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Risk for Non-obese Japanese Workers to Develop Metabolic Syndrome

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Abstract: With regard to metabolic syndrome-related risks (MS risks), obese workers have been the focus of attention, and less attention has been paid to non-obese subjects as if they were free from the risks. The present analysis was initiated to know if no-obesity means no-MS risks. Participants of the study were 804 male workers, who showed no pathological findings in 12 MS-related and other health parameters in 2003, and had complete sets of data in 2008. They were classified by BMI in 2003 into lean (<18.5), normal (≥18.5 to <25) and obese groups (≥25). Proportion of MS in 2008 was examined by use of the second phase of MS criteria. Proportions for the lean, normal and obese subjects who met MS criteria in 2008 were 3.2, 4.8 and 5.3%, respectively, with no significant difference in proportions among them. In the non-obese (i.e., lean+normal) group, age was not significantly influential to increase BMI. Thus, the MS risk exists even in non-obese young workers. Anti-MS effort should be directed not only to obese but to non-obese workers, and care should be extended irrespective of ages.

Key words: Body composition, Follow-up, Metabolic syndrome, Leanness, Obesity, Risk factor

Introduction

World Health Organization published a report late in last century on the definition of metabolic syndrome, in addition to the diagnostic criteria for diabetes mellitus, as an etiology possibly common to various lifestyle-related chronic diseases[1]. Since then, metabolic syndrome (MS) and related risk factors have been among the foci of attention of health staff in many organizations both in developed and developing countries. In Japan in particular, a nation-wide campaign has been launched since a new health examination system for employed workers was promulgated early in 2008[2], and the Ministry of Health, Labour and Welfare has been active on an anti-MS program by requesting all employers to offer special health examination (designated to detect early signs of the syndrome) followed by finding-based health guidance not only to their employees but to the dependants of the employees.

A number of survey reports have been published on the prevalence of MS among various working populations and general public in Japan[3–11] as well as people in east Asia[12–19]. Success in solving MS problems[20] has also been reported through improvement in food habits[21] or introduction of gentle yet daily-repeated physical exercise (typically 40 min walk) in combination with diet guidance[22].

The focus of attention in these studies was placed on obese workers at middle ages (e.g., ≥40 yr) as a possible high-risk group to develop metabolic syndrome. A question naturally arises in occupational health service is if younger workers or those with lean or normal body composition are free from the risk, and in case they also have risks, what would be the extent of their risks relative to the risks for expected high-risk group of middle-aged obese workers.

The present study was initiated to find answers to

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these questions of occupational as well as public health importance. For this purpose, analyses were conducted by use of two sets of records obtained through routine annual health examinations 5 yr apart.

Subjects and Methods

Subjects studied

Among the workers who underwent routine annual health examinations in 2003, 2,042 adult men showed no pathological or borderline findings in their health records (the original group) (for examination items, see below). Most of them were followed up every year as a part of routine occupational health service, and a complete set of data on each and all examination items for 2008 (i.e., 5 yr later) were available for 804 male workers (the selected group). Preliminary analyses to compare the selected group with the original group by unpaired *t*-test on 19 items (including age, height, weight, etc.; ALT, AST, γ-GTP and triglyceride were after logarithmic conversion) did not show significant difference (p>0.01) in most cases, except for age, γ-GTP and triglyceride (p<0.01). The differences between the two groups were however small, i.e., 3.3 yr for age, 5.6 units/l for γ-GTP and 3.5 mg/100 ml for triglyceride (the latter two values were the differences after anti-logarithmic conversion). Smoking did not show significant difference (p<0.01) between the two groups when examined by Mann-Whitney test. Thus, the possible selection bias was considered to be not meaningful from biomedical viewpoints.

During this 5 yr period, the regulation-based intensive health guidance[2)] was yet to be given as it was before the regulatory enforcement, although routine guidance had been provided. The 2003 and 2008 health examination data for these 804 men were subjected to statistical evaluation.

