[Environmental Health and Preventive Medicine 9, 243–250, November 2004]

Original Article

Low Fasting Serum Insulin in Japanese Alcohol Consumers Does Not Imply Improved Coronary Risk Factors

Yuichi YAMADA[1], Yuka NOBORISAKA[1], Masao ISHIZAKI[1], Ikiko TSURITANI[1] and Ryumon HONDA[1]

[1]*Department of Social and Environmental Medicine (Hygiene), Kanazawa Medical University, Ishikawa, Japan*

Abstract

Objective: The effects of alcohol consumption on coronary risk factors (CRFs) and insulin resistance (IR) have seemed equivocal in previous studies. This study aimed to clarify the implications of low fasting blood insulin observed in alcohol consumers as related to CRFs and IR.

Methods: A cross-sectional observation in 2133 middle-aged healthy Japanese men for associations of increases in alcohol consumption, fasting serum insulin concentration and serum gamma-glutamyltransferase (GGT) activity with the major CRFs of high systolic blood pressure (SBP), fasting serum glucose, triglycerides (TG), total- and LDL-cholesterol (tCh & LDLc) and low serum HDL-cholesterol (HDLc).

Results: Increased alcohol consumption was related to higher SBP, serum GGT, glucose and HDLc, and lower serum LDLc and insulin. Although high serum insulin was significantly related to all of the CRFs in all nondrinkers, moderate drinkers consuming up to 59 ml of alcohol per day and excessive drinkers consuming more, the means of SBP, serum glucose and HDLc were significantly higher and serum LDLc was lower in drinkers than in nondrinkers at any level of serum insulin, indicating that the good and bad profiles of CRFs in alcohol consumers are independent of their low fasting serum insulin. High serum GGT related to increased alcohol consumption and/or body weight was significantly associated with high serum insulin and all of the CRFs in all categories of alcohol consumption.

Conclusions: Low fasting serum insulin observed in drinkers does not imply improved CRFs, and thus may not imply improved IR. High serum GGT may reflect increased IR in both drinkers and nondrinkers.

Key words: alcohol consumption, insulin, glucose, coronary risk factors, insulin resistance, serum gamma-glutamyltransferase.

Introduction

Moderate alcohol consumption may protect not only against the development of coronary heart disease (1–3) but also type-2 diabetes mellitus (4–8) and the metabolic syndrome (9, 10), which are considered to be related to a high insulin resistance (IR) state. On the other hand, alcohol consumers, particularly those having an elevated serum gamma-glutamyltransferase (GGT) level, show a high risk of developing hypertension (11–13), type-2 diabetes (14–16) and the metabolic syndrome (17–19). The effects of alcohol consumption, particularly moderate consumption, on the development of coronary risk factors (CRFs) and IR, therefore, have seemed equivocal in previous epidemiological studies.

On the other hand, the exact measurement of IR, such as by insulin clamp method, is time-consuming, while even intravenous or oral glucose load tests are impractical for large-scale population studies. The most widely used method for assessing IR in populations is measuring insulin concentration in the fasting blood, or calculating an IR index from fasting blood insulin and glucose concentrations based on the homeostasis model assessment (HOMA-IR) (20). Recent studies have demonstrated that fasting blood insulin and HOMA-IR are lower in alcohol consumers than in non-consumers (21–25), and which has been advocated as evidence of improved insulin sensitivity in moderate alcohol consumers (21, 24). However, blood pressure and glucose concentrations in the blood are

Received Apr. 26, 2004/Accepted Jul. 8, 2004
Reprint requests to: Yuichi YAMADA
Department of Social and Environmental Medicine (Hygiene), Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, 920-0293 Japan
TEL: +81(76)286-8001, FAX: +81(76)286-9723
E-mail: u1yamada@kanazawa-med.ac.jp

often elevated in drinkers showing low blood insulin (21, 25), and thus the implications of the low fasting blood insulin observed in drinkers as related to the improvements of CRFs and IR remain unclear.

In the present study, the associations of alcohol consumption, fasting serum insulin concentration and serum GGT activity with the major CRFs of high systolic blood pressure (SBP), serum triglycerides (TG), total-cholesterol (tCh), LDL-cholesterol (LDLc) and low serum HDL-cholesterol (HDLc) were analyzed and compared between alcohol-consuming and non-consuming middle-aged healthy Japanese men, to clarify the implications of low fasting blood insulin observed in alcohol consumers.

Methods

The target middle-aged healthy men were recruited from an occupational population presented in our previous studies (19, 25). Among the 2656 male workers aged between 35 and 64 years, 276 men who had been confirmed by health records to have diseases possibly affecting the study results, such as cardiovascular disease, non-alcoholic liver disease or renal disease, or dyslipidemia, diabetes mellitus or hypertension being treated with medicines, were excluded from the study subjects. Furthermore, 121 men who did not have records of any of these diseases but showed a body mass index (BMI) of 30 kg/m^2 or higher, blood pressure (BP) of 180/110 mmHg or higher, or fasting serum glucose of 126 mg/dl (7.0 mmol/l) or higher in the health check-ups, were excluded to avoid the effects of marked obesity, severe hypertension and latent diabetes mellitus on the study results. Because of incompleteness of measurements in the health check-ups, 126 men were further excluded. In total, 2133 middle-aged men were defined as the healthy male subjects. Written informed consent was obtained from all subjects.

