Table 3 – Logistic analysis of 11β-HSD1 SNPs with the risk of metabolic syndrome adjusted by age and sex (both) or by age (men or women).

	MS n/n' (%)	Control n/n' (%)	OR (95%C.I.)	P	Pcorr
Both					
+9410T>A	61/370 (14.2)	91/686 (11.7)	1.5 (1.0–2.2)	0.041	NS
+17925C>T	249/182 (57.8)	453/324 (58.3)	1.0 (0.7–1.2)	0.683	NS
+27447G>C	118/313 (27.4)	199/578 (25.6)	1.1 (0.8–1.4)	0.632	NS
Men					
+9410T>A	45/286 (13.6)	16/182 (8.1)	1.9 (1.1–3.5)	0.029	NS
Women					
+9410T>A	16/84 (16.0)	75/504 (13.0)	1.1 (0.6–2.1)	0.683	NS

MS: metabolic syndrome, n: number of minor homozygote and heterozygote, n': number of major homozygote, %: $n/(n+n') \times 100$, 95%C.I.: 95% confidence interval.
Odds ratio and 95%C.I. is expressed as per copy of the minor allele for additive model.
Pcorr is P values after Bonferroni correction.
NS means not significance.

and age (OR = 1.5 for allelic effect, 95%C.I., 1.0–2.2; $P = 0.041$ and Bonferroni corrected $P = 0.123$). In only men, +9410T>A SNP was nominally associated with metabolic syndrome, while the higher frequency of metabolic syndrome in men lead to the higher power in comparison with women. Taken together all, after considering multiple comparisons we could not find any statistically significant association between metabolic syndrome and SNPs in the HSD11B1 gene. Furthermore, we could not find any significant association between metabolic syndrome of the ATP III criteria and these three SNPs, respectively. We next performed the covariance analysis of the traits related to metabolic syndrome including BMI, waist circumference, systolic and diastolic blood pressures, fasting glucose, HbA1c, and triglyceride and HDL-cholesterol levels in person with or without the +9410T>A SNP, but the SNP did not affect these clinical parameters in total population or only men (Table 4).

Next we studied haplotypes of the HSD11B1. The association between haplotypes comprising SNP-5, -6, and -7 and metabolic syndrome revealed that any haplotype could not have a significant susceptibility to metabolic syndrome (Table 5). The ATG haplotype was nominally associated with a increased risk of metabolic syndrome in men (metabolic syndrome 7.1%, control 4.0%; OR = 1.82, 95%C.I., 1.01–3.25; $P = 0.042$ and Bonferroni corrected $P = 0.168$), while the TTG haplotype was nominally associated with a decreased risk of metabolic syndrome in men (metabolic syndrome 26.4%, control 32.6%; OR = 0.74, 95%C.I., 0.57–0.98; $P = 0.033$ and Bonferroni corrected $P = 0.132$). Although only the TTG haplotype had decreased risk effect among haplotypes with +9410T, the association of these haplotypes with metabolic syndrome is mainly explained by +9410T>A SNP.

4. Discussion

This study was a case–control study using a population-based urban Japanese cohort. Metabolic syndrome was diagnosed according to the 2005 Japanese definition [18] and the control subjects were defined as having none of the components of this syndrome. Using these criteria, we obtained 431 individuals with metabolic syndrome and 777 control subjects for

Table 4 – Comparison of clinical parameters in urban Japanese men and women ($n = 3005$) according to 11β-HSD1 gene +9410T>A genotype.

	Men ($n = 1370$)			Women ($n = 1635$)		
	TT ($n = 1180$)	TA + AA ($n = 189$)	P	TT ($n = 1400$)	TA + AA ($n = 235$)	P
BMI (kg/m^2)	24.1 ± 0.1	23.0 ± 2.9	0.502	22.9 ± 0.1	23.0 ± 0.2	0.622
Waist (cm)	87.7 ± 0.2	87.5 ± 0.6	0.800	84.4 ± 0.3	84.1 ± 0.6	0.695
SBP (mmHg)	132.6 ± 0.6	133.8 ± 1.5	0.442	129.8 ± 0.5	129.3 ± 1.3	0.686
DBP (mmHg)	79.9 ± 0.3	80.4 ± 0.8	0.587	77.1 ± 0.3	77.2 ± 0.7	0.834
FBG (mmol/l)	5.83 ± 0.04	5.96 ± 0.11	0.256	5.47 ± 0.03	5.55 ± 0.07	0.309
HbA1c (%)	5.61 ± 0.03	5.70 ± 0.07	0.233	5.45 ± 0.02	5.47 ± 0.05	0.607
TG (mmol/l)	1.47 ± 0.03	1.44 ± 0.07	0.732	1.12 ± 0.02	1.15 ± 0.04	0.582
HDLc (mmol/l)	1.35 ± 0.01	1.38 ± 0.03	0.369	1.64 ± 0.01	1.62 ± 0.03	0.418

SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, TG: triglycerides, HDLc: HDL cholesterol. Data are shown as the adjusted mean ± SE. These values were obtained after adjusting for age by the least squares method. The laboratory data reported in milligram per deciliter can be converted to SI units as follows: total cholesterol, HDL cholesterol: mg/dl × 0.02586 = mmol/l; triglycerides: mg/dl × 0.01129 = mmol/l; fasting blood glucose: mg/dl × 0.05556 = mmol/l.
P-values for the comparison between TT and TA + AA genotype groups.

Table 5 – Frequency of 11β-HSD1 gene haplotypes constructed by SNPs + 9410T>A, +17925C>T, and +27447G>C and their association with metabolic syndrome.

Gender	Haplotype	Total	MS	Control	χ^2	OR	95%C.I.	P	Pcorr
Both	TCG	0.515	0.514	0.510	0.040	1.02	0.86–1.20	0.841	NS
	TTG	0.277	0.266	0.290	1.653	0.88	0.73–1.07	0.199	NS
	TCC	0.133	0.147	0.140	0.225	1.06	0.84–1.34	0.635	NS
	ATG	0.074	0.073	0.060	1.609	1.24	0.89–1.73	0.205	NS
Men	TCG	0.509	0.526	0.477	2.323	1.21	0.95–1.56	0.128	NS
	TTG	0.280	0.264	0.326	4.563	0.74	0.57–0.98	0.033	NS
	TCC	0.138	0.139	0.157	0.617	0.87	0.61–1.23	0.432	NS
	ATG	0.073	0.071	0.040	4.141	1.82	1.01–3.25	0.042	NS
Women	TCG	0.521	0.475	0.521	1.427	0.83	0.62–1.12	0.232	NS
	TTG	0.275	0.270	0.278	0.055	0.96	0.69–1.35	0.814	NS
	TCC	0.129	0.175	0.135	2.290	1.36	0.91–2.04	0.130	NS
	ATG	0.075	0.075	0.066	0.488	1.22	0.70–2.14	0.485	NS

MS: metabolic syndrome, 95%C.I.: 95% confidence interval.
Pcorr is *P* values after Bonferroni correction.
NS means not significance.

the case–control study. We could not find any significant association between SNPs in the HSD11B1 gene and metabolic syndrome.

