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泌尿器科学

最新の膀胱癌初期治療

——病理の視点から

An updated initial treatment for bladder cancer
——From a pathological point of view

膀胱癌は初期症状が乏しく，進行癌で発見されることもまれではない．加えて，前立腺癌の PSA (prostatic specific antigen)に相当するような有用なスクリーニングのマーカーがなく，尿細胞診がもっとも有効・簡便で安価な検出法として定着している．欧米では尿検体を用いた FISH(fluorescence *in situ* hybridization)法(UroVysion, Abbott)が尿細胞診よりも精度がよい(高感度)との報告から実用化されているが，コストの問題などからわが国での導入は研究レベルの段階である．一方，膀胱癌の病理組織学的診断および治療の目的で行われる TUR(transurethral resection)に関しては，1990 年代から T1 high grade 腫瘍(粘膜固有層浸潤があるが，筋層浸潤のない high grade の膀胱癌)に対する second TUR の重要性が提唱されている．ここでは膀胱癌の初期治療の際に，尿細胞診と病理の情報をいかに有効に活用するかについて解説する．

尿細胞診でどこまでわかるか

尿細胞診は尿中に剝離した腫瘍細胞を顕微鏡で観察して診断する方法で，尿路上皮癌に対する感度はおよそ 40〜60%，特異度は 90〜100%である．grade 1 の尿路上皮癌では細胞が剝離しにくいために尿細胞診の感度は約 10%と低いが，grade 3 や上皮内癌の感度は 70%を超える．つまり緊急性の高い高異型度尿路上皮癌の多くは，尿細胞診で検出可能である．

尿細胞診で予測可能な病理所見としては，①grade，②組織型，③浸潤の有無がある．さらに，扁平上皮や腺管への分化を示すもの，および micropapillary variant, plasmacytoid variant など粘膜固有層浸潤以上(T1 以上)の可能性がきわめて高い組織亜型も細胞診で予測可能なことがある．壊死性の背景は，通常は T1 以上の浸潤癌でのみ認められる．

病理標本でどこまでわかるか

病理に提出される TUR 検体は，大きく 2 つに分けられる．1 つは腫瘍のサイズが比較的小さく，粘膜面と垂直方向に腫瘍組織を切出すことが可能な適切な検体

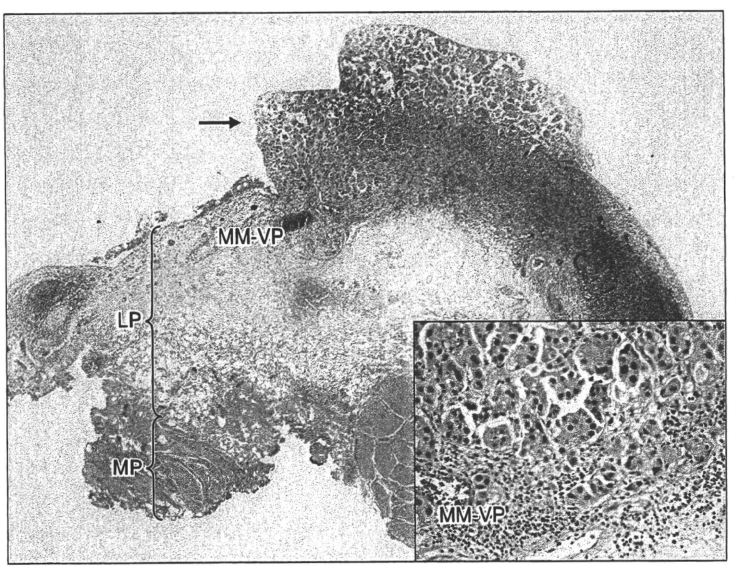

図 1　固有筋層(MP)を含み，垂直方向に切り出された適切な病理標本
pT1 high grade, micropapillary variant の尿路上皮癌(矢印)で粘膜固有層(LP)内の粘膜筋板(MM)-血管叢(VP)に浸潤がある．右下は腫瘍の中拡大像．深部断端は陰性．Second TUR は必要であろうか？

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告書

富山職域コホート研究

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研究要旨

富山職域コホートは、富山県にある企業の従業員を追跡する職域コホートである。就労中の男女、特に地域ではコホート設定が困難な働き盛りの中高年男性における循環器疾患のリスクの評価や、リスクと就業状態の関連等の検討を行っている。

今回、動脈硬化性疾患の代表的な指標である血清脂質と食事のグリセミックインデックスとの関連につき検討を行った。35 歳以上の従業員（男 2,257 名、女 1,598 名）を対象に、2003 年に食事歴法質問票による栄養調査を行い習慣的な食事の GI、GL を求めた。同年の健診にて血清脂質を測定した。GI と血清脂質の間に有意な関連は認められなかった。GL は男女とも HDL コレステロールと負の関連を認め、女性においてはさらに nonHDL コレステロール、LDL コレステロール、中性脂肪とも正の関連を認めた。高 GL 食は、特に女性において血清脂質と強く関連しており、高 GL 食は血清脂質異常を介して動脈硬化を進展させている可能性がある。

A. 研究目的

富山県にある企業の従業員を追跡する職域コホートである。就労中の男女、特に地域ではコホート設定が困難な働き盛りの中高年男性における循環器疾患のリスクの評価や、リスクと就業状態の関連等の検討を行っている。

B. 研究方法

コホートの概要

富山県にあるアルミ製品製造業企業の黒部事業所及び滑川事業所従業員を対象としたコホートである。1980 年以降、研究者が産業医として従業員の健康管理を 25 年にわたり行っている。コホート規模は約 8,000 人で、男女比は約２対１である。

本コホートは職域コホートであるため、従業員全体が毎年 95%以上の受診率で健診を受診しており、各種検査値の高い率での経年追跡が可能である。また現業系従業員では転勤が少なく、また、途中退職も比較的少ないため長期の追跡が可能である。

本コホート研究グループは本事業所での産業医活動を通して、詳細なエンドポイント発生の把握を実施している。すなわち、在職中の脳卒中、虚血性心疾患、悪性新生物、精神疾患等の発症および死亡の把握、健診データ追跡による在職中の高血圧、糖尿病、高脂血症等の発症の把握である。また、一般に職域

コホートでは定年退職後の疾患発症の追跡が困難であるが、本コホートでは退職後も近隣に在住するものがほとんどのため、1990年以降退職者については郵送による退職後健康調査を毎年実施し、生活習慣病の治療状況、脳血管疾患・心疾患の発症および死亡を追跡している。在職中および退職後の脳心事故発症者については同意を得た上で、医療機関での医療記録調査を実施している。

以上より、本コホートの特色としては、(1)地域ではコホート設定が困難な青壮年期の男性を多く含むコホートであること、(2)青壮年期男性のライフスタイルや危険因子に影響が大きいと考えられる職業面での要因について詳細な情報が収集されていること、(3)各種危険因子の経年推移が高い追跡率で把握されていること、が挙げられる。

C. 研究結果

研究の成果

Nakashima M, Sakurai M, Nakamura K, Miura K, Yoshita K, Morikawa Y, Ishizaki M, Murakami K, Kido T, Naruse Y, Sasaki S, Nakagawa H. Dietary Glycemic Index, Glycemic Load and Blood Lipid Levels in Middle-Aged Japanese Men and Women. J Atheroscler Thromb 17(10):1082-95, 2010.

