いずれも骨の健康維持に必要なビタミンである。これらの骨における意義をどのように考えるかは、食事摂取基準の策定に大きく影響することから、これらを研究対象としたものである。

まずビタミンDに関しては、従来わが国では、同一対象者に対して、食事調査と血液検査を同時に行う調査がほとんどなされてこなかった。日照機会の乏しい施設入居高齢者を対象に調査したところ、目安量を大幅に上回る量の摂取にも関わらず、血液中25OHDは非常に低く、5 μg/日の介入ではほとんど改善せず、20 μg/日でも、25OHD濃度が基準値の20 ng/mLに達したのは半数以下であった。すなわち、日照機会の乏しい高齢者にとっては、現行の目安量を大きく上回る量の摂取を要する可能性が示唆された。

ビタミンKに関しては、血液中PIVKA-Ⅱ・ucOC濃度を、肝臓・骨におけるビタミンK作用不足の指標として調査したところ、目安量を大きく上回る摂取量にも関わらず、ucOC 濃度が基準値を上回る対象者の割合が高かった。現行の目安量が肝臓におけるビタミンK作用を指標として策定されており、骨作用を考慮していないことを考えると、これは当然の結果とも言えるが、ビタミンK不足は、肝臓より骨においてより起こりやすいことが確認された。

今回主成分分析によって解析したところ、血液中ビタミンD・K低濃度は、全般的低栄養の指標とは異なった内容を表しており、単なる全般的低栄養の反映ではないことが示唆された。

今後食事摂取基準の策定にむけて、さらに多くの臨床的研究が望まれる。例えば今回の我々の結果は、あくまで日照機会の乏しい高齢者に対する調査結果であり、外出機会の多い対象者であれば、結果は異なる可能性もある。

E. 結論

高齢者において、骨の健康維持のためには、かなり多い量のビタミンD・K摂取を必要とする可能性が高い。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

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REGULAR ARTICLE

Abdominal circumference should not be a required criterion for the diagnosis of metabolic syndrome

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Abstract

Background Metabolic syndrome (MetS) is an established concept. However, it is characterized by a number of different definitions as well as different cut-off points (COPs) for waist circumference (WC) and different modes for incorporating WC into the diagnostic criteria.

Methods Abdominal ultrasonography was performed in 2,333 subjects who also underwent comprehensive medical examinations between April and July 2006. The odds ratios for the number of MetS components were calculated by taking central obesity status into account and considering concurrent fatty liver as an independent variable. We compared the areas under the receiver operating characteristic (ROC) curves for fatty liver and MetS using several MetS criteria.

Results Regardless of the WC criterion selected, we observed a strong linear trend for an association (trend $P < 0.0001$) between MetS and the number of components. The odds ratio (OR) of subjects without central obesity but with all three MetS components was 9.69 (95% confidence interval 3.11–30.2) in men and 55.3 (6.34–483) in women. The COP for the largest area under the curve in men and women was ≥82 cm (OR 0.701) and ≥77 cm (OR 0.699), respectively, when WC was considered as a component. When WC distribution is taken into consideration, practical and appropriate COPs should be ≥85 cm for men and ≥80 cm for women.

Conclusion We suggest that a WC of ≥85 cm for men and ≥80 cm for women would be optimal COPs for the central obesity criteria in the Japanese population. In addition, central obesity should be incorporated as a component of MetS rather than an essential requirement for the diagnosis of MetS.

Keywords Central obesity · Diagnostic criteria · Metabolic syndrome · ROC curve

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Introduction

The prevention of metabolic syndrome (MetS), for which visceral fat accumulation and insulin resistance are considered upstream factors, has recently attracted the attention of the medical world as a useful approach to protect against lifestyle-related diseases typified by arteriosclerotic diseases [1–8]. Visceral fat accumulates for many reasons, including hyperalimentation and inadequate exercise, among others, and causes the abnormal functioning of fat cells and excessive secretion of hormones that are involved in various pathological conditions [9, 10]. Excessive secretion of these hormones is thought to act in combination with other factors to cause arteriosclerotic and other serious diseases, such as renal failure, blindness, lower limb amputation, cerebral apoplexy, cardiac arrest, and cerebrovascular diseases. The progression of conditions, from obesity into serious diseases, is sometimes referred as the metabolic domino effect [11, 12], and includes fatty liver disease.

Diagnostic criteria for MetS have been published by the World Health Organization [13], American National Cholesterol Education Programs, Adult Treatment Panel III (NCEP–ATP III) [14], and International Diabetes Federation (IDF) [15] for Asian countries, including Japan [16]. In Japan, the Examination Committee for Criteria of MetS introduced diagnostic criteria for Japanese metabolic syndrome (JMetS) [16], which are similar to the ones defined by IDF. The criteria essentially include central obesity and several other components, such as hypertension, hyperglycemia, and abnormal lipid metabolism. In Japan, the most prominent difference between the IDF and Examination Committee criteria for evaluating central obesity is in the cut-off point (COP) for waist circumference (WC), especially that for women: in all countries of the world, with the exception of Japan, the COP for WC is larger for men than that for women.

The relative newness of the MetS concept necessitates that the diagnostic criteria be updated as and when needed. The association between the diagnosis of MetS and downstream diseases in the metabolic domino needs to be addressed in prospective studies. In the study reported here, we applied several criteria to examine the association between metabolic status and concurrent fatty liver, which we used as a specific example of a disease in the metabolic domino. Our aim was to identify preliminary criteria and COPs for WC that can be used in diagnosing MetS.