Heath examination items

The examination items included identification of age, measurement of height and weight followed by body mass index (BMI) calculation {BMI=[weight (in kg) –1]/[height (in m)]^2 (where weight was measured as clothed and with no footwear, and 1 was subtracted to adjust for weight of clothes), blood pressures [systolic (SBP) and diastolic blood pressure (DBP)], and serum and plasma biochemistry for triglyceride (TG), total cholesterol (TC), high and low density lipoprotein cholesterol (HDL-C, LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GTP), 10-h fasting plasma glucose (FPG), hemoglobin A_{1c} (HbA_{1c}), and uric acid (UA). Serum and plasma biochemistry items were assayed by conventional clinical laboratory methods with due external and internal quality assurance.

Classification of cases in terms of BMI and MS risk factors

The criteria set by Japan Society for the Study of Obesity[23, 24)] was employed in classifying the cases into the lean, normal and obese groups. Thus, the lean, normal and obese groups were for those with BMI <18.5, 18.5≤BMI <25 and BMI≥25, respectively.

With regard to MS-related classification, the first phase screening established by the MS Committee in Japan[25)] requests the measurement of waist circumference at the navel level so that men with the circumference ≥85 cm (≥90 cm for women) are selected. The second phase criteria for MS are TG≥150 mg/100 ml and/or HDL-C<40 mg/100 ml for dyslipidemia, SBP ≥130 mmHg and/or DBP≥85 mmHg for hypertension, and FPG≥110 mg/100 ml for hyperglycemia. Those who met with two or more criteria out of the three (i.e., dyslipidemia, hypertension and hyperglycemia) will be identified as MS[25)]. In the present analyses, no waist circumference data were available for 2003, and BMI was employed as a surrogate for classifying the subjects as described above. A preliminary simple regression analysis with 2008 data for BMI and waist circumference data (both available for 717 subjects in the cohort) showed a close correlation (with r=0.846 and p<0.01) between the two parameters in confirmation of previous findings[26, 27)].

Statistical analysis

A normal distribution was assumed for all parameters except for ALT, AST, γ-GTP and triglyceride for which a log-normal distribution was considered. Accordingly, pairs of arithmetic mean (AM) and arithmetic standard deviation (ASD) or geometric mean (GM) and geometric standard deviation (GSD) were employed to express the distribution for the former and the latter items, respectively.

For statistical analyses, *t*-tests (either paired or unpaired as appropriate, and after logarithmic conversion as necessary) were employed to detect possible significant difference in means. Mann-Whitney test was also employed. In principle, the difference with p<0.01 was taken as significant, considering the low follow-up rate (804/2042=39.4%). Simple and multiple regression analyses were employed to identify influential variables. χ^2 test and Cochran-Armitage trend test were also applied as appropriate. Through-out the analyses, measurements for the year 2003 were taken as baseline data. The difference (Δ) of the measurement in 2008 from that in 2003 was calculated as an increment; for example ΔSBP to show an increase in SBP in 2008 over SBP in 2003.

Results

Demographic data in 2003 and 2008

Demographic data for the year 2003 and 2008 are summarized in Table 1; the 2003 data are for presentation of the baseline values and 2008 data were to show possible changes in the 5 yr period. AMs and MEDs in 2003 data suggested that the subjects were healthy populations in agreement with the selection criteria. It should be noted that AMs agreed with MEDs in most cases, whereas the agreement was achieved only after logarithmic conversion (i.e., GMs) in cases of AST, ALT and γ-GTP.

When the 2008 values were compared with the corresponding 2003 values by paired t-test, significant increases ($p<0.01$) were observed in most of the items including BMI (except for a slight decrease in SBP), suggesting that there occurred deviations from original healthy status in the 5 yr period.

Changes among lean, normal and obese groups

The total 804 cases were classified into 3 different body composition groups based on the BMI values in 2003, i.e., BMI<18.5, 18.5≤BMI<25, BMI≥25 to the lean, normal and obese group, respectively. The AM values (GMs in cases of AST, ALT, γ-GTP and triglyceride) for the three groups are summarized in Table 2 together with statistical evaluation of the differences. As expected, the obese group had greater BMI than other two groups both in 2003 and in 2008, but interestingly the gain in the 5 yr period was smaller (in fact it was a reduction, although small) for the obese group than for other two groups. The net BMI was however still greater for the obese group than for other two groups. Both the lean and the normal groups gained BMI, and the gain tended to be greater for the lean group than in the normal group although the difference was statistically insignificant ($p>0.01$).

