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KEY WORDS atherosclerosis, cardiac magnetic resonance, coronary artery disease, vulnerable plaque

APPENDIX For supplemental tables, please see the online version of this article.

OPEN ACCESS

ORIGINAL ARTICLE

Prognostic impact of blood pressure response plus gadolinium enhancement in dilated cardiomyopathy

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▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2014-307007).

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Received 25 October 2014
Accepted 11 February 2015
Published Online First 11 March 2015

▸ http://dx.doi.org/10.1136/heartjnl-2014-307426

To cite: Tateishi E, Noguchi T, Goto Y, *et al*. *Heart* 2015;**101**:774–780.

ABSTRACT

Objective Late gadolinium enhancement (LGE) is not necessarily ideal for detecting diffuse myocardial fibrosis in idiopathic dilated cardiomyopathy (DCM). Since systolic blood pressure response (SBPR) during exercise has been proposed to reflect cardiac pump reserve in patients with heart failure, we wished to determine whether LGE plus SBPR is a better prognostic factor in patients with DCM.

Methods LGE and cardiopulmonary exercise testing results in consecutive 207 patients with DCM were examined. Patients were divided into four groups according to the presence or absence of LGE and the SBPR cut-off value of +40 mm Hg according to receiver operating characteristic curve analysis: LGE-positive +SBPR <40 mm Hg (n=65), LGE-positive+SBPR ≥40 mm Hg (n=40), LGE-negative+SBPR <40 mm Hg (n=33) and LGE-negative+SBPR ≥40 mm Hg (n=69). The composite end point was cardiac death, cardiac transplantation, LV assist device implantation, life-threatening arrhythmia or heart failure.

Results Forty-two (20%) patients developed the composite end point, with rates of 35%, 20%, 21% and 6% in patients with LGE-positive+SBPR <40 mm Hg, LGE-positive+SBPR ≥40 mm Hg, LGE-negative+SBPR <40 mm Hg and LGE-negative+SBPR ≥40 mm Hg status, respectively. Multivariable Cox regression analysis identified LGE-positive and SBPR <40 mm Hg as a significant independent predictor of cardiac events (HR 2.08, 95% CI 1.06 to 4.11, p=0.034). Of note, there was no significant difference in the cardiac event-free survival rate between the LGE-positive+SBPR ≥40 mm Hg and LGE-negative+SBPR <40 mm Hg groups (p=0.736).

Conclusions The combination of LGE and SBPR provides more clinically relevant information for assessing the risk of cardiac events in patients with DCM than LGE status alone.

INTRODUCTION

Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) has emerged as a first-line non-invasive modality for investigating the aetiology of myocardial dysfunction[1 2] and evaluating cardiac prognosis in patients with ischaemic[3 4] or non-ischaemic cardiomyopathy.[5–7] However, since LGE relies on the difference in signal intensity between focal myocardial fibrosis and normal myocardium, it is limited in its ability to detect diffuse interstitial fibrosis, which is commonly found in idiopathic dilated cardiomyopathy (DCM).[8] Thus, patients at high risk for cardiac events may have been missed in prior studies that investigated the presence of LGE alone.[5–7]

Peak oxygen uptake (peak VO_2) or the regression slope relating minute ventilation to carbon dioxide output (VE/VCO_2 slope) has been used to identify patients with either ischaemic or non-ischaemic cardiomyopathy at high risk for cardiac death or in need of cardiac transplantation.[9 10] As a simpler and more convenient index, Williams *et al*[11] and Kallistratos *et al*[12] reported that peak systolic blood pressure (SBP) during exercise was associated with all-cause mortality and cardiac mortality in patients with chronic heart failure (HF). Blood pressure response (BPR) during exercise has been proposed as a marker of haemodynamic instability in patients with chronic HF.[12–14] Based on these previous studies, systolic BPR (SBPR) during exercise testing may reflect cardiac pump performance reserve, which may correspond to the extent of diffuse interstitial myocardial fibrosis.

We hypothesised that the combination of LGE and SBPR may provide more precise information for risk stratification in patients with DCM than LGE alone. The aim of this study was to evaluate the predictive value of the combination of LGE and SBPR for cardiac outcomes in patients with DCM.

METHODS

Study population

We conducted a prospective observational study of 207 consecutive patients with DCM at National Cerebral and Cardiovascular Center, Suita, Japan, between April 2005 and December 2012. The diagnosis of DCM was made based on WHO criteria.[15] All patients underwent invasive coronary angiography to exclude significant coronary artery stenosis (>50% diameter stenosis). Myocarditis, hypertrophic cardiomyopathy, secondary cardiomyopathy, valvular heart disease and hypertensive heart disease were excluded. Symptom-limited maximal cardiopulmonary exercise testing (CPX) and CMR were performed while the patient was in a clinically stable, non-congested condition (New York Heart Association (NYHA) functional class ≤II). The median duration between hospital admission and CMR and CPX was 15 days and 25 days, respectively.

CMR protocol

CMR examinations were performed using a 1.5-T system (Magnetom Sonata, Siemens, Erlangen,

Germany) with a four-channel surface coil. The procedures used to acquire MR images in this study have been previously described.[16] We identified LGE using a segmented inversion-recovery prepared true fast imaging with steady state precession sequence with ECG triggering at 10 min after the administration of 0.15 mmol/kg body weight of gadolinium diethylenetriamine pentaacetic acid. LGE data was obtained during the mid-diastolic phase with an inversion time of 300 ms.[16 17] Other imaging variables consisted of 65 segments, echo time 1.73 ms, flip angle 60°, field-of-view 340×255 mm, matrix 256×129 and voxel size 1.3×2.0×8.0 mm^3. We also acquired cine imaging using a true fast imaging with steady state precession sequence (echo time 1.3 ms, repetition time 2.6 ms, flip angle 60°, slice thickness 8 mm, gaps 2 mm, inplane resolution 4.17×2.73 mm) over multiple breath holds in contiguous short-axis slices encompassing the entire LV and three standard long-axis slices.

LGE analysis

Two experienced radiologists who were blinded to clinical data and outcomes independently determined the presence and location of LGE. LGE was only considered present if it was visible in two orthogonal views. Figure 1 shows representative LGE-positive (A–C) and LGE-negative (D) cases. LGE pattern was characterised as mid-wall (figure 1A), diffuse (figure 1B) or focal (figure 1C). We categorised LGE-positive patients as having a mid-wall (n=52), diffuse (n=34) or focal LGE pattern (n=19), respectively. Interobserver and intraobserver agreement was evaluated for all study patients, and the κ values for interobserver and intraobserver agreement for the presence of LGE were 0.89 and 0.90, respectively. A third blinded reader adjudicated in cases with disagreement (n=10, 4.8%).

For quantification of LV volumes and LVEF, we manually traced the LV endocardial contours in end-systolic and end-diastolic frames in cine imaging with a dedicated software program (Argus system, Siemens, Erlangen, Germany).

Exercise testing protocol

CPX was performed on a stationary cycle ergometer (AE-300, Minato; Tokyo, Japan). Blood pressure was measured every 60 s during exercise. SBPR was calculated as the difference in SBP between peak exercise and rest. During CPX, peak VO_2 and VE/VCO_2 slope were also measured.

Determination of BNP

Blood samples were collected in tubes containing EDTA, and plasma brain natriuretic peptide (BNP) was measured using a validated and commercially available immunoassay kit (Tosoh Co, Tokyo, Japan).

Follow-up and end points

After CMR data were obtained, study patients were followed at 3 months, 6 months, and 12 months and annually thereafter until the occurrence of one of the following cardiac events: cardiac death, cardiac transplantation, LV assist device implantation, appropriate implantable cardioverter-defibrillator discharge for ventricular tachycardia (VT) or ventricular fibrillation (Vf), and rehospitalisation for HF. Independent attending cardiologists blinded to the patient's LGE and SBPR status reviewed charts to determine if hospitalisations and deaths qualified as cardiac events. No patients were lost to follow-up.

Statistical analysis

All continuous variables are presented as means±SD and unpaired t tests were used to compare groups. Analysis of variance was used to compare means across multiple groups. Non-continuous and categorical variables are presented as frequencies or percentages and were compared using the χ^2 test. If a four-group comparison was statistically significant, then post

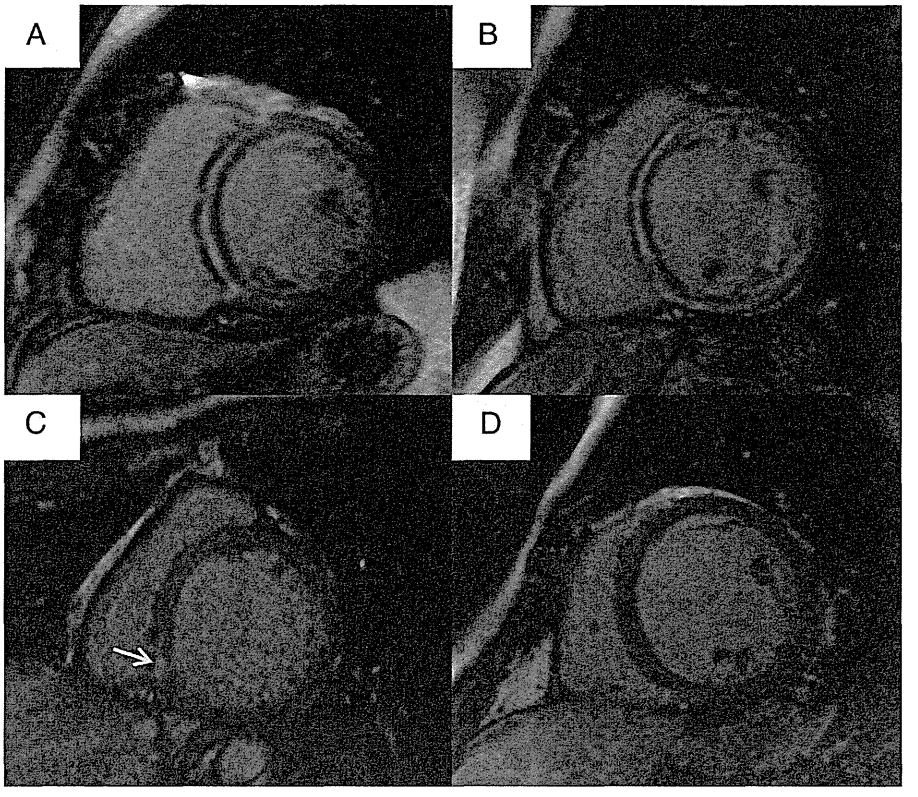

Figure 1 Representative examples of short-axis LGE-positive and LGE-negative images. A, B and C are short-axis images from LGE-positive patients. The typical LGE pattern in DCM is mid-wall enhancement in the interventricular septum (A). A diffuse pattern was observed in 34 out of 105 LGE-positive patients (B). Nineteen patients had focal enhancement (C, arrow). Figure 1D is a representative example of a LGE-negative case. DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement.