Subjects and methods

Height, weight, and WC were measured, and abdominal ultrasonography was performed in 2,333 subjects (1,195 men and 1,138 women) of 2,428 subjects aged 40–79 years. These subjects underwent comprehensive medical examinations at the Kasugai City Medical Center during a 3-month period between April and July 2006. Patients receiving drug treatment(s) for liver diseases, hypertension, diabetes mellitus, or hyperlipidemia were excluded from the study. Height and weight were measured using an automatic scale (Tanita BF-220). The WC was measured in standing subjects with a tape measure placed horizontally at the level of the navel while the subject was gently exhaling. If the abdomen was protuberant and the navel was deviated downwards, the tape measure was placed at the midpoint level between the lower intercostal border and the anterior superior iliac spine.

Fatty liver was diagnosed after discussion with medical technologists (including ultrasound technicians), radiology technologists, and physicians and by taking fatty liver scores (as shown in Table 1) obtained at Kasugai City Medical Center into consideration. These scores were based on previous studies [17–20].

Blood pressure was measured on the right arm using a mercury sphygmomanometer; the subject was in a lying position and had rested for at least 5 min prior to the measurement. Venous blood samples were collected in the morning from subjects after a fasting period of 12 h. Triglyceride (TG) and serum high-density lipoprotein cholesterol (HDL-C) were measured by the direct enzymatic method, and fasting plasma glucose (FPG) was measured by the glucose oxidase method. Their concentrations were measured using an automated analyzer (model 7170S; Hitachi, Japan).

Current JMetS criteria require a central obesity (visceral adipose tissue area $\geq$100 cm^2 or WC $\geq$85 cm for men and $\geq$90 cm for women) and two or more of the following three components: (1) high blood pressure, based on a systolic blood pressure $\geq$130 mmHg and/or diastolic blood pressure $\geq$85 mmHg; (2) hyperglycemia, based on FPG $\geq$110 mg/dl; (3) abnormal lipid metabolism, based on TG $\geq$150 mg/dl and/or HDL-C <40 mg/dl [16]. The Examination Committee for Criteria of MetS in Japan also defined a "risk group for MetS" (yobi-gun) consisting of people who have central obesity and one of the three components listed above (high blood pressure, hyperglycemia, or abnormal lipid metabolism). In our study, as in most epidemiological studies, only WC was considered in our evaluation of central obesity; the visceral adipose tissue area was not assessed.

Our primary aim was to identify and propose new MetS criteria based on our results. Our suggested criteria (our criterion 1) considers central obesity not to be an essential requirement for MetS but as only one of the components of MetS. Accordingly, we defined our patients as having MetS when they demonstrated three or more components of

Table 1 Fatty liver score

Condition	Points
Bright echo pattern	0 or 1
Hepatorenal or hepatosplenic contrast	0 or 1 or 2
Unclear vessels	0 or 1
Deep attenuation	0 or 1 or 2
Fatty bandless sign	0 or 1
Liver swelling	0 or 1

A total score of $\geq$3 points is considered to indicate fatty liver

MetS, regardless of their central obesity status. Similarly, the risk group for MetS consisted of those individuals who demonstrated two components.

Taking the number of MetS components listed above in consideration, we first calculated the odds ratios of fatty liver according to central obesity status in men and women by logistic regression. We then constructed receiver operating characteristic (ROC) curves to assess the detecting power of MetS criteria for concurrent fatty liver and calculated the areas under the curve (AUC) for diagnostic criteria. These procedures were repeated using the IDF COP for WC in the Japanese population, i.e., ≥90 cm for men and ≥80 cm for women (our criterion 2). We also calculated the COP for the largest AUC and suggested an optimal COP for men and women based on the study results. Statistical analyses were performed using the SAS system for Windows (release 9.1.3; SAS Institute, Cary, NC), and the AUC value was obtained to refer to the c statistic in PROC LOGISTIC output. All statistical tests were two-sided, and a P value <0.05 was considered to be significant. The study was approved by the ethics committee of Nagoya City University.

Results

Table 2 shows the number of subjects diagnosed with MetS according to the JMetS criteria and our newly proposed criteria, respectively. This diagnosis was based on the number of MetS components, other than central obesity, calculated by WC status in both men and women. Only 8.4% of the women satisfied the central obesity criterion of JMetS, whereas 26.7% men satisfied the criterion. When the COP for central obesity was changed to ≥80 cm, 36.6% of women satisfied the criterion. Among the 13 men and six women who were newly diagnosed with MetS based on our criteria using the same WC COP, seven men (53.8%) and five women (83.3%) had fatty liver. The