Another point worthy of noting in Table 2 is that all of TG, TC and LDL-C were higher, and HDL-C was lower in accordance with larger BMI in 2003. The difference was less remarkable in 2008 despite the observation that the changes (i.e., Δ) during the 5 yr period did not differ among the three groups.

Table 1. Dermographic data for 804 men analyzed in the study

Parameter		Measurement in 2003			Measurement in 2008				The increment (Δ)[a]		
	(Unit)	AM[b]	ASD[b]	MED[b]	AM	Diff.[f]	ASD	MED	AM	ASD	MED
Age	(yr)	39.3	8.4	39							
Body weight	(kg)	63.5	8.2	62.9	64.3	↑	8.7	63.8	0.8	3.8	0.7
BMI	(kg/m^2)	21.7	2.4	21.6	21.9	↑	2.5	21.85	0.2	1.3	0.1
SBP	(mm Hg)	118.8	10.4	118	115.9	↑	12.5	115	–2.9	13.1	–3
DBP	(mm Hg)	70.9	8.2	71	73.4	↑	9.2	73	2.5	8.6	2
TG	(mg/100 ml)	78.8[d]	1.39[e]	79	87.5[d]	↑	1.54[e]	85	14.4	68.0	7
TC[c]	(mg/100 ml)	180.5	20.5	183	191.5	↑	24.8	190	11.0	18.9	11
HDL-C	(mg/100 ml)	60.5	12.9	59	61.8	↑	14.3	59.5	1.4	9.1	1
LDL-C[c]	(mg/100 ml)	103.9	18.2	105	113.4	↑	22.6	113	9.4	16.8	8.5
AST[c]	(IU/l)	19.5[d]	1.24[e]	19	19.4[d]	ns[g]	1.29[e]	19	0.1	5.7	0
ALT[c]	(IU/l)	18.1[d]	1.44[e]	18	20.2[d]	↑[g]	1.52[e]	19	2.9	10.8	2
γ-GTP[c]	(IU/l)	25.9[d]	1.54[e]	24	28.6[d]	↑[g]	1.67[e]	26	4.5	15.5	2
FPG	(mg/100 ml)	91.2	7.2	91	92.4	↑	9.8	91	1.2	9.1	0
HbA1c[c]	(%)	4.6	0.2	4.6	4.9	↑	0.3	4.9	0.3	0.2	0.3
UA[c]	(mg/100 ml)	5.5	0.9	5.6	5.9	↑	1.0	5.9	0.4	0.7	0.4

[a]The increment=2008 value – 2003 value.

[b]Abbreviations are: AM for arithmetic mean, ASD for arithmetic standard deviation, Min for the minimum, MED for median, and Max for the maximum. GM and GSD are for geometric mean and geometric standard deviation, respectively.

[c]Items not included in the metabolic syndrome criteria.

[d]GM

[e]GSD

[f]Statistical significance of the difference from 2003 values; an arrow is for $p<0.01$ (upward for increase and downward for decrease), and ns is for $p\geq0.01$.

[g]After logarithmic conversion.