hoc pairwise comparisons between each pair were performed to demonstrate which pair was significantly different. The Tukey-Kramer test was used to compare continuous variables and the χ^2 test with Bonferroni correction was used for categorical variables. Cumulative event-free survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. SBPR cut-off values were determined based on receiver operating characteristics (ROC) analysis. Univariable Cox proportional hazards regression models were used to calculate HRs for all cardiac events and 95% CIs. Multivariable Cox regression analysis was performed using covariates that significantly predicted all cardiac events in the univariable analysis, as well as established prognostic risk factors for chronic HF. Stepwise selection with a p value of 0.1 for backward elimination was used to select the best predictive model. All statistical tests were two-sided and p values <0.05 were regarded as statistically significant. Statistical analysis was performed with JMP, V.9.0.2 (SAS Institute, Cary, North Carolina, USA) and STATA, V.12 (StataCorp LP, College Station, Texas, USA).

RESULTS

SBPR cut-off value for predicting the development of cardiac events

During a median follow-up of 44 months (IQR, 23–62 months), cardiac events were observed in 42 of 207 study patients. The median SBPR elevation for patients with or without cardiac events was significantly different, 32 mm Hg and 46 mm Hg, respectively (p<0.001). Based on ROC curve analysis, the optimal SBPR cut-off value for developing cardiac events was 40 mm Hg. The area under the ROC curve was 0.70 (figure 2A). At this value, the sensitivity and specificity for predicting a cardiac event were 72.1% and 66.8%, respectively. Based on this result, we divided the study patients into four groups according to the presence or absence of LGE and the SBPR cut-off value as follows: LGE-positive+SBPR <40 mm Hg (n=65), LGE-positive+SBPR ≥40 mm Hg (n=40), LGE-negative+SBPR <40 mm Hg (n=33) and LGE-negative+SBPR ≥40 mm Hg (n=69) (figure 2B). Of the 65 LGE-positive+SBPR <40 mm Hg patients, 23 (35%) experienced a cardiac event, whereas eight (20%) events occurred in the LGE-positive+SBPR ≥40 mm Hg group (n=40). On the other hand, 7 (21%) of the 33 LGE-negative+SBPR <40 mm Hg patients experienced a cardiac event. Only 4 (6%) of the 69 LGE-negative+SBPR ≥40 mm Hg patients experienced a cardiac event.

Baseline clinical characteristics and cardiac function

Table 1 shows the baseline clinical characteristics of the four groups. The LGE-negative+SBPR ≥40 mm Hg group was significantly younger than the other three groups (p=0.004). Interestingly, among the LGE-positive patients, those with SBPR <40 mm Hg had higher BNP levels and lower peak VO_2 than those with SBPR ≥40 mm Hg (p<0.001), even though LV function and volumes were similar. Similarly, within the LGE-negative stratum, the SBPR <40 mm Hg group had higher BNP levels, reduced exercise tolerance, lower LVEF and larger LV volumes compared with the SBPR ≥40 mm Hg group (p<0.001). Importantly, there were no significant differences in BNP levels, exercise tolerance, and LV function and volumes between the LGE-positive+SBPR ≥40 mm Hg and LGE-negative+SBPR <40 mm Hg groups.

Prognostic value of the combination of LGE and SBPR

Of the 207 study patients, 27 (13.0%) developed HF, 7 (3.4%) received appropriate implantable cardioverter-defibrillator

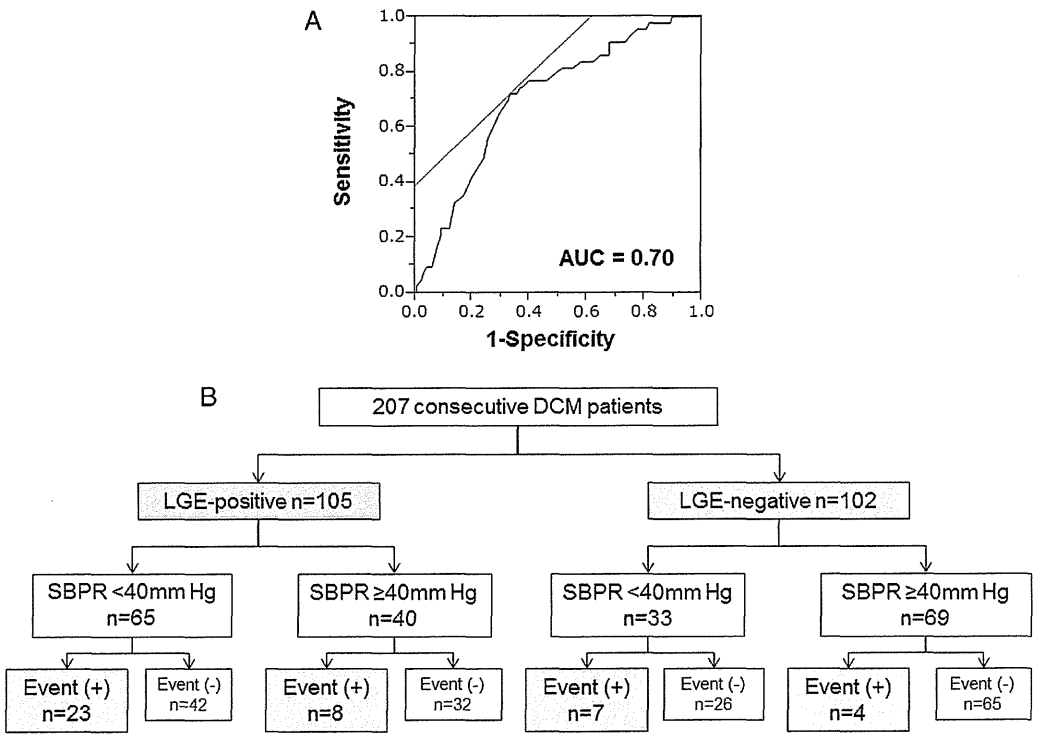

Figure 2 Receiver operating characteristics (ROC) curve analysis for the development of cardiac events and flow chart of study patients on the basis of LGE and SBPR. (A) ROC curve to determine the optimal cut-off value of SBPR for cardiac events. (B) Flow diagram illustrating the number of participants. DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; ROC, receiver operator characteristics; SBPR, systolic blood pressure response.

Table 1 Characteristics of the study patients

	All patients (n=207)	LGE-positive SBPR <40 mm Hg (n=65)	LGE-positive SBPR ≥40 mm Hg (n=40)	LGE-negative SBPR <40 mm Hg (n=33)	LGE-negative SBPR ≥40 mm Hg (n=69)	p Value
Age (years)	50±16	54±16	52±13	51±16	45±16	0.004
Male	165 (80)	50 (77)	37 (93)	24 (73)	54 (78)	0.096
NYHA functional class						0.009
I	58 (28)	15 (23)	14 (35)	3 (9)	26 (38)	
II	58 (28)	23 (35)	10 (25)	13 (39)	12 (17)	
III	26 (13)	10 (15)	5 (13)	7 (21)	4 (6)	
VI	65 (31)	17 (26)	11 (28)	10 (30)	27 (39)	
Hypertension	76 (37)	23 (35)	16 (40)	6 (18)	31 (45)	0.055
Atrial fibrillation	51 (25)	13 (20)	13 (33)	9 (27)	16 (23)	0.178
History of VT/Vf	8 (4)	6 (9)	0	2 (6)	0	0.006
BNP (mg/dL)	93 (38–213)	170 (72–404)	93 (40–176)	131 (39–252)	50 (13–108)	<0.001
Creatine (mg/dL)	0.85±0.23	0.85±0.23	0.81±0.20	0.91±0.19	0.85±0.25	0.377
ECG parameters						
QRS duration (ms)	117±30	125±37	115±21	119±28	109±25	0.023
QTc interval (ms)	437±53	452±43	430±66	442±59	424±45	0.015
Medications						
β-blocker	196 (95)	65 (100)	37 (93)	31 (94)	63 (91)	0.032
ACE-I/ARB	173 (84)	60 (92)	31 (78)	26 (79)	56 (81)	0.106
Aldosterone antagonist	86 (42)	37 (57)	14 (35)	14 (42)	21 (30)	0.014
Loop diuretics	120 (58)	37 (57)	14 (35)	14 (42)	21 (30)	0.009
Digoxin	41 (20)	15 (23)	6 (15)	10 (30)	10 (14)	0.220
Amiodarone	22 (11)	14 (22)	4 (10)	2 (6)	2 (3)	0.004
Exercise testing						
HR at rest (beats/min)	79±15	77±14	74±15	84±12	80±16	0.029
SBP at rest (mm Hg)	114±18	112±20	111±16	111±18	118±17	0.151
Peak SBP (mm Hg)	157±31	135±22	168±24	135±22	181±24	<0.001
Peak VO_2 (mL/min/kg)	22±6	19±5	23±5	20±5	25±7	<0.001
VE/VCO_2 slope	29±6	31±7	28±5	31±8	26±4	<0.001
CMR parameters						
LVEF (%)	27±11	24±10	25±11	23±10	32±10	<0.001
LVEDVI (mL/m^2)	143±57	161±64	152±54	153±66	117±34	<0.001
LVESVI (mL/m^2)	109±56	126±63	117±51	123±66	81±33	<0.001
LV mass (g)	149±49	149±6	162±8	142±9	147±6	0.296
RVEF (%)	36±10	35±10	37±10	35±11	38±10	0.351