Table 2 Criteria of metabolic syndrome and number of subjects

Number of components[a]	Criteria of JMetS	Our criteria	Number of patients diagnosed with MetS	Criteria of JMetS	Our criteria	Number of patients diagnosed with MetS
Men						
	Waist circumference <85 cm			*Waist circumference ≥85 cm*		
0	Normal	Normal	391 (32.7%)	Normal	Normal	93 (7.8%)
1	Normal	Normal	357 (29.9%)	Risk MetS	Risk MetS	152 (12.7%)
2	Normal	Risk MetS	115 (9.6%)	MetS	MetS	61 (5.1%)
3	Normal	MetS	13 (1.1%)	MetS	MetS	13 (1.1%)
Total			876 (73.3%)			319 (26.7%)
	Waist circumference <90 cm			*Waist circumference ≥90 cm*		
0	–	Normal	453 (37.9%)	–	Normal	31 (2.6%)
1	–	Normal	457 (38.2%)	–	Risk MetS	52 (4.4%)
2	–	Risk MetS	151 (12.6%)	–	MetS	25 (2.1%)
3	–	MetS	20 (1.7%)	–	MetS	6 (0.5%)
Total			1,081 (90.5%)			114 (9.5%)
Women						
	Waist circumference <90 cm			*Waist circumference ≥90 cm*		
0	Normal	Normal	603 (53.0%)	Normal	Normal	28 (2.5%)
1	Normal	Normal	357 (31.4%)	Risk MetS	Risk MetS	45 (4.0%)
2	Normal	Risk MetS	76 (6.7%)	MetS	MetS	18 (1.6%)
3	Normal	MetS	6 (0.5%)	MetS	MetS	5 (0.4%)
Total			1,042 (91.6%)			96 (8.4%)
	Waist circumference <80 cm			*Waist circumference ≥80 cm*		
0	–	Normal	458 (40.2%)	–	Normal	173 (15.2%)
1	–	Normal	211 (18.5%)	–	Risk MetS	191 (16.8%)
2	–	Risk MetS	49 (4.3%)	–	MetS	45 (4.0%)
3	–	MetS	4 (0.4%)	–	MetS	7 (0.6%)
Total			722 (63.4%)			416 (36.6%)

JMetS Japanese metabolic syndrome, *Risk MetS* individuals with central obesity and one of three components (high blood pressure, hyperglycemia, or abnormal lipid metabolism), as defined by the Examination Committee for Criteria of MetS in Japan, *MetS* individuals with MetS

[a] Number of the components of MetS other than abdominal obesity

prevalence of fatty liver was much higher than the total prevalence of fatty liver in men and women, i.e., 27.1 and 16.5%, respectively.

Table 3 shows the characteristics of the subjects diagnosed with MetS based on the application of several criteria. The prevalence of MetS using the JMetS criteria was 6.2% in men and 2.0% in women; based on our criteria using the JMetS COP for central obesity, MetS prevalence was 7.3 and 2.5%, respectively. When we applied the criterion for ≥80 cm COP for central obesity in women using our criteria, the prevalence of fatty liver increased to 4.9%. Similarly, the application of the COP increased the prevalence among the MetS risk group to 21.1%, which was close to that observed in men according to our criteria which include the ≥85 cm COP for central obesity. Since central obesity is an essential criterion for determining JMetS or the JMetS risk group, the subjects in these categories are much more obese than those falling in the normal category. The difference in WC and BMI between subjects in the MetS group and the normal group was 12.1 cm and 3.5 kg/m^2, respectively, in men and 17.6 cm and 5.7 kg/m^2 in women. When our criteria were used, these differences decreased to 10.4 cm and 3.0 kg/m^2, respectively, in men and 14.5 cm and 5.0 kg/m^2 in women.