Table 2. Comaprison by body composition among 3 groups or between 2 groups

		Year	Classification by BMI[a, b]						Comparison[c]			
			Lean (L)		Normal (N)		Obese (O)		3 groups	L vs. N	N vs. O	L vs. O
No. of cases			63		666		75					
Parameter[d]												
Age	(yr)	’03	39.5		39.2		40.2		ns			
Weight	(kg)	’03	51.7		63.1		76.5		*	↑	↑	↑
		’08	53.0	↑	64.0	↑	76.0	ns	*	↑	↑	↑
		Δ	1.4		0.9		–0.4		*	ns	↓	↓
BMI	(kg/m^2)	’03	17.7		21.6		26.3		*	↑	↑	↑
		’08	18.1	↑	21.8	↑	26.0	ns	*	↑	↑	↑
		Δ	0.4		0.2		–0.3		*	ns	↓	↓
SBP	(mmHg)	’03	117		119		121		ns	ns	ns	ns
		’08	116	ns	116	↓	119	ns	ns	ns	ns	ns
		Δ	–1.6		–3.1		–2.0		ns	ns	ns	ns
DBP	(mmHg)	’03	70.8		70.6		73.8		*	ns	↑	ns
		’08	72.2	↑	73.0	↑	78.2	↑	*	ns	↑	↑
		Δ	1.4		2.4		4.4		ns	ns	ns	ns
TG	(mg/100 ml)	’03	69.8		78.0		95.7		*	ns	↑	↑
		’08	75.4	ns	87.1	↑	102.4	ns	*	ns	↑	↑
		Δ	10.0		13.2		9.3		ns	ns	ns	ns
TC	(mg/100 ml)	’03	176		180		187		*	ns	↑	↑
		’08	188	↑	191	↑	197	↑	ns	ns	ns	ns
		Δ	12.0		11.0		9.9		ns	ns	ns	ns
HDL-C	(mg/100 ml)	’03	67.3		60.4		55.0		*	↓	↓	↓
		’08	66.4	ns	61.8	↑	58.0	↑	*	↓	ns	↓
		Δ	–0.8		1.4		3.1		ns	ns	ns	ns
LDL-C	(mg/100 ml)	’03	96		104		112		*	↑	↑	↑
		’08	108	↑	113	↑	118	ns	ns	ns	ns	ns
		Δ	11.9		9.7		5.6		ns	ns	ns	ns
AST	(IU/l)	’03[e]	19.6		19.4		20.6		ns	ns	ns	ns
		’08[e]	19.9	ns	19.2	ns	20.7	ns	ns	ns	ns	ns
		Δ	0.5		0.0		0.7		ns	ns	ns	ns
ALT	(IU/l)	’03[e]	16.3		17.7		23.7		*	ns	↑	↑
		’08[e]	18.5	↑	19.9	↑	24.6	ns	*	ns	↑	↑
		Δ	3.0		2.9		3.4		ns	ns	ns	ns
γ-GTP	(IU/l)	’03[e]	25.2		25.3		32.9		*	ns	↑	↑
		’08[e]	27.7	ns	27.9	↑	36.3	↑	*	ns	↑	↑
		Δ	3.2		4.6		5.1		ns	ns	ns	ns
FPG	(mg/100 ml)	’03	90.1		91.1		93.0		ns	ns	ns	ns
		’08	93.0	ns	92.3	↑	93.3	ns	ns	ns	ns	ns
		Δ	2.9		1.2		0.3		ns	ns	ns	ns
HbA1c	(%)	’03	4.6		4.6		4.7		ns	ns	ns	ns
		’08	4.9	↑	4.9	↑	4.9	↑	ns	ns	ns	ns
		Δ	0.3		0.3		0.2		ns	ns	ns	ns
UA	(mg/100 ml)	’03	5.2		5.5		5.7		*	↑	ns	↑
		’08	5.6	↑	5.9	↑	6.2	↑	*	ns	ns	↑
		Δ	0.4		0.4		0.5		ns	ns	ns	ns

[a]Comparison between 2003 and 2008 values is by paired *t*-test; an arrow is for $p<0.01$ (upward for increase and downward for decrease), and ns is for $p \geq 0.01$.
[b]Classification by BMI is Lean for BMI<18.5 for Lean, 18.5≤BMI<25.0 for normal, and BMI≥25.0 for obese group, respectively. Values in the table are AMs unless otherwise specified.
[c]Comparison by ANOVA followed by post-hoc test (Scheffé). * and ns for p<0.01and ns is for $p \geq 0.01$.
[d]Abbreviations are as under Table 1.
[e]GM values; comparison is after logarithmic conversion.