Details regarding the measurements of body height, weight and BP in the subjects, and the collection, storage and analyses of fasting serum samples for glucose, hepatic enzymes, lipids and insulin were mentioned in our previous studies. Briefly, BP was measured with a sphygmomanometer in the sitting position after resting in a chair for 5 minutes or longer. Serum glucose concentration (mg/dl or mmol/l) was measured with a hexokinase/glucose-6-phosphate dehydrogenase method using an automatic analyzer (HITACHI 7450, Hitachi, Japan). Serum GGT activity (U/l) and serum concentrations of TG, tCh and HDLc (mg/dl) were also measured using the automatic analyzer. Serum LDLc was calculated as tCh—HLDc—TG/5 in the subjects showing serum TG of less than 400 mg/dl (26). Serum insulin concentration (μU/ml) was measured with an enzyme immunoassay using an automatic analyzer, IMx (Dinabot, Japan). The detectable limit of this method was 0.8 μU/ml, and all of the subjects showed a concentration above the limit. HOMA-IR was calculated according to the following formula: insulin (μU/ml)×glucose (mmol/l)/22.5. The data of serum GGT, TG, insulin and HOMA-IR were logarithmically transformed for statistical analyses.

The data of alcohol and cigarette consumption and physical activity at leisure time were obtained by a questionnaire and confirmed by experienced nurses. According to the usual alcohol consumption during the preceding year, the subjects were classified into five categories, namely, nondrinkers including those consuming alcohol only less than once a month and those who had quit drinking, drinkers consuming once a month or more but less than 30 ml of alcohol per day on average, and those consuming 30–59 ml, 60–89 ml, and 90 ml or more but not exceeding 120 ml per day. Drinkers who consumed less than 60 ml of alcohol per day were named moderate drinkers and those consuming more as excessive drinkers. Cigarette consumption was classified into five categories, nonsmokers, ex-smokers, current smokers consuming less than 1 pack a day, and those consuming less than 2 packs, and 2 packs or more. Physical activity at leisure was classified into four categories, namely, doing any kind of exercise lasting 30 minutes or longer not more often than once a month, once a week or less, 2 to 4 times a week, or 5 times or more a week. According to the categories, the subjects were scored 0–4 for cigarette consumption and 0–3 for physical activity in the statistical analyses.

The means of SBP, serum GGT, TG, tCh, HDLc, LDLc, glucose and insulin, and HOMA-IR in the five categories of alcohol consumption and those in the quintiles of fasting serum insulin concentration and serum GGT activity distributions were calculated and tested for differences by a generalized linear model (GLM) analysis adjusting for the effects of age, BMI and lifestyle factors. In multiple comparisons, the difference was tested by a method of Least Square Difference. Furthermore, the associations of fasting serum insulin and serum GGT with the CRFs were observed separately in the three alcohol consumption categories of nondrinkers, moderate and excessive drinkers, with adjustment for age and lifestyle factors but not for BMI, and the differences in the means of the CRFs in the three alcohol consumption categories and in the five serum insulin and GGT levels were also tested by a GLM analysis. A program package of SPSS version 11.0 for Windows (SPSS Japan, Tokyo) was used for these statistical analyses, and $p<0.05$ was defined as significant.

Results

The means and standard errors (SEs) of age and BMI, and those of the major CRFs, such as SBP, fasting serum TG, tCh, HDLc, LDLc, glucose and insulin concentrations, and HOMA-IR as well as serum GGT activity in the subjects of the five categories of alcohol consumption are shown in Table 1. The mean age of the subjects consuming 60–89 ml of alcohol per day was significantly higher than those in the other categories of alcohol consumption, while BMI was not different among the five categories. The means of the CRFs were adjusted for the effects of age, BMI and the scores of cigarette consumption and physical activity at leisure time. A significant difference was found in the prevalence of smokers and physically inactive subjects among the five categories of alcohol consumption (25). The means of SBP, serum GGT, HDLc and glucose were significantly increased, while serum LDLc and insulin and HOMA-IR were significantly decreased with increases in alcohol consumption. No significant differences were found in the means of serum TG and tCh in the five categories. SBP, serum GGT and HDLc were significantly higher in drinkers, even those

consuming less than 30 ml of alcohol per day, than in nondrinkers, serum LDLc was significantly lower in those consuming 30 ml or more of alcohol, and serum glucose was higher in those consuming 60 ml or more. A significantly lower mean as compared to that in nondrinkers was found in all categories of drinkers for serum insulin, and in those consuming 30 ml or more for HOMA-IR.