Table 3 Characteristics of the subjects by MetS status

Characteristics	Men			Women		
	Normal	Risk MetS	MetS	Normal	Risk MetS	MetS
Criteria of JMetS (cut-off of WC)	(85 cm)			(90 cm)		
Number (row%)	969 (81.1%)	152 (12.7%)	74 (6.2%)	1,070 (94.0%)	45 (4.0%)	23 (2.0%)
Fatty liver prevalence (%)	20.6%	46.1%	73.0%	14.5%	40.0%	65.2%
Age (years)	63.0 ± 8.8	63.3 ± 8.4	63.4 ± 7.9	61.6 ± 8.0	65.8 ± 8.1	64.4 ± 6.7
BMI (kg/m^2)	22.3 ± 2.4	25.8 ± 2.4	25.8 ± 2.5	21.7 ± 2.6	27.2 ± 3.4	27.4 ± 3.1
WC (cm)	77.8 ± 6.4	89.6 ± 5.3	89.9 ± 4.9	76.5 ± 7.5	95.0 ± 5.1	94.1 ± 3.7
Systolic blood pressure (mmHg)	122.6 ± 15.1	126.5 ± 16.0	136.2 ± 12.4	122.2 ± 17.0	132.0 ± 13.8	142.3 ± 14.7
Diastolic blood pressure (mmHg)	71.9 ± 8.6	75.0 ± 8.9	79.9 ± 8.2	70.5 ± 9.3	74.6 ± 8.3	79.3 ± 7.0
Triglycerides (mg/dl)	114.3 ± 70.8	142.7 ± 71.6	196.2 ± 150.0	97.5 ± 49.8	120.7 ± 52.7	204.5 ± 101.1
HDL-cholesterol (mg/dl)	62.1 ± 16.4	53.3 ± 12.6	51.9 ± 14.8	72.2 ± 17.1	64.7 ± 14.3	54.1 ± 13.6
Fasting glucose (mg/dl)	96.0 ± 17.2	100.0 ± 18.1	122.9 ± 48.1	92.4 ± 15.8	95.1 ± 13.5	117.3 ± 30.9
Our criteria 1 (cut-off of WC)	(85 cm)			(90 cm)		
Number (row%)	841 (70.4%)	267 (22.3%)	87 (7.3%)	988 (86.8%)	121 (10.6%)	29 (2.5%)
Fatty liver prevalence (%)	17.6%	43.1%	70.1%	12.7%	35.5%	69.0%
Age (years)	62.7 ± 8.9	63.9 ± 8.1	64.2 ± 8.0	61.3 ± 8.0	64.7 ± 7.9	64.8 ± 6.8
BMI (kg/m^2)	22.2 ± 2.5	24.5 ± 2.7	25.2 ± 2.6	21.7 ± 2.6	24.0 ± 3.7	26.7 ± 3.2
WC (cm)	77.6 ± 6.6	84.9 ± 7.2	88.0 ± 6.7	76.4 ± 7.6	84.3 ± 10.1	90.9 ± 7.6
Systolic blood pressure (mmHg)	120.5 ± 14.1	130.8 ± 15.9	137.1 ± 11.9	120.7 ± 16.3	137.2 ± 14.0	143.9 ± 14.4
Diastolic blood pressure (mmHg)	71.0 ± 8.3	76.1 ± 9.0	79.4 ± 8.0	69.9 ± 9.1	76.8 ± 8.7	79.9 ± 7.5
Triglycerides (mg/dl)	103.8 ± 50.2	159.2 ± 103.1	197.4 ± 140.9	91.2 ± 40.2	152.1 ± 76.4	207.7 ± 92.4
HDL-cholesterol (mg/dl)	63.2 ± 16.0	54.4 ± 15.0	51.3 ± 14.8	73.0 ± 16.8	63.3 ± 16.7	55.2 ± 14.0
Fasting glucose (mg/dl)	93.2 ± 12.2	105.3 ± 24.5	124.5 ± 45.0	91.2 ± 13.9	100.3 ± 21.6	121.9 ± 33.2
Our criteria 2 (cut-off of WC)	(90 cm)			(80 cm)		
Number (row%)	941 (78.7%)	203 (17.0%)	51 (4.3%)	842 (74.0%)	240 (21.1%)	56 (4.9%)
Fatty liver prevalence (%)	19.6%	50.2%	74.5%	10.3%	27.9%	60.7%
Age (years)	62.8 ± 8.8	64.0 ± 8.2	63.9 ± 7.9	60.6 ± 8.0	64.9 ± 7.2	64.6 ± 7.7
BMI (kg/m^2)	22.5 ± 2.5	24.3 ± 3.0	25.6 ± 3.3	21.3 ± 2.5	23.9 ± 3.1	25.4 ± 2.9
WC (cm)	78.6 ± 6.9	84.3 ± 8.2	88.8 ± 8.6	75.0 ± 7.4	84.3 ± 7.4	87.8 ± 6.6
Systolic blood pressure (mmHg)	121.2 ± 14.4	133.4 ± 15.5	138.2 ± 11.5	118.1 ± 14.9	135.5 ± 15.2	143.1 ± 14.8
Diastolic blood pressure (mmHg)	71.5 ± 8.4	76.9 ± 9.1	80.2 ± 7.9	68.8 ± 8.6	76.1 ± 8.8	79.8 ± 8.0
Triglycerides (mg/dl)	107.6 ± 53.0	172.0 ± 112.7	211.2 ± 172.3	87.0 ± 36.5	126.3 ± 56.4	195.5 ± 102.1
HDL-cholesterol (mg/dl)	62.2 ± 15.9	54.7 ± 16.1	50.1 ± 14.9	74.6 ± 16.6	64.2 ± 15.7	56.4 ± 13.3
Fasting glucose (mg/dl)	93.9 ± 13.4	109.7 ± 28.2	131.1 ± 49.9	90.8 ± 14.4	95.4 ± 14.7	115.5 ± 30.7

Data are given as the mean ± standard deviation (SD)

WC Waist circumference, *BMI* body mass index, *HDL* high-density lipoprotein

When the COP of ≥80 cm was applied, the differences decreased to 12.8 cm and 4.1 kg/m^2, respectively.

Table 4 shows the odds ratios and 95% confidence interval (CI) for fatty liver according to the number of MetS components other than central obesity by WC status. Regardless of sex and the WC COP selected, a strong linear trend was observed for the association (trend $P < 0.0001$) with the number of components. The odds ratio for subjects without central obesity and with all three components of MetS was 9.69 (95% CI 3.1130.2) in men and 55.3 (6.34–483) in women. Using the ≥90 and ≥80 cm COP criterion for central obesity in men and women, respectively, the odds ratio was 55.3 (6.34–483) and 62.4 (6.23–626). These point estimates of odds ratios were higher than those of MetS subjects with two risk factors other than obesity among women, and even among men, they were higher than those of the risk group for MetS who satisfied the central obesity criterion.

Figure 1 shows the ROC curves for the diagnosis of fatty liver according to MetS status by the JMetS criteria and by our criteria. The AUC for the JMetS criteria and our criteria 1 and 2 in men was 0.638, 0.681, and 0.655, respectively. In women, the AUC for our criteria using ≥90 and ≥80 cm COPs for central obesity were 0.625 and 0.681, respectively, whereas that for the JMetS criteria was only 0.570. Based on the findings of our study, the largest AUC was recorded using our criterion 1 (≥85 cm) in men and our criteria 2 in women (≥80 cm). The shapes of the ROC curves of our criterion 2 for men and our criterion 1 for women were very similar, with the coordinates (false positive rate, true positive rate) for MetS and the risk group for MetS being (0.030, 0.188) and (0.204, 0.543), respectively, for men and (0.023, 0.181) and (0.205, 0.537), respectively for women. In addition, when WC was considered as a component, the COP for the largest AUC among men and women was ≥82 cm (0.701) and ≥77 cm (0.699), respectively. We therefore conclude that it would be both practical and appropriate to take WC into consideration, with WC COPs of ≥85 cm for men and ≥80 cm for women. In our study population, 26.7% of the men and 36.6% the women satisfied the criteria.