11β-HSD1 is expressed abundantly in adipose tissue and reactivates cortisone to cortisol [1]. Recent experiments using transgenic and knockout mice suggest that 11β-HSD1 plays a critical role in metabolic deterioration [6–9]. When cortisol generation is increased in peripheral tissues, the overall cortisol reaction is also increased. In humans, 11β-HSD1 expression is heightened in the adipose tissue of obese individuals [10]. Therefore, 11β-HSD1 is a promising target for the pharmacological inhibition in metabolic syndrome patients [11–13].

A previous study showed that a HSD11B1 gene polymorphism is associated with BMI and insulin resistance in a group of obese Pima Indian children [16] with type 2 diabetes mellitus and hypertension and reported that 11β-HSD1 mRNA concentrations were associated with adiposity [14,15]. The T → G polymorphism in the 3rd intron (rs12086634) protects against diabetes in Pima Indians [14] and reduces 11β-HSD1 gene transcription in vitro [19], which is consistent with reduced cortisol generation within cells. The rs12086634 polymorphism was completely in linkage disequilibrium with the rs932335 SNP (+27447G>C) that was analyzed in this study. We did not find a positive association between the +27447G>C SNP and metabolic syndrome in Japanese men.

There are some limitations in this study. First limitation was the Japanese criteria for metabolic syndrome, which is different from the ATP III criteria. Third, there were deviations in social factors, including age, gender, race/ethnicity, geographic location, and socioeconomic status. This cohort consisted of urban citizens residing in a subtropical area with a temperate climate. Most subjects were Asian with a higher percentage of elderly people.

In summary, the HSD11B1 gene is not associated with metabolic syndrome in Japanese. However, taken together with previous results, 11β-HSD1 might be involved in metabolic syndrome pathogenesis by modulating lipid metabolism and gluconeogenesis. Further studies are needed to investigate the role of 11β-HSD1 in metabolic syndrome.

Conflict of interest

The authors state that they have no conflict of interest.

Acknowledgments

We are grateful to the following people for their support in our population survey: Dr. Yasushi Kotani, President; Dr. Katsuyuki Kawanishu, the Co-President; other members of the Suita City Medical Association; and Mr. Kinzo Harada, Director of the City Health Center. We also thank the members of our participants' group (Satsuki-Junyu-kai) for their cooperation with and support of our survey of risk factors and prevention of cardiovascular disease. We also thank Dr. Soichiro Kitamura, President of the National Cardiovascular Center, for encouraging our work. This study was supported by the Program for the Promotion of Fundamental Studies in Health Science of the Organization for Pharmaceutical Safety and Research of Japan, the Research Grant from Special Coordination Funds for Promoting Science and Technology (JST) and the National Institute of Biomedical Innovation (NIBIO) of Japan and the Research Grant for Cardiovascular Diseases from the Ministry of Health, Labour and Welfare of Japan.

REFERENCES

[1] J.R. Seckl, B.R. Walker, Minireview: 11beta-hydroxysteroid dehydrogenase type 1-a tissue-specific amplifier of glucocorticoid action, Endocrinology 142 (2001) 1371–1376.
[2] I.J. Bujalska, S. Kumar, P.M. Stewart, Does central obesity reflect "Cushing's disease of the omentum"? Lancet 349 (1997) 1210–1213.
[3] R.S. Lindsay, D.J. Wake, S. Nair, J. Bunt, D.E. Livingstone, P.A. Permana, et al., Subcutaneous adipose 11 beta-hydroxysteroid dehydrogenase type 1 activity and messenger ribonucleic acid levels are associated with adiposity and insulinemia in Pima Indians and Caucasians, J. Clin. Endocrinol. Metab. 88 (2003) 2738–2744.

[4] M. Shimojo, M.L. Ricketts, M.D. Petrelli, P. Moradi, G.D. Johnson, A.R. Bradwell, et al., Immunodetection of 11 beta-hydroxysteroid dehydrogenase type 2 in human mineralocorticoid target tissues: evidence for nuclear localization, Endocrinology 138 (1997) 1305–1311.
[5] J.W. Tomlinson, E.A. Walker, I.J. Bujalska, N. Draper, G.G. Lavery, M.S. Cooper, et al., 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response, Endocr. Rev. 25 (2004) 831–866.
[6] H. Masuzaki, J. Paterson, H. Shinyama, N.M. Morton, J.J. Mullins, J.R. Seckl, et al., A transgenic model of visceral obesity and the metabolic syndrome, Science 294 (2001) 2166–2170.
[7] H. Masuzaki, H. Yamamoto, C.J. Kenyon, J.K. Elmquist, N.M. Morton, J.M. Paterson, et al., Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice, J. Clin. Invest. 112 (2003) 83–90.
[8] Y. Kotelevtsev, R.W. Brown, S. Fleming, C. Kenyon, C.R. Edwards, J.R. Seckl, et al., Hypertension in mice lacking 11beta-hydroxysteroid dehydrogenase type 2, J. Clin. Invest. 103 (1999) 683–689.
[9] N.M. Morton, M.C. Holmes, C. Fievet, B. Staels, A. Tailleux, J.J. Mullins, et al., Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11beta-hydroxysteroid dehydrogenase type 1 null mice, J. Biol. Chem. 276 (2001) 41293–41300.
[10] E. Rask, B.R. Walker, S. Soderberg, D.E. Livingstone, M. Eliasson, O. Johnson, et al., Tissue-specific changes in peripheral cortisol metabolism in obese women: increased adipose 11beta-hydroxysteroid dehydrogenase type 1 activity, J. Clin. Endocrinol. Metab. 87 (2002) 3330–3336.
[11] B.R. Walker, A.A. Connacher, R.M. Lindsay, D.J. Webb, C.R. Edwards, Carbenoxolone increases hepatic insulin sensitivity in man: a novel role for 11-oxosteroid reductase in enhancing glucocorticoid receptor activation, J. Clin. Endocrinol. Metab. 80 (1995) 3155–3159.
[12] R.C. Andrews, O. Rooyackers, B.R. Walker, Effects of the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes, J. Clin. Endocrinol. Metab. 88 (2003) 285–291.
[13] T.C. Sandeep, R. Andrew, N.Z. Homer, R.C. Andrews, K. Smith, B.R. Walker, Increased in vivo regeneration of cortisol in adipose tissue in human obesity and effects of the 11beta-hydroxysteroid dehydrogenase type 1 inhibitor carbenoxolone, Diabetes 54 (2005) 872–879.
[14] S. Nair, Y.H. Lee, R.S. Lindsay, B.R. Walker, P.A. Tataranni, C. Bogardus, et al., 11beta-Hydroxysteroid dehydrogenase type 1: genetic polymorphisms are associated with Type 2 diabetes in Pima Indians independently of obesity and expression in adipocyte and muscle, Diabetologia 47 (2004) 1088–1095.
[15] P.W. Franks, W.C. Knowler, S. Nair, J. Koska, Y.H. Lee, R.S. Lindsay, et al., Interaction between an 11betaHSD1 gene variant and birth era modifies the risk of hypertension in Pima Indians, Hypertension 44 (2004) 681–688.
[16] L. Gelernter-Yaniv, N. Feng, N.G. Sebring, Z. Hochberg, J.A. Yanovski, Associations between a polymorphism in the 11 beta hydroxysteroid dehydrogenase type I gene and body composition, Int. J. Obes. Relat. Metab. Disord. 27 (2003) 983–986.
[17] J. Robitaille, C. Brouillette, A. Houde, J.P. Despres, A. Tchernof, M.C. Vohl, Molecular screening of the 11beta-HSD1 gene in men characterized by the metabolic syndrome, Obes. Res. 12 (2004) 1570–1575.
[18] K. Reynolds, J. He, Epidemiology of the metabolic syndrome, Am. J. Med. Sci. 330 (2005) 273–279.
[19] N. Draper, E.A. Walker, I.J. Bujalska, J.W. Tomlinson, S.M. Chalder, W. Arlt, et al., Mutations in the genes encoding 11beta-hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase interact to cause cortisone reductase deficiency, Nat. Genet. 34 (2003) 434–439.

