4–8] Given that the associations of FFA quartile with AIx and PPa were independent of antihypertensive medication, our results might be nondifferential and independent of the class effects of antihypertensive drugs.

Perspectives

In conclusion, we found that serum FFA level is an important factor influencing central hemodynamics. Our results might help identify the as yet unidentified mechanisms behind the favorable effects of insulin resistance and type 2 diabetes mellitus on the central hemodynamic profile.

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Disclosures

The authors have no conflicts of interest to disclose.

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Novelty and Significance

What Is New?

- Elevated serum–free fatty acid (FFA) levels were strongly associated with reduced magnitude of arterial reflection pressure wave and relatively low central blood pressure.
- Central pressure differs by ≈4.9 mm Hg because of serum FFA levels and diabetic status.

What Is Relevant?

- Insulin resistance and diabetic status have been shown to be favorably associated with arterial waveform and central blood pressure.

Serum FFA was a more prominent determinant of arterial waveform than insulin.

Summary

Serum FFA was a factor that was favorably associated with central hemodynamics. A favorable association of FFA with central BP and arterial waveform suggests the importance of insulin signaling as a modulator of central hemodynamics.

SUPPLEMENTAL MATERIALS

Association of serum free fatty acid level with reduced reflection pressure wave magnitude and central blood pressure The Nagahama Study

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Table S1. Correlation coefficient for serum FFA levels (study panel)

Factors	r	*P*
Age (years old)	0.087	<0.001
Body mass index (kg/m^2)	-0.084	<0.001
Brachial SBP (mmHg)	0.057	0.002
Central SBP (mmHg)	0.018	0.243
DBP (mmHg)	0.009	0.547
Glucose (mg/dl)	0.016	0.295
Insulin (μU/ml)	-0.023	0.125
HOMA-IR	-0.010	0.503
Total cholesterol (mg/dl)	0.085	<0.001
HDL cholesterol (mg/dl)	0.190	<0.001
LDL cholesterol (mg/dl)	-0.004	0.807
Triglyceride (mg/dl)	-0.034	0.027

HOMA-IR, homeostasis model assessment of insulin resistance.

Table S2. Differences in metabolic parameters among the FFA quartile (study panel)

		Q1	Q2	Q3	Q4	*P*	
Range (mEq/l)	Male	<0.45	0.45 to 0.57	0.58 to 0.72	>=0.73	Crude	Adjusted
	Female	<0.56	0.56 to 0.69	0.70 to 0.86	>=0.87		
No. of subjects		(1,042)	(1,069)	(1,103)	(1,108)		
Age (years old)		50±13	53±13	54±13	55±14	<0.001	
Body height (cm)		161.1±8.5	160.5±8.2	159.9±8.3	159.2±8.3	<0.001	
Body weight (kg)		57.4±10.0	57.8±11.2	57.1±10.9	55.8±11.2	<0.001	
Heart rate (beats/min)		66±9	68±10	70±10	72±11	<0.001	
Glucose (mg/dl)		88±10	91±12	91±14	92±16	<0.001	<0.001
Insulin (μU/ml)		5.0±3.0	5.1±3.0	5.2±3.2	4.9±3.0	0.306	0.053
HOMA-IR		1.10±0.74	1.16±0.79	1.19±0.84	1.15±0.88	0.081	0.004
HbA1c (%)		5.4±0.4	5.5±0.4	5.5±0.5	5.5±0.7	<0.001	0.005
Total cholesterol (mg/dl)		203±33	206±33	208±34	211±35	<0.001	<0.001
HDL cholesterol (mg/dl)		64±16	64±17	66±17	69±17	<0.001	<0.001
LDL cholesterol (mg/dl)		122±30	124±31	123±30	124±32	0.437	0.866
Triglyceride (mg/dl)		86±47	92±54	93±56	92±72	0.022	0.030

Values are mean ± standard deviation. Study subjects were divided into FFA quartile within sex and then combined to avoid potential sex differences. Statistical significance was assessed by analysis of variance (crude model). *P*-values adjusted for age, sex, body height, body weight, and use of antihyperglycemic or lipid level-lowering drugs were obtained by linear regression analyses (adjusted model). HOMA-IR, homeostasis model assessment of insulin resistance; FFA, free fatty acid