Values are means±SD, n (%), or median (first quartile, third quartile).
ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; HR, heart rate; LGE, late gadolinium enhancement; NYHA, New York Heart Association; peak VO_2, peak oxygen uptake; SBP, systolic blood pressure; SBPR, systolic blood pressure response; VE/VCO2 slope, regression slope relating minute ventilation to carbon dioxide output; Vf, ventricular fibrillation; VT, ventricular tachycardia.

discharge for VT or Vf, 3 (1.4%) received a LV assist device and 1 (0.5%) underwent heart transplantation during the follow-up period (table 2). There were four cardiac deaths (1.9%); two patients each died of progressive end-stage HF and sudden cardiac death. Among the four groups, LGE-positive+SPBR <40 mm Hg status was associated with a higher rate of reaching the all cardiac events end point ($p<0.001$). Kaplan-Meier analysis showed that the cardiac event-free survival rate was lowest

Table 2 Incidence of cardiac events during follow-up

	All patients (n=207)	LGE-positive SBPR <40 mm Hg (n=65)	LGE-positive SBPR ≥40 mm Hg (n=40)	LGE-negative SBPR <40 mm Hg (n=33)	LGE-negative SBPR ≥40 mm Hg (n=69)	p Value
All cardiac events	42 (20)	23 (35)	8 (20)	7 (21)	4 (6)	<0.001
Cardiac death	4 (2)	4 (6)	0	0	0	0.024
Cardiac transplantation	1 (0.5)	1 (2)	0	0	0	0.507
LVAD implantation	3 (1)	0	1 (3)	2 (6)	0	0.075
ICD discharge for VT/Vf	7 (3)	3 (5)	2 (5)	2 (6)	0	0.117
Rehospitalisation for HF	27 (13)	15 (23)	5 (13)	3 (9)	4 (6)	0.026

Values are numbers (%).
HF, heart failure; ICD, implantable cardioverter-defibrillator; LVAD, LV assist device; SBPR, systolic blood pressure response; Vf, ventricular fibrillation; VT, ventricular tachycardia.

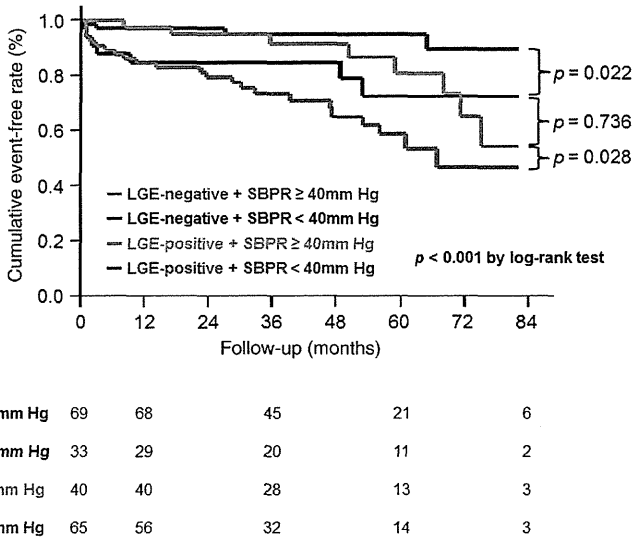

Figure 3 Kaplan-Meier curves comparing the probability of all cardiac events. The LGE-positive+SBPR <40 mm Hg group had the worst prognosis. Importantly, the all cardiac event rate in the LGE-negative+SBPR <40 mm Hg group was intermediate, but comparable with the rate in the LGE-positive+SBPR ≥40 mm Hg group (p=0.736). LGE, late gadolinium enhancement; SBPR, systolic blood pressure response.

No. at risk					
LGE-negative + SBPR ≥ 40mm Hg	69	68	45	21	6
LGE-negative + SBPR < 40mm Hg	33	29	20	11	2
LGE-positive + SBPR ≥ 40mm Hg	40	40	28	13	3
LGE-positive + SBPR < 40mm Hg	65	56	32	14	3

in the LGE-positive+SBPR <40 mm Hg group and highest in the LGE-negative+SBPR ≥40 mm Hg group (p<0.001 by the log-rank test). Importantly, the all cardiac event rate in the LGE-negative+SBPR <40 mm Hg group was intermediate, but comparable with the rate in the LGE-positive+SBPR ≥40 mm Hg group (p=0.736) (figure 3). Online supplementary figure S2 shows the Kaplan-Meier curves comparing the probability of all cardiac events according to the number of risk factors (LGE-positive status and SBPR <40 mm Hg) present when the two intermediate groups were merged.

Univariable analysis showed that a history of VT or Vf, BNP, serum creatine, QRS duration (per 10 ms increments), QTc interval (per 10 ms increments), heart rate and SBP at rest, SBPR <40 mm Hg, LVEF, LV volumes and presence of LGE were all significant predictors for all cardiac events (p<0.05) (table 3). When these factors were further analysed in a stepwise multivariable Cox model adjusted for factors that were significant in the univariable analysis as well as established risk factors (age, gender, NYHA functional class, peak VO_2, VE/VCO_2), a history of VT/Vf, LV end-diastolic volume index, presence of LGE and SBPR <40 mm Hg were significant independent predictors for all cardiac events (table 4, Model 1). When SBPR was considered as a continuous variable, it was still a significant predictor of cardiac risk in the univariable and multivariable analyses (see online supplementary table S2). To further investigate whether the combination of the presence of LGE and a SBPR cut-off value of 40 mm Hg is a better cardiac prognostic factor, we performed an alternative multivariable Cox regression analysis (table 4, Model 2). When this combination was used, LGE-positive+SBPR <40 mm Hg was significantly associated with cardiac events (HR 4.05, 95% CI 1.41 to 14.55, p=0.008). Since the number of cardiac events was relatively low in our study population, we demonstrated that the best predictive model adjusted for significant predictors selected in a stepwise Cox regression analysis based on Models 1 and 2. As a result, LGE-positive+SBPR <40 mm Hg (HR 2.08, 95% CI 1.06 to 4.11, p=0.034) remained a significant indicator of future cardiac events (table 4, Model 3).

DISCUSSION

The major finding of this study is that the combination of LGE status and SBPR during exercise is a significant and independent predictor of future cardiac events in patients with DCM. To the best of our knowledge, this is the first clinical study that demonstrates that a combination of structural (LGE) and simple physiological (SBPR on exercise testing) indices is a relevant prognostic marker of cardiac outcomes compared with either the presence of LGE or SBPR alone.

The prognostic impact of the combination of LGE and SBPR in patients with DCM

Myocardial fibrosis is associated with worsening ventricular systolic function, progressive remodelling and increased ventricular

Table 3 Univariable Cox regression analysis of risk factors for all cardiac events

	HR	95% CI	p Value
Age (per 5 years)	1.02	0.92 to 1.12	0.821
Male	1.27	0.60 to 3.10	0.563
NYHA class on admission	1.17	0.91 to 1.52	0.222
Hypertension	0.58	0.28 to 1.12	0.105
Atrial fibrillation	1.42	0.71 to 2.67	0.308
History of VT/Vf	5.16	1.93 to 11.6	0.002
BNP (per 10 mg/dL increments)	1.02	1.01 to 1.02	0.001
Creatine	3.65	1.05 to 11.0	0.042
ECG parameters			
QRS duration (per 10 ms increments)	1.12	1.02 to 1.22	0.022
QTc interval (per 10 ms increments)	1.11	1.04 to 1.18	0.003
Exercise testing			
Heart rate at rest (per 10 bpm increments)	0.81	0.66 to 1.00	0.048
SBP at rest (per 10 mm Hg increments)	0.75	0.62 to 0.90	0.002
SBPR <40 mm Hg	3.31	1.74 to 6.75	<0.001
Peak VO_2 (per 1 mL/min/kg decrement)	1.04	0.98 to 1.10	0.134
VE/VCO_2 slope	1.01	0.95 to 1.06	0.724
CMR parameters			
LVEF (per 10% decrements)	1.60	1.18 to 2.21	0.002
LVEDVI (per 10 mL/m^2 increments)	1.01	1.06 to 1.14	<0.001
LVESVI (per 10 mL/m^2 increments)	1.11	1.06 to 1.15	<0.001
LV mass	0.99	0.99 to 1.00	0.99
RVEF (per 10% decrements)	1.18	0.89 to 1.56	0.251
Presence of LGE	3.00	1.55 to 6.25	0.001

BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LGE, late gadolinium enhancement; NYHA, New York Heart Association; peak VO_2, peak oxygen uptake; SBP, systolic blood pressure; SBPR, systolic blood pressure response; VE/VCO_2 slope, regression slope relating minute ventilation to carbon dioxide output; Vf, ventricular fibrillation; VT, ventricular tachycardia.