Atherosclerosis 209 (2010) 290–294

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Triglycerides and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort: The Suita study

Tomonori Okamura[a,*], Yoshihiro Kokubo[a], Makoto Watanabe[a], Aya Higashiyama[a], Yuu Ono[a], Yoshihiro Miyamoto[b], Yasunao Yoshimasa[b], Akira Okayama[c]

[a] Department of Preventive Cardiology, National Cardiovascular Center, Osaka, Japan
[b] Department of Atherosclerosis and Diabetes, National Cardiovascular Center, Osaka, Japan
[c] The First Institute for Health Promotion and Health Care, Japan Anti-tuberculosis Association, Tokyo, Japan

ARTICLE INFO

Article history:
Received 15 July 2009
Received in revised form 18 August 2009
Accepted 3 September 2009
Available online 12 September 2009

Keywords:
Triglycerides
Myocardial infarction
Stroke
Cohort studies
Lipids and lipoprotein

ABSTRACT

Objective: The impact of elevated triglycerides (TG) and non-high density lipoprotein cholesterol (non-HDLC) on the incidence of stroke and myocardial infarction (MI) has not been well evaluated in Asian populations such as in Japan, which have a lower incidence of myocardial infarction, but a higher risk of stroke than Western populations.
Methods: The authors conducted an 11.7-year prospective study ending in 2005 of 5098 Japanese aged 30–79 living in an urban population, initially free of stroke or MI. The relationship between serum lipids and the risk for stroke and MI was determined by dividing the participants into four groups stratified by the combination of serum levels of TG and non-HDLC. The cut-off value was 1.7 mmol/L for TG and 4.9 mmol/L for non-HDLC.
Results and conclusion: The total person-years were 59,774 (27,461 for men and 32,313 for women). During the follow-up period, there were 113 cases of MI and 180 of stoke (with 116 cerebral infarctions). Compared with the low TG/low non-HDLC group, the hazard ratio (95% confidence interval) for MI in the high TG/high non-HDLC group was 2.55 (1.53–4.24) after adjustment for other cardiovascular risk factors. The hazard ratio for cerebral infarction in the high TG alone group was 1.63 (1.03–2.56); however, the risk of cerebral infarction was not significantly increased in the other groups. High serum levels of TG and non-HDLC are both important targets for the prevention of cardiovascular disease in Japan.

1. Introduction

Previous studies suggested that high levels of serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) are causal risk factors for coronary artery disease (CAD) [1–4] and possibly for ischemic stroke [5]. However, less attention has been paid to high serum levels of triglycerides (TG) [6–8]. Furthermore, although the US National Cholesterol Education Program Adult Treatment Panel guideline III (NCEP-ATP III) has set goals for non-high-density lipoprotein cholesterol (non-HDLC) after the achievement of LDL-C goals in patients with elevated TG [9], the impact of TG and non-HDLC on the incidence of cardiovascular disease (CVD) has not been evaluated in the Japanese population, which has a lower incidence of CAD but a higher risk of stroke than Western populations [10].

Therefore, our a priori hypothesis was that the coexistence of high serum TG and non-HDLC increases the risk of CAD and stroke in the Japanese population. To investigate this hypothesis, we performed a long-term prospective study in an urban, community-dwelling Japanese population.

2. Methods

2.1. Populations

The Suita study, a cohort study for CVD of urban residents was established in 1989. The details of this study have been described elsewhere [4,11–14]. Briefly, 6485 men and women aged 30–79 years had a baseline survey at the National Cardiovascular Center between September 1989 and March 1994. Of these, a total of 1387 were excluded for the following reasons: past history of coronary heart disease or stroke ($n=210$), lack of participation in the baseline survey ($n=79$), non-fasting visit ($n=166$), use of lipid-lowering agents ($n=125$), missing data ($n=109$), and lost to follow-up ($n=698$). Data from the remaining 5098 participants (2404 men and 2694 women) were included in the analysis. This

* Corresponding author at: Department of Preventive Cardiology, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan. Tel.: +81 6 6833 5012x2228/2188; fax: +81 6 6833 5300.
E-mail address: okamurat@hsp.ncvc.go.jp (T. Okamura).

0021-9150/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2009.09.012

cohort study was approved by the Institutional Review Board of the National Cardiovascular Center.

2.2. Baseline examination

Blood samples were collected after the participants had fasted for at least 10 h. The samples were centrifuged immediately and a routine blood examination was performed that included serum total cholesterol (TC), HDL cholesterol, TG and glucose levels.

Blood pressure was measured in triplicate on the right arm after 5 min of rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used for analysis. Hypertension was defined as either a systolic blood pressure (SBP) ≥ 140 mmHg, a diastolic blood pressure (DBP) ≥ 90 mmHg or the use of antihypertensive agents. Diabetes was defined as a fasting serum glucose ≥ 7.0 mmol/L (126 mg/dL), the use of anti-diabetic agents, or both. Height with bare feet and weight in light clothing were measured. Waist circumference (WC) was measured at umbilical level in a standing position. Metabolic syndrome (MetS) was defined using modified NCEP-ATP III criteria [13], of which abdominal obesity was defined according to the International Obesity Task Force central obesity criteria for Asia [15].

Public health nurses obtained information on the smoking, drinking and medical histories.

2.3. Endpoint determination

The endpoint determination was previously reported [4,11–14]. The endpoints of the present study were: (1) the first myocardial infarction (MI) or stroke event; (2) death; (3) leaving Suita city; or (4) December 31, 2005.

The first step in the survey for MI and stroke involved checking the health status of all participants by repeated clinical visits every two years and yearly questionnaires by mail or telephone. In the second step, in-hospital medical records of participants who were suspected of having an MI or stroke were reviewed by registered hospital physicians or research physicians, who were blinded to the baseline information. The criteria for stroke were defined according to the US National Survey of Stroke criteria [16]. For each stroke subtype [i.e., cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage], a definite diagnosis was established based on the computed tomography, magnetic resonance imaging, or autopsy. The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project [17]. Sudden deaths of unknown origin that occurred within 24 h of the onset were classified as MI in the present study.