【目的】グリセミックインデックス(GI)は、食品を摂取した際の血糖値の上昇の程度を、基準食品（ブドウ糖）を100として数値化した指標である。またグリセミックロード(GL)は、GI値に炭水化物摂取量を掛けた指標である。近年、欧米を中心にGI値とメタボリックシンドロームの代表的な病態の一つである脂質異常症との関連が報告されている。今回、日本人中年男女におけるGI、GL値と血清脂質との関連を検討した。

【方法】北陸の某製造業事業所の35歳以上の男性2,257名、女性1,598名に自記式食事歴法質問票(DHQ)を用いた食事調査を行い、習慣的な食事のGI値、GL値を計算した。男女別のGI値、GL値各5分位における総コレステロール(TC)、中性脂肪(TG)、HDLコレステロール(HDLc)、LDLコレステロール(LDLc)の年齢・BMIで調整、および多変量（年齢・BMI・飲酒・喫煙・身体活動量・閉経(女性)・摂取総熱量・食物繊維摂取量・飽和脂肪酸・一価不飽和脂肪酸・n-3 多価不飽和脂肪酸・n-6 多価不飽和脂肪酸・食事性コレステロール）で調整した平均値を共分散分析にて算出し，群間で比較した。

【結果】GI値とTC、TG、HDLc、LDLc、non HDLcのいずれとの間にも有意な関連は認めなかった。GL値5分位における多変量モデルにおいて、HDLc(平均値±標準誤差)は、男性では61.0±0.7、59.4±0.6、57.8±0.6、58.1±0.6、56.8±0.8 (p for trend = 0.001)、女性では70.7±1.0、70.6±0.9、67.0±0.8、67.0±0.8、64.3±1.18 (p for trend <0.001)と、男女ともにGL値が高いものほどHDL-Cは有意に低値だった。さらに女性ではGL値5分位における多変量調整モデルおいて、TGで62.5 (58.9-66.4)、63.8 (60.5-67.3)、66.5 (63.3-69.9)、68.2 (64.8-71.9)、71.3 (66.6-76.2)、(p for trend=0.011)、LDLcで122.3±2.0、125.0±1.8、126.6±1.6、129.1±1.7、129.0±2.2 (p for trend=0.035)、non HDLcで136.4±2.1、139.3±1.9、141.6±1.8、144.7±1.9、145.4±2.4 (p for trend=0.010)と有意な正の関連を認めた。

【まとめ】日本人中年男女において、GLとHDLcは負に関連していた。また女性において、GLは、LDLc、nonHDLcと正に関連していた。女性において、高GL食は低HDLc血症、高LDLc血症、高nonHDLc血症を介して動脈硬化を促進させている可能性が示唆された。

D. まとめ

富山職域コホートでは、職域の特徴を生かしたコホート研究を、引き続き継続して展開していく予定である。現在、働き盛りの中年労働者の生活習慣、職業的要因と循環器疾患危険因子との関連を検討中であり、今後横断研究、縦断研究として肥満・メタボリックシンドロームの疫学に関する研究の成果を発表していく。

E. 研究発表

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F. 知的財産権の出願・登録状況（予定を含む）

なし

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表雑誌	巻号	ページ	出版年
Hirokawa W, Nakamura K, Sakurai M, Morikawa Y, Miura K, Ishizaki M, Yoshita K, Kido T, Naruse Y, Nakagawa H.	Mild metabolic abnormalities, abdominal obesity and the risk of cardiovascular diseases in middle-aged Japanese men	J Atheroscler Thromb	17	934-943	2010
Nakashima M, Sakurai M, Nakamura K, Miura K, Yoshita K, Morikawa Y, Ishizaki M, Murakami K, Kido T, Naruse Y, Sasaki S, Nakagawa H.	Dietary Glycemic Index, Glycemic Load and Blood Lipid Levels in Middle-Aged Japanese Men and Women.	J Atheroscler Thromb	17	1082-95	2010
Nakamura K, Sakurai M, Miura K, Morikawa Y, Ishizaki M, Yoshita K, Kido T, Naruse Y, Nakagawa H.	Homeostasis model assessment of insulin resistance and the risk of cardiovascular events in middle-aged non-diabetic Japanese men.	Diabetologia	53	1894-902	2010

Original Article

Mild Metabolic Abnormalities, Abdominal Obesity and the Risk of Cardiovascular Diseases in Middle-Aged Japanese Men

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***Aim*:** We investigated the individual and population impacts of mild abnormalities associated with metabolic syndrome (blood pressure, lipids and glucose) and abdominal obesity, for which lifestyle modification is initially applicable, on cardiovascular disease risk.

***Methods*:** Using a cohort study of 2,685 Japanese men aged 35 to 59 years with an 11-year follow-up period, we calculated the relative risks for cardiovascular diseases due to mild metabolic abnormalities that included at least one of the following three conditions: 1) systolic blood pressure 130–139 mmHg and/or diastolic blood pressure 85–89 mmHg; 2) triglycerides 150–299 mg/dL and/or high-density lipoprotein cholesterol 35–39 mg/dL; and 3) fasting plasma glucose 110–125 mg/dL and/or abdominal obesity. Participants with a mild metabolic abnormality were compared to participants with no metabolic abnormality or abdominal obesity. The population attributable fraction of these abnormalities for cardiovascular diseases was also estimated.

***Results*:** At baseline, 9.8% and 21.8% of the total population had a mild metabolic abnormality with or without abdominal obesity, respectively, while 7.5% had isolated abdominal obesity without any metabolic abnormality. A mild metabolic abnormality with or without abdominal obesity and isolated abdominal obesity increased the risk of cardiovascular disease by 2.68-fold, 1.49-fold, and 2.36-fold, respectively. Approximately 20% of cardiovascular diseases in the total population were attributable to either mild metabolic abnormalities or isolated abdominal obesity.

***Conclusion*:** The importance of lifestyle modification should be acknowledged, especially in cases of mild metabolic abnormality and/or abdominal obesity, which may contribute to approximately 20% of the population burden for cardiovascular diseases.

J Atheroscler Thromb, 2010; 17:934-943.

Key words; Abdominal obesity, Blood pressure, Cardiovascular diseases, Glucose, Lipids

Introduction

Cardiovascular risk factors, such as elevated blood pressure, abnormal lipid profiles and disordered glucose metabolism, have a graded linear relationship with the risk of cardiovascular diseases, including coronary heart disease and stroke[1-5]. On the basis of this evidence, more rigorous intervention is applicable for worse conditions. Thus, individuals with moderate-to-severely abnormal findings are generally required to be under medical control. Individuals with only mildly abnormal findings are usually encouraged to improve these abnormalities, using non-pharmacological therapy, at health checkups and with healthcare advice,

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even though the individuals may have several mildly abnormal findings.

In 2008, the Japanese national government introduced a nationwide public health strategy to reduce the burden of cardiovascular diseases due to abdominal obesity and associated metabolic disorders, mainly elevated blood pressure, high triglycerides, low high-density lipoprotein (HDL) cholesterol, and disordered glucose metabolism[6-8]. In this strategy, which is influenced by the Japanese concept and diagnostic criteria of metabolic syndrome[9], priority is given to obese individuals who have metabolic disorders, with the concept that such individuals should modify their lifestyle in order to decrease the accumulation of abdominal fat, which in turn may lead to the control of blood pressure and lipid and glucose levels. In addition, the severity of metabolic disorders is also considered to determine whether individuals should be treated first using pharmacological or non-pharmacological therapies. Although non-obese individuals with a metabolic abnormality are not prior candidates in this strategy, appropriate healthcare advice should be provided for such non-obese individuals. Non-obese individuals with a mild metabolic abnormality are also in need of non-pharmacological therapy initially, but this therapy is, at least partially, different from what is required for obese individuals with a mild metabolic abnormality. There is therefore a need to examine the risk of developing cardiovascular diseases, taking into account the above situations as they apply to the Japanese population. It is particularly important for public health purposes, such as medical checkups and healthcare advice, to estimate the population burden of cardiovascular diseases due to mild metabolic abnormality with and without abdominal obesity, for which appropriate non-pharmacological therapy should be applied, depending on the presence or absence of abdominal obesity. To the best of our knowledge, little is known about the risk of developing cardiovascular diseases due to mild metabolic abnormalities associated with metabolic syndrome and/or abdominal obesity in the Japanese population, as previous studies have mainly examined the association between metabolic disorders (or morbid conditions pursuant to this syndrome) and the risk of these diseases, without considering the severity of the metabolic disorders and excluding individuals who are taking medication for metabolic disorders[10-18]. We used a cohort study in middle-aged Japanese men to investigate the individual and population impacts of mild abnormalities associated with metabolic syndrome and/or abdominal obesity on the risk of cardiovascular diseases.

Participants and Methods

Study Design and Participants

The study population consisted of Japanese men who worked for a metal products factory in Toyama prefecture, Japan. The Industrial Safety and Health Law in Japan requires employers to conduct annual health examinations for all employees. Details of this study population have been reported previously[15, 19, 20]. A total of 2,952 male employees aged 35 to 59 years, who underwent a health examination in 1996, were enrolled in the study, with subsequent follow-up for 11 years until March 2007. The present cohort study was approved by the Institutional Review Committee of Kanazawa Medical University for Ethical Issues.