Table 4 Multivariable Cox regression analysis of risk factors for all cardiac events

	Model 1*			Model 2†			Model 3‡		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
History of VT/Vf	3.16	1.26 to 7.89	0.014	2.83	1.03 to 6.67	0.044	2.96	1.06 to 6.98	0.037
QTc interval (per 10 ms increments)	1.01	1.00 to 1.01	0.063	1.04	0.97 to 1.11	0.324	1.04	0.97 to 1.12	0.270
LVEDVI (per 10 mL/m^2 increments)	1.01	1.00 to 1.01	0.001	1.07	1.02 to 1.12	0.004	1.08	1.03 to 1.12	0.012
Presence of LGE	1.96	1.01 to 3.78	0.046						
SBPR <40 mm Hg	1.93	1.02 to 3.65	0.042						
LGE-negative+SBPR <40 mm Hg				2.62	0.77 to 10.19	0.122			
LGE-positive+SBPR ≥40 mm Hg				2.26	0.69 to 8.65	0.179			
LGE-positive+SBPR <40 mm Hg				4.05	1.41 to 14.55	0.008	2.08	1.06 to 4.11	0.034

*Multivariable Cox model selected by a stepwise method with factors that were significant in the univariable analysis and established risk factors for prognosis (age, gender, NYHA class, peak VO_2, VE/VCO_2 slope).
†Model with the combination of LGE and SBPR, adjusted for predictors selected by Model 1.
‡Best predictive model, adjusted for significant predictors selected by a stepwise Cox regression analysis based on Models 1 and 2.
EDVI, end-diastolic volume index; LGE, late gadolinium enhancement; NYHA, New York Heart Association; peak VO_2, peak oxygen uptake; SBPR, systolic blood pressure response; VE/VCO_2 slope, regression slope relating minute ventilation to carbon dioxide output; Vf, ventricular fibrillation; VT, ventricular tachycardia.

stiffness in patients with DCM.[18] Recently, Gulati *et al*[19] suggested that mid-wall LGE was independently associated with cardiovascular mortality and cardiac transplantation in the largest cohort of patients with DCM to date. Although many previous studies have suggested the prognostic value of LGE in patients with DCM, Schalla *et al*[20] reported that the presence of fibrosis detected by LGE was not correlated with the amount of interstitial fibrosis detected on endomyocardial biopsy. Therefore, LGE status alone may be an insufficient prognostic indicator in patients with DCM.

To avoid missing patients at high risk for cardiac events who cannot be identified with LGE alone, we added SBPR during exercise testing to create a simple, convenient index for predicting outcomes in patients with DCM. SBP on exercise has been established as an important prognostic marker of cardiac events.[21] Kitaoka *et al*[13] reported that postexercise BPR was a simple and useful predictor of adverse cardiac events in patients with DCM. Since SBPR reflects the ability of the heart to increase stroke volume in response to exercise,[11–14 22] that is, systolic and diastolic performance reserve during exercise, patients with SBPR <40 mm Hg may have underlying myocardial functional impairment that is not detected by morphological assessment such as LGE with CMR. In the present study, SBPR of 40 mm Hg was identified as the best cut-off value for predicting prognosis based on ROC curve analysis (figure 2A). Therefore, we divided the study patients into four groups according to the presence or absence of LGE and the SBPR cut-off. Indeed, the incidence of cardiac events was highest in the LGE-positive+SBPR <40 mm Hg group and lowest in the LGE-negative+SBPR ≥40 mm Hg group. Importantly, the event rate in the LGE-positive+SBPR ≥40 mm Hg and LGE-negative +SBPR <40 mm Hg groups were intermediate (figure 3). Based on the different rates for cardiac events in the four groups, our study demonstrated that the combination of LGE and SBPR provides more detailed risk stratification in patients with DCM than LGE or SBPR alone.

Regarding the combination of CMR and exercise testing for predicting prognosis in patients with DCM, Yamada *et al*[23] reported that LGE-CMR combined with peak VO_2-CPX can provide additional prognostic information on cardiac events. However, compared with our study, their study population had clinically mild DCM (prevalence of NYHA functional class I and II; 93% vs 56%). Furthermore, on multivariable analysis, peak VO_2 was not an independent predictor of cardiac events in our study. Therefore, since our study population included patients with clinically moderate to severe DCM and there were more cardiac events, our present study provides more comprehensive information for assessing the risk of cardiac events in a broader spectrum of patients with DCM.

Recently, several studies have proposed that the measurement of T1 relaxation time, called T1 mapping, is potentially valuable for quantitative assessment of myocardial tissue composition on a global or regional level[24 25] and that it is a promising technique for directly quantifying diffuse interstitial fibrosis in chronic HF.[26] Furthermore, Dass *et al*[27] suggested that since T1 values determined by T1 mapping are strongly correlated with impaired myocardial energetics, T1 mapping may detect functional changes in the myocardium prior to the development of fibrosis as evaluated by LGE. However, the relationship between T1 mapping and future cardiac events has not been fully elucidated. In addition, associations between myocardial T1 values and known prognostic physiological parameters in patients with DCM remain insufficiently characterised. Therefore, further investigations with larger samples are required to address this important issue.

Study limitations

Several limitations should be mentioned for the present study. First, since this was an observational study, we could not avoid differences in background characteristics among the four groups. Second, this study was limited by the relatively small number of patients examined and the small number of patients who experienced the primary end point during the study. A higher number of events is needed to provide adequate statistical power to fully evaluate whether a novel risk marker contributes additional prognostic information to an established set of risk factors in a multivariable model. Third, although lower glomerular filtration rate has been reported to be a prognostic factor in patients with chronic HF,[28] patients with chronic renal insufficiency were excluded due to the risk of nephrogenic systemic fibrosis associated with gadolinium. Finally, the results from the stepwise selection process are potentially biased as a result of overfitting the derivation data set.

CONCLUSION

This study highlights the utility of the combination of LGE and SBPR during exercise for risk stratification in patients with DCM, and it cautions against overconfidence in risk stratification based on LGE assessment alone.

Key messages

What is already known on this subject?
Late gadolinium enhancement (LGE) has been established as a prognostic indicator in non-ischaemic cardiomyopathy. However, it is limited in its ability to detect diffuse interstitial fibrosis, which is commonly found in idiopathic dilated cardiomyopathy (DCM).

What might this study add?
To avoid missing patients at high risk for cardiac events by assessing LGE-positive status alone, we added systolic blood pressure response (SBPR) during exercise testing to a simple, convenient index for predicting outcomes in patients with DCM.

How might this impact on clinical practice?
The cardiac event rate in the LGE-negative+SBPR <40 mm Hg group was comparable with the rate in the LGE-positive+SBPR ≥40 mm Hg group. This finding cautions against overconfidence in risk stratification based on LGE-positive status alone. This combination of physiological (SBPR) and structural (LGE) indices can be used for risk stratification of cardiac events in patients with DCM.

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Funding The present work was supported in part by the Takeda Science Foundation and the Japan Cardiovascular Research Foundation.

Competing interests None.

Patient consent Obtained.

Ethics approval The institutional review board and the ethics committees of the National Cerebral and Cardiovascular Center.

Provenance and peer review Not commissioned; externally peer reviewed.

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Heart

Prognostic impact of blood pressure response plus gadolinium enhancement in dilated cardiomyopathy

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Heart 2015 101: 774-780 originally published online March 11, 2015
doi: 10.1136/heartjnl-2014-307007

J Epidemiol 2015;25(6):407-414
doi:10.2188/jea.JE20140172

Original Article

HOMA-IR Values are Associated With Glycemic Control in Japanese Subjects Without Diabetes or Obesity: The KOBE Study

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Received September 10, 2014; accepted January 7, 2015; released online May 23, 2015

ABSTRACT

Background: Several studies have reported that insulin resistance was a major risk factor for the onset of type 2 diabetes mellitus in individuals without diabetes or obesity. We aimed to clarify the association between insulin resistance and glycemic control in Japanese subjects without diabetes or obesity.

Methods: We conducted a community-based cross-sectional study including 1083 healthy subjects (323 men and 760 women) in an urban area. We performed multivariate regression analyses to estimate the association between the homeostasis model assessment of insulin resistance (HOMA-IR) values and markers of glycemic control, including glycated haemoglobin (HbA1c), 1,5-anhydroglucitol (1,5-AG), and fasting plasma glucose (FPG) levels, after adjustment for potential confounders.

Results: Compared with the lowest tertile of HOMA-IR values, the highest tertile was significantly associated with HbA1c and FPG levels after adjustment for potential confounders, both in men (HbA1c: $\beta = 1.83$, $P = 0.001$; FPG: $\beta = 0.49$, $P < 0.001$) and women (HbA1c: $\beta = 0.82$, $P = 0.008$; FPG: $\beta = 0.39$, $P < 0.001$). The highest tertile of HOMA-IR values was inversely associated with 1,5-AG levels compared with the lowest tertile ($\beta = -18.42$, $P = 0.009$) only in men.

Conclusions: HOMA-IR values were associated with markers of glycemic control in Japanese subjects without diabetes or obesity. Insulin resistance may influence glycemic control even in a lean, non-diabetic Asian population.

Key words: homeostasis model assessment of insulin resistance; glycemic control; epidemiology

INTRODUCTION

Insulin resistance is a clinical condition characterized by a decreased sensitivity to insulin in peripheral tissues and is strongly associated with metabolic diseases, such as type 2 diabetes mellitus and obesity.[1–3] Prospective cohort studies in subjects without diabetes have also revealed that increased insulin resistance worsened glycemic control and contributed to the development of type 2 diabetes mellitus.[4–6] However, in all previous reports, the average body mass index (BMI) of the subjects was high (28–33 kg/m^2), and >50% of the subjects were obese.[4–6] Thus, it is unclear whether insulin resistance affects glycemic control in subjects without obesity or diabetes.

For assessing glycemic control, temporal variations in the indicative parameters are more important than values obtained at a single point in time. Glycated hemoglobin (HbA1c) and 1,5-anhydroglucitol (1,5-AG) levels are generally used to

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evaluate glycemic control in clinical practice. HbA1c levels are the gold standard marker of glycemic control in patients with diabetes, and they reflect average plasma glucose levels during the past 2–3 months.[7] In contrast, 1,5-AG levels are used as an index that reflects glycemic control during the past few days or weeks and glycemic control fluctuations.[8,9] Thus, it is necessary to use several indices in various time periods to evaluate glucose metabolism. However, to the best of our knowledge, no earlier studies have investigated the association between insulin resistance and glucose metabolism using multiple markers of glycemic control.

Therefore, in the present study, we aimed to investigate the impact of insulin resistance on glucose metabolism of Japanese subjects without diabetes or obesity. We used three markers that are commonly used to evaluate glucose metabolism in Japanese populations: HbA1c, 1,5-AG, and fasting plasma glucose (FPG) levels.