2.4. Statistical analysis

The relationship between serum lipids and the risk of MI and stroke was described by dividing the participants into four groups stratified by the combination of serum levels of TG and non-HDLC. We used 1.7 mmol/L (150 mg/dL) of serum TG as a cut-off point for high serum TG according to the classification of NCEP-ATP III [9] and that of the Japan Atherosclerosis Society [3]. The category of non-HDLC ≥4.9 mmol/L (190 mg/dL) was defined as a high serum non-HDLC, which was equivalent to 6.2 mmol/L (240 mg/dL) of TC or 4.1 mmol/L (160 mg/dL) of LDL-C, because non-HDLC was usually 0.8 mmol/L (30 mg/dL) higher than LDL-C [9,18–19].

Continuous variables between groups were compared by analysis of variance and categorical variables were compared by a chi-square test. The hazard ratio (HR) for MI or stroke was calculated using a proportional hazards model adjusted for age, hypertension (dichotomous variable), diabetes, HDL-C, body mass index (BMI), smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker) (model 1). Sex-combined analysis with further adjustment for sex was also performed. Another statistical model after replacement of BMI and hypertension with WC and SBP level (continuous variable) was also performed (model 2).

All confidence intervals were estimated at the 95% level and significance was set at a P value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 15.0J, Tokyo, Japan) was used for all the analyses.

3. Results

The median and interquartile range of serum TG in the baseline survey was 1.29 mmol/L (0.90, 1.90) in men and 0.98 mmol/L (0.73, 1.41) in women. The mean baseline serum non-HDLC was 3.93 ± 0.91 mmol/L in men and 4.03 ± 1.03 mmol/L in women.

The means or prevalence of major cardiovascular risk factors in each group stratified by the combination of serum levels of TG and non-HDLC are summarized in Table 1. There was no significant difference in mean age and the prevalence of smoking among the TG and non-HDLC groups for men. There were significant differences in all other variables. Mean BMI, waist circumference and the prevalence of hypertension and diabetes were highest in the high-TG/high non-HDLC group, whereas the values of these parameters were lowest in the low-TG/low-non-HDLC group for both sexes. The prevalence of Mets was much higher in the high-TG groups than in the low-TG groups irrespective of non-HDLC level.

The total person-years were 59,774 (27,461 for men and 32,313 for women), with a mean follow-up period of 11.7 years. During the follow-up period, there were 113 first MIs and 180 first strokes. The strokes consisted of 28 intracerebral hemorrhages, 116 cerebral infarctions, 21 subarachnoid hemorrhages and 15 unclassified cases.

Table 2 shows the number of cases, age and multivariable-adjusted HRs for MI stratified by TG and non-HDLC. Compared with the low TG/low non-HDLC group, the HR for MI in the high TG/high non-HDLC group was 2.05 (95% confidence interval, CI, 1.08–3.90) in men, 3.79 (95% CI, 1.58–9.14) in women and 2.55 (95% CI, 1.53–4.24) in both sexes combined in multivariable adjusted model 1. We did not observe a significant increase in the HR for MI in the other groups. Similar results were observed after replacement of BMI and hypertension with WC and SBP level (model 2).

Table 3 shows the multivariable-adjusted HRs for cerebral infarction stratified by levels of TG and non-HDLC. Compared with the low TG/low non-HDLC group, the HR for cerebral infarction in the high TG alone group (high TG/low non-HDLC group) was 1.45 (95% CI, 0.84–2.50) in men, 2.09 (95% CI, 0.92–4.73) in women and 1.63 (95% CI, 1.03–2.56) in both sexes combined in statistical model 1. There was no significant increase of cerebral infarction in the other groups. Similar results were also observed in statistical model 2.

The incidence of total stroke, intracerebral hemorrhage and subarachnoid hemorrhage was not related to TG and non-HDLC levels in either sex. When the participants were divided into two groups by age (<60 and ≥60), the results of all the analyses listed above were similar in both age groups (data not shown).

4. Discussion

To our knowledge, this is the first cohort study in Japan to clarify the risk for MI and ischemic stroke of high serum level of TG, non-HDLC and both. The risk for MI of both high serum TG and non-HDLC was considerably higher than the risk without both or with only one. This relationship was similarly observed in both men and

Table 1
Means and prevalence of major cardiovascular risk factors in each group stratified by the combination of serum levels of triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDLC).

Variables	Low TG/low Non-HDLC		Low TG/high Non-HDLC		High TG/low Non-HDLC		High TG/high Non-HDLC		*P* value
Men									
No. of subjects	1532		117		550		205		
Non-HDLC (stratum mean), mmol/L	3.6	(0.7)	5.4	0.4	4.0	0.6	5.5	0.5	
Triglycerides (stratum median), mmol/L	1.0	(0.8, 1.3)*	1.3	(1.0, 1.5)*	2.2	(1.9, 2.9)*	2.4	(2.0, 3.7)*	
Age, years	55.8	(13.5)	57.4	(12.9)	54.8	(12.7)	54.8	(11.8)	0.16
HDLC, mmol/L	1.4	(0.3)	1.3	(0.3)	1.1	(0.3)	1.1	(0.2)	<0.01
BMI, kg/m^2	22.2	(2.8)	23.1	(3.1)	23.8	(2.6)	24.2	(2.6)	<0.01
Waist circumference, cm	80.8	(7.9)	82.7	(8.6)	85.7	(7.0)	86.3	(6.9)	<0.01
Systolic blood pressure, mmHg	127	(21)	129	(20)	130	(20)	132	(21)	<0.01
Diastolic blood pressure, mmHg	78	(12)	79	(12)	81	(11)	82	(11)	<0.01
Hypertension, %	30.0		35.0		36.4		38.0		0.01
Diabetes, %	4.8		4.3		7.5		9.3		0.02
Metabolic syndrome, %**	4.5		4.3		45.1		47.8		<0.01
Smoking, %									
Current smoker	49.9		43.6		53.5		47.3		0.51
Ex-smoker	30.3		35.0		28.4		32.7		
Never-smoker	19.8		21.4		18.2		20.0		
Drinking, %									
Current drinker	76.0		63.2		76.4		69.3		0.02
Ex-drinker	3.6		6.0		2.9		5.4		
Never-drinker	20.4		30.8		20.7		25.4		
Women									
No. of subjects	1956		290		256		192		
Non-HDLC (stratum mean), mmol/L	3.6	(0.7)	5.5	(0.5)	4.2	(0.5)	5.8	(0.8)	
Triglycerides (stratum median), mmol/L	0.9	(0.7, 1.1)*	1.2	(0.9, 1.4)*	2.0	(1.8, 2.4)*	2.4	(2.0, 3.0)*	
Age, years	51.5	(12.9)	59.3	(9.6)	57.9	(11.2)	60.7	(8.8)	<0.01
HDLC, mmol/L	1.5	(0.3)	1.4	(0.3)	1.2	(0.3)	1.1	(0.3)	<0.01
BMI, kg./m2	21.7	(3.1)	22.9	(3.1)	23.6	(3.3)	24.2	(3.1)	<0.01
Waist circumference, cm	75.5	(9.8)	79.8	(9.7)	82.7	(10.0)	83.5	(9.7)	<0.01
Systolic blood pressure, mmHg	121	(21)	131	(21)	132	(21)	137	(21)	<0.01
Diastolic blood pressure, mmHg	73	(12)	79	(12)	79	(12)	80	(13)	<0.01
Hypertension, %	20.4		37.9		37.1		48.4		<0.01
Diabetes, %	2.4		4.5		6.6		7.8		<0.01
Metabolic syndrome, %**	7.5		19.3		66.8		74.5		<0.01
Smoking, %									
Current smoker	11.8		8.6		14.5		16.1		0.04
EX-smoker	3.5		2.8		2.7		6.3		
Never-smoker	84.7		88.6		82.8		77.6		
Drinking, %									
Current drinker	34.9		29.3		28.5		24.5		<0.01
Ex-drinker	1.8		0.3		0.8		4.2		
Never-drinker	63.3		70.3		70.7		71.4		

TG, triglycerides; non-HDLC, non-high-density lipoprotein cholesterol; BMI, body mass index. Brackets indicate standard deviation.
Analysis of variance was used for comparisons of multiple group means and the chi-square test was used to compare proportions.