Table 4 Odds ratio and 95% confidence interval for fatty liver according to the number of the components of MetS other than obesity by waist circumstance status

Number of the components[a]	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Men				
	Waist circumference <85 cm		*Waist circumference ≥85 cm*	
0	1.00	Reference	5.49	3.25–9.27
1	1.99	1.32–3.01	7.09	4.51–11.1
2	5.34	3.26–8.74	18.4	9.78–34.4
3	9.69	3.11–30.2	99.7	12.6–786
P for trend	<0.0001		<0.0001	
	Waist circumference <90 cm		*Waist circumference ≥90 cm*	
0	1.00	Reference	7.66	3.59–16.32
1	1.88	1.33–2.66	11.91	6.34–22.39
2	5.17	3.40–7.85	19.96	7.67–51.93
3	14.71	5.45–39.72	31.53	3.62–274.34
P for trend	<0.0001		<0.0001	
Women				
	Waist circumference <90 cm		*Waist circumference ≥90 cm*	
0	1.00	Reference	9.59	4.32–21.3
1	2.32	1.56–3.46	7.37	3.80–14.3
2	5.42	3.10–9.48	17.4	6.45–46.8
3	55.3	6.34–483	44.2	4.85–403
P for trend	<0.0001		<0.0001	
	Waist circumference <80 cm		*Waist circumference ≥80 cm*	
0	1.00	Reference	6.67	3.82–11.7
1	2.67	1.45–4.92	8.63	5.04–14.8
2	6.02	2.70–13.4	26.0	12.5–54.1
3	62.4	6.23–626	125	14.4–1084
P for trend	<0.0001		<0.0001	

[a] Number of the components of metabolic syndrome other than abdominal obesity

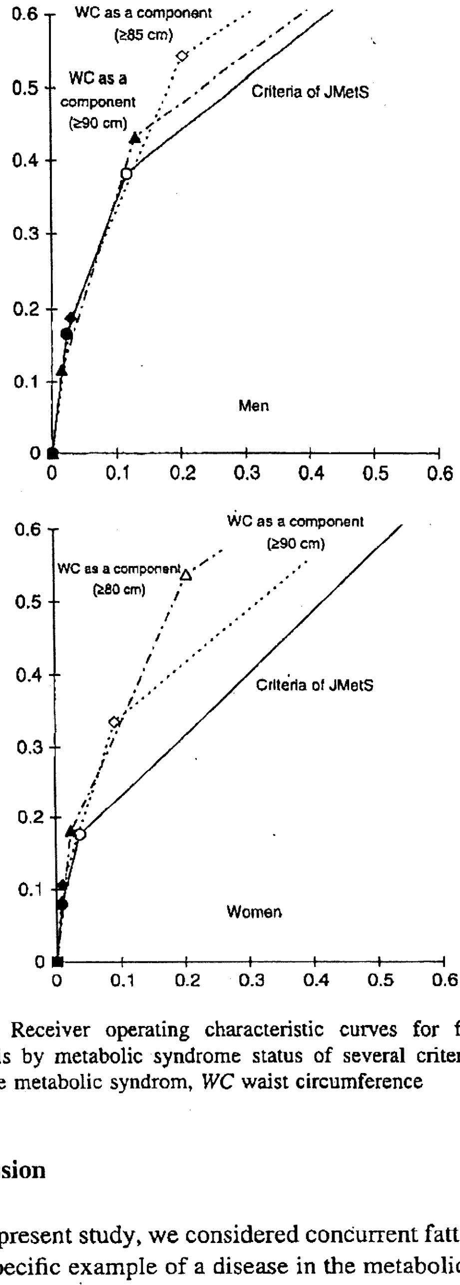

Fig. 1 Receiver operating characteristic curves for fatty liver diagnosis by metabolic syndrome status of several criteria. *JMetS* Japanese metabolic syndrom, *WC* waist circumference

Discussion

In the present study, we considered concurrent fatty liver to be a specific example of a disease in the metabolic domino of MetS and observed that the accumulation of MetS components was associated with higher odds ratios, even without the central obesity component. Taking these results as a whole, we observed stronger associations between MetS and fatty liver in men and women when we considered central obesity as a component rather than an essential requirement for the diagnosis of MetS. We therefore suggest that individuals with an accumulation of components should be regarded as having MetS even in the absence of central obesity, since fatty liver is a component of the metabolic domino. In addition, these individuals may belong to a risk group for other metabolic diseases, including cardiac arrest and cerebrovascular diseases. We also suggest that the optimal COP for WC should be ≥85 cm for men and ≥80 cm for women.

Although the main concepts of MetS are consistent, the COPs for defining central obesity for MetS are controversial, especially in Japan [21]. Several studies have been performed to elucidate the optimal COPs in which ROC analyses with obesity and two or more MetS components other than obesity [22–25] were used. The results suggested that the optimal cut-offs for men and women are 84–90 and 78–82 cm, respectively. Our results are consist with these reported values. However, these earlier studies were based on the internal consistency of obesity and MetS components other than obesity. Further ROC analyses need to be performed to establish the optimal COP for WC, and these should include certain diseases not currently included in MetS. This study is one such analysis.

An important question is whether central obesity should be considered as a requirement for the diagnosis of MetS or as a component of MetS. To answer this question, we need to examine the association between the number of MetS components and particular diseases stratified by central obesity. To date, there have been only two prospective cohort studies [26, 27] from Japan on cardiovascular diseases. Results from NIPPON DATA [26] show the existence of risk accumulation among non-obese subjects, whereas those from Hisayama-cho [27] indicate there is no risk accumulation in such subjects. Data from many studies, including those from our study, are required to facilitate further discussion on this question. However, before the absence of risk accumulation can be established among non-obese individuals, it is possible to treat central obesity as a component of MetS as a precautionary measure.