METHODS

Subjects

We used data from the baseline survey in the Kobe Orthopedic and Biomedical Epidemiological (KOBE) study. The KOBE study is a population-based prospective cohort study of risk factors for cardiovascular disease or worsening of quality of life in Kobe City, a major urban area in Japan, that has been ongoing since 2010. The KOBE study has been described in detail elsewhere.[10] The present study was approved by the Ethics Committee of the Institute of Biomedical Research and Innovation (Committee approval number: 11-12). Written informed consent was obtained from all participants.

A total of 1118 subjects (342 men and 776 women) participated in the baseline survey from July 2010 to December 2011. None of the participants had past history of cardiovascular disease or cancer, and none were under therapy with medications for hypertension, dyslipidemia, or diabetes at the time of the survey. We excluded 34 participants who were diagnosed with diabetes or obesity on the basis of FPG level of $\geq$7.0 mmol/L ($n = 8$) and/or HbA1c level of $\geq$6.5% ($n = 22$) or BMI of $\geq$30 kg/m^2 ($n = 4$) at baseline. A participant with missing data ($n = 1$) was also excluded. We ultimately analysed data of 1083 subjects (323 men and 760 women) without diabetes or obesity in this study.

Measurements

Each subject completed a self-reported questionnaire to assess past medical history and lifestyle factors, such as smoking status, alcohol consumption, and regular exercise habits, and trained researchers directly confirmed the responses to the questionnaire. Waist circumference was measured at the level of the umbilicus in a standing position. Height and body weight were measured with patients wearing socks and light clothing, and BMI was calculated by dividing weight in kilograms by the squared height in meters.

Fasting blood samples were drawn from all participants after they had fasted for at least 10 hours. Blood samples were transported to a single commissioned clinical laboratory centre (SRL Inc., Tokyo, Japan) for measurements. Plasma glucose levels (mmol/L) were determined using the glucose oxidase method. 1,5-AG levels were measured using an enzymatic method. HbA1c levels were measured using high-performance liquid chromatography and were expressed as National Glycohemoglobin Standardization Program units and International Federation of Clinical Chemistry and Laboratory Medicine values for the current analysis.[11] Serum immunoreactive insulin (IRI) levels (pmol/L) were determined using the chemiluminescence enzyme immunoassay (CLEIA) method, and homeostasis model assessment-insulin resistance (HOMA-IR) values were calculated using the following formula: HOMA-IR = IRI × glucose/22.5.[12] Estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR (mL/min per 1.73 m^2) = 194 × creatinine$^{-1.094}$ × age$^{-0.287}$ (× 0.739 if female),[13] and chronic kidney disease (CKD) defined as eGFR of <60 mL/min per 1.73 m^2. High-molecular-weight adiponectin (HMW-adiponectin) levels were measured using the CLEIA method.

Statistical analysis

Gender-specific analyses were performed in light of observed gender differences in HOMA-IR distribution. HOMA-IR values were divided into tertiles to compare the characteristics. Data were presented as means (standard deviations [SDs]) or medians (interquartile ranges) for continuous variables, or numbers (percentages) for categorical variables. We used one-way analysis of variance for continuous variables and the chi-square test or Fisher's exact test for categorical variables to compare the characteristics among the groups. Multiple adjustments were performed with linear regression models to estimate the association between HOMA-IR values and markers of glycemic control, such as FPG, 1,5-AG, and HbA1c levels. We also performed multivariate logistic regression analysis to clarify the association between HOMA-IR values and any of the higher percentiles (80th or 90th percentile) of HbA1c levels, lower percentiles (10th or 20th percentile) of 1,5-AG levels or higher percentiles (80th or 90th percentile) of FPG levels. Multivariable analyses were adjusted for potential confounders in the following steps: (1) age; (2) BMI, regular exercise habits, current smoking, current alcohol drinking, CKD, and HMW-adiponectin levels, in addition to the variables in step 1; and (3) waist circumference substituted for BMI in step 2. The adjusted coefficient of determination (adjusted R^2) was also calculated. Two-tailed P values of <0.05 were considered statistically significant. All analyses were performed using STATA SE 11 data analysis and statistical software (Stata Corp LP, College Station, TX, USA).

Table 1. Characteristics of the participants according to HOMA-IR values by gender

	HOMA-IR tertile			*P* value
	1st (low)	2nd	3rd (high)	
Men (*n* = 323)				
Number of participants	109	107	107	
HOMA-IR	<3.397	3.397–5.596	≥5.596	
HbA1c (NGSP; %), mean (SD)	5.47 (0.30)	5.43 (0.25)	5.63 (0.36)	<0.001
HbA1c (IFCC; mmol/mol), mean (SD)	36 (3)	36 (3)	38 (4)	<0.001
1,5-AG (μmol/L), mean (SD)	145.9 (46.9)	139.4 (45.0)	123.4 (40.9)	<0.001
FPG (mmol/L), mean (SD)	4.91 (0.34)	5.00 (0.35)	5.38 (0.50)	<0.001
IRI (pmol/L), mean (SD)	11.2 (3.1)	19.8 (3.0)	36.6 (12.4)	<0.001
Age (years), mean (SD)	61.1 (8.6)	60.0 (9.5)	61.3 (8.9)	0.495
Body mass index (kg/m^2), mean (SD)	21.2 (2.2)	22.8 (2.1)	24.5 (2.3)	<0.001
Waist circumference (cm), mean (SD)	78.1 (6.6)	82.7 (6.0)	87.9 (7.7)	<0.001
Regular exercise, *n* (%)	70 (64.2%)	69 (64.5%)	66 (61.7%)	0.916
Current smoker, *n* (%)	15 (13.8%)	15 (14.0%)	5 (4.7%)	0.036
Current alcohol drinker, *n* (%)	86 (78.9%)	82 (76.6%)	82 (76.6%)	0.903
Chronic kidney disease, *n* (%)	9 (8.3%)	12 (11.2%)	15 (14.0%)	0.407
HMW-Adiponectin (μg/mL), median (IQR)	3.6 (2.6–5.2)	3.2 (2.0–4.7)	2.5 (1.6–3.7)	<0.001
Women (*n* = 760)				
Number of participants	254	255	251	
HOMA-IR	<3.126	3.126–4.819	≥4.819	
HbA1c (NGSP; %), mean (SD)	5.53 (0.31)	5.55 (0.27)	5.63 (0.29)	<0.001
HbA1c (IFCC; mmol/mol), mean (SD)	37 (3)	37 (3)	38 (3)	<0.001
1,5-AG (μmol/L), mean (SD)	105.6 (31.8)	107.1 (32.3)	109.5 (38.0)	0.444
FPG (mmol/L), mean (SD)	4.68 (0.34)	4.86 (0.33)	5.08 (0.40)	<0.001
IRI (pmol/L), mean (SD)	11.1 (2.7)	18.3 (2.4)	30.7 (10.1)	<0.001
Age (years), mean (SD)	57.0 (8.9)	58.4 (8.7)	58.5 (8.4)	0.094
Body mass index (kg/m^2), mean (SD)	19.5 (2.1)	21.0 (2.3)	22.1 (2.6)	<0.001
Waist circumference (cm), mean (SD)	73.9 (7.3)	78.5 (7.3)	81.9 (7.6)	<0.001
Regular exercise, *n* (%)	141 (55.5%)	139 (54.5%)	124 (49.4%)	0.341
Current smoker, *n* (%)	7 (2.8%)	2 (0.8%)	6 (2.4%)	0.200
Current alcohol drinker, *n* (%)	107 (42.1%)	79 (31.0%)	89 (35.5%)	0.031
Chronic kidney disease, *n* (%)	18 (7.1%)	18 (7.1%)	20 (8.0%)	0.924
HMW-Adiponectin (μg/mL), median (IQR)	6.6 (4.6–8.8)	5.5 (3.9–7.8)	4.4 (3.1–6.1)	<0.001

1,5-AG, 1,5-anhydroglucitol; FPG, fasting plasma glucose; HMW-Adiponectin, high-molecular-weight adiponectin; HOMA-IR, homeostasis model assessment of insulin resistance; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; IQR, interquartile range; IRI, immunoreactive insulin; NGSP, National Glycohemoglobin Standardization Program; SD, standard deviation.

RESULTS

Baseline characteristics of participants

Table 1 shows the characteristics of the participants according to HOMA-IR category by gender. The mean (SD) age was 60.8 (9.0) and 58.0 (8.7) years in men and women, respectively. Participants in higher HOMA-IR categories had higher HbA1c and FPG levels, both in men and women, and only men had lower 1,5-AG levels. Participants in higher HOMA-IR categories also had higher BMI and waist circumference, as well as lower HMW-adiponectin levels, both in men and women.