* Inter-quartile range.

** MetS was defined using modified NCEP-ATP III. Abdominal obesity was defined as a waist circumference ≥0.90 m in men and ≥ 0.80 m in women. High blood pressure was defined as average systolic/diastolic blood pressures of ≥ 130/85 mm Hg and/or current medication for hypertension. High triglyceride was defined as serum triglycerides of ≥1.7 mmol/L. Low HDL cholesterol was defined as serum HDL cholesterol levels of <1.03 mmol/L in men and of <1.29 mmol/L in women. High blood glucose was defined as fasting blood glucose of ≥6.1 mmol/L and/or current use of anti-diabetic medication. MetS was defined as the presence of three or more of these components.

women. In contrast, the risk for ischemic stroke was highest in the participants with high TG alone.

TG-rich lipoproteins have been shown to be atherogenic, and thus, they are associated with coronary atherosclerosis [9,19–20]. As NCEP-ATP III pointed out [9], elevated non-HDLC is a good therapeutic target in patients with high TG, because the serum concentration of non-HDLC reflects not only LDL-C but also the cholesterol content of all other TG-rich and apolipoprotein B containing lipoproteins, such as very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), small dense LDL particles and their remnant lipoproteins [19–20]. In the Helsinki Heart study [21], most of the risk for coronary heart disease (CHD) was confined to participants with high levels of both TG and LDL-C. In the West of Scotland Coronary Prevention Study [22], a higher incidence of CHD was observed in men in both the pravastatin and placebo groups when TG was at or above the median level. Pischon et al. suggested that TG added significant information to non-HDLC for CAD risk prediction in a nested case-control study [23]. Our findings are consistent with previous studies.

Similar to previous studies in Japan [4,10], we found no association between non-HDLC and cerebral infarction even in the presence of high serum TG, which may be due to a lower prevalence of atherothrombotic infarction than in Western populations. The ARIC study indicated that TC was associated with increased risk of non-lacunar, non-embolic stroke (atherothrombotic infarction), but not with lacunar or embolic stroke [24]. A recent report from a Japanese rural population showed that LDL-C is a risk factor for only atherothrombotic infraction [25]. Unfortunately, due to the relatively small stroke cases in our study, we were not able to demonstrate an association between any subtype of cerebral infarction and non-HDLC.

It is not clear why participants with high TG alone showed the increased risk for cerebral infarction in the present study. In a meta-analysis of 26 cohort studies in Asia-Pacific area, partici-

Table 2
Age and multivariable-adjusted hazard ratios (95% confidence intervals) for myocardial infarction stratified by TG and non-HDLC groups in an 11.7-year prospective study of 5098 Japanese men and women.

	Low TG/low Non-HDLC	Low TG/high Non-HDLC	High TG/low Non-HDLC	High TG/high Non-HDLC
Men				
Person-years	17410	1288	6358	2404
Case, *n*	45	6	11	14
Age adjusted	1.00	1.63 (0.70-3.83)	0.76 (0.39-1.48)	2.74(1.50-5.02)
Model 1[a]	1.00	1.48 (0.62-3.49)	0.63 (0.32-1.26)	2.05(1.08-3.90)
Model 2[b]	1.00	1.55 (0.66-3.66)	0.64 (0.32-1.29)	2.10 (1.10-3.98)
Women				
Person-years	23652	3455	2936	2270
Case, *n*	14	5	6	12
Age adjusted	1.00	1.59 (0.57-4.40)	2.28 (0.88-5.94)	4.88 (2.25-10.6)
Model 1[a]	1.00	1.63 (0.58-4.26)	1.99 (0.71-5.57)	3.79 (1.58-9.14)
Model 2[b]	1.00	1.55 (0.55-4.38)	1.92 (0.69-5.34)	3.18 (1.34-7.52)
Men and women				
Person-years	41062	4743	9294	4674
Case, *n*	59	11	17	26
Age adjusted	1.00	1.51 (0.79-2.89)	1.04 (0.60-1.78)	3.42 (2.15-5.44)
Model 1[a]	1.00	1.42 (0.74-2.74)	0.86 (0.49-1.53)	2.55 (1.53-4.24)
Model 2[b]	1.00	1.45 (0.75-2.79)	0.87 (0.49-1.54)	2.48 (1.49-4.10)

TG, triglycerides; non-HDLC, non high-density lipoprotein cholesterol.

[a] Multivariable adjusted for age, body mass index, hypertension, diabetes, HDL (high-density lipoprotein) cholesterol, cigarette smoking and alcohol intake by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] Replacement of body mass index and hypertension as covariates in model 1 with waist circumference and systolic blood pressure level.

pants grouped in the highest fifth of serum TG had a 50% increased risk of stroke compared with those in the lowest fifth [26]. Recent reviews have also concluded that hypertriglyceridemia seems to be a causal risk factor for ischemic stroke [7–8]. However, above-mentioned findings were not able to explain the low incidence of cerebral infarction in the high TG/high non-HDLC group in the present study. An elevated risk for MI might mask the relationship between TG and cerebral infarction; because there would be no further follow-up after a first MI. Another large study concerning about the relationship between serum TG and stroke should be needed.

Recently, we have reported that high serum LDLC and non-HDLC are both associated with an increased risk of MI; and the predictive value of non-HDLC for MI is almost similar to that of LDL-C [4]. However, we did not use serum TG as a covariate to avoid over-adjustment, because difference between serum level of LDLC and non-HDLC was automatically determined by serum TG level when serum LDLC value was calculated by the Friedewald formula [27]. Considering all the findings together, non-HDLC and TG may be recommended as beneficial screening markers for primary prevention of CAD in the Japanese community, as they are less expensive and more convenient because non-HDLC can be calculated irrespective of serum TG level.

The present study has some limitations. First, the single TG and non-HDLC measurement at the baseline survey may have underestimated the relationship between these lipids and cardiovascular disease due to regression dilution bias. Furthermore, we did not evaluate longitudinal trend for each risk factor and its medication status after baseline survey. Especially, hypertriglyceridemia is associated with not only present existence of metabolic components, such as hypertension and diabetes, but also new onset

Table 3
Age and multivariable-adjusted hazard ratios (95% confidence intervals) for cerebral infarction stratified by TG and non-HDLC groups in an 11.7-year prospective study of 5098 Japanese men and women.