In general, if a factor is considered to be an essential requirement for the diagnosis of a certain disease, then that factor should not only be etiologically essential but also amenable to accurate measurement in practice; at the very least, the COP should be a sensitive measure. Otherwise, a considerable number of cases would not be detected by the criterion. In fact, the COPs based on the IDF criteria (≥94 cm for men and ≥80 cm for women), with central obesity as a requirement, are more sensitive than those of the NCEP-ATP III criteria (≥102 cm for men and ≥88 cm for women), wherein central obesity is considered a component. Although the JMetS definition is similar to the IDF definition, the JMetS COP for WC in women (≥90 cm) is much less sensitive than the COP of the IDF (≥80 cm). The COP for central obesity for the diagnosis of JMetS is based on the association between visceral fat area and WC [16]. The committee reported that simple correlation analysis of the regression line in women indicated that a WC corresponding to 100 cm^2 of visceral fat was 92.5 cm. However, the correlation coefficient was only 0.65, and more than half of the women with a visceral fat area

≥100 cm^2 would not be found using the WC COP of ≥90 cm (meaning that sensitivity is <0.5). The poor sensitivity of the WC in detecting abdominal adiposity is directly linked to the poor sensitivity of the JMetS criteria, in which WC is an essential requirement.

Conclusion

Based on the findings of our study, we suggest that a WC of ≥85 cm for men and ≥80 cm for women would be optimal COPs for central obesity for the diagnosis of MetS in the Japanese population. We also suggest that central obesity should be used as a component of MetS rather than an essential requirement for the diagnosis of MetS. No definite conclusion has yet been reached regarding the most appropriate diagnostic criteria for MetS. However, within the framework of our study in which fatty liver was considered to be an independent variable, we found that defining abdominal circumference as a component of MetS was less likely to cause errors of oversight and was thus more appropriate than considering abdominal circumference to be a required criterion. The challenge for the future is to identify pathologic conditions that are responsible for MetS and to find better diagnostic criteria through further similar studies that consider factors, other than fatty liver, involved in the metabolic domino effect [11, 12] as independent variables.

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ORIGINAL ARTICLE

Alcohol Drinking May Not Be a Major Risk Factor for Fatty Liver in Japanese Undergoing a Health Checkup

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Abstract The question of whether alcohol drinking is a risk factor for fatty liver as shown by ultrasonography was investigated by both cross-sectional and longitudinal approaches in Japanese undergoing a health checkup. In this cross-sectional study, 32,438 males (49.0 ± 11.9 years old) and 31,009 females (48.2 ± 11.6 years old) receiving a health checkup from 2000 to 2005 were included. Longitudinally, 5,444 males (49.8 ± 10.7 years old) and 4,980 females (50.4 ± 9.3 years old) participating in both 2000 and 2005 were included. Multiple logistic regression analyses were performed for both sexes, adjusted for age, BMI, and smoking. The prevalence of fatty liver in non-, occasional, daily moderate, and daily heavy drinkers was 28.5, 27.5, 18.7, and 19.1% in men and 12.4, 7.7, 5.4, and 6.7% in women, respectively (inverse association, $P \leq 0.05$ for both). Occasional, daily moderate, and daily heavy drinking in men and occasional and daily moderate drinking in women were inversely associated with fatty liver in the cross-sectional study. Daily moderate and heavy drinking appeared protective in men in the longitudinal study. Alcohol drinking may not be a major risk for fatty liver in Japanese undergoing a health checkup.

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Keywords Alcohol drinking · Fatty liver · Multiple logistic regression analysis · Health checkup · Screening and diagnosis

Abbreviations

BMI Body mass index
OR Odds ratio
FBG Fasting blood glucose

Introduction

Fatty liver due to intrahepatic accumulation of lipids is a widely recognized disease, thought to be linked to obesity and alcohol consumption [1–3]. Non-alcoholic fatty liver is recognized as the hepatic consequence of the metabolic syndrome, characterized by abdominal obesity, hypertriglycemia, hyperglycemia, and hypertension [4–6].

It has been controversial whether alcohol drinking causes obesity, although consumption was associated with a greater waist-to-hip ratio, overweight, and fatty liver [7–12]. Alcohol abuse and obesity were found to be equally strong risk factors for fatty liver in the Guangzhou area of China [13]. On the other hand, alcohol drinking may not increase the risk of obesity among US adults, drinking frequency further being inversely associated with the increase in waist circumference and obesity [9–11].

Low to moderate alcohol drinking may lower the risk of type 2 diabetes as well as the metabolic syndrome and cardiovascular mortality [14–19]. Protective effects of low to moderate alcohol drinking on type 2 diabetes may be related to improved insulin sensitivity [20–23]. It is possible that low to moderate alcohol drinking may therefore reduce the fatty liver, which is closely related to insulin resistance [5, 24]. Moderate alcohol drinking may also be a weaker risk factor for fatty liver than obesity from results for the general population of Northern Italy [25]. Low alcohol drinking, less than 20 g alcohol/day, did not increase the risk for fatty liver in Japanese at a health checkup [26]. Low to moderate alcohol drinking attenuated liver steatosis and non-alcoholic steatohepatitis in severely obese individuals in the USA, possibly by reducing insulin resistance [27]. Moreover, modest wine drinking decreased the prevalence of non-alcoholic fatty liver disease in the Third National Health and Nutrition Survey [28].

Most earlier studies excluded subjects with regular alcohol consumption of more than 20 g/day. Some 54–70% of men and 13% of women in Japan consume more than 23 g alcohol/day [29, 30], drinking behavior being to some extent determined by genetic polymorphisms of alcohol metabolism genes and alcohol-induced liver damage being influenced by the genetic variation of cytochrome P4502EI and alcohol dehydrogenase [31–33]. Therefore, exclusion and selection of categories of drinkers may give rise to misleading results.

