Table 2a. Percent changes in lipid parameters according to %dWC quartiles

Variables	%dWC quartiles				*p* for trend
	First (range: −21.2–−3.4)	Second (range: −3.4–−0.1)	Third (range: 0.0–3.2)	Fourth (range: 3.2–33.3)	
Women					
%dLDL	−1.24±14.32	0.44±14.68	0.39±15.80	1.43±15.31	0.127
%dHDL	−0.41±10.97	−0.35±11.93	−0.53±11.02	−0.64±10.90	0.989
%dTG	2.92±35.05	1.49±33.53	9.02±40.49	8.60±37.33	0.034
Men					
%dLDL	−0.26±17.05	−0.36±15.56	−0.31±17.25	0.38±14.93	0.040
%dHDL	2.15±13.23	0.36±11.83	0.08±12.17	−0.21±11.35	0.016
%dTG	−1.25±39.56	5.17±47.12	6.67±53.51	9.66±53.00	0.009

Table 2b. Percent changes in lipid parameters according to %dBMI quartiles

Variables	%dBMI quartiles				*p* for trend
	First (range: −21.8–−1.8)	Second (range: −1.8–−0.2)	Third (range: −0.2–1.4)	Fourth (range: 1.4–15.6)	
Women					
%dLDL	−1.48±16.44	−1.26±12.79	−0.06±14.24	3.42±15.81	<0.001
%dHDL	0.78±12.40	−1.38±10.75	−0.62±9.46	−0.76±11.59	0.147
%dTG	−2.31±33.46	3.58±33.84	6.59±41.32	13.90±35.91	<0.001
Men					
%dLDL	−4.34±16.61	−0.96±15.58	0.01±15.69	2.80±16.68	<0.001
%dHDL	2.94±13.12	0.75±11.37	−0.40±10.50	−1.18±13.29	<0.001
%dTG	−10.21±33.76	1.90±40.05	7.07±48.69	23.13±63.63	<0.001

Discussion

In the current study, both %dWC and %dBMI were positively associated with %dLDL and %dTG in both genders. In addition, %dWC and %dBMI were inversely associated with %dHDL in men, but not in women; however, the association between percent changes in these obesity parameters and percent changes in lipid parameters, when present, was weak. Similar results were obtained when either %dWC or %dBMI was used as a potent predictor of percent changes in lipid data; however the correlation between %dWC and %dBMI was found to be relatively weak, especially in women; the correlation coefficient was 0.47 in men and 0.24 in women. Stepwise multiple regression analysis showed that %dBMI, but not %dWC, was identified as an independent factor predicting % changes in lipid data tested. Notably, even when %dBMI was excluded from the variables, %dWC was not identified as a predictor of %dHDL in women.

Several previous studies showed an association between changes in obesity indexes and lipid parameter changes. For example, in a community-based sample of 3,325 young adults, a 10-year weight gain tended to confer adverse changes in levels of LDL-C, HDL-C, and TG[7]. Bonithon-Kopp *et al.* reported that changes in BMI and the waist to hip ratio (WHR) were positively associated with changes in TG[8]. Williams *et al.* reported that changes in BMI as well as WC had a greater probability of inducing hypercholesterolemia during 7 years of follow-up[9]. In middle-aged subjects free from known cardiovascular diseases and diabetes[10], a gain or loss of WC over 9 years significantly affected serum lipid data and the incidence of metabolic syndrome[11].

On the other hand, only a few studies have investigated whether WC change was associated with changes in lipid parameters independent of BMI. Wing *et al.* analyzed whether changes in WHR led to improvements in serum lipid concentrations independent of weight change in subjects with no history of

Table 3. Stepwise multiple regression analysis between percent changes in lipid parameters and age, %dWC, and %dBMI

	Women					Men				
	β	95%CI		Standardized β	p value	β	95%CI		Standardized β	p value
Model 1										
Dependent variable, %dLDL										
%dBMI	0.72	0.44	0.99	0.15	<0.001	0.86	0.62	1.10	0.16	<0.001
age						−0.08	−0.15	−0.01	−0.05	0.019
Dependent variable, %dHDL										
%dBMI	−0.23	−0.43	−0.03	−0.07	0.026	−0.70	−0.88	−0.53	−0.17	<0.001
Dependent variable, %TG										
%dBMI	2.08	1.42	2.75	0.18	<0.001	4.47	3.78	5.16	0.28	<0.001
Model 2										
Dependent variable, %dLDL										
%dWC	0.16	0.05	0.26	0.08	0.005	0.25	0.09	0.41	0.07	0.002
age						−0.11	−0.18	−0.04	−0.07	0.003
Dependent variable, %dHDL										
%dWC						−0.24	−0.36	−0.12	−0.09	<0.001
Dependent variable, %TG										
%dWC	0.33	0.06	0.60	0.07	0.015	1.12	0.64	1.60	0.10	<0.001

Model 1. Independent variables include age, %dWC, and %dBMI. For model 2, independent variables included age and %dWC. Standardized β values are the estimates resulting from analysis performed on standardized variables.

heart disease or hypertension[12]. They found that changes in WHR were associated with changes in total cholesterol and triglycerides in men; however, statistical significance was lost after controlling for changes in BMI. On the other hand, after controlling for changes in WHR, changes in BMI remained to be associated with changes in total cholesterol and triglycerides in both genders. Of note, even before controlling for changes in BMI, WC change was not found to be associated with either total cholesterol or triglycerides in women. Wing *et al.* concluded that changes in WHR may not be independently related to changes in cardiovascular risk factors. Pascale *et al.* showed that in subjects participating in a year-long weight loss program, weight loss, but not reductions in WHR, was significantly related with improvements in fasting glucose, fasting insulin, and HbA1, although the magnitude of WHR reduction was strongly related to the amount of weight lost especially in men[13].

Similar to Wing *et al.*'s study, the current study indicated certain gender differences in the association between WC change and lipid parameter change, especially in the model not controlled for BMI. As HDL-C and TG are closely related to insulin sensitivity, and thus visceral fat mass, the closer relationship of %dBMI than %dWC with %dHDL and %dTG was rather unexpected. It is possible that WC measurements may be less reliable than weight and height measurements, which reduced the predictive power of %dWC for lipid changes. The correlation between %dWC and %dBMI was relatively weak, especially in women. This finding may indicate that a loss (gain) of BMI did not necessarily result in a loss (gain) in WC over a one-year period, and that men appear to lose (or gain) weight in their abdominal area more readily than women, which was consistent with previous observations[8, 12]. The finding that %dWC did not predict lipid changes independently of %dBMI may suggest that changes in BMI might be a more reliable goal to avoid adverse lipid changes than changes in WC.

It has recently been demonstrated that measuring both general and abdominal adiposity provides a better assessment of the risk of death[14]; therefore, we cannot lessen the importance of reducing WC and thus control visceral adiposity; in this sense, whether percent changes in abdominal fat demonstrated by computed tomography will have a greater impact on serum lipid data than %dWC should be examined in future studies[15].

The current study has several potential limitations. First, individuals who, for unknown reasons, did not visit our institute in the second year were not enrolled in the current study, which may cause some bias. Second, we do not have sufficient information

on the extent to which modifications of lifestyle and dietary habits affect the observed changes in general/abdominal obesity[16]. Third, we excluded subjects who were taking lipid-lowering drugs at either visit, and these individuals may, in general, have higher motivation to obtain information on how to improve serum lipid levels effectively as compared with those not taking such drugs. Finally, a longer follow-up should be performed in future studies.

In summary, during a one-year period, percent changes in BMI (%dBMI) were associated positively with percent changes in LDL-C and TG and negatively with those in HDL-C, especially in both genders. Although percent changes in WC (%dWC) also tended to confer adverse changes in lipid parameters, this relationship did not remain significant after controlling for %dBMI.