Association between HOMA-IR values and markers of glycemic control

The association between HOMA-IR values and markers of glycemic control, such as HbA1c, 1,5-AG, and FPG levels, in the multivariate linear regression analysis are shown according to gender in Table 2 (men) and Table 3 (women). HbA1c and FPG levels were significantly higher in the highest tertile group of HOMA-IR values than in the lowest tertile group, both in men and women. 1,5-AG levels were significantly lower in the highest tertile group of HOMA-IR values than in the lowest tertile group in men but not in women. The association between HOMA-IR values and markers of glycemic control was unchanged after adjusting for potential confounders, including BMI, waist circumference, and HMW-adiponectin levels. We performed multiple linear regression analysis to estimate the association between HOMA-IR values and markers of glycemic control according to BMI and gender. The results showed that the absolute values of coefficient were larger in the group with high BMI than in the group with low BMI in men (eTable 1), which suggested a strong association between HOMA-IR and these glycemic control parameters; however, these findings were not clearly observed in women (eTable 2). We also performed multivariate logistic regression analysis to clarify the association between HOMA-IR values and any of the higher percentiles of HbA1c levels, lower percentiles of 1,5-AG levels, or higher percentiles of FPG levels, both in men (eTable 3) and women (eTable 4). Compared with the lowest tertile group of HOMA-IR values, the highest tertile group

Table 2. Associations between HOMA-IR values and markers of glycemic control in men (n = 323)

Dependent variables		Independent variables: HbA1c (mmol/mol)				Independent variables: 1,5-AG (μmol/L)				Independent variables: FPG (mmol/L)			
		Coefficient	95% CI	Standardized Coefficient	*P* value	Coefficient	95% CI	Standardized Coefficient	*P* value	Coefficient	95% CI	Standardized Coefficient	*P* value
Model 1													
HOMA-IR	1st (<3.397)	Reference				Reference				Reference			
	2nd (3.397–5.596)	−0.22	(−1.09, 0.65)	−0.03	0.621	−7.36	(−19.11, 4.39)	−0.08	0.219	0.10	(−0.01, 0.21)	0.10	0.064
	3rd (≥5.596)	1.77	(0.90, 2.64)	0.24	<0.001	−22.27	(−34.00, −10.53)	−0.23	<0.001	0.47	(0.36, 0.57)	0.49	<0.001
Age (10 years)		0.95	(0.55, 1.35)	0.25	<0.001	−7.86	(−13.23, −2.49)	−0.16	0.004	0.10	(0.05, 0.15)	0.20	<0.001
		Adjusted coefficient of determination (R^2) = 0.12				Adjusted coefficient of determination (R^2) = 0.06				Adjusted coefficient of determination (R^2) = 0.23			
Model 2													
HOMA-IR	1st (<3.397)	Reference				Reference				Reference			
	2nd (3.397–5.596)	−0.33	(−1.24, 0.58)	−0.05	0.470	−7.04	(−19.16, 5.09)	−0.07	0.254	0.12	(0.01, 0.23)	0.12	0.034
	3rd (≥5.596)	1.65	(0.60, 2.70)	0.22	0.002	−18.62	(−32.60, −4.63)	−0.19	0.009	0.49	(0.36, 0.61)	0.51	<0.001
Age (10 years)		1.03	(0.59, 1.46)	0.26	<0.001	−6.42	(−12.25, −0.60)	−0.13	0.031	0.09	(0.04, 0.14)	0.18	0.001
Body mass index (kg/m^2)		0.09	(−0.07, 0.26)	0.07	0.258	0.30	(−1.89, 2.50)	0.02	0.786	−0.01	(−0.03, 0.01)	−0.04	0.486
Regular exercise (yes)		−0.12	(−0.92, 0.67)	−0.02	0.758	4.20	(−6.36, 14.75)	0.04	0.434	−0.01	(−0.10, 0.09)	−0.01	0.912
Current smoking (yes)		1.02	(−0.18, 2.21)	0.09	0.094	30.94	(15.05, 46.82)	0.21	<0.001	−0.21	(−0.35, −0.06)	−0.14	0.005
Current alcohol drinking (yes)		−0.84	(−1.70, 0.02)	−0.10	0.056	−1.74	(−13.19, 9.72)	−0.02	0.766	0.07	(−0.03, 0.18)	0.07	0.161
Chronic kidney disease (yes)		0.08	(−1.08, 1.24)	0.01	0.895	−4.52	(−20.00, 10.96)	−0.03	0.566	−0.08	(−0.22, 0.06)	−0.06	0.240
HMW-Adiponectin (μg/mL)		0.32	(−0.31, 0.94)	0.06	0.319	3.57	(−4.74, 11.88)	0.05	0.399	0.02	(−0.06, 0.09)	0.03	0.613
		Adjusted coefficient of determination (R^2) = 0.13				Adjusted coefficient of determination (R^2) = 0.09				Adjusted coefficient of determination (R^2) = 0.25			
Model 3													
HOMA-IR	1st (<3.397)	Reference				Reference				Reference			
	2nd (3.397–5.596)	−0.25	(−1.15, 0.66)	−0.03	0.595	−6.93	(−18.97, 5.11)	−0.07	0.258	0.12	(0.01, 0.23)	0.12	0.033
	3rd (≥5.596)	1.83	(0.79, 2.86)	0.25	0.001	−18.42	(−32.20, −4.64)	−0.19	0.009	0.49	(0.36, 0.61)	0.51	<0.001
Age (10 years)		1.00	(0.57, 1.44)	0.26	<0.001	−6.50	(−12.32, −0.69)	−0.13	0.028	0.09	(0.04, 0.14)	0.18	0.001
Waist circumference (10 cm)		0.13	(−0.41, 0.67)	0.03	0.635	0.83	(−6.33, 8.00)	0.01	0.819	−0.03	(−0.09, 0.04)	−0.04	0.441
Regular exercise (yes)		−0.11	(−0.90, 0.69)	−0.01	0.790	4.30	(−6.29, 14.89)	0.05	0.425	−0.01	(−0.10, 0.09)	−0.01	0.861
Current smoking (yes)		1.03	(−0.16, 2.23)	0.09	0.091	30.91	(15.00, 46.82)	0.21	<0.001	−0.21	(−0.35, −0.06)	−0.14	0.005
Current alcohol drinking (yes)		−0.84	(−1.70, 0.02)	−0.10	0.056	−1.76	(−13.22, 9.70)	−0.02	0.763	0.07	(−0.03, 0.18)	0.07	0.158
Chronic kidney disease (yes)		0.12	(−1.04, 1.29)	0.01	0.834	−4.38	(−19.82, 11.07)	−0.03	0.578	−0.09	(−0.23, 0.05)	−0.06	0.221
HMW-Adiponectin (μg/mL)		0.29	(−0.34, 0.91)	0.05	0.373	3.57	(−4.79, 11.93)	0.05	0.402	0.02	(−0.06, 0.09)	0.02	0.643
		Adjusted coefficient of determination (R^2) = 0.13				Adjusted coefficient of determination (R^2) = 0.09				Adjusted coefficient of determination (R^2) = 0.25			

1,5-AG, 1,5-anhydroglucitol; CI, confidence interval; FPG, fasting plasma glucose; HMW-Adiponectin, high-molecular-weight adiponectin; HOMA-IR, homeostasis model assessment of insulin resistance. Multivariate adjustment; Model 1: adjusted by age; Model 2: adjusted by age, body mass index, regular exercise (yes/no), current smoking (yes/no), current alcohol drinking (yes/no), chronic kidney disease (yes/no) and high-molecular-weight (HMW)-Adiponectin (log-transformed); Model 3: adjusted by age, waist circumference, regular exercise (yes/no), current smoking (yes/no), current alcohol drinking (yes/no), chronic kidney disease (yes/no) and HMW-Adiponectin (log-transformed).

Table 3. Associations between HOMA-IR values and markers of glycemic control in women (n = 760)

Dependent variables		Independent variables: HbA1c (mmol/mol)				Independent variables: 1,5-AG (μmol/L)				Independent variables: FPG (mmol/L)			
		Coefficient	95% CI	Standardized Coefficient	*P* value	Coefficient	95% CI	Standardized Coefficient	*P* value	Coefficient	95% CI	Standardized Coefficient	*P* value
Model 1													
HOMA-IR	1st (<3.126)	Reference				Reference				Reference			
	2nd (3.126–4.819)	0.18	(−0.36, 0.72)	0.03	0.516	1.90	(−4.03, 7.84)	0.03	0.529	0.16	(0.10, 0.22)	0.20	<0.001
	3rd (≥4.819)	1.00	(0.45, 1.54)	0.15	<0.001	4.35	(−1.61, 10.31)	0.06	0.152	0.38	(0.32, 0.44)	0.46	<0.001
Age (10 years)		0.88	(0.62, 1.13)	0.24	<0.001	−3.18	(−6.19, −0.59)	−0.09	0.018	0.11	(0.08, 0.14)	0.25	<0.001
		Adjusted coefficient of determination (R^2) = 0.07				Adjusted coefficient of determination (R^2) = 0.01				Adjusted coefficient of determination (R^2) = 0.23			
Model 2													
HOMA-IR	1st (<3.126)	Reference				Reference				Reference			
	2nd (3.126–4.819)	0.01	(−0.55, 0.57)	0.001	0.974	0.83	(−5.34, 6.99)	0.01	0.792	0.16	(0.10, 0.22)	0.19	<0.001
	3rd (≥4.819)	0.80	(0.19, 1.41)	0.12	0.010	2.28	(−4.45, 9.00)	0.03	0.507	0.37	(0.31, 0.44)	0.45	<0.001
Age (10 years)		0.73	(0.44, 1.02)	0.20	<0.001	−3.06	(−6.28, 0.15)	−0.08	0.062	0.10	(0.07, 0.13)	0.23	<0.001
Body mass index (kg/m^2)		0.07	(−0.02, 0.17)	0.06	0.130	0.96	(−0.11, 2.03)	0.07	0.077	0.01	(−0.004, 0.02)	0.04	0.286
Regular exercise (yes)		0.19	(−0.30, 0.68)	0.03	0.438	−2.19	(−7.58, 3.20)	−0.03	0.425	0.04	(−0.02, 0.09)	0.05	0.160
Current smoking (yes)		−1.12	(−2.73, 0.50)	−0.05	0.174	16.49	(−1.27, 34.25)	0.07	0.069	−0.01	(−0.19, 0.17)	−0.003	0.934
Current alcohol drinking (yes)		−0.62	(−1.08, −0.15)	−0.09	0.009	−2.01	(−7.12, 3.11)	−0.03	0.441	0.04	(−0.01, 0.09)	0.05	0.136
Chronic kidney disease (yes)		0.67	(−0.18, 1.52)	0.05	0.122	0.09	(−9.27, 9.44)	0.001	0.985	0.07	(−0.02, 0.17)	0.05	0.128
HMW-Adiponectin (μg/mL)		0.03	(−0.41, 0.47)	0.01	0.884	1.74	(−3.08, 6.57)	0.03	0.479	−0.001	(−0.05, 0.05)	−0.001	0.982
		Adjusted coefficient of determination (R^2) = 0.08				Adjusted coefficient of determination (R^2) = 0.01				Adjusted coefficient of determination (R^2) = 0.23			
Model 3													
HOMA-IR	1st (<3.126)	Reference				Reference				Reference			
	2nd (3.126–4.819)	0.02	(−0.54, 0.58)	0.002	0.956	0.64	(−5.53, 6.80)	0.01	0.840	0.17	(0.11, 0.23)	0.20	<0.001
	3rd (≥4.819)	0.82	(0.21, 1.43)	0.12	0.008	2.09	(−4.59, 8.77)	0.03	0.539	0.39	(0.32, 0.45)	0.46	<0.001
Age (10 years)		0.70	(0.41, 1.00)	0.19	<0.001	−3.49	(−6.76, −0.22)	−0.09	0.036	0.10	(0.07, 0.14)	0.23	<0.001
Waist circumference (10 cm)		0.22	(−0.09, 0.53)	0.06	0.166	3.52	(0.09, 6.94)	0.08	0.044	0.0004	(−0.03, 0.04)	0.001	0.979
Regular exercise (yes)		0.20	(−0.29, 0.69)	0.03	0.425	−2.17	(−7.55, 3.21)	−0.03	0.428	0.04	(−0.01, 0.09)	0.05	0.144
Current smoking (yes)		−1.07	(−2.69, 0.54)	−0.05	0.192	17.11	(−0.64, 34.85)	0.07	0.059	−0.01	(−0.18, 0.17)	−0.002	0.956
Current alcohol drinking (yes)		−0.65	(−1.11, −0.18)	−0.10	0.007	−2.44	(−7.57, 2.69)	−0.03	0.350	0.04	(−0.01, 0.09)	0.05	0.141
Chronic kidney disease (yes)		0.68	(−0.17, 1.53)	0.05	0.119	0.18	(−9.17, 9.53)	0.001	0.971	0.07	(−0.02, 0.17)	0.05	0.130
HMW-Adiponectin (μg/mL)		0.03	(−0.41, 0.47)	0.01	0.883	1.98	(−2.87, 6.82)	0.03	0.424	−0.01	(−0.05, 0.04)	−0.01	0.811
		Adjusted coefficient of determination (R^2) = 0.08				Adjusted coefficient of determination (R^2) = 0.01				Adjusted coefficient of determination (R^2) = 0.23			