In the present cross-sectional and longitudinal investigation, we therefore included all alcohol drinkers in an assessment of risk factors including alcohol drinking for fatty liver assessed by ultrasonography. Adjustment was made for age, body mass index (BMI), and smoking in Japanese undergoing a health checkup.

Methods

Design of Study

This study included both cross-sectional and retrospective longitudinal analyses to investigate whether alcohol consumption, determined by questionnaire, is associated with fatty liver, assessed by ultrasonography, in apparently healthy Japanese undergoing a health checkup. Informed consent was obtained from all participants.

Subjects of the Cross-Sectional Study

A total of 179,646 participants (men: 95,977, 51.7 ± 11.6 years old; women: 83,669, 51.4 ± 11.1 years old) underwent medical examinations including ultrasonography at Okazaki City Medical Association, Public Health Center, between April 2000 and March 2006. Since more than half of the participants repeatedly underwent medical checkups, the participants undergoing a checkup for the first time during this period were included. These comprised 34,593 men and 32,743 women. After exclusion of participants who had past or present histories of hepatic diseases induced by drugs, autoimmune conditions, or unknown etiology based on questionnaire and positive results for hepatitis virus, a total of 63,447 participants (men: 32,438, 49.0 ± 11.9 years old; women: 31,009, 48.2 ± 11.6 years old) were included.

Subjects of the Longitudinal Study

The numbers of participants undergoing medical checkups including ultrasonograpy in 2000 and 2005 were 26,247 (men: 14,627; women: 11,620) and 32,548 (men: 17,207; women: 15,341), respectively. After exclusion of participants who had past or present histories of hepatic diseases induced by drugs, autoimmune conditions, or unknown etiology based on questionnaire and positive results of hepatitis virus, a total of 12,453 participants in both 2000 and 2005 (men: 6,924, 49.5 ± 10.5 years old; women: 5,529, 50.7 ± 9.3 years old) were included. Since 2,029 cases (men: 1,480, 21.4%; women: 549, 9.9%) were assessed as having fatty liver in 2000 on ultrasonography, a total of 10,424 participants (men: 5,444, 49.8 ± 10.7 years old; women: 4,980, 50.4 ± 9.3 years old) without fatty liver in 2000 were longitudinally analyzed to determine risk factors for newly developed fatty liver on ultrasonography in 2005.

Questionnaire

Subjects provided data for alcohol consumption and smoking status in a self-administered questionnaire that was then checked during individual interview by expert nurses in the center. Alcohol consumption was recorded using questions on both frequency and quantity. Frequency of drinking was classified into occasional (1–6 days/week) and daily (7 days/week). One drink was defined as one bottle (500 ml) of beer containing 4–5% alcohol or 1 gou (180 ml) of Japanese sake containing 14% alcohol, which is equivalent to 23 g alcohol [29, 30]. Quantities of drinks were recorded as one, two, or three and more than three drinks per day. Amounts of alcohol consumed per week were estimated by assessing both frequency and numbers of drinks only in the daily drinkers since it was difficult to accurately determine amounts of alcohol in the occasional drinkers. The amounts of alcohol in the participants having daily one, two, and three or more than three drinks were estimated to be 161 g/week, 322 g/week, and 483 g or more than 483 g/week, respectively.

The drinkers were divided into three categories: occasional drinkers, daily moderate drinkers who have one drink (23 g alcohol) per day, and daily heavy drinkers who have two and three or more than three drinks (46 g and 69 g or more than 69 g alcohol, respectively) per day. These categories were determined according to the previous reports demonstrating that less than 30 g alcohol/day prevented cardiovascular diseases and the risk threshold for alcohol-induced liver disease was more than 30 g alcohol/day [34, 35].

Measurements

Body weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. BMI was categorized into three categories: <25, 25–29.9, and ≤30 according to the criteria determined by the Japan Society for the Study of Obesity. Age was categorized into four categories: <40, 40–49, 50–59, and <60.

Blood samples were taken from each participant after overnight fasting. Fasting blood glucose (FBG) was measured by Hitachi autoanalyzer models 7600 and 7700 (Hitachi Medical, Co., Tokyo, Japan).

Fasting hyperglycemia was defined if serum FBG was ≤110 mg/dl. Elevated blood pressure or hypertension was diagnosed if resting blood pressures was ≤130/85 mmHg or if the participants had either a history of hypertension or antihypertensive medication, respectively.

Abdominal ultrasonographic examination was performed using convex-type real-time electronic scanners (SSA 250 and 300, Toshiba Medical, Co., Tokyo, Japan) by ten technicians lacking any information about the subjects, including alcohol history. All images were printed on sonograph paper and reviewed by other technicians and physicians. Fatty liver was assessed according to the modified criteria reported previously [36, 37]. These include a comparative assessment of liver brightness (diagnosed by a difference of more than 10 in the average liver and renal cortical echo amplitudes), attenuation of echo penetration, and decreased visualization of veins.

Statistical Analyses

Multiple logistic regression analyses were performed to determine the influence of drinking as a risk factor for fatty liver in both men and women, both adjusted for age and for age, BMI, and smoking in the cross-sectional and longitudinal studies. Adjustment was also made for age, BMI, smoking, and either FBG or elevated blood pressure and hypertension. The analyses were further performed after excluding daily heavy drinkers.

Statistical differences among groups were identified using one-way analysis of variance, followed by multiple comparisons using Bonferroni method. The $m \times n$ chi-square test and Fisher's test were used for comparison of prevalence of fatty liver. Logistic regression analyses were performed using computer software (SPSS version 13.0 for Windows). P values less than 0.05 were considered significant.