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Impacts of Changes in Obesity Parameters for the Prediction of Blood Pressure Change in Japanese Individuals

Nobukazu Ishizaka[a] Yuko Ishizaka[c] Ei-Ichi Toda[c] Kazuhiko Koike[b]
Minoru Yamakado[c] Ryozo Nagai[a]

Departments of [a]Cardiovascular Medicine and [b]Infectious Diseases, University of Tokyo Graduate School of Medicine, and [c]Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital, Tokyo, Japan

Key Words
Waist circumference · Body mass index · Blood pressure · Health screening

Abstract
Aims and Methods: By analyzing data from 2,861 individuals who underwent general health screening 2 years running, we have investigated the impact of changes in waist circumference (WC) and body mass index (BMI) over a 1-year period on systolic blood pressure (BPs). We termed WC, BMI, and BPs at the first visit as WC1, BMI1, and BPs1, respectively, and those at the second visit as WC2, BMI2, and BPs2, respectively. The %dWC, %dBMI, and %dBPs was defined as (WC2 – WC1)/WC1 × 100, (BMI2 – BMI1)/BMI1 × 100, and (BPs2 – BPs1)/BPs1 × 100, respectively. ***Results:*** In multivariate regression analysis using age, BPs1, WC1, and %dWC as independent variables, %dWC was a significant predictor for %BPs only in men. %dBMI was a significant predictor for %BPs in both genders when age, BPs1, BMI1, and %dBMI were used as independent variables. Compared with individuals with both %dWC <0 and %dBMI <0, age-adjusted %dBPs was significantly greater in those with both %dWC <0 and %dBMI ≥0; however, it did not significantly differ in those with both %dWC ≥0 and %dBMI <0. ***Conclusion:*** Our data suggest that the impact of BMI change might be greater than WC change in terms of BPs change during this short period.

Introduction

Much evidence supports a positive association between obesity parameters and hypertension [1–4], although the strength of such an association may differ according to the parameter used [5]. In addition, a loss or gain in body weight may affect blood pressure levels [6, 7], even in relatively lean or non-obese individuals [8, 9]. Therefore, weight control may be an important target for better blood pressure control, leading to a reduction in mortality from heart and cerebrovascular disease [4]. Compared with weight, or body mass index (BMI), less information seems to be available on whether, or to what extent, a loss (or gain) in waist circumference (WC) would result in a change in blood pressure. We previously reported that a reduction or gain in obesity parameters may affect the status of chronic kidney disease in individuals who underwent general health screening [10]. To this end, here we investigated the mode of association be-

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Dr. Nobukazu Ishizaka, Department of Cardiovascular Medicine
University of Tokyo Graduate School of Medicine
Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655 (Japan)
Tel +81 3 3815 5411, ext. 37156, Fax +81 3 5842 5586
E-Mail nobuishizka-tky@umin.ac.jp

tween changes in WC or BMI over a 1-year period and changes in blood pressure levels in Japanese individuals. We analyzed the data separately for each gender, because there may be gender differences in the strength of the association between various obesity parameters and blood pressure [11].

Subjects and Methods

Study Population

The study was approved by the Ethical Committees of University of Tokyo and Mitsui Memorial Hospital. Between October 2005 and October 2006, 3,312 (1,203 women, 2,109 men) individuals underwent general health screening (visit 1), and they visited our institute again in the following year (visit 2). Among these 3,312 individuals, 2,861 (1,114 women, 1,747 men) who reported not taking antihypertensive drugs at both visits were enrolled in the present study. After about 10 min of rest, systolic blood pressure (BPs) and diastolic blood pressure (BPd) were measured in the sitting position by automated sphygmomanometer, BP-203RVIII (Omron Colin, Tokyo, Japan). Blood pressure was measured twice and the mean of these data were taken. With the subject standing, WC was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians [12]. After changing into a robe from our institute, height and weight were measured, and the weight of the robe was subtracted from the value indicated by the scales. Age, WC, BMI, and BPs at visit 1 were designated age1, WC1, BMI1, and BPs1, respectively. Similarly, WC, BMI, and BPs at visit 2 were designated WC2, BMI2, and BPs2, respectively. %dWC, %dBMI, and %dBPs were defined as (WC2 – WC1)/WC1 × 100, (BMI2 – BMI1)/BMI1 × 100, and (BPs2 – BPs1)/BPs1 × 100, respectively.

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), HDL cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method, hemoglobin A_{1C} was determined using the latex agglutination immunoassay. Serum creatinine was measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) using commercially available kits, Accuras Auto CRE (Shino-test, Tokyo, Japan), according to the manufacturer's instructions. Accuracy control was performed every day by constructing X-bar and R charts using commercially available standards. Estimated glomerular filtration rate (eGFR) was calculated by the following equation: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ (× 0.739 if female) [13]. Serum insulin was measured by enzyme immunoassay. Homeostasis model assessment insulin resistance (HOMA-IR) was calculated in these individuals according to the following formula: HOMA-IR = [fasting immunoreactive insulin (μU/ml) × fasting plasma glucose (mg/dl)]/405 [14].

Statistical Analysis

Data are expressed as the mean ± SD unless stated otherwise. Analyses of variance with trend analysis, Tukey's post-hoc analysis and multiple regression analysis were conducted as appropriate to assess the statistical significance of differences between groups using computer software Dr. SPSS II (SPSS, Inc., Chicago, Ill., USA). A value of $p < 0.05$ was taken to be statistically significant.

Results

Baseline Characteristics

As described in the Methods section, among the 3,312 individuals who underwent general health screening visited our institute again in the following year; 2,861 (1,114 women, 1,747 men) who reported not taking antihypertensive drugs at both visits were enrolled in the current study (table 1). The mean ± SD of the interval between the two visits of the individuals enrolled was 355 ± 52 days. The mean ± SD age of the enrolled women (51.3 ± 9.9 years) and men (52.5 ± 10.1 years) was significantly smaller than that of the women (60.7 ± 8.3 years) and men (59.0 ± 8.5 years), respectively ($p < 0.001$), who were excluded because of the antihypertensive medication at either or both visits. Similarly, the mean BMI values of enrolled women (21.2 ± 2.9) and men (23.5 ± 2.7) were significantly smaller than those of the excluded women (22.5 ± 3.2) and men (25.0 ± 2.8), respectively ($p < 0.001$).

WC1 ranged between 51.8 and 118.5 cm, and a WC1 ≥90 cm was found in 71/1,114 women (6.4%), and a WC1 ≥85 cm was found in 183/1,114 men (16.4%). BMI1 ranged between 13.1 and 39.4. A BMI1 ≥25 was found in 110/1,114 women (9.9%) and 453/1,747 men (25.9%), and BMI1 ≥30 was found only in 12/1,114 (1.1%) women and 33/1,747 (1.9%) men. The correlation coefficients between %dWC, %dBMI, %dBPs, WC1, BMI1, and BPs1 are described in table 2. The correlation between %dWC and %dBMI was found to be moderate in men ($r = 0.476$), whereas it was weak in women ($r = 0.241$). The relationship between %dBMI and %dBPs was found to be statistically significant in the both genders. On the other hand, the relationship between %dWC and %dBPs was statistically significant only in men. Among the study subjects, it was reported that 60 subjects experienced a WC change of –10 cm or less, and 94 subjects experienced a WC change of +10 cm or more. After excluding these 154 individuals from the study population, the results obtained were not essentially changed (data not shown). It was calculated that a 10% weight gain (loss) over a 1-year period was associated with a 3.88 mm Hg BPs gain (loss) in women and a 9.86 mm Hg BPs gain (loss) in men.

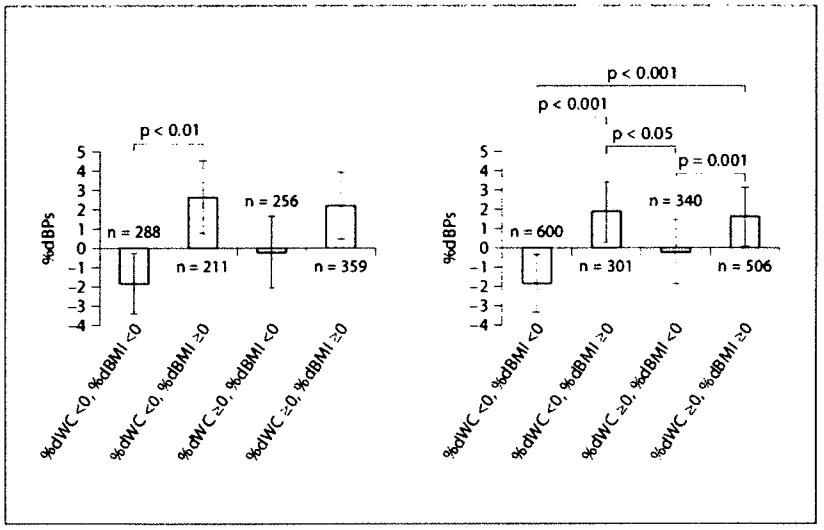

Fig. 1. Comparison of the age-adjusted %dBPs in four subgroups categorized according to the gain or loss of %dWC and %dBMI values. p values were from the result of the Tukey's post-hoc analysis following analyses of variance. Mean ± 95% confidence interval is shown in each group.

