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Research article

Association of cardiorespiratory fitness with elevated hepatic enzyme and liver fat in Japanese patients with impaired glucose tolerance and type 2 diabetes mellitus

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Abstract
No study has so far determined whether a favorable level of cardiorespiratory fitness (CF) contributes to a reduced risk of elevated hepatic enzymes and a high degree of liver fat in patients having various metabolic risks. This study investigated the association between the maximal oxygen uptake (VO_2 max) and the prevalence of elevated liver enzymes and high liver fat, while considering such factors as abdominal obesity, hyperinsulinemia and the other metabolic risks. The study enrolled newly diagnosed Japanese patients (n = 84; 52 males and 32 females; aged 25-69 years) with impaired glucose tolerance (IGT) and type 2 diabetes mellitus (Type2DM) who did not receive any intervention or pharmacological therapy. The subjects were divided into 3 groups according to the distribution of the VO_2max for each sex. The odds ratios (ORs) for the prevalence of elevated aspartate and alanine aminotransferase (AST and ALT) and high degree of liver fat adjusted for age, sex, disease type, daily ethanol intake, and current smoking were significantly lower in the moderate- and high CF groups in comparison to the low CF group. In addition, a significant OR for AST was maintained in the moderate and high CF group after adjusting for abdominal obesity and/or hyperinsulinemia. The significant ORs for the prevalence of elevated ALT and a high degree of liver fat were attenuated after adjusting for abdominal obesity and/or hyperinsulinemia. No significant OR for the prevalence of elevated gamma-glutamyl transferase (GGT) was recognized in all logistic models. These results indicated that CF was negatively and independently associated with the prevalence of elevated AST even in Japanese diabetic patients having various metabolic risks. It was concluded that the AST level might be useful as a simple marker reflecting physical inactivity in such subjects.

Key words: Cardiorespiratory fitness, hepatic enzyme, non-alcoholic fatty liver, abdominal obesity, insulin resistance.

Introduction

Hepatic enzymes are primary indices for the diagnosis of non-alcoholic fatty liver disease (NAFLD), which is noticed as one of phenotypes of metabolic syndrome (André et al., 2007). Furthermore, elevated hepatic enzymes have been noted as a predictor of metabolic syndrome, type 2 diabetes mellitus (Type2DM) and cardiovascular disease (André et al., 2006; Cho et al., 2007; Doi et al., 2007, Monami et al., 2008; Nakanishi et al., 2004; Rector et al., 2008; Sattar et al., 2004). Hepatic enzymes might therefore be a general marker reflecting the pathology of these diseases.

On the other hand, cardiorespiratory fitness (CF), which is a direct index of physical activity, plays a role of suppressing the onset of type 2 DM, metabolic syndrome, cardiovascular diseases and mortality (LaMonte et al., 2005; Lakka et al., 2002; Sawada et al., 2003; Sui et al., 2007; Lyerly et al., 2009). In addition, recent cross-sectional studies reported an inverse association between CF and NAFLD (Church et al., 2006; Lawlor et al., 2005; Nguyen-Duy et al., 2003; Perseghin et al., 2007). It is therefore naturally expected that a favorable level of CF might be related not only with a low prevalence of NAFLD, but also elevated levels of hepatic enzymes.

A recent study (Messier et al., 2010) has demonstrated that metabolically healthy but obese women who were in the upper quartile of insulin sensitivity values had significantly lower concentrations of ALT, AST, and GGT as well as a lower fatty liver index in comparison to individuals in the lower 3 quartiles. However, this study did not evaluate either the physical activity or CF. A survey performed on adults aged 17 yrs of age or older in US (n = 15676) (Clark et al., 2003) reported unexplained aminotransferase elevation, which was significantly associated with a higher body mass index, waist circumference, triglyceride levels, fasting insulin, and lower HDL. It is well-known that these indices are strongly influenced by physical activity; however, no description regarding lifestyle was made in that report. Furthermore, the most of those studies are conducted in normal populations, and no study has yet investigated the impact of the maximal oxygen uptake on both liver fat and liver enzymes while taking other metabolic risks into consideration in specific subjects having a number of metabolic abnormalities.

The current study therefore investigated whether the prevalence of high degree of liver fat and elevated liver enzymes could be associated with low level of CF in newly diagnosed impaired glucose tolerance (IGT) and Type2DM patients with various metabolic risks but not consuming excessive amounts of alcohol.