Of the 2,952 participants, 267 were excluded due to either a history of previous cardiovascular disease ($n=11$), taking medications for either hypertension, hypercholesterolemia, hypertriglyceridemia and/or diabetes ($n=211$), missing information at the time of the baseline survey ($n=12$), or failure to obtain information in the follow-up survey ($n=33$). The remaining 2,685 participants were included in the analyses.

Baseline Examination

Data collected at study entry included age, medical history, smoking and alcohol drinking habits, leisure-time physical activity, and anthropometric indices, including waist circumference, blood pressure, serum total cholesterol, HDL cholesterol, triglycerides and fasting plasma glucose. Fasting blood samples were obtained by cubital venipuncture and then shipped to one laboratory (BML, Inc., Toyama, Japan) for analysis. Plasma glucose levels were measured enzymatically using an automatic analyzer. Total cholesterol and triglyceride levels were measured by enzyme assay using another automatic analyzer, while HDL cholesterol levels were measured by a direct determination method. A single blood pressure measurement was carried out by trained staff using a mercury sphygmomanometer after the participants had rested for five minutes in the seated position. Waist circumference was measured above the iliac crest and below the lowest rib margin during minimal respiration in the standing position. Medical history, cigarette smoking and alcohol drinking habits, and leisure-time physical activity were evaluated using a self-administered questionnaire.

Definition of the Absence or Presence of Mild or Moderate-to-Severe Metabolic Abnormalities and Abdominal Obesity

Abnormalities in blood pressure, lipids (triglycer-

Table 1. Definition of normal, mildly abnormal and moderate-to-severely abnormal levels of blood pressure, lipids and glucose

	Normal	Abnormal	
		Mildly	Moderate-to-severely
Blood pressure	SBP <130 mmHg and DBP <85 mmHg	SBP 130-139 mmHg and/or DBP 85-89 mmHg	SBP ≥140 mmHg and/or DBP ≥90 mmHg
Lipids	TG <150 mg/dL and HDLC ≥40 mg/dL	TG 150-299 mg/dL and/or HDLC 35-39 mg/dL	TG ≥300 mg/dL and/or HDLC ≥34 mg/dL
Glucose	FPG <110 mg/dL	FPG 110-125 mg/dL	FPG ≥126 mg/dL

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.
The present definitions were based on the Japanese metabolic syndrome criteria[9] and the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on metabolic syndrome) criteria[6-8]; the lower cut-off value of mildly abnormal glucose was defined using the former criteria.

ides and/or HDL cholesterol) and glucose were defined using the criteria of the Japanese Society of Internal Medicine on behalf of the Japanese Committee to Evaluate Diagnostic Standards for Metabolic Syndrome[9]. Each abnormality was then classified further as being either mildly or moderate-to-severely abnormal, using the criteria adopted by the Japanese health checkups and healthcare advice, with particular focus on metabolic syndrome ("*Tokutei Kenshin Tokutei Hoken Shidou*")[6-8]. Mildly abnormal blood pressure, lipids (triglycerides and/or HDL cholesterol), and glucose were defined as meeting the criteria for which individuals need support to modify their undesirable lifestyle in order to improve metabolic disorders according to the criteria of the *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on metabolic syndrome). Moderately-to-severely abnormal blood pressure, lipids and glucose were defined as meeting the criteria for which individuals should be advised to consult a physician. Details of this classification are shown in **Table 1**. The lower cut-off value for mildly abnormal glucose was set as 110 mg/dL, which represents the Japanese metabolic syndrome criteria[9] and not 100 mg/d, the criteria used in the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on metabolic syndrome)[6-8].

The study participants were diagnosed as having no, mild, or moderate-to-severe metabolic abnormality after comprehensive evaluation of blood pressure, lipids, and glucose (**Table 2**). Participants who did not have abnormal blood pressure, lipid profile or glucose levels were classified as having "no metabolic abnormality". Participants who had at least one mild abnormality of either blood pressure, lipids or glucose without moderate-to-severely abnormal blood pressure, lipids or glucose were classified as having a "mild metabolic abnormality". Participants who had at least one moderate-to-severe abnormality in either blood pressure, lipids or glucose were classified as having a "moderate-to-severe metabolic abnormality".

Abdominal obesity, defined as a waist circumference ≥85 cm, was treated separately from abnormal blood pressure, lipids and glucose, as the criteria for Japanese metabolic syndrome regards it as a mandatory element[9].

Follow-Up Survey

Vital status and the incidence of cardiovascular diseases were ascertained in March 2007, representing a follow-up period of over 11 years. For participants who stayed at the target factory, questionnaires on medical history at annual health checkups and medical certifications of sickness absence were used to obtain information on the cardiovascular disease history during the follow-up period. For retired participants, questionnaires on cardiovascular disease history were sent annually by mail. For deceased participants, information was obtained from family members. The medical records of every participant who was considered as having a history of cardiovascular disease from this procedure were reviewed to confirm the diagnosis, without knowledge of the variables at baseline. In some deceased cases, death certifications were referenced. If a participant had died or a retired participant did not reply to the questionnaire on cardiovascular disease history, follow-up was stopped at that point.

Table 2. Definition of no, mild, or moderate-to-severe metabolic abnormality after comprehensively evaluating blood pressure, lipids and glucose

No metabolic abnormality	Mild metabolic abnormality	Moderate-to-severe metabolic abnormality
Having all the following conditions: 1) Normal blood pressure (SBP < 130 mmHg and DBP < 85 mmHg) 2) Normal lipids (TG < 150 mg/dL and HDLC ≥ 40 mg/dL) 3) Normal glucose (FPG < 110 mg/dL)	Having at least one of the following conditions: 1) Mildly abnormal blood pressure (SBP 130-139 mmHg and/or DBP 85-89 mmHg) 2) Mildly abnormal lipids (TG 150-299 mg/dL and/or HDLC 35-39 mg/dL) 3) Mildly abnormal glucose (FPG 110-125 mg/dL) without any of the following conditions: 1) Moderate-to-severely abnormal blood pressure (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) 2) Moderate-to-severely abnormal lipids (TG ≥ 300 mg/dL and/or HDLC ≥ 34 mg/dL) 3) Moderate-to-severely abnormal glucose (FPG ≥ 126 mg/dL)	Having at least one of the following conditions: 1) Moderate-to-severely abnormal blood pressure (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) 2) Moderate-to-severely abnormal lipids (TG ≥ 300 mg/dL and/or HDLC ≥ 34 mg/dL) 3) Moderate-to-severely abnormal glucose (FPG ≥ 126 mg/dL)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.

The diagnostic criteria for myocardial infarction were modified from those of the MONItoring trends and determinants of CArdiovascular disease (MONICA) project conducted by the World Health Organization[21]. Myocardial infarction was defined as suffering typical chest pain with findings of abnormal and persistent Q or QS waves on an electrocardiogram and/or changes in cardiac enzyme activity. Sudden cardiac death was defined as death within one hour of onset, a witnessed cardiac arrest or abrupt collapse. Angina pectoris was also included as a coronary heart disease event in individuals who underwent coronary artery angioplasty or bypass surgery. Stroke was defined as suffering a focal neurological disorder with rapid onset, which persisted for at least 24 hours or until death, with supporting evidence from imaging examinations, such as computed tomography or magnetic resonance imaging. The diagnosis of stroke subtype was classified on the basis of the imaging examinations.

The outcome used in the present study was a first-ever incident event of all cardiovascular diseases that included coronary heart disease and stroke. The former included myocardial infarction, sudden cardiac death, and angina pectoris requiring an intervention for the coronary arteries, while the latter included cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and unspecified stroke.

Statistical Analysis

The three metabolic abnormality groups (i.e., no, mild, or moderate-to-severe metabolic abnormality) defined in the previous section (**Table 2**) were stratified further according to the presence or absence of abdominal obesity. This yielded the following six groups: 1) no metabolic abnormality without abdominal obesity; 2) mild metabolic abnormality without abdominal obesity; 3) moderate-to-severe metabolic abnormality without abdominal obesity; 4) no metabolic abnormality with abdominal obesity; 5) mild metabolic abnormality with abdominal obesity; and 6) moderate-to-severe metabolic abnormality with abdominal obesity. Hazard ratios, compared to the no metabolic abnormality without abdominal obesity group, were calculated for the five other groups. A Cox proportional hazard model was used to calculate the hazard ratios and their corresponding 95% confidence intervals for the outcomes in each group. This model incorporated the following variables as covariates: age (35-39, 40-44, 45-49, 50-54, 55-59 years), smoking habits (current, former, never smoked), drinking habits (heavy, light, occasional, no drinking), leisure-time physical activity (hard, moderate, light, no activity) and non-HDL cholesterol level (< 170, ≥ 170 mg/dL). Non-HDL cholesterol was calculated as total cholesterol - HDL cholesterol and was used as a covariate instead of low-density lipoprotein cholesterol, the level of which could not be calculated for participants with extremely high triglyceride levels[22].