Table 1. Clinical characteristics and laboratory data at the first visit

Variables	Whole	%dBPs				p value
		first (range: −40 ~ −7)	second (range: −7 ~ 0)	third (range: +1 ~ +6)	fourth (range: +6 ~ +52)	
Number	2,861	714	809	639	699	
Women/men	1,114/1,747	288/426	314/495	251/388	261/438	0.712
Age, years	52.0 ± 10.1	52.8 ± 10.1	51.4 ± 9.9	51.8 ± 10.0	52.2 ± 10.2	0.047
Height, cm	164.8 ± 8.4	164.5 ± 8.3	165.2 ± 8.5	164.7 ± 8.5	164.7 ± 8.6	0.379
Weight, kg	61.8 ± 11.5	61.8 ± 11.4	62.0 ± 11.6	61.5 ± 11.3	61.8 ± 11.7	0.883
BMI, kg/m^2	22.6 ± 3.0	22.7 ± 3.0	22.6 ± 3.1	22.5 ± 3.0	22.6 ± 3.1	0.781
WC, cm	81.8 ± 9.1	82.0 ± 9.1	81.8 ± 9.3	81.5 ± 9.0	81.9 ± 9.0	0.851
Systolic BP, mm Hg	120.9 ± 18.0	128.7 ± 18.3	121.8 ± 17.0	118.5 ± 16.7	114.2 ± 16.8	<0.001
Diastolic BP, mm Hg	76.4 ± 11.4	79.3 ± 11.3	76.8 ± 10.9	75.5 ± 11.0	73.7 ± 11.5	<0.001
LDL cholesterol, mg/dl	129.2 ± 31.1	131.4 ± 31.5	128.3 ± 29.5	127.1 ± 30.9	130.1 ± 32.4	0.051
HDL cholesterol, mg/dl	61.2 ± 15.3	60.8 ± 15.0	61.8 ± 15.7	61.4 ± 15.6	60.7 ± 15.0	0.465
Triglyceride, mg/dl	109.9 ± 71.4	115.7 ± 69.9	104.7 ± 61.8	109.8 ± 81.0	110.1 ± 73.4	0.030
Uric acid, mg/dl	5.4 ± 1.3	5.4 ± 1.3	5.5 ± 1.3	5.4 ± 1.4	5.5 ± 1.4	0.688
Fasting glucose, mg/dl	95.2 ± 20.0	96.8 ± 20.4	95.1 ± 21.1	94.2 ± 18.0	94.7 ± 20.0	0.072
Hemoglobin A1C, %	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	0.506
HOMA-IR	1.5 ± 1.1	1.6 ± 1.1	1.5 ± 1.1	1.4 ± 1.0	1.5 ± 1.0	0.066
Blood urea nitrogen, mg/dl	14.0 ± 3.4	13.8 ± 3.7	14.0 ± 3.2	14.2 ± 3.4	14.1 ± 3.5	0.245
Serum creatinine, mg/dl	0.8 ± 0.3	0.8 ± 0.4	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.764
Estimated glomerular filtration rate	68.6 ± 11.8	68.3 ± 11.4	69.3 ± 12.0	68.4 ± 11.8	68.1 ± 11.8	0.177
Antidiabetic medication, n (%)	51 (1.8)	12 (1.7)	20 (2.5)	10 (1.6)	9 (1.3)	0.335
Current smoker, n (%)	680 (23.8)	179 (25.0)	184 (22.7)	139 (21.8)	178 (25.5)	0.298

Data are means ± SD, unless stated otherwise. BMI = Body mass index; WC = waist circumference; HOMA-IR = homeostasis model assessment of insulin resistance. %dBPs was calculated by the following equation: (BPs at the second visit − BP1 at the second visit)/(BP1 at the second visit) × 100 (%). p value is for trend.

Table 2. Pearson's correlation coefficient of obesity indices and blood pressure parameters

	%dWC	%dBMI	%dBPs	WC1	BMI1	BPs1
Women						
%dWC						
r	–					
p value	–					
%dBMI						
r	0.241	–				
p value	<0.001	–				
%dBPs						
r	−0.014	0.097	–			
p value	0.635	0.001	–			
WC1						
r	−0.317	−0.053	−0.028	–		
p value	<0.001	0.078	0.350	–		
BMI1						
r	−0.026	−0.087	−0.029	0.787	–	
p value	0.393	0.004	0.331	<0.001	–	
BPs1						
r	−0.025	−0.055	−0.325	0.365	0.409	–
p value	0.396	0.064	<0.001	<0.001	<0.001	–
Men						
%dWC						
r	–					
p value	–					
%dBMI						
r	0.476	–				
p value	<0.001	–				
%dBPs						
r	0.116	0.232	–			
p value	<0.001	<0.001	–			
WC1						
r	−0.268	−0.089	−0.031	–		
p value	<0.001	<0.001	0.189	–		
BMI1						
r	−0.054	−0.071	−0.026	0.830	–	
p value	0.023	0.003	0.286	<0.001	–	
BPs1						
r	−0.090	−0.077	−0.327	0.308	0.322	–
p value	<0.001	0.001	<0.001	<0.001	<0.001	–

BPs = Systolic blood pressure; WC = waist circumference; BMI = body mass index. BPs at visit 1 and visit 2 were designated BPs1 and BPs2, respectively. BMI at visit 1 and visit 2 were designated BMI1 and BMI2, respectively, and WC at visit 1 and visit 2 were designated WC1 and WC2, respectively. %dBMI, %dWC, and %dBPs were calculated by the equation (BMI2 − BMI1)/BMI1 × 100 (%), (WC2 − WC1)/WC1 × 100 (%), and (BPs2 − BPs1)/BPs1 × 100 (%), respectively.

Table 3. Multiple regression analysis between %dBPs and age1, WC1, BMI1, %dWC, and %dBMI

	β	95% CI	Standardized β	p value
Women				
Model 1				
BPs1	−0.23	−0.27 to −0.20	−0.38	<0.001
Age1	0.11	0.05 to 0.18	0.10	0.001
WC1	0.11	0.03 to 0.19	0.09	0.005
%dWC	0.01	−0.06 to 0.09	0.01	0.733
Model 2				
BPs1	−0.24	−0.28 to −0.21	−0.40	<0.001
BMI1	0.47	0.25 to 0.70	0.13	<0.001
Age1	0.13	0.07 to 0.19	0.12	<0.001
%dBMI	0.34	0.15 to 0.53	0.10	0.001
Model 3				
BPs1	−0.24	−0.28 to −0.21	−0.40	<0.001
BMI1	0.65	0.28 to 1.03	0.17	0.001
Age1	0.14	0.07 to 0.20	0.13	<0.001
%dBMI	0.39	0.19 to 0.60	0.11	<0.001
WC1	−0.08	−0.21 to 0.05	−0.06	0.244
%dWC	−0.08	−0.17 to 0.01	−0.06	0.071
Men				
Model 1				
BPs1	−0.22	−0.25 to −0.19	−0.35	<0.001
WC1	0.15	0.08 to 0.22	0.11	<0.001
%dWC	0.28	0.17 to 0.39	0.11	<0.001
Age1	0.02	−0.03 to 0.07	0.02	0.467
Model 2				
BPs1	−0.22	−0.25 to −0.19	−0.35	<0.001
%dBMI	0.80	0.64 to 0.96	0.22	<0.001
BMI1	0.41	0.23 to 0.59	0.10	<0.001
Age1	0.05	0.00 to 0.10	0.05	0.035
Model 3				
BPs1	−0.22	−0.25 to −0.19	−0.35	<0.001
%dBMI	0.82	0.63 to 1.00	0.22	<0.001
BMI1	0.38	0.04 to 0.72	0.10	0.027
Age1	0.05	0.00 to 0.10	0.05	0.046
WC1	0.01	−0.11 to 0.14	0.01	0.845
%dWC	−0.03	−0.16 to 0.11	−0.01	0.705

BPs = Systolic blood pressure; WC = waist circumference; BMI = body mass index. Standardized β values are the estimates resulting from an analysis performed on variables that were standardized. BPs at visit 1 and visit 2 were designated BPs1 and BPs2, respectively. BMI at visit 1 and visit 2 were designated BMI1 and BMI2, respectively, and WC at visit 1 and visit 2 were designated WC1 and WC2, respectively. %dBMI, %dWC, and %dBPs were calculated by the equation of (BMI2 − BMI1)/BMI1 × 100 (%), (WC2 − WC1)/WC1 × 100 (%), and (BPs2 − BPs1)/BPs1 × 100 (%), respectively.