Methods

Subjects

One hundred fifty-seven Japanese outpatients (114 males and 43 females, aged 25 to 81 years) who were newly-diagnosed to have IGT and Type2DM based on a 75g oral glucose tolerance test (75g OGTT) participated in the present study. The pathological state was classified based

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on the diagnostic criteria of the Committee of Japan Diabetes Society (Kuzuya et al., 2002). Though 2-24 months passed from the time that the patients were noted to have an elevated blood glucose level at a group medical checkup, none of the subjects had received pharmacological therapy or intervention until the diagnosis.

The patients answered a questionnaire to assess their alcohol consumption and current smoking habits. The type, amount, and frequency of alcohol consumption were assessed, from which the total amount of alcohol consumption was calculated and converted to the daily ethanol intake. Sixty-five subjects whose daily ethanol intake was more than 20g in males and 10g in females (Hashimoto, 2004), were excluded from the analysis. In addition, any cases including missing data needed for an analysis (n = 8) were also excluded. Finally, the data of 84 patients (52 male and 32 female, aged 25 to 69 years) were used for the analysis of the present study. Informed consent was obtained from each patient and the study was approved by The Ethics Committee of Institute of Health Science in Kyushu University.

Anthropometric measurement and protocol for computed tomography

The BMI was calculated as the weight (kilograms) divided by height (meters) squared. The waist circumference was measured at the level of the umbilicus. The visceral (VFA) and subcutaneous fat areas (SFA) were assessed by computed tomography (CT; VIGOR LAU DATOR, Toshiba, Japan). The subjects were examined following overnight fasting and in the supine position. Scanning was performed using the usual clinical assessment settings, i.e., 120kV and 200mA, 400mm field of view, 5mm thickness, and 2sec scanning time. The regions of interest were determined by the clinical specialists by tracing an outline of the adipose tissue on the CT image at the umbilical level. The whole abdominal and visceral fat areas were computed automatically based on the pixels for the X-ray attenuation range of these areas (Tokunaga et al., 1983). The SFA values were derived by subtracting the VFA from the whole abdominal fat area. In addition, liver fat deposition was evaluated using a CT image including both the liver and spleen derived from the twelfth thoracic vertebra level to the second lumbar vertebra level. The analysis of the mean CT attenuation values derived for the liver and spleen were performed by clinical specialists in diagnostic imaging. The ratio of the liver/spleen attenuation value (L/S ratio) was defined as an index of liver fat (Church et al., 2006).

Measurements of clinical data

Following overnight fasting of at least 9 hrs, blood samples were drawn from antecubital vein for the analysis as below; sampling tubes of EDTA 2K-NaF and plain were used. A 75g OGTT was performed on the subjects' blood samples obtained at 30, 60, 120, and 180 minutes. The fasting insulin and fasting blood glucose concentrations were measured using a radioimmunoassay and an enzymatic method, respectively. The levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were determined as indices of the hepatic function, using a method recommended by the Japanese Society of Clinical Chemistry for determining the catalytic amounts of enzymes. Tests for hepatitis B or C virus and other liver diseases were performed on the subjects whose AST and/or ALT were over 100 IU/L. The levels of fasting triglyceride, total cholesterol, and high-density lipoprotein cholesterol were assessed using an enzymatic method. The resting systolic (SBP) and diastolic blood pressure (DBP) were determined 3 times following a 30-minute rest period using a mercury sphygmomanometer, with the lowest values used as the resting blood pressure. The subjects newly diagnosed to have IGT or Type2DM were instructed to undergo an anthropometric evaluation and a fitness test within 2 to 3 weeks following the diagnostic tests.

Criteria for abnormalities of parameters

The definition of elevated liver enzymes based on a statement by The Ministry of Health, Labour and Welfare in Japan, 2007. The abnormal criteria for each enzyme were as follows; elevated AST: AST > 30U/L, elevated ALT: ALT > 30U/L, and elevated GGT: GGT > 50U/L. Furthermore, a patient with an L/S ratio less than 0.9, which is a cutoff value usually adopted in domestic medical institutions (Hashimoto, 2006), was regarded as having high liver fat.

Patients whose VFA levels were more than 100 cm^2 were defined as having excess visceral fat (The Examination Committee of Criteria for "Obesity Disease" in Japan, 2002). The fasting insulin equivalent was determined to be 7μU/mL, a 75th percentile value of fasting insulin in Japanese male workers (Tamakoshi et al., 2003) as the basic criteria for hyperinsulinemia in this study.

Evaluation of cardiorespiratory fitness

Graded exercise tests were performed by a skilled examiner using a cycle ergometer (Monark, Stockholm, Sweden) to evaluate the CF. The heart rate, electrocardiogram, and blood pressure were monitored and recorded during the test. The exercise intensity was increased 3 or 4 times every 4 minutes until the heart rate reached 70% of the maximum or higher. Maximal oxygen uptake (VO_2max), which is regarded as an index of CF, was determined according to the nomogram of Åstrand & Rhyming (1954), a modality that is generally used to predict the VO_2max.