Table 2 shows the means and SEs of age and BMI, and those of the CRFs in the subjects of the five serum insulin levels, corresponding to the quintiles of the serum insulin distribution in the subjects as follows: 0.8–2, 3, 4, 5–6, and 7–75 μU/ml. The means of age in the subjects were significantly lower in the higher quintiles of serum insulin than in the lower quintiles, while those of BMI were significantly higher in the higher quintiles. After adjustments for age, BMI, alcohol and cigarette consumption, and physical activity, all of the means of the CRFs were significantly different in the five serum insulin levels. SBP was significantly higher in the subjects showing a serum insulin of 4 μU/ml or above, and serum GGT was significantly higher in the highest quintile of 7–75 μU/ml in comparison with that in the lowest quintile of 0.8–2 μU/ml. A linear increase with increases in serum insulin was observed in the means of serum TG, glucose and HOMA-IR, and a linear decrease in those of serum HDLc. The means of serum tCh and LDLc were markedly low in the lowest quintile of serum insulin, but the means in the upper four quintiles did not mark-

Table 1 Means and standard errors (SE) of age and BMI, and those of systolic BP, serum GGT activity, fasting serum lipids, glucose and insulin concentrations and HOMA-IR with adjustment for age, BMI, cigarette consumption and physical activity at leisure time in middle-aged healthy men, divided by the average volume of alcohol consumed per day

	Nondrinker n=538		Less than 30 ml/day n=479		30–59 ml n=581		60–89 ml n=375		90 ml or more n=160		
Parameters	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	ρ[a]
Age (years)	44.4	0.28	44.4	0.30	44.9	0.27	45.7	0.34[b]	44.7	0.52	0.015
BMI (kg/m^2)	23.1	0.11	23.0	0.12	22.9	0.11	23.2	0.13	23.1	0.20	0.410
Systolic BP (mmHg)	116	0.5	118	0.6[b]	118	0.5[b]	121	0.6[b]	124	1.0[b]	<0.001
Serum GGT (U/l)[c]	17.8	1.03	21.6	1.03[b]	25.8	1.02[b]	34.7	1.03[b]	37.4	1.05[b]	<0.001
TG (mg/dl)[c]	100	1.02	99	1.02	96	1.02	98	1.03	101	1.04	0.551
tCh (mg/dl)	204	1.4	205	1.5	203	1.4	203	1.7	202	2.6	0.804
HDLc (mg/dl)	45.4	0.51	49.4	0.54[b]	51.8	0.49[b]	55.2	0.61[b]	56.7	0.94[b]	<0.001
LDLc (mg/dl)[d]	136	1.4	132	1.4	129	1.3[b]	124	1.6[b]	120	2.5[b]	<0.001
glucose (mg/dl)	88.2	0.38	89.2	0.40	88.9	0.37	91.8	0.46[b]	90.9	0.70[b]	<0.001
insulin (μU/ml)[c]	4.9	1.02	4.5	1.03[b]	4.2	1.02[b]	4.1	1.03[b]	4.0	1.04[b]	<0.001
HOMA-IR[c]	1.05	1.02	0.99	1.02	0.93	1.02[b]	0.92	1.03[b]	0.88	1.05[b]	<0.001

[a] Significance of the difference in the means of the five alcohol consumption categories.
[b] Significant difference ($p<0.05$) in comparison with the means of nondrinkers.
[c] Geometric means and geometric standard errors.
[d] Serum LDLc was calculated only in the subjects showing serum TG of less than 400 mg/dl.
[e] For the definitions of abbreviations, refer to text.

Table 2 Means and standard errors (SE) of age and BMI, and those of systolic BP, serum GGT activity, fasting serum lipids and glucose concentrations and HOMA-IR with adjustment for age, BMI, alcohol and cigarette consumption and physical activity at leisure time in middle-aged healthy men, divided by the quintiles of fasting serum insulin (μU/ml) distribution

	Serum insulin 0.8–2 μU/ml n=375[a]		3 μU/ml n=393		4 μU/ml n=352		5–6 μU/ml n=501		7–75 μU/ml n=512		
Parameters	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	ρ[b]
Age (years)	45.6	0.34	45.3	0.33	45.0	0.35	44.4	0.29[c]	44.1	0.29[c]	0.002
BMI (kg/m^2)	21.2	0.12	22.3	0.11[c]	22.7	0.12[c]	23.6	0.10[c]	24.6	0.10[c]	<0.001
Systolic BP (mmHg)	116	0.7	117	0.6	119	0.7[c]	119	0.6[c]	121	0.6[c]	<0.001
Serum GGT (U/l)[d]	24.1	1.03	22.2	1.03	24.0	1.03	23.7	1.03	27.9	1.03[c]	<0.001
TG (mg/dl)[d]	79	1.03	87	1.03[c]	95	1.02[c]	105	1.03[c]	124	1.04[c]	<0.001
tCh (mg/dl)	198	1.8	204	1.7[c]	204	1.8[c]	206	1.5[c]	205	1.6[c]	0.020
HDLc (mg/dl)	54.8	0.64	52.1	0.59[c]	51.5	0.62[c]	49.3	0.52[c]	47.0	0.55[c]	<0.001
LDLc (mg/dl)[e]	125	1.7	132	1.6[c]	131	1.7[c]	133	1.4[c]	129	1.5	0.003
glucose (mg/dl)	86.1	0.47	87.7	0.44[c]	89.3	0.46[c]	89.9	0.39[c]	92.9	0.41[c]	<0.001
HOMA-IR[d]	0.40	1.03	0.65	1.03[c]	0.87	1.03[c]	1.19	1.03[c]	2.18	1.03[c]	<0.001

[a] Considerable difference in the number of subjects at each quintile was due to rounding the decimal fraction.
[b] Significance of the difference in the means of the five serum insulin levels.
[c] Significant difference ($p<0.05$) in comparison with the means of the lowest quintile of serum insulin.
[d] Geometric means and geometric standard errors.
[e] Serum LDLc was calculated only in the subjects showing serum TG of less than 400 mg/dl.
[f] For the definitions of abbreviations, refer to text.

edly differ from each other. The similar means of serum tCh and LDLc in the upper four quintiles may have reflected the adjustments for BMI, because more linear associations of serum insulin with serum tCH and LDLc were observed in the analyses not adjusted for BMI, although not shown in the table.