Model 1 = Independent variables include age, BPs1, WC1, and %dWC; model 2 = independent variables include age, BPs1, BMI1, and %dBMI; model 3 = independent variables include model 1 + BMI1, and %dBMI.

Multiple Linear Regression Analysis

In multiple regression analysis, in which age1, WC1, BPs1, and %dWC were used as independent variables (model 1), %dWC was found to be an independent predictive value for %dBPs in men, but not in women (table 3). In a model where age1, BMI1, BPs1, and %dBMI were used as independent variables (model 2), %dBMI was found to be an independent predictive value for %dBPs in the both genders. After including all of the age1, BPs1, WC1, BMI1, %dWC, and %dBMI in a model as independent variables (model 3), %dBMI remained to be a predictor for %dBPs in both genders. In model 3, the variance inflation factor scores of all applied independent variables were <10 (data not shown)

Comparison between Individuals with BMI Gain or Loss together with WC Gain or Loss

We then compared the %BPS values between individuals with both WC loss (%dWC <0) and BMI loss (%dBMI <0), those with both WC loss and BMI gain (%dBMI ≥0), both WC gain and BMI loss, and those with both WC gain and BMI gain during a 1-year period (fig. 1). Age-adjusted %dBPs was significantly greater in individuals with both WC loss and BMI gain compared with those with both WC loss and BMI loss. On the other hand, age-adjusted %dBPs did not significantly differ between individuals with both WC loss and BMI loss and those with WC gain and BMI loss in both genders. When the same analysis was performed after excluding 154 subjects who experienced WC change of –10 cm or less or +10 cm or more, the results obtained were not essentially changed (data not shown).

Discussion

By analyzing data from individuals who underwent general health screening for 2 consecutive years, we showed that a percent difference in BMI (%dBMI) was a statistically significant predictor for a percent difference in BPs (%dBPs) in both genders. A percent difference in WC (%dWC) was also found to be a predictor for %dBPs in men; however, it lost statistical significance after further adjustment for BMI at the first visit and %dBMI, and it was not significant in women before and after such further adjustment.

A body of evidence indicates an association between obesity parameters and blood pressure levels [15, 16]. A reduction in body weight may result in a lowering of blood pressure in overweight or obese subjects [17, 18], although the results may not be always uniform. Moore et al. [19] showed that modest weight loss over a 4-year period substantially lowered the long-term risk of hypertension in overweight adults in Framingham. Haung et al. [20] showed that weight loss occurring after 18 years of age was related to a significantly lower risk, whereas weight gain was related to greater risk of hypertension in middle-aged women. In addition, Yang et al. [21] showed that in men aged between 40 and 74 years, weight gain occurring after 20 years of age was significantly associated with prehypertension. Most of the reports studying the potential association between changes in obesity parameters and changes in blood pressure were carried over a follow-up period longer than that in the current study. Furthermore, Truesdale et al. [22] have more recently shown that weight change over a 3-year period resulted in change in blood pressure levels; men who had experienced a 10% weight gain over the previous 3 years had BPs that was 2.6 mm Hg higher. They found, however, that the impact of weight change was, albeit present, less prominent in women. Women who had experienced a 10% weight gain over the previous 3 years had BPs that was only 0.9 mm Hg higher, suggesting the presence of gender difference in the extent of association between weight change and blood pressure change. We also showed here that the magnitude of the effect of changes in obesity parameters on blood pressure changes may vary by gender (table 3).

As compared to changes in weight, and thus in BMI, fewer analyses have focused on the relationship between changes in WC and blood pressure alterations. Considering that reductions in WC have been recommended more strongly than before for the purpose of prophylaxis and/or resolution of metabolic syndrome by the government in our country [23], the impact of WC reduction (gain) in terms of alterations of atherogenic risk factors, including blood pressure and levels of glucose and lipids, is becoming a more important issue to be investigated. Therefore, we also assessed whether changes in WC were reflected by the BPs change, and whether this relationship, if present, was independent of BMI change. We found that WC change was predictive of BPs change in men but not in women. In addition, the association between %dWC and %dBPs in men lost statistical significance after controlling for BMI1 and %dBMI (table 3). In contrast, %dBMI was a predictor for %dBPs in both genders regardless of the control of %dWC, suggesting that a reduction in BMI may represent a more essential target than WC reduction in terms of blood pressure control. This concept may be further supported by our finding that mean %dBPs did

not differ significantly between individuals with %dWC <0 and those with %dWC ≥0 among individuals with %dBMI <0. In reverse, %dBPs reduction was significantly greater in individuals with %dBMI <0 than in those with %dBMI ≥0 among individuals with %dWC <0 (fig. 1).

It has been reported that, in individuals with a mean BMI of 31, change in BMI was significantly correlated with change in BPs in both genders, even after adjusting for change in waist-hip ratio [24]. In the same study, it was reported that change in waist-hip ratio was not significantly correlated with change in BPs after adjusting for BMI change in men, and that the relationship between change in waist-hip ratio and BPs change was not significant before any adjustment in women. The results of Wing et al. [24] can be said to be similar to our current observation although there is a difference between WC and waist-hip ratio.

The current study has several limitations. First, we retrospectively analyzed data on individuals who underwent general health screening at our institute for 2 consecutive years; as a result, individuals who did not visit our institute the second year for unknown reasons were not enrolled in the current study, which may cause some biases. Second, we could not specify the reasons for weight gain or loss in individuals, however, very few individuals would have been taking antiobesity medications because only one individual in each gender had a BMI of 35 kg/m^2 or more at the first visit. Third, this study population included many non-obese subjects; a BMI1 ≥30 was found only in 1.1% of women and 1.9% of men. Fourth, we excluded those subjects who were taking antihypertensive drugs at either visit. We found that BMI was significantly greater in these excluded subjects than in the study population for both genders. Lastly, although change in BMI may seem to be superior for predicting BPs change than changes in abdominal obesity, abdominal fat volume should be measured by more reliable methods, such as computed tomography, before conclusion. In addition, we have to follow the subjects for a longer period, as a recent study has shown that surrogate measures of abdominal obesity are stronger predictors of all-cause and cardiovascular death than BMI in the general population [25].

In conclusion, in individuals who underwent general health screening for consecutive years, percent change in WC was significantly associated with percent change in BPs in men, but not in women; although this association in men lost statistical significance after controlling for percent change in BMI. By contrast, percent change in BMI was significantly associated with percent change in BPs regardless of controlling for percent change in WC. Our data suggest that controlling BMI, and thus controlling body weight, may represent a more essential goal than a reduction in WC in terms of blood pressure lowering among Japanese individuals who are not taking antihypertensive medication.

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Original Article

Prolonged treatment with pegylated interferon α 2b plus ribavirin improves sustained virological response in chronic hepatitis C genotype 1 patients with late response in a clinical real-life setting in Japan

Sumio Watanabe,[1] Nobuyuki Enomoto,[2] Kazuhiko Koike,[3] Namiki Izumi,[4] Hajime Takikawa,[5] Etsuko Hashimoto,[6] Fuminori Moriyasu,[7] Hiromitsu Kumada,[8] Michio Imawari[9] and PERFECT Study Group

[1]Department of Gastroenterology, Juntendo University School of Medicine, [3]Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, [4]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, [5]Department of Medicine, Teikyo University School of Medicine, [6]Department of Medicine and Gastroenterology, Tokyo Women's Medical University, [7]Department of Gastroenterology and Hepatology, Tokyo Medical University, [8]Department of Hepatology, Toranomon Hospital, [9]Department of Gastroenterology, Showa University School of Medicine, Tokyo, and [2]First Department of Internal Medicine, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

Aim: This study was conducted to clarify the factors related to sustained virological response (SVR) to pegylated interferon α 2b (PEG-IFN) plus ribavirin (RBV) combination therapy administered for 48 weeks in patients with chronic hepatitis C virus (CHCV) and to evaluate the usefulness of prolonged treatment in patients with late virological response (LVR).