The distributions of VO_2max were divided into tertiles in each sex. The details regarding the range in each group were as follows; the lowest tertile (Low-CF group): $VO_2max \leq 31.8$ml/kg/min in males and $VO_2max \leq 26.2$ in females; the intermediate tertile (Moderate-CF group): $31.8 < VO_2max \leq 35.6$ in males and $26.2 < VO_2max \leq 30.2$ in females; and the highest tertile (High-CF group): $VO_2max > 35.6$ in males and $VO_2max > 30.2$ in females.

Statistical analysis

An analysis of variance (ANOVA) was performed to compare continuous variables of the subjects classified by CF level. TG, fasting glucose and insulin, AST, ALT, and GGT had a skewed distribution and were therefore analyzed following log-transformation. A comparison of categorical variables was analyzed using chi-square analysis. The odds-ratio (OR) and 95% confidence inter-

val (95%CI) for the prevalence of any abnormalities in each group were calculated using 4 logistic regression models. First, ORs adjusted for age, sex, disease type, daily ethanol intake, and smoking as basic confounding factors for the prevalence of these abnormalities were calculated (Model-1). After the analysis using Model-1, the ORs were adjusted for abdominal obesity or hyperinsulinemia (Model-2 and 3), finally, adjustments for both abdominal obesity and hyperinsulinemia were added (Model-4). All statistical analyses were performed using the SPSS version 14.0 software program (SPSS Japan Inc.). Statistical significance was set at a value of $p < 0.05$.

Results

Characteristics of the subjects divided by the CF level

Characteristics of all subjects and those classified by CF levels are indicated in Table 1. The distribution of the subjects' VO_2max was observed to have shifted slightly to a lower level and the whole range was narrower than that in the Japanese healthy population.

The mean value of the VFA in all the subjects ($160.4 \pm 63.2 cm^2$) was substantially higher than the Japanese criteria for abdominal obesity ($\geq 100 cm^2$). The mean value of the fasting insulin level ($7.4 \pm 4.7 \mu U/ml$) was as high as the mean value of the top quartile in Japanese male workers (Tamakoshi et al., 2003). Prevalence of elevated AST, ALT and GGT in all subjects was 23, 49 and 31%, respectively. The subjects having elevated AST accounted for 48, 14 and 7% in the high, moderate and low CF group, respectively. The elevated ALT in each group accounted for 74, 41 and 32%, in addition, the elevated GGT was accounted for 37, 35 and 21%, respectively. Further, prevalence of high liver fat in all subjects was 21%, and 41, 14 and 11% in each fitness level, respectively. The Abdominal and liver fatness, fasting insulin, AST and ALT levels showed a gradual decrease according to the increase of CF level.

Analysis of the prevalence of abnormalities in the groups classified by CF level

As indicated in Table 2, The ORs for the prevalence of elevated AST in the moderate- and high CF group were significantly low in all models in comparison to the low CF group; the ORs ranged from 0.06 to 0.14. The ORs for an elevated ALT in the moderate- and high CF group were also significantly low in model 1, which ranged from 0.15 to 0.25. Model 2 showed a significant OR for elevated ALT only in high CF group. However, the significant ORs were attenuated after adjusting for only hyperinsulinemia (model 3), and after adjusting for both abdominal obesity and hyperinsulinemia (model 4). The ORs for an elevated GGT showed no significance in any group. The OR for high liver fat in the high CF group was significantly low in comparison to the low CF group (OR: 0.21) in model 1; however, the ORs in the other models adjusted for abdominal obesity and/or hyperinsulinemia showed no significance in any group.

Discussion

The main finding in the current study was that a favorable level of CF contributed to the attenuation of the elevated

Table 1. Comparison of characteristics of subjects classified by fitness level.