Table 3 shows the means and SEs of age and BMI, and those of the CRFs in the quintiles of serum GGT distribution: 6–13, 14–17, 18–25, 26–39, and 40–507 U/l. The means of age were not significantly different in the five serum GGT levels, but the means of BMI were increased with increases in the serum GGT level. The means of the CRFs were adjusted for age, BMI, alcohol and cigarette consumption, and physical activity. Except for low serum HDLc, all of the other CRFs were significantly increased with increases in serum GGT levels in a linear manner, with the exception of slightly lower serum LDLc (130 mg/dl) in the highest serum GGT level as compared to the next highest level (135 mg/dl). The means of serum HDLc were higher at higher serum GGT levels, although the differences were barely significant (p=0.049). However, this positive association between serum GGT and HDLc may have also reflected the adjustments for BMI, because an inverse association between them was observed in the analysis not adjusted for BMI.

Table 4 shows the means of age and BMI in the quintiles of serum insulin and serum GGT distributions in the three alcohol consumption categories of nondrinkers, moderate drinkers

Table 3 Means and standard errors (SE) of age and BMI, and those of systolic BP, fasting serum lipids, glucose and insulin concentrations and HOMA-IR with adjustment for age, BMI, alcohol and cigarette consumption and physical activity at leisure time in middle-aged healthy men, divided by the quintiles of serum GGT (U/l) distribution

	Serum GGT 6–13 U/l n=370[a]		14–17 U/l n=393		18–25 U/l n=515		26–39 U/l n=420		40–507 U/l n=435		
Parameters	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	ρ[b]
Age (years)	44.7	0.34	44.6	0.33	44.8	0.29	44.6	0.32	45.2	0.31	0.660
BMI (kg/m^2)	21.9	0.13	22.5	0.12[c]	23.0	0.11[c]	23.5	0.12[c]	24.0	0.12[c]	<0.001
Systolic BP (mmHg)	116	0.7	117	0.6	117	0.5	119	0.6[c]	122	0.6[c]	<0.001
Serum TG (mg/dl)[d]	78	1.03	87	1.03[c]	97	1.02[c]	106	1.03[c]	128	1.04[c]	<0.001
tCh (mg/dl)	195	1.8	199	1.7	202	1.4[c]	210	1.6[c]	212	1.7[c]	<0.001
HDLc (mg/dl)	50.2	0.65	49.4	0.60	50.2	0.52	51.2	0.58	51.9	0.60	0.049
LDLc (mg/dl)[e]	126	1.7	129	1.6	129	1.4	135	1.5[c]	130	1.6	0.009
glucose (mg/dl)	87.7	0.46	88.8	0.45	89.3	0.39[c]	90.2	0.44[c]	90.9	0.43[c]	<0.001
insulin (μU/ml)[d]	3.8	1.03	4.1	1.03	4.4	1.02[c]	4.7	1.03[c]	5.0	1.03[c]	<0.001
HOMA-IR [d]	0.81	1.03	0.88	1.03	0.97	1.03[c]	1.04	1.03[c]	1.13	1.05[c]	<0.001

[a] Considerable difference in the number of subjects at each quintile was due to rounding the decimal fraction.
[b] Significance of the difference in the means of the five serum GGT levels.
[c] Significant difference (p<0.05) in comparison with the means of the lowest quintile of serum GGT.
[d] Geometric means and geometric standard errors.
[e] Serum LDLc was calculated only in the subjects showing serum TG of less than 400 mg/dl.
[f] For the definitions of abbreviations, refer to text.

Table 4 Numbers (N), means (M) and standard errors (SE) of age and BMI in middle-aged healthy men divided by alcohol consumption and the quintiles of fasting serum insulin concentration (μU/ml) or those of serum GGT activity (U/l)

