ORIGINAL

Profiles of atherosclerotic risk factors in gastrectomized men

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Abstract. Postprandial hyperglycemia is an established risk factor for atherosclerotic vascular diseases, and it is frequently observed in gastrectomized subjects. This study sought to examine whether other atherosclerotic risk factors are also common among gastrectomized subjects. The study population comprised of 44 non-diabetic men who previously underwent gastrectomy. The age- and body mass index-matched control population comprised of 278 non-diabetic men without gastrectomy. In addition to traditional atherosclerotic risk factors for atherosclerosis, high sensitivity C-reactive protein (hsCRP) and brachial-ankle pulse wave velocity (baPWV) were also compared between the groups. Fasting plasma glucose was not different between both groups, while glycated hemoglobin (HbA1c) was significantly higher in the gastrectomized men than in the control men. Systolic and diastolic blood pressures and high density lipoprotein cholesterol (HDL-C) were significantly higher, whereas low density lipoprotein cholesterol (LDL-C) was lower in the gastrectomized men than in the control men. baPWV, hsCRP, triglycerides and insulin resistance (as per the homeostasis model assessment) were not different between groups. While levels of certain atherosclerotic risk factors, including HbA1c and blood pressure are higher among gastrectomized men, HDL-C and LDL-C were actually favorable. Additionally, levels of more emerging risk factors, such as hsCRP and baPWV were not altered among gastrectomized men.

Key words: Atherosclerosis, Gastrectomy, Postprandial hyperglycemia, Pulse wave velocity

ORAL glucose tolerance tests (OGTT) among gastrectomized subjects often demonstrate marked hyperglycemia (oxyhyperglycemia) 30 to 60 min after glucose loading [1, 2]. It has been shown that glycated hemoglobin (HbA1c) is increased and serum glycated albumin (GA) more reflecting postprandial and maximal blood glucose levels is furthermore increased in gastrectomized subjects [3].

Postprandial hyperglycemia or hyperglycemia after oral glucose-loading is a known risk for cardiovascular diseases [4, 5]. Thus, gastrectomized subjects may be prone to developing atherosclerotic vascular diseases. However, epidemiological studies have reported that these subjects may actually have lower incidence of cardiovascular events [6, 7]. There have been several reports studying the effects of gastrectomy on the tradi-

tional atherosclerotic risk factors, including blood pressure, serum lipids, insulin resistance, serum uric acids and high sensitivity C-reactive protein (hsCRP) [8-10]. However, it remains unclear whether atherosclerosis preferentially develops in gastrectomized subjects.

Among various surrogate markers for atherosclerosis, pulse wave velocity (PWV) has been shown to have clinical utility as a noninvasive method for predicting future cardiovascular events [11, 12]. In the present study, we sought to investigate whether or not atherosclerotic risk factors including brachial-ankle PWV (baPWV) are commonly present among gastrectomized subjects.

Subjects and Methods

Study subjects

During health examinations at Kinki Central Hospital between August 2006 and March 2009, men with a history of gastrectomy were identified. From this group, 44 men whose fasting plasma glucose (FPG) of <126 mg/dL were selected as the study group.

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Table 1 Baseline characteristics of participants.

	Gastrectomized men	Control men	<i>p</i> value
n	44	278	-
Age (years)	58.8 ± 6.8	58.8 ± 4.3	0.964
BMI (kg/m ²)	22.1 ± 2.7	22.1 ± 1.6	0.944
Current smokers (%)	25.0	26.3	0.860
Drinking habits (%)	75.0	69.8	0.482
Duration after gastrectomy (years)	14.3 ± 11.3	-	-

Data presented as mean ± SD or number. BMI; body mass index.

A total of 1,994 men visited the Health Care Center at Kinki Central Hospital for routine health examination between May 2006 and October 2006. From these subjects, 936 men (mean age; 53.1 ± 7.4 years, mean BMI; 23.9 ± 2.7 kg/m²) without any history of diabetes or evidence of a diabetic pattern on OGTT were identified. In total, 278 age- and BMI-matched men were selected as controls. Exclusion criteria included liver disease (e.g., chronic hepatitis, liver cirrhosis), renal disease, thyroid disease, anemia, administration of glucocorticoid, and treatment for hypertension, dyslipidemia, hyperuricemia and anemia. Clinical characteristics of the study participants are shown in Table 1. Among the 44 gastrectomized men, 18 received gastrectomy because of peptic ulcers while the other 27 had gastric cancers, but were currently confirmed to have no signs of recurrence or metastasis. All study subjects were otherwise healthy with a proper nutritional status. Specifically, subjects had no abnormalities in blood tests, chest X-ray examination and abdominal echography. There were no significant differences in the prevalence of current smokers and that of drinking habits between both groups.