The population attributable fraction, which represents the contribution of mild and moderate-to-severe metabolic abnormalities to cardiovascular disease in the study population, was then estimated as

Table 3. Baseline risk characteristics of the 2,685 male study participants in a workplace, Toyama, Japan (1996). Data are presented for the total study population and also grouped according to metabolic abnormality and abdominal obesity status.

		Without abdominal obesity			With abdominal obesity			
	Overall	No metabolic abnormalitiy	Mild metabolic abnormalitiy	Moder-to-sev metabolic abnormalitiy	No metabolic abnormalitiy	Mild metabolic abnormalitiy	Moder-to-sev metabolic abnormalitiy	*p* values[†]
Participants	2,685	1,015	584	342	202	264	242	
Age (yrs)	45.2 (±6.5)	44.3 (±6.2)	45.3 (±6.3)	47.0 (±6.8)	44.9 (±6.2)	45.0 (±6.2)	47.0 (±6.9)	<0.01
Height (cm)	167.8 (±6.0)	167.4 (±6.0)	167.2 (±6.1)	167.0 (±6.1)	169.1 (±5.8)	169.2 (±6.0)	168.8 (±6.0)	<0.01
Weight (kg)	65.4 (±8.8)	61.4 (±6.7)	62.9 (±6.6)	62.7 (±7.2)	73.8 (±6.5)	75.0 (±7.0)	75.4 (±7.0)	<0.01
Body mass index (kg/m^2)	23.2 (±2.7)	21.8 (±2.0)	22.5 (±2.1)	22.4 (±2.1)	25.8 (±2.0)	26.1 (±2.2)	26.4 (±2.1)	<0.01
Waist circumference (cm)	79.8 (±7.6)	75.4 (±5.4)	77.6 (±4.9)	77.7 (±4.9)	88.7 (±3.7)	89.3 (±4.0)	89.8 (±4.3)	<0.01
Cigarette smoking (%)								0.34
Never	29.1%	29.8%	26.7%	31.9%	29.2%	29.5%	27.3%	
Former	11.3%	10.3%	10.8%	10.5%	15.3%	11.0%	14.9%	
Current	59.6%	59.9%	62.5%	57.6%	55.4%	59.5%	57.9%	
Alcohol drinking (%)								<0.01
No	22.7%	24.5%	20.5%	19.3%	18.3%	23.9%	27.3%	
Occasional	30.9%	31.0%	32.2%	28.9%	32.7%	29.2%	30.2%	
Light	27.6%	28.4%	26.0%	28.9%	29.7%	31.8%	19.4%	
Heavy	18.8%	16.1%	21.2%	22.8%	19.3%	15.2%	23.1%	
Leisure-time physical activity (%)								0.10
No	66.6%	66.7%	67.5%	61.7%	66.8%	68.2%	68.6%	
Light	19.4%	17.1%	19.9%	22.8%	21.3%	18.2%	23.6%	
Moderate	9.9%	11.4%	8.6%	10.8%	8.4%	10.6%	5.4%	
Hard	4.1%	4.8%	4.1%	4.7%	3.5%	3.0%	2.5%	
Systolic blood pressure (mmHg)	121.3 (±13.3)	113.4 (±8.6)	123.8 (±10.7)	135.3 (±14.4)	115.3 (±7.8)	123.6 (±10.0)	132.6 (±14.1)	<0.01
Diastolic blood pressure (mmHg)	76.3 (±10.0)	70.9 (±7.2)	77.1 (±8.2)	86.1 (±10.5)	72.9 (±7.0)	78.3 (±7.3)	84.4 (±10.8)	<0.01
Serum triglycerides (mg/dL)*	99 (70-146)	79 (61-102)	126 (81-173)	115 (72-177)	94 (72-116)	153 (100-190)	164 (110-260)	<0.01
Serum HDL cholesterol (mg/dL)	55.2 (±15.0)	59.9 (±14.1)	54.5 (±14.7)	54.7 (±18.2)	53.0 (±9.7)	48.5 (±11.8)	45.8 (±13.9)	<0.01
Serum non-HDL cholesterol (mg/dL)	148.5 (±34.0)	139.1 (±31.0)	149.6 (±34.9)	150.3 (±36.2)	150.6 (±28.4)	163.3 (±32.2)	166.9 (±32.6)	<0.01
Fasting plasma glucose (mg/dL)*	90 (85-97)	88 (83-93)	91 (85-97)	94 (87-105)	89 (85-95)	92 (86-98)	97 (89-109)	<0.01

Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; Moder-to-sev, Moderate-to-severe.
Values are expressed as the mean (±standard deviation), median (interquartile range) or the % of participants in that category; *median is presented due to the skewed distributions.
[†] One-way analysis of variance, Kruskal Wallis test or chi- square tests were used to compare each risk characteristic among the six groups.

proportion × (hazard ratio −1)/hazard ratio[23], using the proportion of incident cases in the metabolic abnormality group and the multivariate-adjusted hazard ratio derived from this analysis.

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 12.0J for Windows (SPSS Japan Inc., Tokyo, Japan). All probability values were two-tailed and the significance level was set at $p<0.05$.

Results

Characteristics of the Study Population

The baseline characteristics of the 2,685 study participants in total and grouped according to the severity of metabolic abnormality and abdominal obesity status are summarized in **Table 3**. The mean age of the study population was 45.2 years. Of the total participants, 39.1% had neither metabolic abnormal-

Table 4. Hazard ratios for the incidence of cardiovascular disease due to mildly or moderate-to-severely abnormal levels of each metabolic disorder and abdominal obesity, in 2,685 male participants over 11 years of follow-up (1996–2007)

	Participants	Cardiovascular diseases	
		Events	Multivariate-adjusted HR (95% CI)*
Blood pressure			
Normal	1,768	29	1.00 reference
Mildly abnormal	530	13	1.37 (0.70–2.65)
Moderate-to-severely abnormal	387	16	1.99 (1.04–3.79)
Lipids (triglycerides/high- density lipoprotein cholesterol)			
Normal	1,910	34	1.00 reference
Mildly abnormal	591	16	1.11 (0.60–2.07)
Moderate-to-severely abnormal	184	8	1.27 (0.55–2.93)
Glucose			
Normal	2,483	48	1.00 reference
Mildly abnormal	123	5	1.39 (0.54–3. 57)
Moderate-to-severely abnormal	79	5	1.70 (0.65–4.45)
Abdominal obesity status			
Non-obese	1,977	32	1.00 reference
Obese	708	26	1.87 (1.07–3.26)

Abbreviations: HR, hazard ratio; CI, confidence interval.
Hazard ratios, with normal acting as the reference, were calculated using a Cox proportional hazards regression model adjusted for age, smoking habits, drinking habits, leisure- time physical activity, serum non-high-density lipoprotein cholesterol, the three residual factors (blood pressure, lipids, and glucose) and abdominal obesity status.

ity nor abdominal obesity, 21.8% had a mild metabolic abnormality without abdominal obesity, 12.7% had a moderate-to-severe metabolic abnormality without abdominal obesity, 7.5% had isolated abdominal obesity without any metabolic abnormality, 9.8% had a mild metabolic abnormality with abdominal obesity and 9.0% had a moderate-to-severe metabolic abnormality with abdominal obesity. The mean age increased with worsening metabolic abnormalities for participants with and without abdominal obesity. With a few exceptions, mean blood pressure, triglyceride and fasting glucose levels increased with worsening metabolic abnormalities, whereas mean HDL cholesterol decreased with worsening metabolic status. Mean non-HDL cholesterol also increased with worsening metabolic abnormalities.