Methods: Of 2257 patients registered at 68 institutions, those with genotype 1 and high viral load were selected to participate in two studies. Study 1 (standard 48-week group, $n = 1480$) investigated SVR-determining factors in patients who received the treatment for ≤52 weeks, whereas study 2 compared SVR rates between patients with LVR who received treatment for either 36–52 weeks (48-week group, $n = 223$) or 60–76 weeks (72-week group, $n = 73$).

Results: In study 1, SVR rate was 44.9%; that in male subjects (50.4%) was significantly ($P < 0.0001$) higher than in female subjects (36.4%). SVR rate significantly ($P < 0.0001$) decreased with 10-year age increments in both sexes. Multivariate logistic regression analysis revealed that age, F score, platelet count, and HCV load were SVR-related factors. In study 2, SVR rate in the 72-week group (67.1%) was significantly ($P = 0.0020$) higher than in the 48-week group (46.2%).

Conclusions: Patients with CHCV genotype 1 infection should be treated with PEG-IFN plus ribavirin combination therapy as early as possible, and 72 weeks' treatment is recommended in patients with LVR regardless of age.

Key words: chronic hepatitis C virus, elderly patients, pegylated interferon, prolonged treatment, ribavirin

INTRODUCTION

THE TOTAL NUMBER of patients infected with the hepatitis C virus (HCV) is estimated at 170 million worldwide, of whom 1.5–1.7 million are Japanese. Treatment of HCV infection began with interferon (IFN) monotherapy before the discovery of HCV in 1989. At that time, responders to treatment were mostly limited to patients with HCV genotypes 2 or 3 infection, which is highly sensitive to IFN. The sustained virological response (SVR: HCV-RNA negative at 24 weeks after end of treatment) to IFN monotherapy in genotype 1 patients known from that time to be difficult to treat was only about 5%. SVR rate has since increased thanks to concomitant administration of the antiviral drug ribavirin (RBV), and with the development of the long-acting

Correspondence: Dr Sumio Watanabe, Department of Gastroenterology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Email: sumio@juntendo.ac.jp

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IFN product pegylated interferon (PEG-IFN) it has increased to 50%.[1–4] Today, PEG-IFN plus ribavirin regimen is internationally recognized as a standard therapy for chronic hepatitis C virus (CHCV) infection.[5,6] Early clinical trials of this regimen focused on specific patient populations. Subsequently, several multinational studies such as WIN-R,[7] HALT-C,[8] EPIC3,[9] and REPEAT Study[10] have been conducted in the general clinical setting. The results of the IDEAL Study[11] directly comparing PEG-IFN α 2a versus PEG-IFN α 2b have also been published. From these studies, variables predictive of SVR have been identified, including ethnicity, sex, age, and weight as demographic parameters, staging and hepatic steatosis as histological parameters, viral load, genotype, NS5A, and core mutation as virologic parameters, alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) as biochemical parameters, and even the timing of viral negativity as a treatment variable.[12–15] More recently, the SVR rate was reported to increase in association with decrease in the relapse rate with 72-week treatment in patients with delayed HCV-RNA negativity.[15,16] However, the majority of patients participating in previous studies in western countries were aged in their 40s on average, and the influence of aging of the patient population has not been studied adequately.

We therefore examined SVR-determining factors with 48-week PEG-IFN α 2b plus RBV combination therapy in the prevailing Japanese clinical setting characterized by increasing numbers of elderly patients. We also compared SVR rate between 48-week and 72-week treatment in patients with late virological response (LVR) defined as achieving HCV-RNA negativity in the period from weeks 13 to 24 after the start of treatment so as to examine the significance of prolonged treatment.

METHODS

Patients

A MULTICENTER STUDY was conducted at 68 institutions in Tokyo and Yamanashi prefectures (PERFECT Study Group; see Appendix I) to survey the actual state of combination therapy with PEG-IFN α 2b (PegIntron; Schering Plough, Kenilworth, NJ) and RBV (Rebetol, Schering Plough) in 2008. A total of 2257 chronic hepatitis C virus (CHCV) patients seen from December 2004 who completed combination treatment by September 2007 were registered regardless of genotype, history of IFN treatment, and ALT levels. The presence of HCV in serum had to be confirmed by Cobas Amplicor HCV Monitor, version 2.0 (Roche Diagnostic, Tokyo) for registration.

Excluded from this study were pregnant or possibly pregnant and lactating women, and patients with severe heart disease, chronic kidney failure or creatinine clearance of ≤50 mL/min, current or history of severe psychiatric disorder, and autoimmune hepatitis.

Demographic characteristics examined included age, sex, height and weight, the presence or absence of diabetes mellitus, hypertension, heavy drinking, and history of IFN therapy and hepatic cancer. Hepatic histological data recorded were stage (F0–F4) and grade (A0–A3). Laboratory tests recorded were ALT, platelet count, albumin, and α-fetoprotein (AFP) before the start of PEG-IFN α 2b plus RBV combination therapy.

As indicated in Figure 1, of the total 2257 patients registered, patients with genotype 1 and high viral load (>100 KIU/mL: Amplicor PCR quantitation) who satisfied the following conditions were included in this study: patients who received treatment for ≤52 weeks (standard 48-week treatment group, $n = 1480$) in study 1, and patients with LVR who received treatment for either 36–52 weeks (48-week treatment group, $n = 223$) or 60–76 weeks (72-week treatment group, $n = 73$) in study 2.

This multicenter study was approved by IRB at each participating institution. The study protocol was carried out according to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from each patient.

Treatment

PEG-IFN α 2b was administered subcutaneously once weekly at a dose of 1.5 μg/kg. Dose reduction and treatment discontinuation followed the instructions given in the package insert, i.e., the dose was reduced by half if WBC decreased to <1500/mm^3, neutrophils to <750/mm^3 or platelet count to <80000/mm^3, and treatment was discontinued if WBC decreased to <1000/mm^3, neutrophils to <500/mm^3 or platelet count to <50000/mm^3. RBV was administered in two divided doses of 600, 800, or 1000 mg/day in patients weighing <60, 60–<80, and ≥80 kg, respectively. Dose reduction and treatment discontinuation followed the package insert, i.e., dose was reduced from 600 mg/day to 400 mg/day, from 800 mg/day to 600 mg/day, or from 1000 mg/day to 600 mg/day if hemoglobin (Hb) concentration decreased to <10 g/dL, and administration was discontinued if Hb decreased to 8.5 g/dL. Duration of treatment was 48 weeks as a rule. In LVR patients who did

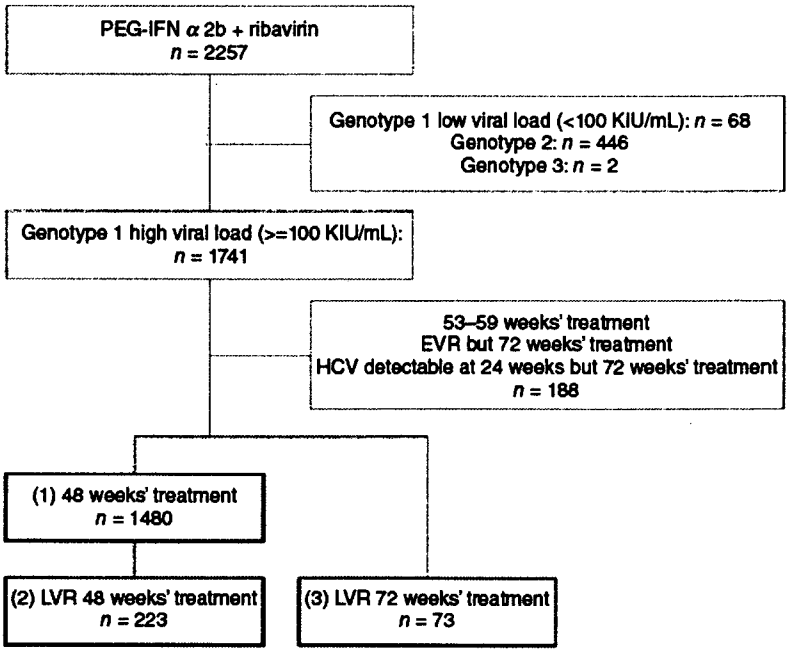

Figure 1 Flow-chart of study subjects. (1) 48 weeks' treatment (48-week standard therapy group): patients with genotype 1 and high viral load who received pegylated interferon α 2b (PEG-IFN α 2b) + ribavirin (RBV) for 52 weeks. Multiple logistic regression analysis was used to evaluate the response to PEG-IFN α 2b + RBV in this group (2) Late virological response (LVR) 48 weeks' treatment: patients with genotype 1 and high viral load who received PEG-IFN α 2b + RBV for 36–52 weeks (3) LVR 72 weeks' treatment: patients with genotype 1 and high viral load who received PEG-IFN α 2b + RBV for 60–76 weeks. SVR rate was compared between LVR 48 weeks' treatment group (2) and LVR 72 weeks' treatment group (3). EVR, early virologic response; HCV, hepatitis C virus.