The study was performed in accordance with the principles of the Declaration of Helsinki as revised in 2000, and the study protocol was approved by the ethics committee of Kinki Central Hospital.

Laboratory analyses

Body height and weight were measured on the same day during the health examination. Blood pressure was measured with an automatic sphygmomanometer with the subject in a sitting position after 5 min of rest. Fasting blood was collected from subjects between 9 AM and 11 AM, and was centrifuged immediately for measurements. Plasma glucose, serum insulin, serum uric acid, total cholesterol, high density lipoprotein cholesterol (HDL-C) cholesterol, and triglycerides were

determined by means of standard laboratory assays. HbA1c was measured with ADAMS-A1c HA-8160 (Arkray Inc., Kyoto, Japan) by HPLC, as described previously [13]. HbA1c (%) is estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%), calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society: JDS) (%) + 0.4%. This formula adjusts for the relative expression of HbA1c (JDS) (%) to a previous Japanese standard substance for HbA1c (NGSP) [14]. Serum low density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation [15]. hsCRP was determined by means of latex-enhanced immunonephelometry on a BNII Analyzer (Dade Behring, Marburg, GmbH), as described previously [16]. Insulin resistance (IR) was estimated by the homeostasis model assessment-IR (HOMA-IR) [fasting insulin (pmol/L) × FPG (mmol/L)]/135 [17]. Ankle-brachial blood pressure index (ABI) and baPWV were measured with the use of a Waveform analyzer (VaSera VS-1000, Fukuda Denshi, Tokyo, Japan), after 5 min rest [18]. The validity and reproducibility of the baPWV measurements have been previously reported [19]. In our laboratory, the coefficients of variations of inter-observer and intra-observer reproducibility were 1.1% and 2.2%, respectively [18]. baPWV was defined as the mean of left and right baPWV. Systolic and diastolic blood pressures in the supine position, determined simultaneously with baPWV, were also expressed as the mean of left and right blood pressures.

Statistical analyses

All data are shown as means ± SD. For statistical analyses, unpaired Student's *t* test was used to compare between two groups, as appropriate. The relationship between FPG levels and different variables was assessed by linear univariate regression analyses. The StatView computer program (Version 5.0 for Windows;

Fig. 1 Fasting plasma glucose (FPG) (A), HbA1c (B), and HOMA-IR (C) in 44 gastrectomized men and in 278 control men.

Fig. 2 Serum triglycerides (A), LDL-cholesterol (LDL-C) (B), and HDL-cholesterol (HDL-C) (C) in 44 gastrectomized men and in 278 control men.

Abacus Concepts, Berkeley, CA) was used for all statistical analyses. A *p* value of <0.05 was considered to be statistically significant.

Results

FPG levels (98 ± 9 mg/dL vs. 100 ± 8 mg/dL, $p=0.120$), as well as HOMA-IR (0.93 ± 0.62 vs. 1.10 ± 0.51 , $p=0.275$; Fig. 1), were not different between groups, whereas HbA1c levels were significantly higher in the gastrectomized men ($5.8 \pm 0.4\%$ vs. $5.6 \pm 0.4\%$, $p=0.013$). Serum LDL-C concentrations were significantly lower in the gastrectomized men than in the control men (110 ± 31 mg/dL vs. 120 ± 29 mg/dL, $p=0.032$), while HDL-C concentrations were higher in

the gastrectomized men (73 ± 19 mg/dL vs. 59 ± 15 mg/dL, $p<0.0001$), and serum triglycerides levels were not different between groups (115 ± 65 mg/dL vs. 125 ± 63 mg/dL, $p=0.335$; Fig. 2). Systolic and diastolic blood pressures in the gastrectomized men (128 ± 65 mmHg and 81 ± 14 mmHg) were significantly higher than those in the control men (120 ± 15 mmHg, $p=0.002$ and 75 ± 11 mmHg, $p=0.002$) (Fig. 3). Systolic (130 ± 19 mmHg vs. 123 ± 15 mmHg, $p=0.009$) and diastolic blood pressures (82 ± 13 mmHg vs. 77 ± 10 mmHg, $p=0.002$) in the supine position, as determined simultaneously with baPWV measurements, were also higher in the gastrectomized men compared to controls. However, resting heart rates were not different between groups (64.5 ± 9.4 /min vs. 63.5 ± 8.3 /min, $p=0.473$). Serum uric acid

Fig. 3 Systolic blood pressure (SBP) (A), diastolic blood pressure (DBP) (B), and serum uric acid (UA) (C) in 44 gastrectomized men and in 278 control men.

Fig. 4 High sensitivity C-reactive protein (hsCRP) (A) and brachial-ankle pulse wave velocity (baPWV) (B) in 44 gastrectomized men and in 278 control men.