Individual Risk of Cardiovascular Diseases Due to Each Metabolic Disorder and Abdominal Obesity

The study involved 26,882 person-years of follow-up in the 2,685 study participants. The mean overall follow-up period was 10.0 years. During follow-up, 58 first-ever incident events of cardiovascular diseases were recorded, including 20 myocardial infarctions, 4 sudden cardiac deaths, 5 cases of angina pectoris with coronary intervention, 17 cerebral infarctions, 8 cerebral hemorrhages, and 4 subarachnoid hemorrhages. The crude incidence rate of cardiovascular diseases in the study population was 2.16/1000 person-years.

Table 4 shows that the increased severity of elevations in blood pressure, dyslipidemia or disordered glucose metabolism was likely to independently increase the risk of cardiovascular disease. Abdominal obesity was also an independent risk factor for cardiovascular diseases.

Individual Risk of Cardiovascular Diseases Due to Mild or Moderate-to-Severe Metabolic Abnormalities and/or Abdominal Obesity

Table 5 shows the hazard ratios for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity. Compared to the absence of any metabolic abnormality and abdominal obesity, a moderate-to-severe metabolic abnormality without abdominal obesity, a mild metabolic abnormality with abdominal obesity and a moderate-to-severe metabolic abnormality with

Table 5. Hazard ratios for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity, in 2,685 male participants over 11 years of follow-up (1996–2007)

	No metabolic abnormalitiy	Mild metabolic abnormalitiy	Moderate-to-severe metabolic abnormalitiy
Without abdominal obesity			
Participants	1,051	584	342
Total person-years of follow-up	10,739	5,821	3,399
Cardiovascular events	11	10	11
Crude rate per 1000 person-years	1.02	1.72	3.24
Age- adjusted HR (95% CI)*	1.00 reference	1.54 (0.65–3.63)	2.51 (1.08–5.82)
Multivariate-adjusted HR (95% CI)**	1.00 reference	1.49 (0.63–3.52)	2.52 (1.08–5.87)
With abdominal obesity			
Participants	202	264	242
Total person-years of follow-up	1,982	2,611	2,329
Cardiovascular events	5	8	13
Crude rate per 1000 person-years	2.52	3.06	5.58
Age-adjusted HR (95% CI)*	2.34 (0.81–6.74)	2.81 (1.13–7.00)	4.36 (1.94–9.82)
Multivariate-adjusted HR (95% CI)**	2.36 (0.81–6.82)	2.68 (1.07–6.73)	4.12 (1.80–9.43)

Abbreviations: HR, hazard ratio; CI, confidence interval.
Hazard ratios were calculated by a Cox proportional hazards regression model, with no metabolic abnormality without abdominal obesity acting as the reference; *adjusted for age; **adjusted for age, smoking habits, drinking habits, leisure-time physical activity and serum non-high-density lipoprotein cholesterol.

abdominal obesity increased the risk of cardiovascular disease by 2.52-fold, 2.68-fold, and 4.12-fold, respectively. All three of these hazard ratios were statistically significant. Mild metabolic abnormality without abdominal obesity and isolated abdominal obesity without any metabolic abnormality also tended to increase the risk of cardiovascular disease by 1.49-fold and 2.36-fold, respectively.

Population Risk of Cardiovascular Diseases Due to Mild or Moderate-to-Severe Metabolic Abnormalities and/or Abdominal Obesity

Fig. 1 shows the estimations of population attributable fractions for cardiovascular disease. These calculations showed that 19.3% of cardiovascular diseases that occurred in the study population were attributable to either a mild metabolic abnormality or abdominal obesity alone without any metabolic abnormality, 5.7% to a mild metabolic abnormality without abdominal obesity, 5.0% to isolated abdominal obesity, and 8.6% to a mild metabolic abnormality with abdominal obesity. Furthermore, 28.4% of cardiovascular diseases were attributable to a moderate-to-severe metabolic abnormality.

Discussion

This cohort study in middle-aged Japanese men demonstrated that the risk of cardiovascular disease was likely to be higher in participants who had a mild metabolic abnormality either with or without abdominal obesity and in participants who had isolated abdominal obesity without any metabolic abnormality for whom non-pharmacological therapy was required initially, compared to participants who had neither a metabolic abnormality nor abdominal obesity. Mild metabolic abnormality or isolated abdominal obesity contributed up to 20% of the cardiovascular diseases that occurred in the study population. The unique feature of this report is that the risk of cardiovascular disease due to the components of metabolic syndrome was evaluated from the viewpoint of intervention as a priority in health checkups and healthcare advice.

The mild metabolic abnormality based on our definitions is usually considered to require non-pharmacological therapy initially to improve the abnormality, regardless of the presence or absence of abdominal obesity. In contrast, moderate-to-severe metabolic abnormality based on our definitions is usually considered to require consultation with a physician[6-8]. Our results are reasonable according to this principle of health checkups and healthcare advice, when we viewed our results separately in obese and non-obese participants. The risk of cardiovascular disease tended to be the first and second highest in participants with a moderate-to-severe metabolic abnormality and in

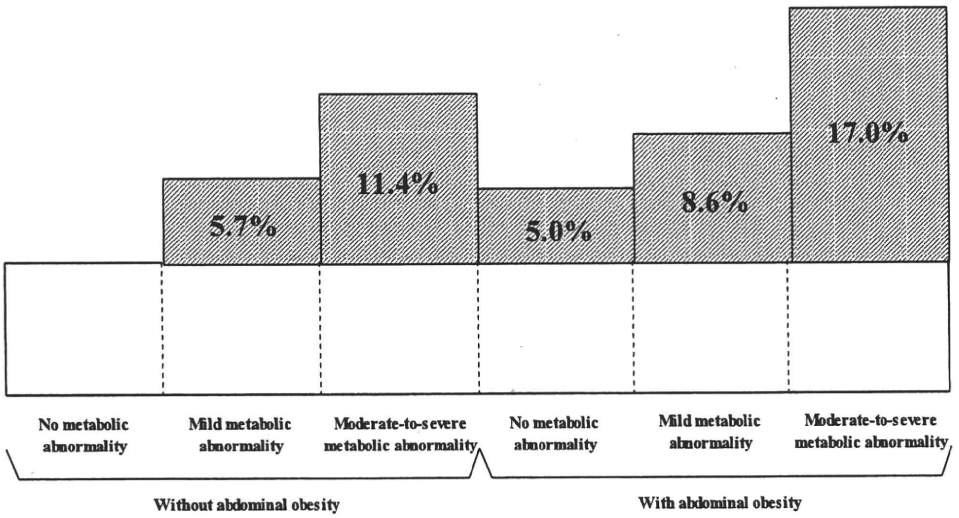

Fig. 1. Population attributable fraction for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity, in the study population over 11 years of follow-up (1996-2007).

participants with a mild metabolic abnormality, respectively, regardless of the abdominal obesity status, despite the corresponding risk originally being higher in participants with abdominal obesity than in those without. Surprisingly, our results indicate that some obese individuals with a mild metabolic abnormality have a cardiovascular risk that is as high as that in non-obese individuals with a moderate-to-severe metabolic abnormality. This suggests that it may be better to advise some obese individuals with a mild metabolic abnormality to consult a physician prior to recommending non-pharmacological therapy, due to their possible high risk of cardiovascular disease. Obese participants with two or more mild metabolic disorders, who met the Japanese metabolic syndrome criteria (i.e., presence of abdominal obesity accompanied by two or more metabolic disorders)[9], may have a higher cardiovascular risk than obese participants with only a single metabolic disorder. This concern arises from the findings of a previous study in a Western population carried out by Vasan and colleagues[24]. They observed that coronary heart disease event rates rose with increasing number of borderline abnormalities in blood pressure (systolic 120–139 mmHg or diastolic 80–89 mmHg), serum low-density lipoprotein cholesterol (100–159 mg/dL), high-density lipoprotein cholesterol (40–59 mg/dL), glucose (fasting 110–125 mg/dL or 2-hour post-prandial 140–199 mg/dL) and smoking habits (former smoking), although this previous study did not investigate abdominal obesity or serum triglycerides, which are components of the metabolic syndrome, but did record serum low-density lipoprotein cholesterol levels and smoking habits[24]. In fact, the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on metabolic syndrome) criteria[6-8] places importance on both the number and severity of metabolic abnormalities in health checkups and healthcare advice. Unfortunately, our study did not include a sufficiently large number of participants or events to conduct additional analyses using the number of mild metabolic abnormalities to further classify the participants. Further studies on a greater number of participants and cases are therefore warranted to clarify whether there is a further increase in cardiovascular disease risk in individuals with a cluster of mild metabolic disorders, compared to individuals with only a single metabolic disorder.

