to atherosclerosis. In addition, chronic kidney disease–related metabolic disorders may affect normal or mildly injured vessels to a lesser extent in normotensives than in hypertensives, and therefore, the 12-year follow-up period of our study may be insufficient to allow for the occurrence of cardiovascular disease.

In the present study, chronic kidney disease was found to be an independent risk factor in men for the occurrence of coronary heart disease but not of ischemic stroke. A possible reason for this discrepancy is competition among causes of cardiovascular disease, whereby our men with chronic kidney disease were more likely to suffer from coronary heart disease than from ischemic stroke, thereby causing possible censorship of data due to coronary death. Also, risk factors may have been modified in response to medical advice and treatment after coronary heart disease events, which would probably have weakened the association between chronic kidney disease and ischemic stroke. In contrast, for women with chronic kidney disease, an opposite phenomenon was observed: the risk of ischemic stroke was significantly elevated, while the risk of coronary heart disease was not. This phenomenon is likely due to both inadequate statistical power and to the low risk of coronary heart disease in Japanese women. Some reports indicate a higher risk of stroke in women [37, 38]. Di Tullio et al [38] have shown that smaller aortic plaques are significantly associated with ischemic stroke in women but not in men. This gender difference may be a consequence of the effects of hypercoagulable states [39, 40], lipid abnormalities [41], or gonadal steroids [42–44] in women. Further studies are necessary to elucidate these gender differences in detail.

Several limitations of our study should be discussed. The primary limitation is the small numbers of both subjects and cardiovascular disease events in the study population. Thus, the generalizability of the study results may be somewhat limited. Nonetheless, we believe that the findings of our study represent the actual association between chronic kidney disease and cardiovascular disease outcomes, since we used a highly accurate method of determining all cardiovascular disease cases.

The second limitation is that our results might be biased, because almost 20% of the target population did not participate. At baseline, the mean age of subjects who did not participate was significantly lower than that of subjects who did participate (53 vs. 60 years old), and the proportion of men was significantly higher among nonparticipants (57% vs. 42%). Unfortunately, we could not obtain information on other risk factors among the nonparticipants. However, it is generally agreed that an acceptable participation rate in a population-based study (i.e., a rate that practically eliminates the threat of selection bias attributable to nonparticipants) is above 70% of the target population [45, 46]. Because of the high participation rate in our study (81%), this bias did not seem to have the potential to alter our findings.

The third limitation is that our GFR estimates, which were made using the simplified prediction equation derived from the MDRD Study and that were based on a single blood sample, might not be sufficiently correct, although this prediction equation, among other equations of its type, is considered to be the most precise estimate of GFR [28]. In addition, a recent report has shown that repeated measurements of serum creatinine are necessary to correct within-person measurement variations of serum creatinine [47], suggesting that some nondifferential misclassifications of cases with chronic kidney disease may have occurred in our study. Given that this limitation can reduce the impact of chronic kidney disease, the true association may be stronger than that shown in our findings.

The fourth limitation is that we have no information regarding the severity or duration of hypertension or other cardiovascular disease risk factors. The fifth limitation is that we also could not provide information regarding the type or number of antihypertensive drugs, medication compliance, and blood pressure control. Although ECG abnormalities, which reflect target-organ damage from hypertension or other risk factors, were used as a confounding factor in the multivariate analysis, these limitations may reduce the accuracy of our findings to some extent. Thus, they have the potential to alter our findings, but they are not likely to do so.

The sixth limitation is that our subjects with chronic kidney disease may have undergone more intense medical surveillance than those without it, resulting in a surveillance bias. However, diagnostic procedures such as echocardiography and scintigraphy were usually performed in subjects who presented symptoms or clinical signs of cardiac ischemia, but were not performed in subjects who did not present cardiac symptoms, even if they had chronic kidney disease. Brain CT/MRI was taken in the similar situation. In addition, as described in the **Methods** section, the diagnosis of cardiovascular disease was in principle based on the acute events of heart and brain attack. We performed almost the same follow-up surveys on all study subjects regardless of the presence or absence of chronic kidney disease. The mean number of health investigations was similar for subjects with or without chronic kidney disease in men (4 ± 4 times in subjects with chronic kidney disease vs. 5 ± 4 times in subjects without chronic kidney disease) and in women (5 ± 4 times vs. 6 ± 4 times). Furthermore, health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination that year or who had moved out of town. Thus, subjects with chronic kidney disease are considered not to have undergone more intense medical surveillance, so the potential for such bias seems to be negligible.