(6.1 ± 1.2 mg/dL vs. 6.2 ± 1.3 mg/dL, $p=0.467$), hsCRP (log-transformed-mg/L; -1.43 ± 0.45 vs. -1.32 ± 0.47 , $p=0.149$) and baPWV (13.5 ± 2.3 m/sec vs. 13.2 ± 1.7 m/sec, $p=0.275$) were not different between gastrectomized *versus* control men (Fig. 4).

Discussion

In the present investigation, we examined the traditional atherosclerotic risk factors and surrogate markers for atherosclerosis in gastrectomized subjects. The rationale for this study was based on the observation that postprandial hyperglycemia, a known risk factor for atherosclerotic vascular diseases, is frequently observed in gastrectomized subjects. It has been shown that blood glucose and serum uric acid levels are lower, and that serum LDL-C and HDL-C levels are higher, in

women *versus* men. In addition, it is well known that the incidence of cardiovascular disease, and the levels of hsCRP and baPWV, are lower in women than in men. Thus, to avoid the potential confounding effects of gender on the parameters studied, the present study focused solely on men. Furthermore, the control subjects in the present study comprised of age- and BMI-matched men without a history of gastrectomy, as age and BMI both directly and indirectly influence atherosclerotic risk. It is generally accepted that the BMI of gastrectomized subjects is lower than that of non-gastrectomized subjects [3]. Recently, bariatric surgery, in addition to by-pass surgery, is offered as a treatment of marked obesity [20]. Therefore, in order to properly assess the results of the present study, the reduced BMI in response to gastrectomy must be considered.

Although FPG levels were not different between

groups, HbA1c levels were significantly higher in the gastrectomized men. These results are consistent with a previous report demonstrating higher glycated albumin levels in gastrectomized subjects compared with control subjects [3]. Taken together, the gastrectomized men in the present study exhibited postprandial hyperglycemia. Compared to diabetic patients, gastrectomized patients experienced a shorter duration of postprandial hyperglycemia. However, a transient rise of plasma glucose levels can cause vascular endothelial injury [21], leading to the progression of atherosclerosis. Insulin resistance, as measured by HOMA-IR, was not significantly different between groups, but was numerically lower in the gastrectomized men. Alterations of hormonal milieu after gastrectomy may influence insulin sensitivity. Further studies including a larger subject sample are necessary to clarify this issue.

In the present study, gastrectomized men exhibited lower LDL-C and higher HDL-C in comparison to healthy controls, in a manner consistent with a previous report [9]. On conversely, we failed to show significant differences in serum triglycerides levels between groups, which is inconsistent with a previous finding of lower serum triglycerides levels in gastrectomized *versus* non-gastrectomized subjects [8]. The discrepancy between these studies may be due to the fact that the control population was BMI-matched in the current, but not in the previous study [8]. Thus, gastrectomy itself may be involved in the decreased LDL-C and the increased HDL-C levels, while decreased BMI related to gastrectomy results in decreased triglycerides levels.

Our study found that both systolic and diastolic blood pressures were higher among gastrectomized men. In contrast, the Honolulu Heart Study on Japanese-American men reported that blood pressure in gastrectomized subjects was lower compared with the control population [8]. Again, such discrepant results may be caused by the BMI-matching of our control group. It

has recently been shown that ghrelin, a peptide produced by the stomach, plays a role in reducing blood pressure [22], and low plasma ghrelin levels are associated with hypertension [23]. Since circulating ghrelin concentrations are depressed after gastrectomy [24], this may be the mechanism by which blood pressure was increased among the gastrectomized men in the present study.

The surrogate marker for atherosclerosis, baPWV, was not different between the two groups. To our knowledge, no prior report examined baPWV in gastrectomized subjects. However, baPWV is well known to be influenced by blood pressure [25]. Nevertheless, although systolic and diastolic blood pressures were significantly higher in the gastrectomized men than in the control men, baPWV was similar across the groups. Atherosclerosis progression is thought to be influenced by a balance between pro- and anti-atherogenic factors [26, 27]. Thus, in gastrectomized men, baPWV might not be elevated because of the balance between postprandial hyperglycemia, and increased blood pressures (pro-atherogenic), as well as decreased LDL-C and increased HDL-C (anti-atherogenic). In the future, other markers of atherosclerosis should be evaluated.

Gastrectomy alters secretions of various hormones, which may also influence atherosclerosis progression. For example, it has been shown that circulating glucagon-like peptide-1 (GLP-1) concentrations are increased in gastrectomized subjects [28]. Given that GLP-1 exerts an anti-atherogenic effect [29], a mechanism by which the increased GLP-1 in gastrectomized subjects prevents atherosclerosis progression may exist. Further studies will be needed to address these issues.

Conflicts of Interest

The authors declare no conflict of interest relevant to this manuscript.

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