When non-obese and obese individuals were combined in our analyses, the burden of cardiovascular disease due to mild metabolic abnormalities and isolated abdominal obesity was equivalent to approximately two-thirds of the corresponding burden due to moderate-to-severe metabolic abnormalities. Approximately 15% of cardiovascular diseases in our study population were attributable to either abdominal obesity in association with a mild metabolic abnormality or isolated abdominal obesity. Ideally, rigorous lifestyle modification that decreases the accumulation of abdominal fat without the administration of medica-

tion is initially applicable. In other words, a value of 15% represents the ideal expected reduction in the burden of cardiovascular disease resulting from rigorous lifestyle modification to decrease abdominal fat accumulation without the need to take medication. On the other hand, other lifestyle modifications, such as reducing dietary sodium intake, are also of importance, especially in non-obese individuals with mild metabolic abnormalities, a group that contributed to approximately 5% of the cardiovascular diseases observed in our study population. This suggests that non-obese individuals with a mild metabolic abnormality should not be overlooked from the viewpoint of public health for the prevention of cardiovascular diseases in the Japanese population, who are relatively lean. The burden of cardiovascular disease due to combined mild and moderate-to-severe metabolic abnormalities was greater in obese participants than in non-obese participants: 30.6% (=5.0%+8.6%+17.0%) vs. 17.1% (=5.7%+11.4%). This pattern contradicts the finding in a previous Japanese study, which showed a greater population attributable fraction for ischemic cardiovascular disease among non-obese men with metabolic disorders (33%) than obese men with metabolic disorders and individuals with obesity alone (22%)[16]. This difference may be partially due to the different characteristics between these two study populations, suggesting that our observed burden of cardiovascular disease due to mild and moderate-to-severe metabolic abnormalities without abdominal obesity is underestimated, whereas the corresponding burden due to mild and moderate-to-severe metabolic abnormalities with abdominal obesity is overestimated.

The present study had several limitations. First, as our study participants consisted solely of male workers in one factory, it is necessary to take care when generalizing our results. Furthermore, participants who had already started to take medication for metabolic disorders prior to study entry were excluded. Second, the metabolic abnormalities in this report included high blood pressure, high triglycerides, low HDL cholesterol, and high glucose, which are components of metabolic syndrome, but did not include high total cholesterol, which is another determinant of cardiovascular disease risk[2]. Dyslipidemia was evaluated using a combination of triglyceride and HDL cholesterol levels based on the Japanese metabolic syndrome criteria[9]. In addition, mildly abnormal glucose control was defined as a fasting glucose level between 110 and 125 mg/dL; however, broadly similar hazard ratios were observed for cardiovascular disease due to mild and moderate-to-severe metabolic abnormalities and/or abdominal obesity, when the lower cut-off value was set as 100 mg/d, based on the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health check-ups and healthcare advice specifically focusing on metabolic syndrome) criteria[6-8] (data not shown). Third, we measured waist circumference, using the landmark above the iliac crest and below the lowest rib margin, which is different from the protocol in Japanese metabolic syndrome criteria, which uses the level of the umbilicus for the measurements[9]; however, one study suggested that the association between waist circumference and cardiovascular diseases is unlikely to depend on the measurement protocol[25]. Fourth, abdominal obesity was treated separately from blood pressure, lipids, and glucose, not only because it is an essential factor in Japanese metabolic syndrome criteria[9], but also because of a lack of evidence of mild and moderate-to-severe increases in waist circumference. Fifth, the follow-up survey protocol differed between participants who stayed at the target factory and retired participants. Although information on cardiovascular disease could be easily and completely obtained for participants staying at the factory, there were difficulties and failures in obtaining the corresponding information from retired participants. While this difference in data collection may have resulted in bias, the follow-up rate of the cohort was very high (99%) and therefore we consider that it is acceptable to disregard this possibility. Finally, we used a composite outcome in which coronary heart disease and stroke events were combined due to the relatively small number of events. In addition, coronary heart disease included cases of angina pectoris that required intervention for the coronary arteries.

In conclusion, obese and non-obese individuals with mildly abnormal blood pressure, lipids and/or glucose, and obese individuals without any metabolic disorders may have, on average, an approximately 2-fold increased risk of cardiovascular disease, compared to individuals with neither metabolic disorders nor abdominal obesity. The importance of lifestyle modification should be acknowledged, especially in cases of a mild metabolic abnormality and/or abdominal obesity, which may contribute to approximately 20% of the population burden of cardiovascular diseases.

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Original Article

Dietary Glycemic Index, Glycemic Load and Blood Lipid Levels in Middle-Aged Japanese Men and Women

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Aims: This study investigated the association between dietary glycemic index (GI)/glycemic load (GL) and serum lipids in middle-aged Japanese men and women.
Methods: The study participants were employees of a metal products factory in Japan: 2,257 men and 1,598 women aged 35 years or older. Dietary GI and GL were assessed using a self-administered diet history questionnaire. Serum lipid levels, adjusted for age, body mass index, alcohol consumption, smoking, physical activity, menopause status, and dietary intake of total energy, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol and fiber, were compared among GI/GL quintiles for each gender.
Results: No significant associations were observed between GI and adjusted serum lipids in men or women. In contrast, GL was inversely associated with HDL-cholesterol in men and women (p for trend=0.001 for men and <0.001 for women), and positively associated with non-HDL-cholesterol (p for trend=0.010), LDL-cholesterol (p for trend=0.035) and triglycerides (p for trend=0.011) in women; however, alcohol drinking affected these associations; there was no association between GL and serum lipids in male nondrinkers and between GL and LDL-cholesterol in female nondrinkers.
Conclusion: GL was inversely associated with HDL-cholesterol and positively associated with non-HDL-cholesterol in Japanese women. These associations in men were not observed in nondrinkers. A high-GL diet for women may have an atherogenic effect through these serum lipid abnormalities.

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Key words; Glycemic index, Glycemic load, HDL-cholesterol, LDL-cholesterol, Japanese

Introduction

In 1981, Jenkins *et al.* noticed that foods with an equivalent carbohydrate content were associated with a variable rise in postprandial glucose and reported glycemic indices (GIs) representing a numerical measure of hyperglycemic response to glucose load for 51 different kinds of food[1]. Dietary GI can be calculated based on the GI for each food and the carbohydrate contribution of each food to the overall diet. Glycemic load (GL) is a measure that considers both dietary GI and the amount of carbohydrate intake[2]. Recently, an association between dietary GI/GL and several diseases, including type 2 diabetes and cancer, has been

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reported[3].

The association between GI and high-density lipoprotein cholesterol (HDL-C) was reported in previous studies involving Western and Asian populations[4-10]; however, some studies conducted in Western countries[11, 12] have reported no significant association between GI/GL and HDL-C. In contrast, a recent U.S. study in middle-aged women reported not only a significant inverse association between GI and HDL-C but also a significant positive association between GI and low-density lipoprotein cholesterol (LDL-C)[7]. Reports on the association between GI/GL and serum lipids are limited, and the results are largely inconsistent.

Previous studies have frequently been conducted in the U.S. and Europe, and only a few reports are from Asian populations[8-10] with higher rice intake and lower fat intake, which is significantly different, in terms of the foods contributing to dietary GI, to the intake of Western populations[13]. Studies from Japan are limited to women, and there are no studies available regarding middle-aged Japanese men. Furthermore, only one study from an Asian population examined the association between GI/GL and LDL-C, and there are no reports evaluating the association between GI/GL and non-HDL-C.

The present study was designed to determine the association between dietary GI/GL and serum lipids in a large population comprised of Japanese middle-aged men and women who had different dietary habits to Western populations.

Methods

Participants

The participants were 4,593 employees (2,813 men and 1,780 women), aged 35-years or older, of a manufacturer that produces zippers and aluminum sashes in Toyama Prefecture, Japan. In 2003, a regular mass health examination and a self-administered diet history questionnaire were conducted. Of the 4,593 employees, 4,327 (94%) (2,590 men and 1,737 women) underwent the health examination and responded to the diet survey. Employees with total calorie intake below 500 kcal or above 5,000 kcal (n = 16), those with extremely high triglycerides (>400 mg/dL) and inadequately calculated LDL-C (n = 46), and those on medication for hyperlipidemia (n = 136), hypertension (n = 226), and diabetes mellitus (n = 48) were excluded. Thus, 3,855 participants (2,257 men and 1,598 women) were analyzed in this report.