1,5-AG, 1,5-anhydroglucitol; CI, confidence interval; FPG, fasting plasma glucose; HMW-Adiponectin, high-molecular-weight adiponectin; HOMA-IR, homeostasis model assessment of insulin resistance. Multivariate adjustment; Model 1: adjusted by age; Model 2: adjusted by age, body mass index, regular exercise (yes/no), current smoking (yes/no), current alcohol drinking (yes/no), chronic kidney disease (yes/no) and high-molecular-weight (HMW)-Adiponectin (log-transformed); Model 3: adjusted by age, waist circumference, regular exercise (yes/no), current smoking (yes/no), current alcohol drinking (yes/no), chronic kidney disease (yes/no) and HMW-Adiponectin (log-transformed).

had significantly higher odds ratios for any of higher percentiles of HbA1c levels, lower percentiles of 1,5-AG levels, or higher percentiles of FPG levels, both in men and women, after adjusting for potential confounders.

DISCUSSION

This is the first report, to the best of our knowledge, to assess the relationship between HOMA-IR values and several indices of glucose metabolism, obtained at various time points, in Japanese subjects without diabetes or obesity. As a result, we found that HOMA-IR values were significantly associated with all indices of glucose metabolism in men, as well as with HbA1c or FPG levels in women.

HOMA-IR is generally considered an index of insulin resistance in the liver.[12] Insulin suppresses the elevation of plasma glucose levels by promoting glucose uptake into cells and by inhibiting glucose release from the liver. However, when insulin resistance increases, the regulatory mechanism fails and blood glucose levels remain elevated.[14–16] In the present study, our results indicate that increased insulin resistance further deteriorates glucose metabolism in patients with not only type 2 diabetes mellitus and obesity but also in those without diabetes or obesity. The relationship between insulin resistance and several indices of glucose metabolism was maintained after adjusting for confounding factors, such as BMI or waist circumference. Multivariate regression analysis in this study revealed that BMI and waist circumference were not correlated with the indices of glucose metabolism. However, in the multivariate regression model that excluded HOMA-IR as an independent variable, BMI (eTable 5) and waist circumference (eTable 6) maintained significant correlation with HbA1c and FPG levels. Therefore, these results indicated that insulin resistance might regulate glucose metabolism downstream of BMI and waist circumference.

The present study showed that HOMA-IR values were not significantly associated with 1,5-AG levels in women. 1,5-AG is monosaccharide excreted in the urine. Approximately, 99%–100% of the excreted 1,5-AG is reabsorbed in the renal tubules, and a constant level is maintained in subjects with normal glucose tolerance. When blood glucose levels reach the threshold at which urinary glucose appears, 1,5-AG levels decrease remarkably because 1,5-AG reabsorption is inhibited.[8,17,18] In other words, 1,5-AG levels do not change if blood glucose levels do not reach the urinary glucose excretion threshold. Considering these mechanisms, it is suspected that most of the participants, especially women, had normal glucose tolerance, although participants both with normal glucose tolerance and mild glucose intolerance were included in the present study. In male participants, HOMA-IR values were weakly correlated with 1,5-AG levels compared to the correlations of HOMA-IR values with HbA1c and FPG levels. Thus, it is possible that the suspected high prevalence of normal glucose tolerance influenced this result.

A cohort study of the general Japanese population revealed that metabolic syndrome increased the risk of onset of type 2 diabetes mellitus, suggesting that insulin resistance contributed to the onset of type 2 diabetes mellitus in the Japanese population.[19] Another cohort study of the general Japanese population showed that both a decrease in insulin secretion ability and an increase in insulin resistance contributed to the onset of type 2 diabetes mellitus.[20] In the present study, a correlation between an index of insulin resistance and several indices of glucose metabolism was observed in Japanese subjects without obesity and with low insulin resistance. These findings suggest that insulin resistance mainly contributed to the onset of type 2 diabetes mellitus in Japanese subjects. Lifestyle interventions, such as healthy diet and regular exercise, have been shown to be effective for the improvement of insulin resistance but not impaired insulin secretion capacity.[21] Thus, we recommend lifestyle interventions for the prevention of onset of type 2 diabetes mellitus not only in obese subjects but also in non-obese subjects. In the present study, we also found that the association between HOMA-IR values and each marker of glycemic control was stronger in subjects with high BMI than in those with low BMI. Therefore, even in non-obese (BMI $<30\,kg/m^2$) Asians, we suggest that the impact of lifestyle intervention on the onset of type 2 diabetes mellitus is larger among subjects with high BMI than among those with low BMI when impaired insulin secretion capacity is suspected.

This study has several limitations. At first, we used HOMA-IR, which is an indirect index for the evaluation of insulin resistance. Although the glucose clamp technique is necessary for direct evaluation,[22] we were unable to apply this test in our subjects. However, a previous study reported that the use of HOMA-IR was appropriate to assess insulin sensitivity in subjects without diabetes.[23] Second, we used a self-reported questionnaire in the present study; thus, recall bias might have affected the evaluation of physical activity. Finally, we could not evaluate postprandial hyperglycemia accurately in this study because we did not measure the blood glucose afterload. We used HbA1c levels as the diagnostic criteria of diabetes in this study; thus, subjects having marked postprandial hyperglycemia were excluded.

In conclusion, the present study showed that HOMA-IR values were significantly associated with several indices of glucose metabolism in Japanese subjects without diabetes or obesity and that insulin resistance prescribed glucose metabolism downstream of BMI or waist circumference. These findings suggest that insulin resistance may mainly influence glycemic control even in non-diabetic subjects without obesity.

ONLINE ONLY MATERIALS

eTable 1. Associations between HOMA-IR values and markers of glycemic control divided by median BMI in men ($n = 323$).

eTable 2. Associations between HOMA-IR values and markers of glycemic control divided by median BMI in women ($n = 760$).
eTable 3. Associations between HOMA-IR values and higher percentile of HbA1c or FPG or lower percentile of 1,5-AG.
eTable 4. Associations between HOMA-IR values and higher percentile of HbA1c or FPG or lower percentile of 1,5-AG.
eTable 5. Associations between BMI and markers of glycemic control in multivariate regression model that excluded HOMA-IR.
eTable 6. Associations between waist circumference and markers of glycemic control in multivariate regression model that excluded HOMA-IR.
Abstract in Japanese.

ACKNOWLEDGEMENTS

This study was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (B 23390178, C 23590835); by Grants from the Regional Innovation Cluster Program, Global Type, Ministry of Education, Culture, Sports, Science and Technology; by a Grant-in-Aid for Researchers, Hyogo College of Medicine, 2010; by a Grant-in-Aid for Young Scientists B 23790711 from the Japan Society for the Promotion of Science; and by Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H26-Junkankitou [Seisaku]-Ippan-001 from Ministry of Health, Labor and Welfare. The authors would like to express their sincere appreciation to the volunteers involved in the administration of the KOBE study and all of the research staff. We thank Enago (www.enago.jp) for editing our article.

Conflicts of interest: None declared.

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Effects of Stroke Education of Junior High School Students on Stroke Knowledge of Their Parents

Tochigi Project

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Background and purpose—Educating the youth about stroke is a promising approach for spreading stroke knowledge. The aim of this study was to verify communication of stroke knowledge to parents by educating junior high school students about stroke.

Methods—We enrolled 1127 junior high school students (age, 13–15 years) and their parents in the Tochigi prefecture, Japan. All students received a stroke lesson, watched an animated cartoon, and read the related Manga comic as educational aids. The students took back home the Manga and discussed what they learned with their parents. Questionnaires on stroke knowledge were given to all at baseline and immediately after the lesson.