	Low TG/low Non-HDLC	Low TG/high Non-HDLC	High TG/low Non-HDLC	High TG/high Non-HDLC
Men				
Person-years	17410	1288	6358	2404
Case, *n*	46	2	22	5
Age adjusted	1.00	0.53 (0.13-2.19)	1.51 (0.91-2.52)	0.99 (0.39-2.51)
Model 1[a]	1.00	0.54 (0.13-2.25)	1.45 (0.84-2.50)	0.92 (0.35-2.38)
Model 2[b]	1.00	0.56 (0.14-2.31)	1.48 (0.86-2.56)	0.75 (0.26-2.14)
Women				
Person-years	23652	3455	2936	2270
Case, *n*	20	8	10	3
Age adjusted	1.00	1.77 (0.78-4.02)	2.62 (1.23-5.60)	0.81 (0.24-2.72)
Model 1[a]	1.00	1.52 (0.66-3.50)	2.09 (0.92-4.73)	0.69 (0.20-2.44)
Model 2[b]	1.00	1.54 (0.67-3.54)	2.10 (0.93-4.73)	0.77 (0.22-2.71)
Men and women				
Person-years	41062	4743	9294	4674
Case, *n*	66	10	32	8
Age adjusted	1.00	1.14 (0.58-2.23)	1.82 (1.19-2.79)	0.94 (0.45-1.95)
Model 1[a]	1.00	1.12 (0.57-2.20)	1.63 (1.03-2.56)	0.79 (0.37-1.69)
Model 2[b]	1.00	1.12 (0.57-2.21)	1.62 (1.03-2.55)	0.69 (0.62-1.88)

TG, triglycerides; non-HDLC, non high-density lipoprotein cholesterol.

[a] Multivariable adjusted for age, body mass index, hypertension, diabetes, HDL (high-density lipoprotein) cholesterol, cigarette smoking and alcohol intake by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] Replacement of body mass index and hypertension (prevalence) as covariates in model 1 with waist circumference and systolic blood pressure levels.

of them in the future [28,29]. Second, we did not measure serum apolipoprotein B (apoB) [22], apolipoprotein A1 (ApoA1) and LP(a) [30], which some previous studies have shown to be strong risk factors for CAD [22]. Third, a recent study indicated that non-fasting TG is a better predictor of CAD than fasting TG [31]. However, in a large individual based meta-analysis in the Asia-Pacific region [26], most blood samples were collected during fasting, and there was a significant positive relationship between serum TG and CAD or stroke.

In conclusion, a combination of higher serum levels of TG and non-HDLC is associated with an increased risk of MI in a Japanese population. Furthermore, the risk for ischemic stroke was highest in the participants with high TG alone; however, further research should be needed. High serum levels of TG and non-HDLC are both important targets for the prevention of cardiovascular disease, which requires evidence-based guidelines for management in the primary care setting.

Acknowledgements

The present study was supported by grants-in-aid from the Ministry of Health, Labor and Welfare (H19-Seishu-017, H19-Seishu-021 and H20-Seishu-013). We sincerely appreciate members of the Suita Medical Foundation and Suita City Health Center. We thank researchers and co-medical staffs in the Department of Preventive Cardiology, National Cardiovascular Center, for their excellent medical examinations and follow-up surveys. We also thank *Satuki-Junyukai*, the society members of the Suita study.

References

[1] Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med 1990;322:1700–7.
[2] Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
[3] Teramoto T, Sasaki J, Ueshima H, et al. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerosis cardiovascular diseases for Japanese. J Atheroscler Thromb 2007;14:267–77.
[4] Okamura T, Kokubo Y, Watanabe M, et al. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study. Atherosclerosis 2009;203:587–92.
[5] Psaty BM, Anderson M, Kronmal RA, et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. J Am Geriatr Soc 2004;52:1639–47.
[6] Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. Circulation 1998;97:1029–36.
[7] Labreuche J, Touboul PJ, Amarenco P. Plasma triglyceride levels and risk of stroke and carotid atherosclerosis: a systematic review of the epidemiological studies. Atherosclerosis 2009;203:331–45.
[8] Antonios N, Angiolillo DJ, Silliman S. Hypertriglyceridemia and ischemic stroke. Eur Neurol 2008;60:269–78.
[9] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.
[10] Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation 2008;118:2702–9.
[11] Kokubo Y, Kamide K, Okamura T, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. Hypertension 2008;52:652–9.
[12] Kokubo Y, Okamura T, Yoshimasa Y, et al. Impact of metabolic syndrome components on the incidence of cardiovascular disease in a general urban Japanese population: the Suita study. Hypertens Res 2008;31:2027–35.
[13] Kokubo Y, Nakamura S, Okamura T, et al. Relationships between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease. The Suita study. Stroke 2009;40:2674–9.
[14] Watanabe M, Okamura T, Kokubo Y, Higashiyama A, Okayama A. Elevated serum creatine kinase predicts first-ever myocardial infarction: a 12-year population-based cohort study in Japan, the Suita study. Int J Epidemiol; in press [25th June 2009. Epub ahead of print].
[15] James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res 2001;9(suppl. 4):228S–33S.
[16] Walker AE, Robins M, Weinfeld FD. The national survey of stroke. Clinical findings. Stroke 1981;12(Pt 2 suppl. 1):I13–44.
[17] World Health Organization. Document for meeting of MONICA Principal Investigators. In: WHO, editor. MONICA Project: Event Registration Data Component, MONICA Manual, Version 1.1. 1986;S-4: 9–11.
[18] Sugimoto K, Isobe K, Kawakami Y, et al. The relationship between non-HDLCholesterol and other lipid parameters in Japanese subjects. J Atheroscler Thromb 2005;12:07–10.
[19] Shimano H, Arai H, Harada-Shiba M, et al. Proposed guidelines for hypertriglyceridemia in Japan with non-HDL Cholesterol as the second target. J Atheroscler Thromb 2008;15:116–21.
[20] Havel RJ. Role of triglyceride-rich lipoproteins in progression of atherosclerosis. Circulation 1990;81:694–6.
[21] Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation 1992;85:37–45.
[22] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.
[23] Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 2005;112:3375–83.
[24] Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley Jr TH, Folsom AR. Risk factors for ischemic stroke subtypes: the atherosclerosis risk in communities study. Stroke 2006;37:2493–8.
[25] Imamura T, Doi Y, Arima H, et al. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. Stroke 2009;40:382–8.
[26] Patel A, Barzi F, Jamrozik K, et al. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation 2004;10:678–86.
[27] Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the ultracentrifuge. Clin Chem 1972;18:499–502.
[28] Laaksonen DE, Niskanen L, Nyyssönen K, Lakka TA, Laukkanen JA, Salonen JT. Dyslipidaemia as a predictor of hypertension in middle-aged men. Eur Heart J 2008;29:2561–8.
[29] Kahn HS, Cheng YJ, Thompson TJ, Imperatore G, Gregg EW. Two risk-scoring systems for predicting incident diabetes mellitus in U.S. adults age 45 to 64 years. Ann Intern Med 2009;150:741–51.
[30] Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the atherosclerosis risk in communities (ARIC) study. Circulation 2001;104:1108–13.
[31] Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 2007;298:309–16.