Alcohol consumption	Serum insulin	0.8–2 μU/ml			3 μU/ml			4 μU/ml			5–6 μU/ml			7–75 μU/ml			Significance[a]
		N	M	(SE)	N	M	(SE)	N	M	(SE)	N	M	(SE)	N	M	(SE)	(Alc/Ins/A*I)
Nondrinker	Age (years)	67	45.1	(0.79)	84	45.6	(0.71)	90	45.3	(0.69)	132	44.2	(0.57)	165	43.1	(0.51)	For age
	BMI (kg/m^2)		20.7	(0.27)		21.9	(0.24)		22.1	(0.23)		23.5	(0.19)		24.8	(0.17)	(#/*/ns)[c]
Up to 59 ml/day	Age (years)	183	45.7	(0.48)	210	45.1	(0.45)	177	44.6	(0.49)	252	44.3	(0.41)	238	43.9	(0.42)	For BMI
	BMI (kg/m^2)		21.2	(0.17)		22.3	(0.15)		22.9	(0.17)		23.4	(0.14)		24.3	(0.15)	(**/**/ns)
60 ml/day or more	Age (years)	125	45.8	(0.58)	99	45.4	(0.65)	85	45.5	(0.71)	117	44.7	(0.60)	109	45.8	(0.62)	
	BMI (kg/m^2)		21.4	(0.20)		22.5	(0.11)		23.1	(0.24)		23.9	(0.21)		24.9	(0.21)	
Alcohol consumption	Serum GGT	6–13 U/l			14–17 U/l			18–25 U/l			26–39 U/l			40–507 U/l			Significance[b]
		N	M	(SE)	N	M	(SE)	N	M	(SE)	N	M	(SE)	N	M	(SE)	(Alc/G/A*G)
Nondrinker	Age (years)	178	44.5	(0.49)	118	44.6	(0.60)	127	44.4	(0.58)	79	44.1	(0.73)	36	43.7	(1.09)	For age
	BMI (kg/m^2)		21.8	(0.18)		22.8	(0.22)		23.7	(0.21)		24.4	(0.27)		24.9	(0.40)	(ns/ns/ns)
Up to 59 ml/day	Age (years)	168	45.1	(0.50)	219	44.3	(0.44)	276	44.6	(0.39)	211	44.6	(0.45)	186	44.9	(0.48)	For BMI
	BMI (kg/m^2)		22.1	(0.19)		22.4	(0.16)		22.8	(0.15)		23.5	(0.17)		23.9	(0.18)	(**/**/*)
60 ml/day or more	Age (years)	24	43.5	(1.33)	56	46.1	(0.87)	112	45.7	(0.62)	130	44.8	(0.57)	213	45.7	(0.45)	
	BMI (kg/m^2)		21.6	(0.49)		22.2	(0.32)		22.7	(0.23)		23.0	(0.21)		23.9	(0.17)	

[a] Significance of the effects of alcohol consumption (Alc), serum insulin levels (Ins) and the interaction (A*I) on the means of age and BMI.
[b] Significance of the effects of alcohol consumption (Alc), serum GGT levels (G) and the interaction (A*G) on the means of age and BMI.
[c] ns: not significant (p≧0.10), #: 0.10>p≧0.05, *: p<0.05, **: p<0.01.

consuming up to 59 ml of alcohol per day, and excessive drinkers consuming more. Mean age was significantly higher in the lower quintiles of serum insulin than in the higher quintiles, and slightly higher in alcohol consumers than in non-consumers at the serum insulin level, although not significantly (p=0.085). The means of BMI were significantly higher in the higher quintiles of serum insulin in both drinkers and nondrinkers, but were significantly higher in drinkers than in nondrinkers, particularly in the lower quintiles of serum insulin. Therefore, the differences in the means of BMI between the low and high serum insulin levels seemed larger in nondrinkers than in drinkers, although the interactive effect of serum insulin with alcohol consumption on BMI level was not significant (p=0.10). On the other hand, no significant difference in mean age was found either among the quintiles of serum GGT or between drinkers and nondrinkers at any serum GGT level. BMI was significantly higher in the higher quintiles of serum GGT in both drinkers and nondrinkers, but the increase in BMI with increases in serum GGT was more marked in nondrinkers than in drinkers, and the interaction of serum GGT with alcohol consumption on BMI was significant (p=0.045).

Considering the complicated associations between serum insulin, GGT, alcohol consumption and BMI in further analyses on the associations of serum insulin and GGT levels with CRFs separately in the three alcohol consumption categories, the means of the CRFs were adjusted for age, smoking and physical activity, but not for BMI. The changes in the means of SBP, serum TG and HDLc with increases in serum insulin levels in the nondrinkers, and moderate and excessive drinkers are illustrated in Fig. 1. The means of SBP and serum TG were significantly elevated, while those of serum HDLc were decreased with increases in serum insulin in all three categories of alcohol consumption. The means of SBP were 2–3 mmHg and 7–8 mmHg higher, and those of serum HDLc were 6 mg/dl and 10 mg/dl higher, respectively, in the moderate and excessive drinkers in comparison with nondrinkers at any serum insulin level. The means of serum TG were similar in the moderate drinkers and nondrinkers, and the differences in the three alcohol consumption categories were not significant (P=0.07). Although not shown in the figure, the association of serum insulin with the means of serum glucose was quite similar to that with SBP, i.e., there was much higher serum glucose in drinkers than in nondrinkers at any level of serum insulin; also, the association with serum tCh was similar to that with serum TG, and the association with serum LDLc mirrored that with serum HDLc, i.e., there was much lower serum LDLc in drinkers than in nondrinkers at any level of serum insulin. The associations of HOMA-IR with these CRFs were similar to those of serum insulin.