not achieve HCV-RNA negativity by week 12, treatment could be extended for 48 weeks or longer based on individual patients' desire and investigators' judgment.

Evaluation of response to treatment

Determination of genotype and measurement of HCV-RNA levels were performed at each center. Pre-treatment HCV-RNA levels were determined by Amplicor PCR quantitation. Viral negativity was defined as HCV below detection limit (<50 IU/mL) by Amplicor qualitative analysis (Roche Molecular Systems, NJ).

SVR was defined as HCV below detection limit at 24 weeks after the end of PEG-IFN α 2b plus RBV combination therapy by Amplicor HCV qualitative analysis.

Statistical analysis

All statistical analyses were performed using SAS, version 9.13 (SAS Institute, Cary, NC). Intergroup comparison of SVR rate was performed by Fisher's exact test; that of background variables by Fisher's exact test and Mann–Whitney *U*-test. Trend of SVR rate by age was assessed by Cochran–Armitage test, and intergroup comparison after adjustment of stratification factors was conducted by Mantel–Haenstzel method. Determination of factors associated with SVR was conducted by a stepwise procedure using the results of logistic univariate analysis ($P < 0.2$) into logistic multivariate analysis. All tests were two-sided, with significance level set at $P < 0.05$.

RESULTS

Study 1: SVR-related factors in patients receiving standard 48-week treatment

AS INDICATED IN Table 1 and Figure 1, 1480 subjects (male, $n = 898$ [60.7%]; median age, 57 [range, 13–79] years) were eligible for analysis. SVR rate based on ITT was 44.9%. SVR rate in subjects who completed and who discontinued treatment was 56.5% ($n = 1110$) and 10.3% ($n = 370$), respectively, a statistically significant difference ($P < 0.0001$). SVR rate in male subjects (50.4%; 453/898) was significantly ($P < 0.0001$) higher than in female subjects (36.4%; 212/582). SVR rate significantly ($P < 0.0001$) decreased as age increased by 10 years in both male and female subjects (Fig. 2); the odds ratio for SVR decreasing with 10-year increase in age was 0.688 (95% CI, 0.604–0.784; $P < 0.0001$) in male subjects and 0.546 (0.449–0.663; <0.0001) in female subjects, indicating that the influence of aging was greater in female than in male subjects. There was no bias of older versus younger age among patients who had and had not previously

Table 1 Pretreatment characteristics of chronic hepatitis C virus (CHCV) patients with HCV-1b RNA who received pegylated interferon α 2b + ribavirin standard therapy for 48 weeks

Characteristic	Value (n = 1480)
Sex (male/female)	898/582
Age (years)	57 (13–79)
History of HCC (yes/no/unknown)	8/1405/67
Previous IFN treatment (yes/no/unknown)	459/688/333
Diabetes (yes/no/unknown)	44/480/956
Hypertension (yes/no/unknown)	105/417/958
Ongoing alcohol use (yes/no/unknown)	157/456/867
Grade (A0/A1/A2/A3/unknown)	14/499/478/55/434
Stage (F0/F1/F2/F3/F4/unknown)	36/469/316/176/48/435
ALT (IU/L)	63 (8.4–910)
Platelets (×10⁴/μL)	16.6 (4.3–47.7)
Viral load (KIU/mL)	1900 (100–5100)

Data expressed as median (range). HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; IFN, interferon.

received IFN. Whereas, multivariate logistic regression analysis revealed that older age (<55/≥55 years), degree of progression of hepatic fibrosis (F0–1/2–4), low platelet count (≥16/<16×10⁴/μL), and high viral load (<1900/≥1900 KIU/mL) are resistance factors to SVR (Table 2). In multivariate logistic regression analysis, sex was not selected.

Study 2: usefulness of prolonged treatment in LVR patients

Of the patients who completed standard 48-week treatment, 223 patients (20.0%) showed LVR (Fig. 1), and median duration of treatment was 48 weeks. Compared with patients who exhibited early virologic response (EVR) defined as HCV-RNA negative within 12 weeks after the start of treatment, those with LVR were older (median age, 58 vs 55 years; $P = 0.0043$) and had higher viral load (median, 2700 vs 1620 KIU/mL; $P < 0.0001$) and lower platelet count (median, 16.5 vs 17.3 × 10⁴/μL; $P = 0.0162$). SVR rate based on treatment analysis was 56.5 in all, 79.2% in EVR and 46.2% in LVR, respectively. In multivariate logistic regression analysis of SVR-related factors in LVR patients who completed standard 48-week treatment, age (10-year groups) was selected as a significant factor.

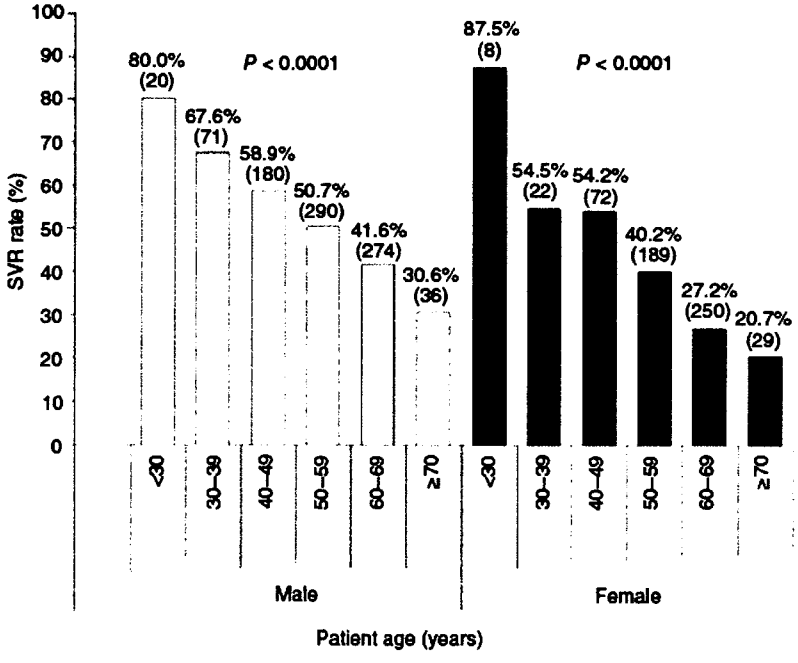

Figure 2 Sustained virological response (SVR) rate to 48 weeks' standard treatment with pegylated interferon α 2b (PEG-IFN α 2b) + ribavirin in male and female patients stratified by age. Cochran–Armitage test was used to study the underlying trend.

Table 2 Independent factors associated with sustained virological response in genotype 1 chronic hepatitis C virus patients who received pegylated interferon α 2b + ribavirin standard therapy for 48 weeks

	Odds ratio	95% confidence interval	*P*-value†
Age <55/≥55 years	0.414	0.293–0.585	<0.0001
Stage 0–1/2–4	0.633	0.442–0.906	0.0124
Platelets <16/≥16 × 10^4/μL	1.876	1.305–2.696	0.0007
Viral load </≥1900 KIU/mL	0.663	0.471–0.935	0.0192

†Multiple logistic regression analysis.