Table S3. Multiple linear regression analysis for central hemodynamic parameters by sex

		PP amplification		AIx		cSBP	baPWV
Sex	Independent variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Male (n=3,031)	Type 2 diabetes	0.034 (0.027)	0.027 (<0.001)	-0.006 (0.662)	-0.006 (0.643)	-0.013 (0.026)	0.077 (<0.001)
	Insulin (log-transformed)	0.060 (0.001)	0.045 (<0.001)	0.033 (0.038)	-0.014 (0.386)	-0.023 (0.001)	0.093 (<0.001)
	AIx (%)		-1.035 (<0.001)				
	FFA (mEq/l)	0.164 (<0.001)	0.026 (<0.001)		-0.134 (<0.001)	-0.063 (<0.001)	0.087 (<0.001)
Female (n=6,362)	Type 2 diabetes	0.039 (<0.001)	0.010 (0.039)	-0.027 (0.006)	-0.029 (0.003)	-0.010 (<0.001)	0.044 (<0.001)
	Insulin (log-transformed)	0.006 (0.629)	0.024 (<0.001)	0.047 (<0.001)	0.018 (0.117)	-0.002 (0.629)	0.080 (<0.001)
	AIx (%)		-1.013 (<0.001)				
	FFA (mEq/l)	0.158 (<0.001)	0.031 (<0.001)		-0.125 (<0.001)	-0.042 (<0.001)	0.040 (<0.001)

Values are standardized regression coefficient (β). *P*-values are shown in parenthesis. Adjusted factors were as follows; age, body height, body weight, taking medication for hypertension or dyslipidemia, SBP, heart rate, total cholesterol and baPWV. In the regression model 6, heart rate and baPWV were not adjusted. AIx, augmentation index; FFA, free fatty acid; baPWV, brachial-to-ankle pulse wave velocity.

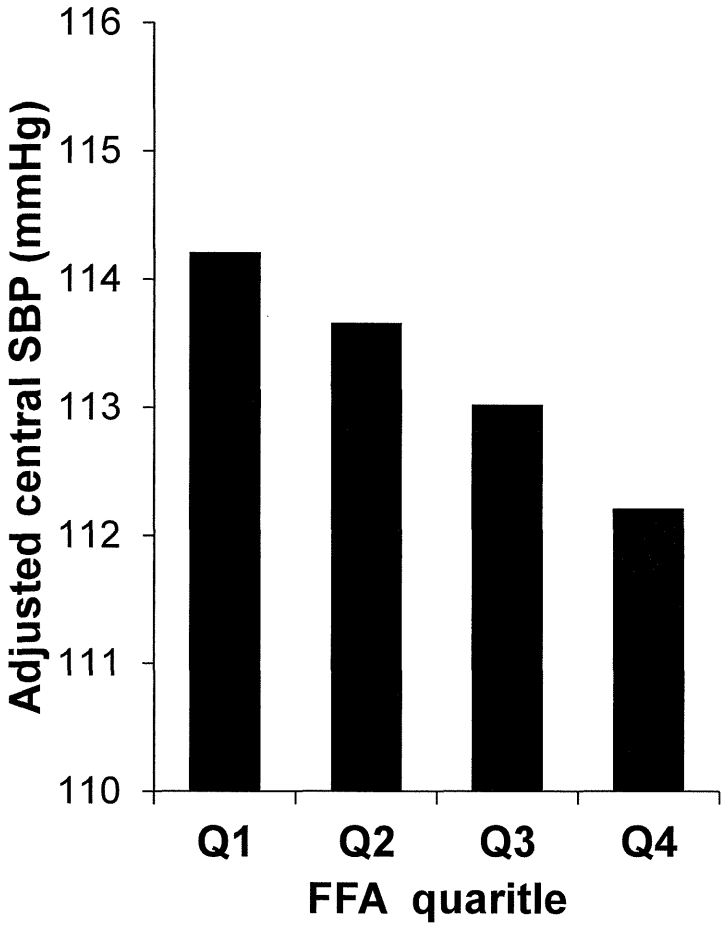

Figure S1 Mean adjusted central SBP levels by FFA quartile (Study panel)

Adjusted factors were as follows: age, sex, body height, body weight, taking medication for hypertension or dyslipidemia, SBP, heart rate, total cholesterol, insulin, baPWV, and type 2 diabetes. Overall *P*-value was <0.001.