Figure 2 shows the means of serum insulin, glucose and HDLc concentrations in the nondrinkers, and moderate and excessive drinkers at the five serum GGT levels. Serum insulin

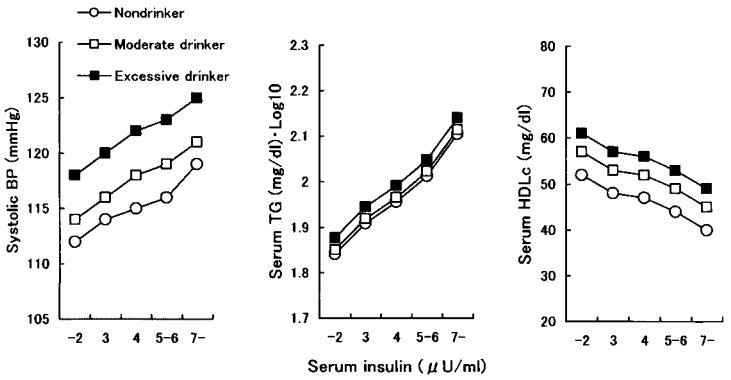

Fig. 1 The means of systolic blood pressure, serum triglycerides and HDL-cholesterol in the quintiles of fasting serum insulin distribution.
Open circles represent nondrinkers, open squares moderate drinkers consuming less than 60 ml of alcohol per day, and closed squares excessive drinkers consuming more.

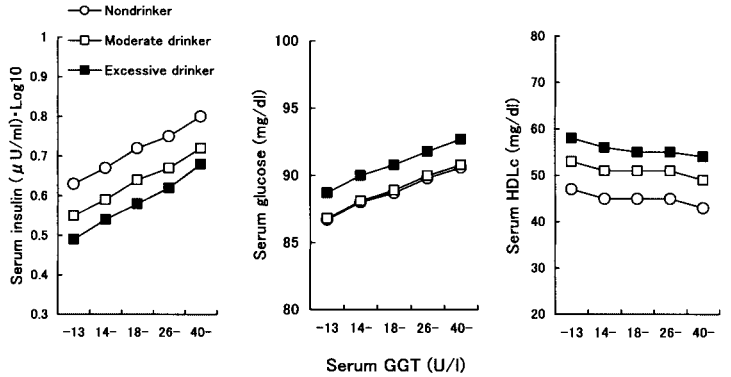

Fig. 2 The means of fasting serum insulin, glucose and HDL-cholesterol concentrations in the quintiles of serum gamma-glutamyltransferase (GGT) distribution.
Open circles represent nondrinkers, open squares moderate drinkers consuming less than 60 ml of alcohol per day, and closed squares excessive drinkers consuming more.

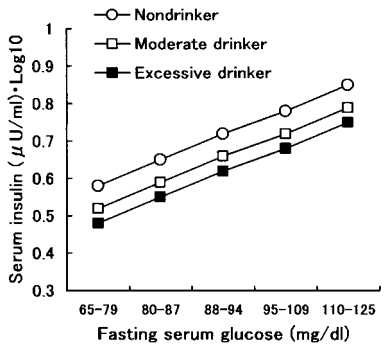

Fig. 3 The means of fasting serum insulin in the five levels of fasting serum glucose.
Open circles represent nondrinkers, open squares moderate drinkers consuming less than 60 ml of alcohol per day, and closed squares excessive drinkers consuming more.

was elevated with elevations of serum GGT in all three categories of alcohol consumption, accompanied by much higher means in nondrinkers than in drinkers at any level of serum GGT. Although the means of serum glucose concentration were significantly different among the three categories of alcohol consumption, the means were very similar between the moderate drinkers and the nondrinkers at the level of serum GGT. Serum HDLc was decreased with increases in serum GGT in all categories of alcohol consumption, with much higher means in drinkers than in nondrinkers at any level of serum GGT. Although not illustrated, BP showed an association with serum GGT similar to that of serum glucose, and serum TG showed an association similar to that of serum insulin with GGT. The changes in serum LDLc also mirrored those of serum HDLc. A quite similar linear association between serum GGT and tCh was observed in all three categories of alcohol consumption.

Figure 3 shows the association between fasting serum glucose and insulin concentrations in nondrinkers, and moderate and excessive drinkers. The five fasting serum glucose levels were defined here as 65–79 mg/dl (normal low), 80–87, 88–94, 95–109 (normal high) and 110–125 (impaired glucose tolerance), considering a possible pathogenic role of upper-normal blood glucose in hypertension (27). The numbers of the subjects in these categories were 240, 711, 645, 470 and 67, respectively. The means of serum insulin were adjusted for age, cigarette consumption and physical activity, but not for BMI. Although elevations of serum glucose were related to increases in the means of serum insulin in all three alcohol consumption categories, the means of serum insulin were significantly lower in drinkers than in nondrinkers, and lower in larger volume alcohol consumers at any level of serum glucose.

Discussion

It is advocated that moderate alcohol consumption improves IR, thereby helping to protect against the development of coronary heart disease, mainly based on the low fasting blood insulin observed in alcohol consumers (21, 24). The present study showed a dose-dependent decrease in traditional indicators of IR, i.e., fasting serum insulin and HOMA-IR, with increases in alcohol consumption up to 120 ml per day in middle-aged healthy Japanese men. At the same time, however, significantly higher SBP was found even in drinkers consuming less than 30 ml of alcohol per day, and higher fasting serum glucose in drinkers consuming 60 ml or more, in comparison with those in nondrinkers, respectively (Table 1). These findings are in good accordance with those of Kiechl et al. (21) in 820 middle-aged healthy Italian men and women consuming up to 100 g or more of alcohol per day.