Results

Cross-Sectional Study

The percentages of occasional, daily moderate, and daily heavy drinkers were 32.9, 17.7, and 9.3% overall, 33.8, 27.6, and 16.5% for men, and 32.1, 7.4 and 1.8% for women, respectively. Age was significantly lower in occasional and daily drinkers than in non-drinkers in both sexes (Table 1). BMI was significantly higher in occasional drinkers and lower in daily drinkers than in non-drinkers in men and was significantly lower in occasional and daily drinkers than in non-drinkers in women. In addition, the overall prevalence of fatty liver was 23.9% in men and 10.3% in women, and the prevalence of fatty liver in daily

Table 1 Age, BMI, prevalence of fatty liver, and ever smoking rates due to drinking habits in the cross-sectional study

	Non-drinkers	Occasional drinkers	Daily moderate drinkers	Daily heavy drinkers
Men				
%	21.7	33.8	27.6	16.5
Age	50.9 ± 12.6	46.4 ± 12.1*	50.7 ± 11.2	49.1 ± 10.7*
BMI	23.1 ± 3.2	23.4 ± 3.1*	22.9 ± 2.8	23.0 ± 2.8
Fatty liver (%)	28.5	27.5	18.7	19.1
Ever smoking rates (%)	41.1	41.3	44.4	59.6
Women				
Number (%)	58.5	32.1	7.4	1.8
Age	50.6 ± 11.4	44.3 ± 11.2*	47.5 ± 10.0*	42.7 ± 10.1*
BMI	22.2 ± 3.3	21.7 ± 3.1*	21.4 ± 2.8*	21.2 ± 3.0*
Fatty liver (%)	12.4	7.7	5.4	6.7
Ever smoking rates (%)	5.9	11.6	17.3	52.4

* $P < 0.05$ compared with non-drinkers

drinkers was significantly lower than in non-drinkers in both sexes.

Multiple logistic regression analysis revealed that occasional and daily moderate drinking both adjusted for age and for age, BMI, and smoking was inversely associated with fatty liver in both sexes (Table 2). Daily heavy drinking fully adjusted for other factors was inversely associated with fatty liver in men, while this relation did not reach statistical significance in women.

Adding FBG or elevated blood pressure and hypertension, the ORs were not changed in both sexes. After removing the daily heavy drinkers (5,370 men and 563 women), the results were not essentially changed (data not shown).

Longitudinal Study

The percentages of occasional, daily moderate, and daily heavy drinkers were 30.6, 20.3, and 9.5% overall, 31.3, 32.3, and 17.0% for men, and 29.9, 7.0, and 1.2% for women, respectively. Age was significantly lower in occasional and daily heavy drinkers in men and in three groups of drinkers in women than in non-drinkers (Table 3). Fatty liver newly developed in 10.2, 12.1, 11.7, and 12.0% of non-, occasional, daily moderate, and daily heavy drinkers, respectively, overall within the 5-year period. Fatty liver was found in 16.4, 16.7, 12.9, and 12.4% of non-, occasional, daily moderate, and daily heavy drinkers in men, respectively, and in 8.2, 6.8, 5.7, and 6.7% of the women, respectively. The risk of newly developed fatty liver was significantly lower in daily moderate and heavy drinkers than non-drinkers in men.

In the multiple logistic regression analysis, daily moderate and heavy drinking was inversely associated with fatty liver adjusted for age, BMI, and smoking in men. Although similar inverse association was observed in women, this did not reach statistical significance (Table 4). Adding FBG or elevated blood pressure and hypertension did not alter the ORs (data not shown). After removing the daily heavy drinkers (928 men and 60 women), daily moderate drinking was the inverse risk factor for fatty liver (ORs 0.72, 95% CI 0.58–0.89) in men, while the results were not changed in women.

Table 2 Multiple logistic regression analysis for fatty liver in the cross-sectional study

	Age-adjusted OR	95% CI	Multivariate OR*	95% CI
Men				
Non-drinkers	1.00	References	1.00	References
Occasional drinkers	0.93	0.87–0.99	0.89	0.83–0.96
Daily moderate drinkers	0.56	0.52–0.60	0.58	0.53–0.63
Daily heavy drinkers	0.56	0.51–0.61	0.57	0.52–0.63
Women				
Non-drinkers	1.00	References	1.00	References
Occasional drinkers	0.74	0.68–0.81	0.77	0.70–0.85
Daily moderate drinkers	0.44	0.37–0.53	0.53	0.43–0.64
Daily heavy drinkers	0.70	0.50–0.98	0.85	0.60–1.23

* Adjusted by age, BMI, and smoking status

Table 3 Age, BMI, and ever smoking rates due to drinking habits in the longitudinal study

	Non-drinkers	Occasional drinkers	Daily moderate drinkers	Daily heavy drinkers
Men				
Number (%)	19.1	31.3	32.3	17.0
Age	51.4 ± 11.2	48.7 ± 11.1*	50.3 ± 10.5	49.0 ± 9.5*
BMI	22.2 ± 2.6	22.5 ± 2.5*	22.4 ± 2.4	22.4 ± 2.4
Ever smoking rates (%)	39.0	41.8	44.6	63.9
Women				
Number (%)	61.5	29.9	7.0	1.2
Age	51.8 ± 9.2	47.9 ± 9.2*	49.6 ± 8.6*	46.8 ± 9.0*
BMI	21.8 ± 2.6	21.8 ± 2.6	21.5 ± 2.5	21.5 ± 2.7
Ever smoking rates (%)	4.3	9.2	17.7	53.5

* $P < 0.05$ compared with non-drinkers