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Association of Serum–Free Fatty Acid Level With Reduced Reflection Pressure Wave Magnitude and Central Blood Pressure: The Nagahama Study

Yasuharu Tabara, Yoshimitsu Takahashi, Takahisa Kawaguchi, Kazuya Setoh, Chikashi Terao, Ryo Yamada, Shinji Kosugi, Akihiro Sekine, Takeo Nakayama and Fumihiko Matsuda on behalf of the Nagahama Study Group

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SYMPOSIUM: 2014 KNEE SOCIETY PROCEEDINGS

The KSS 2011 Reflects Symptoms, Physical Activities, and Radiographic Grades in a Japanese Population

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Abstract

Background Cultural and ethnic differences are present both in subjective and objective measures of patient health, but scoring systems do not always reflect these differences, and so validation of outcomes tools in different cultural settings is important. Recently, a revised version of The Knee Society Score® (KSS 2011) was developed, but to our knowledge, the degree that this tool evaluates clinical symptoms, physical activities, and radiographic grades in the general Japanese population is not known.

Questions/purposes We therefore asked: (1) how KSS 2011 reflects knee conditions and function in the general Japanese population, in particular evaluating changes with increasing patient age; (2) can objective measures of physical function be correlated with KSS 2011; and (3) does radiographic osteoarthritis (OA) grade correlate with KSS 2011?

Methods Two hundred twenty-six people in the general Japanese population, aged 35 to 92 years, with and without knee arthritis, voluntarily participated in this cross-sectional study. Residents who had no serious disease or symptoms based on a self-assessment were recruited. This study consisted of a questionnaire including self-administered KSS 2011, physical examination, and weightbearing radiographs of the knee. Leg muscle strength, Timed Up and Go test, and body mass index (BMI) were examined in all the participants. Radiographs were graded according to the Kellgren and Lawrence scale (KL grade).

Results Multivariable linear regression analysis showed that KSS 2011 correlated with age (coefficient: -0.30 ± 0.12, $p = 0.011$), BMI (coefficient: -1.47 ± 0.42, $p < 0.001$), leg muscle strength (coefficient: 0.41 ± 0.13, $p = 0.002$), and Timed Up and Go Test (coefficient: -1.96 ± 0.92, $p = 0.034$), but not sex, as independent variables by a stepwise method. KSS 2011 was also correlated with radiographic OA evaluated by KL grade (coefficient: -12.2 ± 2.9, $p < 0.001$).

Conclusions KSS 2011 reflects symptoms, physical activities, and radiographic OA grades of the knee in an age-dependent manner in the general Japanese population.

The Nagahama Prospective Genome Cohort for the Comprehensive Human Bioscience (The Nagahama Study) is composed of the following principal investigators: Fumihiko Matsuda (chairperson), Ryo Yamada, Akihiro Sekine, Shinji Kosugi, and Takeo Nakayama (Kyoto University Graduate School of Medicine and School of Public Health).

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All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Level of Evidence Level IV, diagnostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

TKA is used widely to relieve pain and improve functional status in patients with symptomatic knee osteoarthritis (OA) [24]. The number of TKAs performed annually has increased in the United States [27] and in other countries [10, 12]. Patient satisfaction is now recognized as an important measure of healthcare quality [4, 13, 17]. However, despite substantial advances in patient selection, surgical technique, and implant design in primary TKA, a study has indicated that 11% to 18% of the patients are still unsatisfied with the operation [5]. In other words, TKA does not perfectly achieve its goal of relieving pain and restoring function in a substantial proportion of patients. One reason is that some patients expect full recovery of the motion of the knee and the ability to participate actively in recreational and physical activities after receiving TKA [18]. To evaluate the reasons why a certain fraction of patients who undergo TKA are dissatisfied, a proper evaluation of patients undergoing TKA is needed. It is also required that the evaluation method be closely related to physical function and, possibly, radiological grade of the patient.