Previous studies on the associations of alcohol consumption with fasting serum insulin and glucose concentrations, however, have shown considerably different results. Razzay and Heaton (24) observed decreased fasting serum insulin in drinkers consuming 21–30 g of alcohol per day in comparison with that in nondrinkers, while it was high in those consuming 40 g or more. Lu et al. (28) observed lower fasting serum glucose in American Indians consuming 60 ml or more of alcohol per day than in nondrinkers. These discrepancies suggest the considerable influence of factors other than the average volume of alcohol consumed on the fasting blood insulin and glucose concentrations, possibly including selection of the subjects, their age and race, or their nutrition or drinking pattern (29). At least, in the middle-aged healthy Japanese men, the disparity between low fasting serum insulin and high serum glucose concentrations observed in the drinkers consuming 60 ml or more of alcohol per day indicates that low serum insulin in large volume alcohol consumers does not imply improved IR.

Further analyses showed that although higher serum insulin was related to higher CRFs in all of the nondrinkers, and moderate and excessive drinkers, the means of SBP and serum glucose and HDLc were higher, while serum LDLc was lower in drinkers than in nondrinkers at any level of serum insulin, and the differences were more marked in consumers of more alcohol (Table 2 & Fig. 1). These results indicate that although elevations of serum insulin are related at least in part to higher CRFs and thus may reflect higher IR in both drinkers and nondrinkers, the good and bad profiles of CRFs in alcohol consumers are not directly related to their low fasting serum insulin, but to the volume of alcohol consumed. Low fasting serum insulin, even in moderate alcohol consumers, therefore, does not imply improved CRFs and thus may not imply improved IR.

On the other hand, elevated serum GGT was related to increases in all of the CRFs in all of the nondrinkers, and moderate and excessive drinkers (Table 3 & Fig. 2), which is in accordance with the significant associations between elevated serum GGT and the major CRFs irrespective of alcohol consumption previously observed in middle-aged Japanese men and women (15, 17, 19). Although fasting serum insulin concentration was lower in drinkers than in nondrinkers at any serum GGT level, the positive association between serum insulin and GGT in both drinkers and nondrinkers indicates that elevations of serum GGT are related at least in part to increases in IR, irrespective of alcohol consumption. Elevations of serum GGT, which in healthy people must reflect the development of hepatic steatosis due to alcohol consumption or obesity or both, are considered to be related to hepatic IR and then systemic IR (30, 32).

As shown in Fig. 3, the fasting serum insulin concentration

corresponding to the level of fasting serum glucose was lower in alcohol consumers than in non-consumers, and lower in larger volume alcohol consumers. Since glucose concentration in blood directly influences insulin secretion from the pancreas (32), these findings suggest that insulin secretion from the pancreas in response to increases in blood glucose is different between drinkers and nondrinkers, i.e., decreases with increases in alcohol consumption, and thus the implication of fasting serum insulin as an index of IR would no longer be identical between alcohol consumers and non-consumers. The findings of Arima et al. (33), showing a significant association of fasting serum insulin with hypertension in nondrinkers but not in drinkers, are consistent with this contention. The primary effect of alcohol consumption on glucose metabolism is the suppression of gluconeogenesis from the liver (34) due to consumption of NAD, a coenzyme utilized in producing glucose from pyruvate or glycerol in the liver. The suppressed gluconeogenesis from the liver in alcohol consumers may have some correlation to low insulin secretion from pancreatic beta cells. Direct effects of alcohol on the beta cells are also possible, but in any case the exact mechanisms remain unknown.

Although the limitations inherent in any cross-sectional study should be considered, the present results indicate that the low fasting serum insulin observed in alcohol consumers is not related to their good or bad profiles of major CRFs, and suggest that the implication of fasting serum insulin as an indicator of IR in alcohol consumers is different between alcohol consumers and non-consumers. The nature of a change in IR, whether decreased or increased, induced by alcohol consumption continues to be a contentious issue, and requires investigation by methods other than measurements of fasting blood insulin.

References

(1) Colditz GA, Branch LG, Lipnick RJ, et al. Moderate alcohol and decreased cardiovascular mortality in an elderly cohort. Am Heart J. 1985; 109: 886–889.

(2) Dyer AR, Stamler J, Paul O, et al. Alcohol consumption and 17-year mortality in the Chicago Western Electronic Company Study. Prev Med. 1980; 9: 78–90.

(3) Marmot MG, Rose G, Shipley MJ, Thomas BJ. Alcohol and mortality: A U-shaped curve. Lancet. 1981; I: 580–583.

(4) Nakanishi N, Suzuki K, Tatara K. Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. Diabetes Care. 2003; 26: 48–54.

(5) Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle-aged British men. Brit J Med. 1995; 310: 560–564.

(6) Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. Brit J Med. 1995; 310: 555–559.

(7) Tsumura K, Endo G, Hayashi T, Fujii S, Suematsu C, Okada K. Daily alcohol consumption and the risk of type 2 diabetes in Japanese men. The Osaka Study. Diabetes Care. 1999; 22: 1432–1437.