Impact of Diabetes Mellitus on Outcomes in Japanese Patients Undergoing Coronary Artery Bypass Grafting

Kenji Minakata, MD, PhD; Ko Bando, MD, PhD; Shuichiro Takanashi, MD, PhD; Hiroaki Konishi, MD, PhD; Yoshihiro Miyamoto, MD, PhD; Kenji Ueshima, MD, PhD; Tosiya Sato, PhD; Yuichi Ueda, MD, PhD; Yutaka Okita, MD, PhD; Izuru Masuda, MD, PhD; Hitoshi Okabayashi, MD, PhD; Hitoshi Yaku, MD, PhD; Shinji Yasuno, MD, PhD; Shigeki Miyata, MD, PhD; Yoshitaka Okamura, MD, PhD; Michihiro Nasu, MD, PhD; Kazuo Tanemoto, MD, PhD; Koichi Arinaga, MD, PhD; Yosuke Hisashi, MD; Ryuzo Sakata, MD, PhD; the J MAP Study Investigators

Affiliations:
Kyoto University Graduate School of Medicine (K.M., K.U., S.Y., R.S.), International University of Health and Welfare (K.B.), Sakakibara Heart Institute (S.T.), Jichi Medical University (H.K.), National Cerebral and Cardiovascular Center (Y.M., S.M.), Kyoto University School of Public Health (T.S.), Nagoya University Graduate School of Medicine (Y.U.), Kobe University Graduate School of Medicine (Y. Okita.), Takeda Preventive Medicine & EBM Center (I.M.), Iwate Medical University (H.O.), Kyoto Prefectural University of Medicine (H.Y.), Wakayama Medical University (Y. Okamura.), Kobe City Medical Center General Hospital (M.N.), Kawasaki Medical School (K.T.), Kurume University School of Medicine (K.A.), and Kagoshima University Graduate School of Medicine and Dental Science (Y.H.).

Short title: Impact of diabetes on the outcomes of CABG

This study was supported by a Health and Labour Science Research Grant from the Ministry of Health, Labour and Welfare of Japan (Grant ID: 09158533).

Corresponding author:
Ryuzo Sakata, MD, PhD, Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan
Email: sakatar @kuhp.kyoto-u.ac.jp

The total word count: 4,613
The total number of tables: 5

Abstract (219words)

Background: There have been no large scale studies on the impact of diabetes mellitus (DM) on outcomes in Japanese patients undergoing coronary artery bypass grafting (CABG).

Methods: A multi-institutional retrospective cohort study was conducted in 14 Japanese centers. All adult patients who underwent isolated CABG from 2007 to 2008 were included (n=1,522; 1,177 males; mean age: 68.5 years). The definitions of DM were all patients admitted with diagnosis of DM and preoperative HbA1c≥6.5%. Univariate and multivariable analyses were performed to identify the risk of morbidity and mortality.

Results: There were 849 DM and 572 non-DM patients. Preoperative, intraoperative and 3-day average postoperative blood glucose (BG) were 146mg/dl, 172mg/dl and 168mg/dl in the DM group, and 103mg/dl, 140mg/dl and 136mg/dl in the non-DM group (all p<0.0001). Although there were no significant differences in postoperative cardiovascular events, the incidence of infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%, P=0.036). The all-cause death was also higher in the DM group than in the non-DM group (2.1% vs 1.1%, p=0.12), and this was likely related to infection.

Conclusions: DM patients had worse perioperative BG control, higher incidence of infection, and higher mortality than non-DM patients. These results indicate that perioperative BG control guidelines should be standardized to obtain better surgical outcomes in Japanese DM patients.

Key words: complication, coronary artery bypass grafting, diabetes mellitus, infection, mortality

Introduction

The prevalence of diabetes mellitus (DM) has increased dramatically in Western countries over the last several decades, leading in turn to increased mortality due to cardiovascular events [1]. This trend is also apparent in Asian countries, especially in Japan, where the number of DM patients has increased from 6.9 million to 8.9 million in the last decade (a 29% increase) [2]. The most important life-threatening complication in DM patients is obviously coronary artery disease [3]. There has been debate regarding the optimal treatment for DM patients; some physicians favor percutaneous catheter intervention (PCI), while others favor coronary artery bypass grafting (CABG). Some studies have shown that CABG yields better long-term outcomes in DM patients with multivessel disease [4, 5]. However, it is well known that patients with DM who undergo CABG have worse early and late outcomes than CABG patients without DM [6, 7]. Also, it has been shown that intraoperative and postoperative blood glucose (BG) control has a significant effect on complications such as infection and mortality [8-10]. However, there have been no large-scale studies on Japanese DM patients undergoing coronary artery bypass grafting. To better understand the impact of DM on coronary artery surgery and to establish the optimal BG control method during cardiac surgery, we organized a multicenter/multidisciplinary research group, which we called the JMAP study group (Japanese Study to Explore the Impact of Diabetes on Cardiac Surgery for Optimal Glycemic

Control Protocol). Herein, we carried out a retrospective cohort study to identify the impact of DM and BG control on surgical outcomes in Japanese patients undergoing CABG.

Patients and Methods

From 2007 to 2008, a total of 1,522 patients underwent isolated CABG in 14 cardiac surgery centers in Japan. Patients who underwent redo CABG were included, but patients who underwent concomitant procedures such as valvular procedures, aneurysm repair, arrhythmia surgery, repair of ventricular septal perforation, and surgical ventricular restoration procedures were excluded from this study. All the patient characteristics and operative data were extracted from the prospective national database (the Japan Adult Cardiovascular Surgery Database: JACVSD), which is similar to the Society of Thoracic Surgeons (STS) national database in the North America. Other study-specific data like perioperative BG control, as well as other blood laboratory data and postoperative complications including cardiovascular events and individual infections, which are not included in the JACVSD, were obtained from medical records at each study site. These two sets of data were merged and sent to a data center (the EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan).

Demographic variables are listed in Appendix I. Of note, the Japanese Diabetes Society (JDS) value

of HbA1c (%) is converted into the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the following formula according to the JDS guidelines [11]:

$$\text{HbA1c (NGSP) (\%)} = \text{HbA1c (JDS) (\%)} + 0.4\ (\%)$$

Postoperative variables were acute myocardial infarction (MI), cerebrovascular events, acute renal failure and other cardiovascular events (including cardiac tamponade, ventricular tachycardia or fibrillation, and complications after PCI). Postoperative infection was categorized into deep sternal wound infection (anterior mediastinitis), superficial sternal wound infection, graft harvesting site infection, blood stream infection, urinary tract infection, and pneumonia. Details of the definitions of the clinical events are summarized in Appendix II. Hospital death included all-cause death within 30 days of operation or during initial hospitalization. All the aforementioned clinical events were evaluated at the participating centers, and then assessed by the independent clinical events evaluation committee (Appendix III). The primary composite endpoint was defined as a composite of acute MI, cerebrovascular accidents, other cardiovascular events, all infections and their related deaths. Although cardio-cerebrovascular events were thought to be important for DM patients, this prespecified primary composite endpoint was not related to DM. Thus, we added a new composite endpoint, which consisted of all infections, renal failure, and all cause deaths, and conducted an additional analysis.