Results—A total of 1125 students and 915 parents answered the questionnaires. In the students, the frequency of correct answers increased significantly for all questions on stroke symptoms except for headache, and for all questions on risk factors after the lesson. In the parents, the correct answer rates increased for stroke symptoms except for headache and numbness in one side of the body, and for all questions on risk factors except for hypertension. Ninety-one percent of students and 92.7% of parents correctly understood the Face, Arm, Speech, and Time (FAST) mnemonic after the lesson.

Conclusions—Improvement of stroke knowledge immediately after the stroke lesson was observed in parents as well as their children, which indicated that our teaching materials using the Manga was effective in delivering the stroke knowledge to parents through their children. **(*Stroke*. 2015;46:572-574. DOI: 10.1161/STROKEAHA.114.007907.)**

Key Words: acute stroke ■ health education ■ schools

Stroke education is expected to reduce the time from onset of symptom to arrival at the hospital through increasing the knowledge of warning signs for stroke. We and others recently reported the results of studies of stroke educational campaigns for teenagers.[1–5] These results suggest that educating the youth on stroke is effective in spreading stroke knowledge to their families indirectly by communication among their family members.

The Tochigi project was planned to be a campaign of public education of stroke knowledge in collaboration with the local government of Tochigi prefecture between September 2012 and July 2013. The Tochigi prefecture with around 2 million residents is one of the prefectures with the highest rate of mortality for stroke in Japan.

The aim of this study was to verify the effectiveness of stroke education, which is the part of the Tochigi project, in a large population of junior high school students by delivering stroke lessons using an animated cartoon or a Manga.

Methods

Supplemental methods including analysis of data are provided in the online-only Data Supplement.

We enrolled 1127 students of the first to third grades (age, 13–15 years) in 9 public junior high schools and their parents. For recognition of stroke signs and symptoms, we used the Face, Arm, Speech, and

Received October 24, 2014; final revision received November 24, 2014; accepted November 25, 2014.

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*A list of all Participating Investigators of Tochigi Junior High School Stroke Education Group is given in the Appendix.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.007907/-/DC1.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.114.007907**

Time (FAST) mnemonic derived from the Cincinnati prehospital stroke scale.[6,7] After receiving a stroke lesson by a stroke neurologist on how to educate students about stroke using our teaching materials, our collaborators who were Public Health employees gave lectures as teachers on stroke knowledge to the students. Educational posters of FAST[3] were put on the walls of each classroom 1 week before the stroke lesson. The stroke lecture consisted of 3 parts, such as a 20-minute stroke lesson by teachers, watching an animated cartoon for 10 minutes, and reading a Manga comic for 10 minutes. At the close of the lesson, the teacher asked the students to take back home the Manga comic and questionnaire sheets and talk about stroke with their parents while showing the Manga.

Stroke knowledge of students and their parents was assessed at 2 time points: baseline and immediately after the instruction. Questionnaires of stroke knowledge were the same as those reported previously (Table in the online-only Data Supplement).[3,4]

Statistical analyses were performed using SPSS (version 13.0; SPSS Inc, Chicago, IL). Data before the lesson and immediately after the lesson were compared with the 2 sample test of proportions. A $P<0.05$ was considered to indicate statistical significance.

Results

Test scores were evaluated from 1125 of 1127 students (98%) and from 915 parents/guardians (860 parents and 55 guardians) among whom there were 755 mothers and 137 medical professionals; median age was 43 years. In students, the frequency of correct answers increased significantly for all questions on stroke symptoms except for headache, for all questions on risk factors, and for calling an ambulance. Correct test scores were 60.7% before versus 94.3% after the lesson ($P<0.001$; Table 1). In parents/guardians, the correct answer rates for stroke symptoms except for headache and numbness in one side of the body, for all questions on risk factors except for hypertension, and for calling an ambulance increased after the lesson. Correct test scores were 83.0% before versus 92.7% after the lesson ($P<0.001$; Table 2). Ninety-one percent of students and 92.7% of parents/guardians correctly understood the FAST mnemonic after the lesson.

Table 1. Changes in Answer Rates for Questions in the Students

Questions	BL, % (n=1127)	IL, % (n=1125)	*P* Value	95% CI (ΔIL to BL, %)
Stroke signs and symptoms				
Correct symptoms				
Headache	68.3	68.0	0.869	−3.52 to 4.17
Facial weakness in 1 side	45.0	92.4	<0.001	44.2 to 50.7
Visually impaired	22.8	57.5	<0.001	30.9 to 38.5
Speak unclearly	63.1	98.2	<0.001	32.1 to 38.1
Numbness in 1 side of the body	56.3	85.1	<0.001	25.2 to 32.4
Weakness of arm and leg in one side	57.9	89.4	<0.001	28.2 to 35.0
Incorrect symptoms				
Chest pain	10.1	3.50	<0.001	−8.7 to −4.6
Feel like choking	30.8	7.30	<0.001	−26.6 to −20.4
Stomach ache	5.68	0.98	<0.001	−6.2 to −3.2
Foot edema	16.1	3.73	<0.001	−14.7 to −9.9
Joint pain	11.2	3.38	<0.001	−9.9 to −5.7
Weakness of bilateral arms and legs	55.0	14.9	<0.001	−42.5 to −35.2
Adequate action when stroke onset				
Call an ambulance	60.7	94.3	<0.001	30.4 to 36.7
Stroke risk factors				
Correct risk factors				
Alcohol drinking	78.2	95.5	<0.001	14.6 to 20.0
Smoking	63.6	90.3	<0.001	23.4 to 30.0
Hypertension	81.7	92.8	<0.001	8.4 to 13.8
High blood glucose level	57.1	85.5	<0.001	24.8 to 31.9
High cholesterol level	58.1	88.8	<0.001	27.3 to 34.1
Overweight	28.4	76.0	<0.001	44.0 to 51.2
Irregular heart rhythm	44.0	55.9	<0.001	7.8 to 16.0
Incorrect risk factors				
Constipation	8.07	1.78	<0.001	−8.1 to −4.5
Frequent urination	9.49	4.53	<0.001	−7.1 to −2.9
Stiff shoulders	11.4	2.13	<0.001	−11.4 to −7.3

BL indicates before the lesson; CI, confidence interval; and IL; immediately after the lesson.

Discussion

This study showed that for junior high school students, there was an improvement of stroke knowledge immediately after delivering the stroke lesson to the students and that stroke knowledge, especially the FAST mnemonic, could be delivered to the students' parents by giving the students a stroke lesson using the Manga. Because ease of understanding is essential for spreading the stroke education, the Manga, a part of the Japanese culture, could be expected to play an important role in spreading stroke knowledge universally without the need of language just by visual presentation all over the world.

There were several limitations in this study. First, our study is not a randomized controlled study. However, we confirmed the feasibility of delivering stroke knowledge to the parents through their children with a large number of subjects. Second, it could not be determined which teaching materials were more useful in the improvement of stroke knowledge. Third, the stroke lesson was delivered by medical professionals. For spreading stroke knowledge widely through school-based instruction, school teachers rather than medical staff should be trained for delivering stroke knowledge as suggested previously.[4] Fourth, stroke symptoms other than those in the FAST mnemonic were not communicated to the parents. Placing emphasis on the FAST mnemonic may be the reason behind low percentage of correct test scores regarding headache as a stroke symptom.

Conclusions

A lesson on stroke using teaching materials using the Manga in junior high school students improved the stroke knowledge of students immediately after the lesson, and the stroke knowledge was communicated to their parents through their children. Instruction on stroke for children in junior high school is a promising means to spread the stroke knowledge nationwide, and could lead to a reduction of onset to door times in the future.

Table 2. Changes in Answer Rates for Questions in the Parents

Questions	BL, % (n=915)	IL, % (n=915)	*P* Value	95% CI (ΔIL to BL, %)
Stroke signs and symptoms				
Correct symptoms				
Headache	81.1	72.8	<0.001	−12.1 to −4.5
Facial weakness in one side	71.0	83.4	<0.001	8.5 to 16.2
Visually impaired	29.1	60.5	<0.001	27.2 to 35.8
Speak unclearly	90.7	95.5	<0.001	2.5 to 7.1
Numbness in one side of the body	69.3	72.5	0.136	−1.0 to 7.3
Weakness of arm and leg in one side	73.1	81.7	<0.001	4.8 to 12.4
Incorrect symptoms				
Chest pain	2.84	3.17	0.6815	−1.2 to 1.9
Feel like choking	8.31	6.10	0.0570	−4.7 to 0.1
Stomach ache	0.98	0.98	1.0000	−0.9 to 0.9
Foot edema	5.25	1.75	<0.001	−5.2 to −1.8
Joint pain	1.86	1.97	0.8645	−1.1 to 1.4
Weakness of bilateral arms and legs	42.2	29.8	<0.001	−16.7 to −8.0
Adequate action when stroke onset				
Call an ambulance	83.0	92.7	<0.001	6.7 to 12.7
Stroke risk factors				
Correct risk factors				
Alcohol drinking	66.4	87.2	<0.001	17.0 to 24.5
Smoking	82.1	92.9	<0.001	7.8 to 13.8
Hypertension	90.9	91.7	0.561	−1.8 to 3.3
High blood glucose level	45.9	74.4	<0.001	24.2 to 32.8
High cholesterol level	72.8	81.1	<0.001	4.5 to 12.1
Overweight	51.4	65.1	<0.001	9.3 to 18.2
Irregular heart rhythm	29.7	63.0	<0.001	28.9 to 37.5
Incorrect risk factors				
Constipation	5.14	3.61	0.1096	−3.2 to -0.3
Frequent urination	1.97	3.17	0.1041	−0.2 to 2.7
Stiff shoulders	13.0	5.46	<0.001	−10.2 to -4.9

BL indicates before the lesson; CI, confidence interval; and IL, immediately after the lesson.

Appendix

Participating Investigators of Tochigi Junior High School Stroke Education Group

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Sources of Funding

This study was supported by the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-4-1).

Disclosures

None.

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