Prolonged treatment was conducted in 73 LVR patients (Fig. 1), with mean duration of 72 weeks. As shown in Table 3, whereas among LVR patients there were significantly ($P = 0.0061$) more female subjects in 72-week group than 48-week group, no intergroup difference of other factors was observed. Overall, SVR rate based on treatment analysis was significantly ($P = 0.0020$) higher in 72-week treatment group than in 48-week treatment group (67.1% [49/73] vs 46.2% [103/223]; Fig. 3A).

When stratified by sex, SVR rate with 48-week and 72-week treatment was 51.4% and 68.6% ($P = 0.0809$) in male subjects and 37.3% and 65.9% ($P = 0.0039$) in female subjects, with SVR in 72-week treatment being significantly higher in female subjects and indicating that, in LVR patients, efficacy comparable to male subjects is achieved in female subjects with 72-week treatment.

In patients aged <55 years SVR rate in the 48- and 72-week treatment groups was 57.6% and 78.9% ($P = 0.1100$) in male subjects and 40.0% and 76.9% ($P = 0.0724$) in female subjects, respectively, with higher SVR rates for the 72-week treatment group (Fig. 3B). In patients aged ≥55 years this parameter was 44.6% and 53.8% ($P = 0.5619$) in male subjects and 37.1% and 60.7% ($P = 0.0425$) in female subjects, respectively, with higher SVR rates for the 72-week treatment group than for the 48-week treatment group as in the case of the younger age group (Fig. 3C).

DISCUSSION

Study 1: SVR-related factors in patients receiving standard 48-week treatment

SVR RATE WITH standard 48-week treatment in this study was 44.9%, roughly equal to the 45% reported in previous clinical trials in Japan.[4,17–19] The present results are also similar to those of clinical trials conducted in patients aged in their mid-40s in western countries and in the general clinical setting.[1–4] Age was

Table 3 Comparison of clinical and virological characteristics between groups receiving pegylated interferon α 2b + ribavirin therapy for 48 and 72 weeks among patients showing late virological response

	48 weeks' group ($n = 223$)	72 weeks' group ($n = 73$)
Sex (male/female)	140/83*	32/41*
Age (years)	58 (21–75)	56 (22–71)
History of HCC (yes/no/unknown)	1/221/11	0/73/0
Previous IFN treatment (yes/no/unknown)	68/113/42	29/32/12
Diabetes (yes/no/unknown)	11/71/141	1/34/38
Hypertension (yes/no/unknown)	18/62/143	6/29/38
Ongoing alcohol use (yes/no/unknown)	17/75/131	6/27/40
Grade (A0/A1/A2/A3/unknown)	2/66/82/6/67	0/21/26/4/22
Stage (F0/F1/F2/F3/F4/unknown)	7/68/45/32/5/66	2/16/20/12/2/21
ALT (IU/L)	61.5 (14–550)	52 (17–254)
Platelets (×10^4/μL)	16.5 (8.5–43.2)	16.6 (4.3–40.2)
Viral load (KIU/mL)	2700 (160–5100)	2100 (130–5000)

Data expressed as median (range). *$P = 0.006$. ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; IFN, interferon

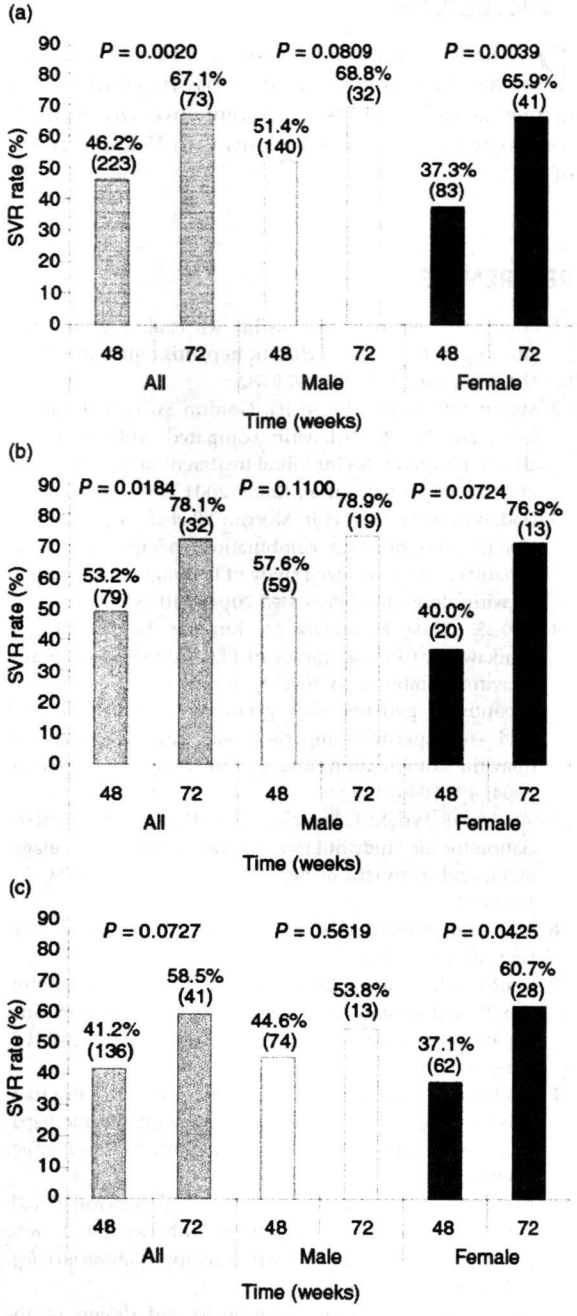

Figure 3 Sustained virological response (SVR) rate based on treatment analysis between groups receiving pegylated interferon α 2b (PEG-IFN α 2b) + ribavirin therapy for 48 and 72 weeks who exhibited late virological response (LVR). (A) Overall; (b) patients aged <55 years; (c) patients aged ≥55 years. Data on age not available for 7 male patients and 1 female patient.

selected among factors for SVR with PEG-IFN plus RBV combination therapy in an aging patient population, the examination of which was the objective of this study, and SVR rate decreased stepwise with 10-year age increase. Of particular note was the greater impact of aging observed in female than male subjects.

Lower efficacy in elderly female patients infected with HCV genotype 1 has already been reported in Japan.[20] A low SVR rate was also observed in elderly female subjects in this study. Although female sex was considered a favorable prognostic factor in some Western studies, there is no established opinion on sex difference. Change associated with aging of the patient population in Japan is considered to account for this phenomenon observed in the present study. This may be due to decrease in compliance among elderly women; on the other hand, however, there was no difference between male and female subjects aged ≥55 years in the rate of completion of treatment. Although the rate of dose reduction of RBV tended to be slightly higher in female subjects (data not shown), the difference was not significant. These findings suggest the influence of factors other than adherence to treatment for the low SVR rate among elderly women. One possible factor for reduced SVR rate among these individuals may be the effect of menopause. In women, insulin resistance begins to worsen after the age of 50 years,[21,22] and this is reported more closely associated with the effect of menopause than age itself.[23]

The presence of insulin resistance has been reported to lower efficacy of PEG-IFN and RBV combination therapy.[24–27] Insulin resistance is also a cause of advanced fibrosis and fatty change of the liver.[28–31] It is possible that such changes combined with other factors associated with metabolic syndrome interact in a complex way to reduce the efficacy of this therapy.[32–35] In fact, the incidence of non-alcoholic fatty liver disease (NAFLD) among elderly Asians was reported higher in women as compared with that in men.[36–38] However, while older age, advanced fibrosis, low platelet count and high HCV load were selected as factors for reduction of SVR rate in our multivariate logistic regression analysis, sex was not selected. It is therefore necessary to examine further the confounding of these selected factors with sex. It also should be taken into consideration that, due to limitations imposed by the retrospective nature of this study, data on factors affecting the efficacy of PEG-IFN plus RBV therapy such as insulin resistance, steatosis, and core mutation are lacking. A large-scale prospective study is

required to examine the lower efficacy observed in elderly women.