The Knee Society Knee Scoring System® developed in 1989 (KSS 1989) is one of the most often used methods to evaluate patients undergoing TKA [8]. This scoring system has several advantages in terms of its reliability and use, and it has been adopted worldwide [2, 11]. However, increasing importance is being placed on the subjective aspects of evaluation, which have changed from those of prior generations, and were not captured by the KSS 1989. Therefore, in 2011, the new Knee Society Knee Scoring System® (KSS 2011) was refined to better characterize the expectations, satisfaction, and physical activities of more diverse populations of patients who undergo TKA [25]. This new scoring system is based on new scales and validation work [19], and its reliability has been evaluated by our research group and by others [14, 26] with satisfactory results. However, what is an appropriate score in this scoring system in a certain age group remains to be unveiled.

In this study, we asked the following questions: (1) how KSS 2011 reflects knee conditions and function in the general Japanese population, in particular evaluating changes with increasing patient age; (2) can objective measures of physical function be correlated with KSS 2011; and (3) does radiographic OA grade correlate with KSS 2011?

Patients and Methods

We conducted a cross-sectional study of the association between KSS 2011 and clinical symptoms and physical activities in a general Japanese population. Subjects were participants in the Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience (the Nagahama Study) [16]. The Nagahama Study participants were recruited from apparently healthy community residents aged older than 30 years living in Nagahama City, a largely rural city of approximately 124,000 inhabitants in Shiga Prefecture located in the center of Japan. The study has been continuously advertised in the city for residents with no serious disease or symptom based on a self-assessment, and a total of 226 residents with and without knee arthritis voluntarily participated in 2012. We did not specifically exclude patients with knee symptoms or prior knee surgery.

We translated the KSS 2011 questionnaire into Japanese. We used the self-administered questionnaire areas of the KSS 2011 questionnaire, including "symptoms," "patient satisfaction," and "functional activities." The questions on "expectations" were excluded because the participants did not plan to undergo TKA. The area "functional activities" comprises four components: "walking and standing," "standard activities," "advanced activities," and "discretionary activities." The full score of these questions is a maximum of 165 points. We supposed that participants did not have applicable answer choices for some of the questionnaire because the participants may have an impairment involving a body part other than the knee. Thus, in the area of "functional activities," we added a new answer: "I cannot do this because of a problem not related to the knee." Participants who chose this answer were excluded from the analyses. A total of 4% (nine of 224) answered this to the question about "walking and standing," 2.2% (five of 224) for "standard activities," 1.3% (three of 224) for "advanced activities," and 2.7%

Table 1. Baseline characteristics of the participants

Demographic	Mean ± SD
Number of participants	212
Female (ratio)	123 (58%)
Age (years)	60.3 ± 12.2
Height (cm)	161.4 ± 9.1
Weight (kg)	59.4 ± 11.8
BMI (kg/m^2)	22.7 ± 3.3
Leg strength (kg)	26.7 ± 10.3
Up and Go time (seconds)	6.2 ± 1.6

BMI = body mass index; Up and Go = Timed Up and Go Test.

Table 2. Demographic data of subgroups (mean ± SD)

Demographic	30s	40s	50s	60s	70s	80s
Number of participants	17	24	47	73	42	9
Female number (ratio)	12 (70%)	15 (62%)	29 (61%)	48 (65%)	18 (43%)	1 (11%)
Height (cm)	163.4 ± 10.4	163.6 ± 9.9	165.0 ± 8.7	159.3 ± 8.3	159.1 ± 8.8	158.6 ± 7.1
Weight (kg)	60.0 ± 13.3	61.2 ± 13.3	63.4 ± 14.0	56.5 ± 10.7	59.0 ± 8.7	56.1 ± 9.1
BMI (kg/m^2)	22.1 ± 3.6	22.7 ± 3.5	23.0 ± 3.7	22.1 ± 3.3	23.2 ± 2.3	22.2 ± 4.1
Leg strength (kg)	26.4 ± 12.4	28.5 ± 9.8	29.7 ± 12.6	25.4 ± 8.4	26.7 ± 9.6	19.1 ± 6.0
Up and Go time (seconds)	5.5 ± 1.0	5.4 ± 0.9	5.7 ± 0.7	6.2 ± 1.3	6.8 ± 1.5	9.0 ± 4.1
Participants with XP (number)				49	32	6
Radiographic knee OA (number)				19	13	4

BMI = body mass index; Up and Go = Timed Up and Go test; OA = osteoarthritis; XP = Xray photography.