Table 3. Number of cases meeting metabolic syndrome criteria

	No. of cases	No. of cases meeting the metabolic syndrome criteria[a]											
		BMI (≥25)[b]	Dyslipidemia			Hypertension			Hyperglycemia	No. of item(s) meeting the criteria[c]			
			TG (≥150 mg/100 ml)	HDL-C (<40 mg/100 ml)	TG and/or HDL-C	SBP (≥130 mmHg)	DBP (≥85 mmHg)	SBP and/or DBP	FPG (≥110 mg/100 ml)	1	2	3	2 or 3
Total	804	57	79	16	85	128	99	169	28	201	33	5	38
	(%)	(7.1)	(9.8)	(2.0)	(10.6)	(15.9)	(12.3)	(21.0)	(3.5)	(25.0)	(4.1)	(0.6)	(4.7)
Classification by 2003 BMI[d]													
Lean (L)	63	0	2	2	3	9	5	13	4	16	2	0	2
	(%)	(0.0)	(3.2)	(3.2)	(4.8)	(14.3)	(7.9)	(20.6)	(6.3)	(25.4)	(3.2)	(0.0)	(3.2)
Normal (N)	666	9	64	10	68	104	75	134	21	155	28	4	32
	(%)	(1.4)	(9.6)	(1.5)	(10.2)	(15.6)	(11.3)	(20.1)	(3.2)	(23.3)	(4.2)	(0.6)	(4.8)
Obese (O)	75	48	13	4	14	15	19	22	3	30	3	1	4
	(%)	(64.0)	(17.3)	(5.3)	(18.7)	(20.0)	(25.3)	(29.3)	(4.0)	(40.0)	(4.0)	(1.3)	(5.3)

[a]Evaluation was made by use of the data in 2008.
[b]BMI (≥25) is considered in place of waist circumference (≥85 cm).
[c]BMI category is not taken into account.
[d]Classification by BMI is BMI<18.5 for lean, 18.5≤BMI<25.0 for normal, and BMI≥25.0 for obese subjects, respectively.

Possible difference in developing MS-risk factors among the three groups of different body composition

The risk to develop MS-related factors during the 5 yr period was compared in the lean, normal and obese groups (Table 3). As a majority of the subjects was in the normal group (666 cases) and those in the lean (63 cases) or obese group (75 cases) were limited, the risk was compared in terms of percentages.

The proportion of developing over-all risk (i.e., having two out of three individual risks of dyslipidemia, hypertension and hyperglycemia) was 3.2, 4.8 and 5.3% for the lean, normal and obese group, respectively (the right-most column in Table 3). Whereas the percentage appeared to increase from the lean, normal to obese group, the difference was statistically insignificant (p>0.10) when examined by χ^2 test. Those who met at least one criterion were 5 or more times larger than those with ≥2 criteria, which was taken to suggest that there existed abundant possible candidates (or reserves) to meet the full criteria later in life. The reserve was not nil even in the lean group although the percentage for the lean or normal group was lower than that for the obese group (the right-most one-third in Table 3). Among the three individual criteria, hypertension criterion was most frequently met through-out the three groups, whereas TG sub-criterion was met by 17% of the obese people.

In order to gain better statistical power, the 804 subjects were divided by BMI into three groups (BMI<21.1, between the two extremes, and >22.7) of an equal size, and subjected to similar analyses as in Table 3. Those who met the full criteria were 7, 10 and 21 subjects in the 1st, 2nd and 3rd tercile groups, respectively. The trend to increase as a function of greater BMI was significant (p<0.01) when examined by Cochran-Armitage test.

Factors related to an increase in BMI

In order to identify factors associated with an increase in BMI, multiple regression analysis was conducted taking ΔBMI as a dependent variable, and age in 2003 and increments (Δ) in each of the 12 clinical parameters as independent variables (thus, 13 independent variables; enzymic parameters were after logarithmic conversion). The results with total 804 subjects (i.e., three groups in combination) showed that three dyslipidemia-related parameters (i.e., triglyceride, HDL-C and LDL-C) were the most influential independent variables followed by two enzymic parameters (p<0.01 for all). R^2 was as large as 0.4, and r (0.634) was statistically significant (p<0.01). Contrary to expectation, age was not an influential independent variable (p>0.10) for ΔBMI. Simple regression analyses of age with other 12 parameters were also essentially insignificant (|r|<0.14) except that ΔSBP showed significant correlation with age (r=0.326, p<0.01).