(8) Wei M, Kampert JB, Gibbons LW, Blair SN, Mitchell TL. Alcohol intake and incidence of type 2 diabetes in men. Diabetes Care. 2000; 23: 18–22.

(9) Dixon JB, Dixon ME, O'Brien PE. Alcohol consumption in the severely obese: relationship with the metabolic syndrome. Obes Res. 2002; 10: 245–252.

(10) Rosell M, De Faire U, Hellenius ML. Low prevalence of the metabolic syndrome in wine drinkers—is it the alcohol beverage or the lifestyle? Eur J Clin Nutr. 2003; 57: 227–234.

(11) Lee DH, Ha MH, Kim JR, Gross M, Jacobs DR. Gamma-glutamyltransferase, alcohol, and blood pressure: a four year follow-up study. Ann Epidemiol. 2002; 12: 90–96.

(12) Miura K, Nakagawa H, Nakamura H, et al. Serum gamma-glutamyl transferase level in predicting hypertension among male drinkers. J Hum Hypertens. 1994; 8: 445–459.

(13) Yamada Y, Ishizaki M, Kido T, et al. Alcohol, high blood pressure, and serum γ-glutamyl transpeptidase level. Hypertension. 1991; 18: 819–826.

(14) Lee DH, Ha MH, Kim JH, et al. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. Diabetol. 2003; 46: 359–364.

(15) Nakanishi N, Nishina K, Li W, Sato M, Suzuki K, Tatara K. Serum gamma-glutamyltransferase and development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. J Intern Med. 2003; 254: 287–295.

(16) Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum γ-glutamyltransferase and risk of NIDDM. Diabetes Care. 1998; 21: 732–237.

(17) Hashimoto Y, Futamura A, Nakarai H, Nakahara K. Relationship between response of γ-glutamyl transpeptidase to alcohol drinking and risk factors for coronary heart disease. Atherosclerosis. 2001; 158: 465–470.

(18) Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesaniemi YA. Gamma-glutamyl transpeptidase and the metabolic syndrome. J Intern Med. 2000; 248: 230–238.

(19) Yamada Y, Noborisaka Y, Suzuki H, Ishizaki M, Yamada S. Alcohol consumption, serum gamma-glutamyltransferase levels, and coronary risk factors in a middle-aged occupational population. J Occup Health. 2003; 45: 293–299.

(20) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentration in man. Diabetol. 1985; 28: 412–419.

(21) Kiechl S, Willeit J, Poewe W, et al. Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). Brit Med J. 1996; 313: 1040–1041.

(22) Lazarus R, Sparrow D, Weiss ST. Alcohol intake and insulin levels. The Normative Aging Study. Am J Epidemiol. 1997; 145: 909–916.

(23) Mayer EJ, Newman B, Quesenberry CP, Friedman G, Selby JV. Alcohol consumption and insulin concentrations. Role of insulin in association of alcohol intake with high-density lipoprotein cholesterol and triglycerides. Circulation. 1993; 88 [part 1]: 2190–2197.

(24) Razzay G, Heaton KW. Moderate alcohol consumption has been shown previously to improve insulin sensitivity in men. Brit J Med. 1997; 314: 443–444.
(25) Yamada Y, Noborisaka Y, Ishizaki M, Tsuritani I, Honda R, Yamada S. Alcohol consumption, homeostasis model assessment indices and blood pressure in middle-aged healthy men. J Hum Hypertens. 2004; 18: 343–350.
(26) Friedewald WT. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of preparative ultracentrifuge. Clin Chem. 1972; 18: 499–509.
(27) Cubeddu LX, Hoffman IS. Insulin resistance and upper-normal glucose levels in hypertension: a review. J Hum Hypertens 2002; 16 (Suppl 1): S52–S55.
(28) Lu W, Jablonski KA, Resnick HE, et al. Alcohol intake and glycemia in American Indians: The Strong Heart Study. Metabolism. 2003; 52: 129–135.
(29) Dorn JM, Hovey K, Muti P, et al. Alcohol drinking patterns differentially affect central adiposity as measured by abdominal height in women and men. J Nutr. 2003; 133: 2655–2662.
(30) Mayes PA. Gluconeogenesis and control of the blood glucose. In: Murray RK, Granner DK, Mayes PA, Rodwell VW eds. Harper's Biochemistry 25th ed. New York: McGraw-Hill, 2000: 208–218.
(31) den Boer M, Voshol PJ, Kuipers F, Havekes LM, Romjin JA. Hepatic steatosis: a mediator of the metabolic syndrome. Lessons from animal models. Artherioscler Thromb Vasc Biol. 2004; 24: 644–649.
(32) Saglam K, Kilic R, Yilmaz MI, Gulec M, Baykal Y, Kutlu M. Insulin resistance in patients with steatohepatitis. Hepatogastroenterology. 2003; 50: 456–459.
(33) Arima H, Kiyohara Y, Kato I, et al. Alcohol reduces insulin-hypertension relationship in a general population. The Hisayama study. J Clin Epidemiol. 2002; 55: 863–869.
(34) Bell DSH. Alcohol and the NIDDM patient. Diabetes Care. 1996; 19: 509–513.