(six of 224) for "discretionary activities." In total, 5.4% (12 of 224) participants were excluded for this reason. The female ratio, average age, and body mass index (BMI) of the 212 participants were 58% (123 of 212), 60.3 ± 12.2 years, and 22.7 ± 3.3 kg/m^2, respectively (Table 1).

Anthropometry measurements included height and weight, which were used to calculate BMI as weight in kg/height in m^2. Quadriceps strength was measured twice on both sides during a 3-second isometric contraction of the knee extensors with a handheld dynamometer (μ-Tas F-1; Anima Co, Chofu, Japan). With the participant in a seated position, the hip and the knee were positioned at 90° angles, and the force sensor was placed 10 cm above the lateral malleolus. The average bilateral maximum muscle strength was used to represent maximum muscle strength. Participants also performed the Timed Up and Go Test [23], which measures the time it takes a participant to stand up from a chair, walk a distance of 3 m, turn, walk back to the chair, and sit down as quickly as possible.

We evaluated weightbearing AP radiographs of both knees, which were performed by experienced radiology technicians. Eighty-eight of the 124 participants who were older than 60 years agreed to the examination. Radiographs of the knee were graded according to the scale described by Kellgren and Lawrence (KL grade) [9]. Two experienced orthopaedists (NT, HI), who were blinded with regard to participant status, read the radiographs in consultation. Knee OA was defined as a KL Grade 2 or higher in either knee. Radiographic knee OA was present in 41% (36 of 87) of the participants who completed the radiographic examination (Table 2). We used the average score of both knees as the variable for analysis.

Simple linear regression analysis was used to identify correlations between the KSS 2011 and age. We divided participants into six subgroups according to age. Because only one participant was older than 90 years, we included this participant in the 80s age group. In the analysis, relationships between the KSS 2011 and physical functions and those between the KSS 2011 and other factors were examined. After excluding weight and height, a stepwise method was applied for multivariable linear regression analysis. The relationship between the KSS 2011 and KL grade was evaluated by simple linear regression analysis separately because of the limited number of participants older than 60 years with radiographic data. All data were analyzed using the statistical package R (http://www.r-project.org/).

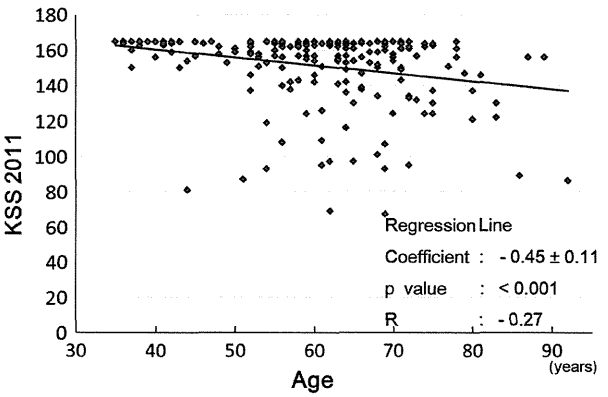

Fig. 1 Correlation of KSS 2011 and age is shown. Linear regression analysis showed a significant correlation between KSS 2011 and age.

Results

We found that increased age was correlated with decreasing scores on KSS 2011 (Fig. 1). Because age is an essential factor when deciding a therapeutic strategy, we divided the whole group into six subgroups according to their age. The total scores of the subgroups are 163.5 ± 3.7 in 30s, 158.3 ± 17.1 in 40s, 152.3 ± 18.4 in 50s, 148.0 ± 23.8 in 60s, 152.6 ± 16.1 in 70s, and 127.0 ± 25.8 in 80s (Table 3). The satisfaction component

Table 3. Details of each component in KSS 2011 in subgroups (mean ± SD)