Discussion

The present analyses of changes in a 5-yr period among the male workers apparently healthy at the baseline survey made it clear that the risk of developing MS is present not only among obese workers (with BM≥25) but also in workers with normal body composition (18.5 ≤BMI<25) and even in lean subjects (BMI<18.5). The proportions for the lean, normal and obese subjects who met with MS criteria in 5 yr were 3.2, 4.8 and 5.3%, respectively. The ratio did not differ from each other statistically ($p>0.10$), although the ratio appeared to increase in accordance with BMI values, and the trend was significant ($p<0.01$) when the 804 cases were classified into BMI-based tertile groups for comparison. Thus the analyses clearly show that the MS risk does exist even in the lean or normal group. Kawamoto *et al*.[28] also reported, in preventing atherosclerosis, the importance of examining subjects who were with normal or slightly elevated BMI.

Multiple regression analysis showed that the changes in three dyslipidemia parameters of TG, HDL-C and LDL-C was most influential to the increase in BMI among non-obese (i.e., lean+normal) group as expected, whereas the influence of age was not statistically significant. In other words, care to prevent MS risks should not be limited to aged people but expanded equally to younger subjects. In agreement with the present observation, Matsuoka *et al*.[11] analyzed data of routine health examination on transportation workers and concluded that anti-MS health guidance should be given to workers younger than 40 yr of age, as to the older workers.

Possible MS-related health risks among those with lean or normal body composition has been calling attention in these 10 yr. Karelis *et al*.[29] classified obesity into three categories in comparison with healthy subjects who are normal both in body composition and in metabolism, i.e., 'at risk' obese, metabolically obese with normal weight, and metabolically normal but obese. Here physical obesity is represented by high BMI and body fat mass, whereas metabolic obesity is characterized by high visceral fat and TG with low insulin sensitivity. Thus, in spite of normal BMI, metabolically obese subjects may have high visceral fat, high TG and low insulin sensitivity. De Lorenzo *et al*.[30] could identify 'normal-weight obese syndrome' cases in women who were normal in weight and BMI, but fat mass was in excess of 30% of body weight. In contrast, the presence of physically obese but metabolically normal cases[31] should also be considered who are high in BMI, but low in visceral fat and TG with high HDL-C.

There are several major draw-backs in the study. First of all, the follow-up rate was low (39.4%) in the present study. This was primarily due to a long follow-up period of 5 yr when the turn-over among the working population was high. Nevertheless, preliminary analyses ruled out biomedically meaningful selection bias as discussed above. Secondly, no waist circumference data were available for the baseline time of the year 2003, and BMI was employed as a surrogate. This lack of data was due to the fact that the baseline items were set up before the legal enactment of the health examination system which includes the circumference measurement. A preliminary analysis with 2008 data has shown that a significant correlation ($p<0.01$) existed between the two parameters as expected (see the Subjects and Materials section). Nevertheless, it is known that the employment of BMI alone may lead to misclassification of obesity[32] as discussed above.

The sizes of the lean and obese groups (63 and 75 subjects, respectively) were much smaller than that for the normal group (666 subjects), being only about 10% each of the latter. The small sizes are basically due to the fact that apparently healthy subjects were selected in 2003 and it is rather natural that a majority of the selected belonged to the normal group. Nevertheless, it would be desired for better statistical power to have more non-normal subjects in conducting comparison, as the results of tercile analysis suggested. A research is under progress to confirm the present conclusions with a cohort of an expanded scale.

Lastly, data from routine health examination were employed in the present analyses with no additional examination items such as body fat mass and insulin sensitivity. Thus, it was not possible to carry out in-depth analysis in possible mechanism for pathological findings among the subjects of non-obese body composition[29, 30].

Conclusions

It is clear from the present analysis that the risk of developing MS is present not only among obese workers with BM≥25 but also in workers with normal body composition 18.5≤BMI<25 and even in lean subjects with BMI<18.5. The effort to prevent metabolic syndrome should be directed not only to obese but to non-obese workers, and the care should be extended irrespective of ages.

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