Study 2: usefulness of prolonged treatment in LVR patients

EVR (viral load reduced by 2 log or undetected in week 12) has been used for determining continuation or discontinuation of treatment in western countries. Recently, however, EVR was divided into complete EVR (HCV RNA <50 IU/mL at week 12) and partial EVR (>2 log drop in HCV RNA but still detectable [>50 IU/mL]). Fried *et al.*[15] and Berg *et al.*[16] reported that the SVR rate was a high 68–84% in patients showing complete EVR but only 17–29% in those with partial EVR with treatment for 48 weeks. They also reported that treatment for 72 weeks was effective in patients with partial EVR. In the clinical study for health registration in Japan, the SVR rate by timing of HCV-RNA negativity at 4, 12, and 24 weeks was 100%, 71.1%, and 36.4%, respectively, and no patient with HCV-RNA negativity after 25 weeks achieved SVR.[4] With these studies as reference, patients with LVR were defined as those who were positive (>50 IU/mL) at week 12 and became negative (<50 IU/mL) by week 24. To minimize the influence of treatment discontinuation, only patients who completed the standard duration of treatment were selected as subjects in this study. In the comparison of patient background, there was no significant intergroup difference except for a significantly greater number of female subjects in the 72-week treatment group. This finding might be related to the observation that it was already widely believed that efficacy in elderly women in Japan is low and that duration of treatment was at the discretion of individual physicians. Nevertheless, it is noteworthy that the SVR rate was significantly higher in the 72-week treatment group than in the 48-week treatment group and that a high 60% SVR rate was achieved with 72-week treatment in elderly female patients, a population in whom a relatively low SVR was observed with standard 48-week treatment.

This retrospective study had the limitation that duration of treatment was at the sole discretion of each participating physician. A prospective study is necessary to demonstrate whether 72-week treatment in elderly women with LVR is more efficaous than 48-week treatment in male patients. Although the number of younger subjects examined was rather low, it is noteworthy that an SVR rate of >75% was observed with 72-week treatment in both male and female patients. This also should be confirmed by prospective study.

CONCLUSIONS

PATIENTS WITH CHCV genotype 1 infection should be treated with PEG-IFN and ribavirin combination therapy as early as possible. Seventy-two weeks' treatment is recommended in patients with LVR, regardless of age.

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APPENDIX I

IN ADDITION TO the study authors, the investigators in the PEG-IFN and Ribavirin, Find Evidence of Chronic Hepatitis C Therapy in Tokyo (PERFECT) Study Group included: Hiroyasu Adachi, Department of Internal Medicine, Tobu Chiki Hospital; Yoshio Aizawa, Department of Internal Medicine, The Jikei University School of Medicine, Aoto Hospital; Masatoshi Akamatsu, Department of Gastroenterology, JR Tokyo General Hospital; Masahiro Arai, Department of Gastroenterology, Toshiba General Hospital; Yasuhiro Asahina, Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital; Yoshimichi Chuuganji, Department of Gastroenterology, Tokyo Metropolitan Bokutoh Hospital; Yoshiyuki Fujita, Department of Gastroenterology, St. Luke's International Hospital; Yukiya Hakozaki, Department of Internal Medicine, Self-Defence Forces Central Hospital; Naoaki Hashimoto, Department of Gastroenterology, Tokyo Teishin Hospital; Katsuya Hattori, Department of Gastroenterology, Kohsei Chuo General Hospital; Seishu Hayashi, Division of Hepatology, Tokyo Metropolitan Komagome Hospital; Masanori Hirano, Department of Gastroenterology Tokyo Metropolitan Police Hospital; Keiichi Hirata, National Hospital Organization Disaster Medical Center; Department of Gastroenterology; Yuuichi Hirose, Department of Internal Medicine, Yamanashi Prefectural Central Hospital; Toshiya Horibe, International University of Health & Welfare Mita Hospital, Gastroenterology Center; Kazuhiko Hosoda, Department of Gastroenterology and Hepatology Yamanashi Hospital of Social Insurance; Hiroaki Igarashi, Department of Gastroenterology, Kawakita General Hospital; Yoshida Ikuma, Department of Internal Medicine, Kasai Cardiology & Neurosurgery Hospital; Tetsuya Irie, Department of Internal Medicine, Nakano General Hospital; Koji Ishii, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University School of Medicine; Takayoshi Ito, Department of Gastroenterology, Department of Medicine, Showa University School of Medicine; Naohiro Kawamura, The Third Department of Internal Medicine, Kyorin University School of Medicine; Tateo Kawase, Department of Gastroenterology, Kanto Central Hospital of the Mutual Aid Association of Public School Teachers; Hirokazu Komeichi, Department of Internal Medicine, Division of Cardiology, Hepatology, Geriatrics and Integrated Medicine, Nippon Medical School; Sadanori Kubo, Department of Internal Medicine, Showa University Toyosu Hospital; Naohiko Masaki, Division of Gastroenterology, International Medical Center of Japan, Toyama Hospital; Akihisa Miyazaki, Department of Gastroenterology, Juntendo University Nerima Hospital; Mitsuhiko Moriyama, Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University of School of Medicine; Naoya Murashima, Department of Gastroenterology, Mishuku Hospital; Hikaru Nagahara, Department of Gastroenterology, Aoyama Hospital Tokyo Women's Medical University; Hisato Nakajima, Department of Gastroenterology and Hepatology, Jikei University School of Medicine Daisan Hospital; Ikuo Nakamura, Department of Gastroenterology, Tokyo Medical Univsrsity; Ryo Nakata, Department of Gastroenterology, Japanese Red Cross Medical Center; Katsuhisa Nakatsuka, Division of Gastroenterology, Department of Internal Medicine Nippon Medical School; Yasuhiro Nishizaki, Department of Gastroenterology, Tokai Univsrsity Tokyo Hospital; Osamu Noguchi, Division of Gastroenterology and Hepatology, Ome Municipal General Hospital; Toshihiko Nouchi, Department of Gastroenterology, Showa General Hospital; Yuki Ogura, Department of Medicine, Tokyo Metropolitan Fuchu Hospital; Masanaru Ozawa, Yoshikawa Hospital; Shigehiko Sainokami, Fussa Hospital; Naoya Sakamoto, Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University; Minoru Sakamoto, Department of Internal Medicine, Faculty of Medicine, University of Yamanashi; Mina Sasaki, Department of Gastroenterology, Tokyo Metropolitan Geriatric Hospital; Yoshiyuki Sato, Department of Internal Medicine, Tokyo Kosei Nenkin Hospital; Koichi Shiraishi, Division of Gastroenterology and Hepatology, Tokai University Hachioji Hospital; Satoko Suzuki, Department of Gastroenterology, Juntendo University School of Medicine; Tomohiko Suzuki, Department of Internal Medicine, Tokyo Metropolitan Health and Medical Treatment Corporation Ohkubo Hospital; Fumitaka Suzuki, Department of Hepatology, Toranomon Hospital; Kazumi Tagawa, Department of Gastroenterology, Mitsui Memorial Hospital; Ichiro Takagi, Division of Gastroenterology and Hepatology, Depeartment of Internal Medicine, Jikei University School of Medicine; Seiichirou Takahashi, Department of Internal Medecine, Fujiyoshida Municipal Medical Center; Atsushi Tanaka, Department of Medicine, Teikyo University School of Medicine; Takuma Teratani, Department of Gastroenterology, Kanto Medical Center NTT EC; Katsutoshi Tokushige, Department of Medicine and Gastroenterology, Tokyo Women's Medical University; Masahiko Tomimatsu, Department of Medicine, Tokyo

Women's Medical University Medical Center East; Shigeki Tsukada, Department of Gastroenterology, Juntendo Tokyo Koto Geriatric Medical Center; Hiroyuki Watanabe; Department of Gastroenterology, Yamanashi Red Cross Hospital; Michiyasu Yagura, Department of Gastroenterology, National Hospital Organization, Tokyo National Hospital; Haruki Yamada, Department of Internal Medicine, Social Insurance Central General Hospital; Toshio Yamada, Department of Gastroenterology, Tokyo Rinkai Hospital; Taro Yamanaka, Department of Gastroenterology, Itabashi Chuo Medical Center; Kiyomi Yasuda, Depatment of Hepatology, Kiyokawa Hospital; Yuji Yoshikawa, Department of Gastroenterology, Sanraku Hospital; Yoko Yoshioka, Department of Gastroenterology, Shiseikai-dainihospital; Hiroshi Yotsuyanagi, Department of Infectious Diseases, Internal Medicine, Graduate School of Medicine, University of Tokyo; Mikio Zeniya, Department of Gastroenterology, Jikei University Graduate School of Medicine.