Factor	30s	40s	50s	60s	70s	80s
Symptoms	24.7 ± 0.8	24.2 ± 2.3	22.5 ± 4.1	22.1 ± 4.3	23.3 ± 3.2	19.6 ± 4.8
Patient satisfaction	39.5 ± 1.5	37.9 ± 1.5	34.8 ± 7.0	34.4 ± 7.8	35.5 ± 7.9	31.8 ± 5.6
Walking and standing	30.0 ± 0.0	28.4 ± 5.2	29.1 ± 3.3	27.3 ± 5.5	27.5 ± 6.2	22.0 ± 6.9
Standard activities	29.8 ± 0.7	29.4 ± 1.9	28.4 ± 3.4	27.9 ± 3.8	28.8 ± 2.1	23.7 ± 6.5
Advanced activities	24.7 ± 1.0	24.0 ± 3.4	23.6 ± 2.8	22.7 ± 4.2	23.4 ± 2.6	18.8 ± 5.5
Discretionary activities	14.8 ± 0.7	14.5 ± 1.5	13.9 ± 1.9	13.5 ± 2.5	14.2 ± 2.0	11.2 ± 3.0
Sum of KSS 2011	163.5 ± 3.7	158.3 ± 17.1	152.3 ± 18.4	148.0 ± 23.8	152.6 ± 16.1	127.0 ± 25.8

KSS 2011 = 2011 The Knee Society Score®.

Table 4. Correlation analysis of KSS 2011 and other factors (simple and multivariable linear regression analysis) (mean ± SD)

Factor	Simple		Multivariable	
	Coefficient	p value	Coefficient	p value
Age	−0.45 ± 0.11	< 0.001†	−0.30 ± 0.12	0.011*
Sex	0.74 ± 2.87	0.796	Excluded by a stepwise method	
Height	0.19 ± 0.16	0.218		
Weight	−0.12 ± 0.12	0.309		
BMI	−1.22 ± 0.43	0.005*	−1.47 ± 0.42	< 0.001†
Leg strength	0.42 ± 0.14	0.003*	0.41 ± 0.13	0.002*
Up and Go	−3.42 ± 0.87	< 0.001†	−1.96 ± 0.92	0.034*

* Significant risk ratio ($p < 0.05$); †significant risk ratio ($p < 0.001$); KSS 2011 = 2011 The Knee Society Score®; BMI = body mass index; Up and Go = Timed Up and Go Test.

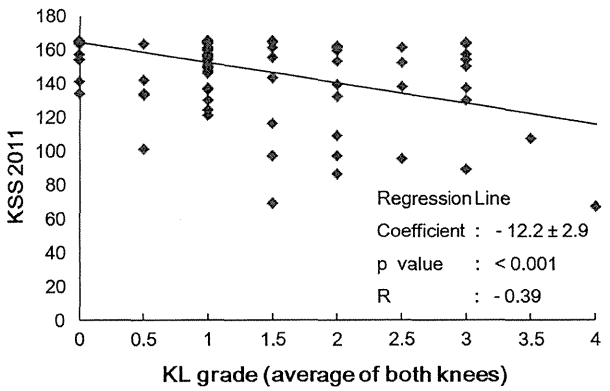

Fig. 2 Correlation between the KSS 2011 and the KL grade is shown. Linear regression analysis showed a significant correlation between KSS 2011 and KL grade.

declined steadily from ages 30s to 50s and was stable from ages 50s to 70s. The scores of people in their 80s were lower than those in the younger age groups for all components.

We found that several measures of physical function and anthropometrics correlated with the score on KSS 2011. Multivariable linear regression analysis showed that KSS 2011 correlated with age (coefficient: −0.30 ± 0.12, $p = 0.011$), BMI (coefficient: −1.47 ± 0.42, $p < 0.001$), leg muscle strength (coefficient: 0.41 ± 0.13, $p = 0.002$), and the Timed Up and Go Test (coefficient: −1.96 ± 0.92, $p = 0.034$), but not sex, as independent variables by a stepwise method (Table 4).

The presence of radiographic arthritis was associated with lower KSS 2011 scores. We found a moderate correlation between the KSS 2011 score and KL grade (Fig. 2). The regression line using the KSS score as an outcome variable (y) and KL grade as a predictor variable (x) was $y = -9.8x + 158.9$ (coefficient: −9.8 ± 2.5, $p < 0.001$, $R = -0.39$).

Discussion

KSS 2011 was designed primarily to evaluate the results of TKA. However, knee function and physical activities vary among patients and are influenced by age and sex, so what should be expected as a desirable score in KSS 2011 after TKA remains unclear. To have a clearer idea about this, some population-derived normative data are important, and it is important that these normative data be determined from relevant national, cultural, and ethnic populations. We found in this study from the general Japanese population, including patients with and without arthritis of the knee, that (1) as age increased, KSS 2011 decreased; (2) objective measures of physical function correlated well with KSS 2011; and (3) the presence of radiographic arthritis was moderately correlated with lower KSS 2011.