DM patients were defined as those patients who were admitted to the participating hospitals with a diagnosis of DM. Patients without a previous diagnosis of DM who had preoperative HbA1c $\geq$ 6.5% (NGSP) were also included [12]. The intraoperative BG was an average of 3-4 BG measurements taken during surgery. The postoperative 3-day BG average was a composite average of the daily mean BG levels (BG was measured up to 12 times per day following surgery) from the day of the surgery to postoperative day 3.

Perioperative BG control methods varied from hospital to hospital, however, in all the participating institutions, it was standard practice to treat hyperglycemia with continuous insulin infusion whenever BG exceeded 200mg/dl.

Statistical Analyses

Baseline characteristics of the DM and the non-DM groups are described as mean $\pm$ standard deviation for continuous variables and proportions for categorical variables. P-values were calculated by the t-test and the chi-squared test. We compared the proportions of primary and additional composite endpoints and their components between the DM and the non-DM groups. Risk ratios and associated 95% confidence intervals were calculated.

Logistic regression analyses were conducted to estimate the magnitude of the effect of DM on the additional composite endpoint, all infections, and all cause deaths adjusted by age (in 10-year increments), gender, body mass index, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, left ventricular ejection fraction < 50%, operative status (elective vs urgent or emergency), bilateral internal thoracic artery use, and intraoperative steroid use. Of note, two patients undergoing CABG as salvage were excluded from the analyses. Odds ratios and their associated 95% confidence intervals were calculated. All analyses were performed with JMP 8.0 statistics software (SAS Institute Inc., Cary, NC, USA). The two-sided alpha level was set to 5%.

This study was approved by the Internal Review Board at all the participating hospitals and the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All the patients and their families gave written consent at the time of operation for participation in the JACVSD.

Results

A total of 1,522 enrolled patients were classified into two groups: the DM group (n=849) and the non-DM group (n=572). Because there were no preoperative HbA1c data for 101 patients without a previous diagnosis of DM, these patients were excluded from this study. Patients' baseline characteristics are shown in Table 1. There were no differences in terms of age, gender and body mass index (BMI). However, depressed left ventricular systolic function (ejection fraction < 50%), renal insufficiency, and peripheral artery disease were significantly higher in the DM group than in the non-DM group. On the other hand, chronic obstructive pulmonary disease was less common in the DM group. There was no difference in terms of usage of bilateral internal thoracic artery, however intraoperative administration of intravenous steroids was more common in the non-DM group. There were no differences in operative status. Off-pump techniques were used frequently in both groups (about 70% of patients in each group).

Preoperative fasting, intraoperative and 3-day average postoperative BG were 146mg/dl, 172mg/dl and 168mg/dl in the DM group, and 103mg/dl, 140mg/dl and 136mg/dl in the non-DM group, respectively. At all measurement points, DM patients had significantly higher BG levels ($p<0.0001$). As shown in Table 2, the all-cause deaths were 2.1% (n=18) in the DM group and 1.1% (n=6) in non-DM group ($p=0.124$). There was no significant difference in the primary composite endpoint, however, the additional composite endpoint was significantly higher in the DM group. In terms of

complications, although there were no significant differences in the incidence of postoperative cardiovascular events and cerebrovascular accidents, the incidence of overall infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%, P=0.036). In particular, the incidence of deep sternal wound infection was much higher in the DM group (2.0%) than in the non-DM group (1.1%) although this did not reach statistically significance (p=0.163). The cause of death in the DM group was predominantly related to infection (10/18), while in the non-DM group there was only one patient who died of infection (1/6). On multivariable logistic regression analyses, the statistically significant risk factors for the additional composite endpoint included female gender, BMI, renal insufficiency, and chronic obstructive pulmonary disease (Table 3). Also, the statistically significant risk factors for infection were female gender, BMI and renal insufficiency (Table 4). Finally, the statistically significant risk factors for all-cause death were renal insufficiency, congestive heart failure, and emergency surgery (Table 5). The presence of DM was not identified as a statistically significant risk factor for any of the endpoints and complications including infection by multivariable analyses.

Discussion

In 2009, the Society of Thoracic Surgeons Blood Glucose Management Task Force published their guidelines regarding BG management during adult cardiac surgery [13]. According to these

guidelines, it is highly desirable to maintain BG < 180mg/dl during surgery and during the immediate postoperative period with intravenous insulin infusion in DM patients. Although it is unnecessary to use intravenous continuous insulin infusion in non-DM patients during surgery, both DM and non-DM patients benefit from maintaining BG < 180mg/dl in order to prevent morbidity and mortality [13]. Based on the current findings, our BG management approach seems to be reasonable given the intraoperative and postoperative 3-day average BG with 172mg/dl and 168mg/dl, respectively, in the DM group. This begs the question of how low the target should be. Furnary et al. reported from their prospective observational study that there was a highly significant relationship between mortality and postoperative glucose levels rising above 175mg/dl [10]. Our current BG levels in DM patients were barely below this cut-off value.

It has been reported that the presence of DM in patients undergoing CABG is a significant risk factor for hospital mortality and morbidity including stroke, deep sternal wound infection and length of hospital stay from the STS database analyses [13]. In addition, DM patients have worse long-term survival than non-DM patients after surgery [6]. Our results show that DM has a significant influence on the additional composite endpoint consisting of all-cause death, infection and acute renal failure (10.8% vs 7.3%, p=0.027). Looking at each complication, infection was the most significant factor contributing to this result (9.2% in DM group vs 6.1% in non-DM group, p=0.036).

Also, DM patients tended to have higher mortality than non-DM patients (2.1% vs 1.1%, p=0.124). Moreover, DM patients tended to have a much higher incidence of deep sternal wound infection than non-DM patients (2.0% vs 1.1%, p=0.163), although this difference did not reach statistical significance. However, the complication of infection definitely influenced mortality rates because the majority of deaths were related to infection in the DM group. There is no doubt that DM patients have unfavorable baseline characteristics such as diffuse coronary artery disease, peripheral artery disease, high BMI, and worse renal function, all of which would contribute to worse short and long-term outcomes compared to non-DM patients. The Portland Diabetic Project, which is an on-going prospective study of over 5,000 DM patients, aims to show that tight glucose control from the end of surgery until the 2nd postoperative day with continuous insulin infusion may eliminate the diabetic disadvantage [15]. They showed that tight glucose control with a full 3 days of continuous insulin infusion (the Portland Protocol) significantly reduced mortality (by 65%), deep sternal wound infection (by 63%), and length of hospital stay (average 2-day reduction). Therefore, they concluded that DM is not the true risk factor for the seemingly unfair diabetic disadvantage in terms of increased mortality and morbidity. Since we showed that DM patients still have excess mortality and morbidity compared to non-DM patients in the current study, we might be able to reduce these excess complications by implementing tighter glucose control protocols.