Continuous variables	All subject (M=52, F=32)		Fitness level Low (M=18, F=9)		Moderate (M=17, F=12)		High (M=17, F=11)		p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (yrs)	50.9	10.7	47.4	11.5	53.6	10.4	51.4	9.6	N.S.
BMI ($kg \cdot m^{-2}$)	25.1	4.1	27.7	4.4	24.8	3.2	22.9	3.2	< .001
Waist girth (cm)	88.4	10.1	94.3	10.8	88.0	7.5	83.0	8.8	< .001
Daily ethanol intake (g)	3.0	5.2	1.7	3.6	3.9	5.5	3.4	6.1	N.S.
Type 2 DM (%)	60.0 (71.4)		20.0 (74.1)		21.0 (72.4)		19.0 (67.9)		
Current smoking (%)	26.0 (31.0)		10.0 (37.0)		6.0 (20.7)		10.0 (35.7)		N.S.
Visceral fat area (cm^2)	160.4	63.2	197.6	70.4	155.2	44.9	129.8	55.2	< .001
Subcutaneous fat area (cm^2)	172.1	86.0	202.1	104.1	165.7	78.6	149.8	66.7	N.S.
L / S ratio †	1.03	0.26	0.90	0.28	1.09	0.17	1.08	0.26	< .005
AST (U/L)	26.3	12.5	33.9	14.3	22.6	8.9	22.8	10.6	< .001
ALT (U/L)	38.8	31.0	57.6	39.3	29.3	17.3	30.5	25.3	< .001
GGT (U/L)	43.7	26.8	53.0	31.9	42.2	25.7	36.3	19.7	N.S.
VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)	32.1	5.7	27.5	3.8	31.1	3.0	37.5	4.9	< .001
Total cholesterol (mg/dL)	217.6	35.9	211.0	39.1	226.6	31.2	214.7	36.8	N.S.
Triglyceride (mg/dL)	134.4	78.3	140.1	77.8	127.9	67.2	135.5	90.8	N.S.
HDL-C (mg/dL)	51.4	12.5	47.1	11.0	55.3	14.9	51.6	10.1	N.S.
Fasting glucose (mg/dL)	136.1	33.5	136.3	41.8	140.9	32.8	131.0	24.3	N.S.
Fasting insulin (μU/mL)	7.4	4.7	10.3	5.8	6.3	3.3	5.6	3.3	< .001
Systolic blood pressure (mmHg)	127	17	133	16	124	18	124	17	N.S.
Diastolic blood pressure (mmHg)	80	11	84	11	79	11	76	9	< .05

Abbreviations are denoted in text. Data are expressed as means±S.D. or number of patients. The percentage in each group is shown in parenthesis. One-way ANOVA or Chi-square test was performed for statistical analysis. N.S. not significant.

Table 2. Odds ratios for the elevated hepatic enzymes and NAFL in the groups classified by fitness level (n = 84).

	Model 1 [a]			Model 2 [b]			Model 3 [c]			Model 4 [d]		
	OR	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Elevated AST												
Moderate CF	**.11**	**.02-.55**	**.007**	**.12**	**.02-.58**	**.009**	**.13**	**.02-.78**	**.025**	**.14**	**.02-.85**	**.033**
High CF	**.06**	**.01-.36**	**.002**	**.06**	**.01-.42**	**.004**	**.07**	**.01-.49**	**.008**	**.07**	**.01-.58**	**.013**
Elevated ALT												
Moderate CF	**.25**	**.06-.94**	**.041**	.28	.07-1.07	.063	.48	.11-2.02	.314	.52	.12-2.29	.390
High CF	**.15**	**.04-.58**	**.006**	**.20**	**.05-.83**	**.027**	.29	.07-1.25	.096	.39	.09-1.79	.226
Elevated GGT												
Moderate CF	.99	.28-3.47	.981	1.08	.31-3.81	.906	1.15	.29-4.65	.842	1.30	.32-5.25	.714
High CF	.52	.14-1.90	.320	.66	.17-2.53	.545	.60	.14-2.52	.488	.78	.18-3.37	.740
High liver fat												
Moderate CF	.35	.08-1.49	.155	.37	.09-1.63	.191	1.04	.18--5.86	.963	1.06	.19-5.92	.950
High CF	**.21**	**.05-.99**	**.048**	.28	.06-1.33	.109	.62	.10-3.63	.592	.77	.12-4.77	.778

These odds ratios are referring for that in the low CF group. Abbreviations are denoted in text. [a]: Adjusted for age, sex, disease type, daily ethanol intake and current smoking. [b]: Added adjusting for abdominal obesity to the Model 1. [c]: Added adjusting for hyperinsulinemia to the Model 1. [d] Added adjusting for abdominal obesity and hyperinsulinemia to the Model 1. CI: confidence interval.

AST, independent of the pathology frequently observed in the diabetic subjects. The prevalence of elevated AST was below one fourth of all subjects, whereas one half of them were included in the low CF group. On the other hand, the association of elevated ALT or high liver fat with CF depended on the presence of abdominal obesity and/or hyperinsulinemia in diabetic subjects. No association found between CF level and elevated GGT.