This study has several limitations. First, sampling bias certainly exists in many ways in this study. Community residents voluntarily participated in this study and motivated residents would be inclined to participate. Also, residents with a concern or symptoms in their knees may tend to participate. Furthermore, the protocol stipulated

that the radiographic examination was limited to participants older than 60 years, and only two-thirds of these participants agreed to receive this examination. Participants with a higher grade of radiographic OA may have agreed with radiographic examination. Therefore, some sampling bias likely influenced the results. Second, any physical function-related comorbidity may affect the results. Based on this speculation, excluded were patients who had disability unrelated to the knee that could influence patients' scores on KSS 2011; a small percentage (5.4% [12 of 224]) of participants were excluded because they had such disability. Conversely, this also demonstrates that the questionnaire can be answered by most patients without influence from other kinds of disabilities. Third, the component related to "patient expectation" was unavailable in this study because the participants had no plans to receive surgery. However, it is important to point out that patients' expectations about surgery affect their satisfaction with TKA [17], and the results of this study may differ from those in patients who undergo TKA. Fourth, because there is a clear ceiling effect in the KSS 2011, parametric techniques should be cautiously used in statistical analyses. We tested the correlations with a nonparametric analysis and obtained similar results, indicating simple and multiple regression analyses with a general linear model are usable. Also, regression lines by Torbit model are similar to those in the general linear model, supporting the results obtained in this study. Even so, the results obtained here should be handled with the greatest caution. Finally, we used a Japanese version of the questionnaire, but the translated version has not been validated by the cultural adaptation method. Even minor changes in question content can influence patients' estimation of knee pain and disability [21]. A validation study of the translated version is underway.

As expected, KSS 2011 declined with age, which is consistent with other reports [3]. In a previous study, knee function declined gradually with age, and the rate of decrease accelerated in people older than 85 years [18]. Our results are consistent with these previous findings. Collectively, older patients, especially in their 80s, can set much lower goals after TKA compared with younger patients.

It is noteworthy that the KSS 2011 scores correlated with BMI, leg muscle strength, and the Timed Up and Go Test in both the simple and multivariable liner regression analyses (Table 4). These correlations raise several issues. First, greater BMI is associated with knee pain and prevalence of radiographic OA [1, 29] and substantially limits physical activities. This study confirmed that the KSS 2011 score reflects the effects of BMI. Second, a previous study found that lower knee extension strength was associated with knee pain [22, 29]. The strong associations of KSS 2011 with leg muscle strength and the Timed Up and Go Test along with other reports [7, 22] collectively suggest that increased strength can improve the KSS 2011 as well as symptoms and satisfaction. Finally, the simple test of quadriceps strength and the Timed Up and Go Test were well tolerated; these tests are representative tests of knee functions as well as symptoms and satisfaction [29]. These relationships are worth investigating further.

In the current study, 41% (36 of 87) of participants had radiographic knee OA; this percentage agrees with previous reports on the prevalence of OA in the general population [6, 20, 28]. This implies that the participants in this study can be regarded as representative of the general population. The present study showed that KSS 2011 declines with increasing KL grade, which suggests that the severity of radiographic knee OA correlates with knee symptoms and functions and patient satisfaction. However, previous studies showed that the degree of radiographic OA does not correlate strongly with knee pain [15, 20, 29], and symptoms have been more emphasized in therapeutic strategies for OA [24]. Those and this study collectively indicate that KSS 2011 is more suitable than a radiological evaluation when deciding therapeutic strategies.

In summary, this is the first study to our knowledge to apply the KSS 2011 in the general (Japanese) population. The present study has three key findings: (1) In the general population, the KSS 2011 score declined with age. (2) The KSS 2011 score correlated independently not only with age, but also with BMI, the Timed Up and Go Test, and leg muscle strength but not with sex. (3) The KSS 2011 score correlated significantly with KL grade in people older than 60 years. Because TKA is one of the most prevalent operations worldwide, KSS 2011 should be tested in correlation with many aspects of symptoms and functions in a variety of ethnicity, nationality, belonged society, and lifestyle to set an appropriate goal for a patient who undergoes TKA.

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