Data Collection

Body height and weight were measured during a regular annual health examination conducted at the company in 2003. Body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Total cholesterol, triglycerides, and HDL-C were measured using fasting blood samples. Total cholesterol and triglycerides were measured enzymatic ally, and HDL-C was measured directly. Quality control was conducted for the lipid measurements based on the Centers for Disease Control and Prevention / US Cholesterol Reference Method Laboratory Network. LDL-C was calculated using the Friedewald formula as described below[14]:

LDL-C (mg/dL) = total cholesterol (mg/dL) − HDL-C (mg/dL) − triglycerides (mg/dL) × 0.2

Non-HDL cholesterol (non-HDL-C) was calculated as total cholesterol minus HDL-C.

Smoking status (presence or absence of a smoking habit), intensity of physical activity (none, mild, moderate or severe), and the menopause status for women were determined based on a health examination questionnaire.

Dietary Assessment

Dietary habits during the preceding month were assessed using a self-administered diet history questionnaire (DHQ)[15]. The DHQ was developed to estimate the dietary intake of macronutrients and micronutrients for epidemiological studies in Japan. A detailed description of the methods used for calculating dietary intake and the validity of the DHQ have been published previously[13, 16-18]. Estimates of dietary intake for 147 food and beverage items, energy and nutrients were calculated using an ad hoc computer algorithm developed for the DHQ based on the Standard Tables of Food Composition in Japan.

Calculation of Dietary GI and GL

The GI of a food is defined as the 2-hour incremental area under the blood glucose response curve after consumption of a food portion containing a specific amount (usually 50 g) of available carbohydrate, divided by the corresponding area after consumption of a portion of a reference food (usually glucose or white bread) containing the same amount of available carbohydrate, and multiplied by 100 to be expressed as a percentage[2]. We calculated dietary GI by multiplying the percentage contribution of each individual food to daily available carbohydrate intake by the GI value of the food and summed these products. Available carbohydrate was calculated as total carbohydrate

minus dietary fiber[2]. We also calculated dietary GL by multiplying the dietary GI by the total amount of daily available carbohydrate intake (divided by 100). Of the 147 food and beverage items included in the DHQ, six (4.1%) are alcoholic beverages, eight (5.4%) contain no available carbohydrate and 63 (42.9%) contain less than 3.5 g available carbohydrate per serving. The calculation of dietary GI and GL was thus based on the remaining 70 items with GI values ranging from 16 to 91. A detailed description of the calculation of dietary GI and GL used in the present study as well as a table of GI values for each item have been published elsewhere[9, 13].

Statistical Analysis

The gender-specific mean values of age, height, weight, BMI, and serum lipids (total cholesterol, triglycerides, HDL-C, LDL-C, and non-HDL-C) in each GI/GL quintile were determined. The mean serum lipid levels were calculated in each GI/GL quintile adjusted for age and BMI (model 2) or for multiple variables (i.e. age, BMI, alcohol consumption, smoking status, degree of habitual exercise, menopausal status (women), total energy intake, dietary intakes of saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), n-3 polyunsaturated fatty acids (PUFA), n-6 PUFA, dietary cholesterol and dietary fiber) (model 3) through analysis of covariance. For each variable, categorization and dummy variable adjustment were performed; three categories of alcohol consumption determined by the DHQ for men (nondrinker, consumed less than 20 g/day, consumed 20 g or more) and two categories of alcohol consumption for women (nondrinker or drinker), two categories of smoking status (current smoker or not), three categories for the degree of habitual exercise (no, light, moderate to strong), and five categories (quintile) for total energy intake (kcal/day), SFA (g/day), MUFA (g/day), n-3 PUFA (g/day), n-6 PUFA (g/day), dietary cholesterol (mg/day) and dietary fiber intake (g/day). Triglycerides were converted logarithmically for analysis. Linear trends with increasing levels of dietary GI and GL were tested by assigning each participant the median value for the category and modeling this value as a continuous variable. Similar analyses were conducted in subgroups based on drinking status (nondrinkers or drinkers) in both men and women, and in subgroups based on the menopausal status (pre- or postmenopause) in women. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS version 17.0J; SPSS, Tokyo, Japan). $P<0.05$ was considered significant.

Results

The characteristics of the study participants are shown in **Supplemental Table 1**. The mean ages were 47.4 years for men and 47.0 years for women. The mean BMIs were 23.3 kg/m^2 for men and 22.4 kg/m^2 for women. Thirty-nine percent of women were postmenopausal. The mean carbohydrate and fat intake (% of energy) were 57.8% and 21.4% for men and 59.2% and 25.8% for women, respectively. The mean dietary GIs were 69.3 for men and 68.0 for women. The mean dietary GLs (/1,000 kcal) were 88.2 for men and 89.2 for women. White rice was the largest contributor to dietary GI/GL (61.6% for men and 53.6% for women), followed by bread (6.9%), noodles (5.5%), and confectionery (5.1%) for men and confectionery (10.1%), bread (8.9%), and sugar (5.3%) for women (data shown in **Supplemental Table 2**).

In men and women, being in the higher GI and GL quintiles was associated with a significantly higher mean age, and no significant association between either GI or GL and BMI was observed (GL results are shown in **Table 1** and **2**). Higher GL was also associated with less alcohol, a lower habitual exercise rate, lower dietary energy intake, lower fatty acid intake, and higher carbohydrate intake.

GI was not significantly associated with serum lipids in men, and higher GI was associated with significantly higher triglycerides and non-HDL-C in women (data shown in **Supplemental Table 3**). When the mean serum lipid levels in the GI quintiles adjusted for multiple variables were determined, GI was significantly and inversely associated only with TG for men (p for trend=0.029), and no significant association between GI and serum lipids was observed for women (data not tabulated).

The mean serum lipid levels in each GL quintile are shown in **Table 3** and **4**. In men (**Table 3**), higher GL was associated with significantly lower HDL-C and higher LDL-C and non-HDL-C in the univariate analyses (model 1) and age and BMI-adjusted models (model 2). When adjusted for multiple variables (model 3), higher GL was significantly associated only with lower HDL-C. The association between GL and LDL-C or non-HDL-C was not significant when drinking status was included in the model (data not tabulated), and also in the multivariate-adjusted model (model 3). In women (**Table 4**), higher GL was associated with significantly lower HDL-C, higher total cholesterol, triglycerides, LDL-C, and non-HDL-C (model 1). Higher GL was significantly associated with lower HDL-C and with higher triglycerides, LDL-C, and non-HDL-C in the age and BMI-

Table 1. Baseline characteristics of male study participants according to glycemic load quintiles