It is highly important to identify the difference in the strength of association with CF among these enzymes. This remains a matter for speculation, but might be due to a difference in the location of these enzymes. While ALT and GGT exist mainly in hepatic cells, AST exists not only in the hepatic cells, but also in cardiac and muscle cells. In the current study, the prevalence of elevated AST among the subjects with a high degree of liver fat was 50%, which was obviously lower than that in the subjects demonstrating both high liver fat and elevated ALT or GGT (88.9 and 72.2%, respectively). It is speculated that AST might therefore reflect either cell injury or inflammation beside hepatic tissue in such subjects having various metabolic abnormalities. At this point, the robust inverse relationship between CF and elevated AST can be attributed to the findings of recent studies reporting an inverse association of directly measured CF and such inflammation markers as C-reactive protein, fibrinogen and cytokine, etc (Kullo et al., 2007; Jae et al., 2008). In addition, a recent clinincal study showed a significant correlation between the carotid intimal media thickness and hepatic enzymes, including AST (Abdou et al., 2009). However, these explanations remain mere speculation. Further accumulation of evidence is thus needed to clarify the association between the CF and AST levels in the future.

On the other hand, ALT which mainly exists in the hepatic cells might be directly affected by higher levels of liver fat, which is related to both abdominal fat and insulin resistance (Messier et al., 2010). Results from recent animal experiments, which examined the effect of daily aerobic exercise (Rector et al., 2008), the cessation of exercise (Rector et al., 2008) and a genetically low aerobic capacity (Thyfault et al., 2009) to the hepatic oxidative capacity, are all consistent with the hypothesis that regular aerobic exercise or a favorable CF improve the hepatic oxidative capacity. Such evidence could therefore help us to explain both the low prevalence of high liver fat and the elevated ALT levels observed in the high CF group. However, the prevalence of both abnormalities was dependent on abdominal obesity and/or hyperinsulinemia rather than on the CF level in diabetic subjects; the result in the current study agreed with that in the prior-mentioned study (Messier et al., 2010).

No association between CF and elevated GGT found in the logistic model adjusted for basic confounders including disease type. Considerable number of prospective studies reported elevated GGT was a strong predictor of Type 2 DM (André et al., 2005, André et al., 2006, André et al., 2007, Doi et al, 2007, Lee et al., 2003, Nakanishi et al., 2004). The GGT level was closely correlated with the insulin level in the present study ($r = 0.452$, $p < 0.0001$, data not shown). Taking these evidences into consideration, it was speculated that GGT level in diabetic subjects was affected by insulin resistance rather than aerobic capacity strongly reflecting muscle oxidative capacity and cardiac function.

The present study has some limitations. The design of the study was cross-sectional and thus unable to identify causality between CF and elevated hepatic enzymes or high liver fat. In addition, the results of the current study were derived from diabetic patients; it should not be regarded as phenomena in healthy population. The VO_2max data was calculated using heart rate during exercise, thus few errors in the values of VO_2max might occur, though VO_2max measurements were performed by a skilled examiner. The daily ethanol intake was self-reported, and may therefore be biased or inaccurate. Tests for hepatitis B or C virus were only performed for the patients who were suspected of having these viruses. At least a 3-year treatment regimen by the subjects' primary doctor and at least a 1-year follow-up of lifestyle modification was performed for almost all subjects after the assessment of the present study; however, no onset of hepatitis B or C was recognized.

Conclusion

The current study is thus considered to demonstrate, for the first time, a favorable level of cardiorespiratory fitness could contribute to a reduced risk of elevated aminotransferase and high liver fat in Japanese patients newly diagnosed as IGT or type 2 DM. An independent and inverse association between the CF level and the prevalence of an elevated AST level was observed, the possibility that AST may potentially be useful as a simple marker concerning physical inactivity should therefore be assessed. Prospective cohort studies in the general population, exercise-intervention for high-risk populations, and a biochemical approach are required to address the effect of physical activity on both the hepatic enzyme levels and liver fat levels in the future.

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Key points

- The prevalence of elevated AST was negatively, and strongly associated with the CF level independent of abdominal obesity, hyperinsulinemia, and the other confounders in the subjects with glucose intolerance.
- The association between the CF level and both an elevated ALT level and a high degree of liver fat, as defined by the L/S ratio of CT images depended on abdominal fat and/or hyperinsulinemia in the subjects with glucose intolerance.
- No association was recognized between CF and elevated GGT in the subjects with glucose intolerance in the subjects with glucose intolerance.
- Having a favorable level of CF could lead to a reduced risk of hepatic-related abnormalities even in diabetic patients having the other metabolic risks.

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