	Quintiles of dietary glycemic load					
Glycemic load (/1,000 kcal)	Q1 (lowest) n=452 ≤73.0	Q2 n=451 73.1-83.4	Q3 n=452 83.5-91.9	Q4 n=451 92.0-103.3	Q5 (highest) n=451 ≥103.4	p
Age (years)	46.7±6.9	47.6±6.8	47.0±6.8	47.7±6.9	47.9±6.9	0.010
Body height (cm)	169.1±6.1	169.7±6.1	169.4±5.9	168.9±6.1	168.5±6.5	0.041
Body weight (kg)	67.0±9.4	67.5±9.3	67.5±9.8	65.9±8.7	66.5±9.8	0.076
Body mass index (kg/m^2)	23.3±2.7	23.4±2.8	23.4±3.0	23.0±2.8	23.3±3.1	0.481
Current smoker (%)	58.8	53.7	54.2	47.0	54.1	0.011
Alcohol drinker (%)						<0.001
Nondrinkers	2.2	8.4	13.7	22.6	36.6	
Light drinkers (<20 g/day)	20.4	36.8	45.4	50.3	50.3	
Moderate/heavy drinkers (≥20 g/day)	77.4	54.8	40.9	27.1	13.1	
Habitual exercise (%)						0.003
No	65.9	65.6	68.1	67.0	74.9	
Light	19.2	20.4	18.4	19.5	16.0	
Moderate/Strong	14.2	14.0	13.1	12.9	8.6	
Energy intake (kcal/day)	2,417±625	2,268±554	2,191±582	2,103±548	2,024±644	<0.001
Carbohydrate intake (g/day)	278.5±72.6	303.1±75.7	316.9±87.5	326.1±87.1	350.6±113.6	<0.001
Fat intake (g/day)	69.3±30.9	60.0±21.9	54.1±20.5	46.8±16.2	35.2±14.9	<0.001
Protein intake (g/day)	77.5±27.1	71.0±23.2	65.5±21.3	61.1±17.6	52.5±18.4	<0.001
Carbohydrate intake (%Energy)	46.3±5.6	53.4±3.1	57.8±2.7	62.0±2.9	69.3±4.5	<0.001
Fat intake (%Energy)	25.5±7.5	23.6±5.7	22.0±5.2	19.9±4.4	15.6±4.3	<0.001
SFA (g/day)	17.3±8.2	15.1±6.0	13.9±5.8	12.1±4.5	9.2±4.3	<0.001
MUFA (g/day)	25.6±12.4	21.7±8.3	19.4±7.5	16.5±6.2	12.1±5.5	<0.001
n3PUFA (g/day)	3.6±1.8	3.0±1.3	2.6±1.1	2.3±0.9	1.7±0.8	<0.001
n6PUFA (g/day)	13.6±6.0	11.9±4.3	10.6±3.8	9.3±3.3	7.3±3.0	<0.001
Dietary cholesterol (mg/day)	353.2±171.1	301.4±140.6	259.2±124.6	226.5±106.8	158.6±94.2	<0.001
Fiber intake (g/day)	12.3±4.9	11.8±4.5	11.2±4.2	10.6±3.9	9.6±4.0	<0.001
Dietary glycemic index	67.1±4.5	68.4±3.6	69.1±3.4	70.1±3.2	71.5±3.1	<0.001
Glycemic index-white rice (%)	52.8±23.7	58.0±20.6	60.3±20.1	65.1±19.6	71.3±19.6	<0.001
Glycemic index-bread (%)	7.1±8.4	7.8±8.3	7.4±8.3	6.6±7.9	5.4±7.7	<0.001
Glycemic index-noodles (%)	7.2±7.4	5.9±5.1	5.5±5.1	4.6±4.9	4.0±4.4	<0.001
Glycemic index-confectioneries (%)	6.1±5.7	5.4±4.7	5.0±4.0	4.7±3.8	3.2±3.9	<0.001
Glycemic index-sugar (%)	6.1±4.0	5.2±3.5	5.0±3.5	4.3±3.2	3.5±2.7	<0.001
White rice intake (g/day)	285.9±148.4	359.4±148.1	403.6±159.7	463.4±175.1	579.8±244.6	<0.001

Values are the mean±standard deviation or %.

adjusted model (model 2) and also in the multivariate-adjusted model (model 3).

Because drinking status had a large effect on the multivariate-adjusted model results, we analyzed the subgroups separately based on drinking status in men and women. Compared to nondrinkers, dietary GL and carbohydrate intake were lower in both male and female drinkers, while fat intake was higher in male drinkers but lower in female drinkers (data in **Supplement Table 4**). In male nondrinkers (n=377), no associations between GL and serum lipid levels were observed (**Table 5**). In male drinkers (n=1,880) the associations between GL and serum lipid levels were similar to those of all men. In female nondrinkers (n=949), higher GL was associated with significantly lower HDL-C, higher triglycerides, and higher non-HDL-C, but was not associated with LDL-C (**Table 6**). In female drinkers (n=649), higher GL was associated with significantly lower HDL-C, higher non-HDL-C and higher LDL-C.

Table 2. Baseline characteristics of female study participants according to glycemic load quintiles

	Quintiles of dietary glycemic load					
Glycemic load (/1,000 kcal)	Q1 (lowest) n=320 ≤76.8	Q2 n=320 76.9-84.8	Q3 n=319 84.9-92.0	Q4 n=320 92.1-101.3	Q5 (highest) n=319 ≥101.4	p
Age (years)	45.4±6.4	45.8±6.6	46.9±6.9	47.4±6.8	49.5±6.3	<0.001
Body height (cm)	156.8±5.4	156.4±5.5	156.0±5.2	156.0±5.7	154.4±5.7	<0.001
Body weight (kg)	55.1±8.7	54.6±8.8	54.5±8.3	54.8±8.8	53.5±8.9	0.044
Body mass index (kg/m^2)	22.4±3.4	22.3±3.4	22.3±3.3	22.5±3.4	22.4±3.5	0.668
Menopause (%)	31.3	31.3	39.5	41.9	53.0	<0.001
Current smoker (%)	4.7	4.7	3.1	1.6	3.1	0.160
Alcohol drinker (%)						<0.001
Nondrinkers	41.6	50.9	58.6	67.2	78.7	
Light drinkers (<20 g/day)	50.6	47.8	39.5	31.3	21.0	
Moderate/heavy drinkers (≥20 g/day)	7.8	1.3	1.9	1.6	0.3	
Habitual exercise (%)						0.007
No	73.4	75.9	80.6	81.9	85.6	
Light	13.4	12.2	11.6	8.8	6.6	
Moderate/Strong	12.5	11.9	7.2	9.1	7.5	
Energy intake (kcal/day)	2,112±614	1,977±452	1,846±407	1,744±471	1,568±461	<0.001
Carbohydrate intake (g/day)	265.6±78.4	274.9±65.2	271.2±60.9	273.1±75.5	268.0±80.0	0.830
Fat intake (g/day)	76.5±27.4	63.5±16.2	54.1±15.1	44.7±13.7	32.5±12.2	<0.001
Protein intake (g/day)	75.4±23.2	67.0±17.5	59.5±13.6	54.2±15.2	43.2±14.3	<0.001
Carbohydrate intake (%Energy)	50.3±4.2	55.5±2.5	58.8±2.5	62.6±2.8	68.4±4.2	<0.001
Fat intake (%Energy)	32.3±4.9	28.8±3.2	26.1±3.2	22.9±2.9	18.4±3.7	<0.001
SFA (g/day)	19.8±7.8	17.0±5.3	14.4±4.9	11.8±4.2	8.6±3.8	<0.001
MUFA (g/day)	27.6±10.9	22.2±6.0	18.8±5.6	15.1±4.9	10.9±4.2	<0.001
n3PUFA (g/day)	3.7±1.6	2.9±1.0	2.5±0.9	2.1±0.8	1.5±0.6	<0.001
n6PUFA (g/day)	14.7±5.5	12.1±3.3	10.4±2.9	8.6±2.6	6.5±2.2	<0.001
Dietary cholesterol (mg/day)	340.6±149.2	296.3±120.4	236.8±82.3	200.1±80.2	137.9±80.5	<0.001
Fiber intake (g/day)	14.1±5.4	13.1±4.3	12.0±3.7	11.0±3.7	9.0±3.4	<0.001
Dietary glycemic index	65.3±4.0	67.1±3.3	68.1±3.0	68.7±3.1	70.6±3.0	<0.001
Glycemic index-white rice (%)	41.3±21.1	48.7±18.1	54.0±18.6	58.2±17.8	65.5±17.4	<0.001
Glycemic index-bread (%)	9.7±7.9	9.9±8.0	9.0±8.1	8.7±9.0	6.7±7.7	<0.001
Glycemic index-noodles (%)	5.5±5.0	4.8±4.7	4.0±3.9	4.3±4.3	3.4±4.2	<0.001
Glycemic index-confectioneries (%)	11.9±7.9	11.1±6.3	9.8±6.1	8.4±6.0	7.5±6.0	<0.001
Glycemic index-sugar (%)	6.2±3.6	5.7±3.4	5.1±3.5	5.0±3.8	4.1±2.6	<0.001
White rice intake (g/day)	212.8±119.0	273.6±115.3	305.7±111.3	337.5±123.2	392.3±136.1	<0.001

Values are the mean±standard deviation or %.

Women were analyzed separately in subgroups based on the menopausal status (pre- or postmenopause, data shown in **Supplement Table 5**). Although no difference in GI was observed between pre- and post-menopause, postmenopausal women were associated with a higher GL than premenopausal women, higher carbohydrate intake, and lower fat intake. Postmenopausal women showed higher mean serum lipids than premenopausal women. The associations between GL and serum lipid levels were similar between pre- and postmenopausal women.

Discussion

The present study investigated the association between serum lipids and dietary GI/GL in a large population of Japanese middle-aged men and women. The results indicated a significant inverse association