CONCLUSION

Chronic kidney disease was found to be an independent risk factor for the incidence of cardiovascular disease in a general Japanese population. Our findings suggest that subjects with chronic kidney disease should be considered a high-risk population for cardiovascular disease and be recommended for more intensive preventive management of cardiovascular disease, including active detection and strict treatment of cardiovascular risk factors. An additional clinical intervention trial is needed to evaluate preventive measures of cardiovascular disease in subjects with chronic kidney disease.

Reprint requests to Toshiharu Ninomiya, M.D., Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582 Japan.
E-mail: nino@intmed2.med.kyushu-u.ac.jp

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(日本語要約)

地域住民における CRP レベルと糖尿病発症の関係：久山町研究

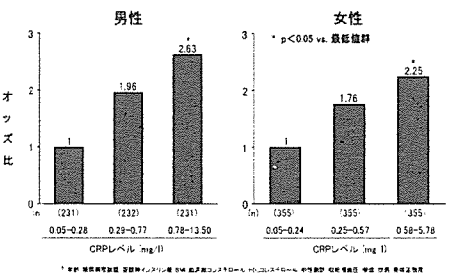
土井康文、清原裕、久保充明、二宮利治、湧川佳幸、米本孝治、岩瀬正典、飯田三雄
九州大学大学院医学研究院病態機能内科学

【背景と目的】近年、慢性炎症の示標である C 反応性蛋白（CRP）と心血管病との関係が注目されている。一方、CRP が糖尿病発症の危険因子であるとする報告が欧米で散見されるが、わが国でこの問題を検討した報告は極めてまれである。そこで本研究では、福岡県久山町の地域住民を対象にした追跡調査において、CRP レベルと糖尿病発症との関係を検討した。

【対象と方法】1988 年の久山町の循環器健診を受けた 40-79 歳の住民のうち、糖尿病（ADA 基準）がなくかつ CRP の測定が可能であった 2,207 名を追跡対象とした。この集団のうち、1993 年-1998 年に再度健診を受診し糖尿病の有無を判定できた 1,759 名（男性 694 名、女性 1,065 名、追跡率 79.7%、平均追跡期間 9.0 年）を本研究の対象とした。

【結果】対象者を CRP レベルの 3 分位で 3 群に分けると、年齢調整後の糖尿病の累積発症率は、男性では低値群 4.4%、中間値群 11.3%、高値群 13.1% (p=0.002)、女性ではそれぞれ 3.5%、6.0%、9.2% (p=0.001) と、CRP レベル上昇とともに有意に増加した。年齢、糖尿病家族歴、空腹時インスリン値、body mass index (BMI)、総コレステロール、HDL コレステロール、中性脂肪、収縮期血圧、飲酒、喫煙、身体活動度を交絡因子とした多変量解析では、CRP 低値群に対する高値群の糖尿病発症のオッズ比は、男性 2.63(95%信頼区間 1.23-5.65、p for trend=0.014)、女性 2.25 倍(1.01-5.01、p for trend=0.049)と、CRP 高値は男女で糖尿病発症の独立した有意な危険因子となった。

次に男女合わせて層別解析を行うために、対象者を BMI、中性脂肪、HDL コレステロールの 3 分位で 3 群に分け、高血圧、飲酒、喫煙の有無別に 2 群に分けた。性・年齢調整後の CRP 値と糖尿病発症の関係は、BMI および中性脂肪の低値群、HDL コレステロールの高値群、非高血圧群、非飲酒群、喫煙群と非喫煙群で有意であった。その他の層では、CRP 値と糖尿病発症の間に有意な関係を認めなかった。



CRPレベル別の糖尿病発症に対するオッズ比
(久山町住民1759名 40-79歳 1988-1998年 多変量調整)

【結論】久山町では、CRP 高値は糖尿病発症の有意な危険因子であった。この関係は、インスリン抵抗性の小さな群と非飲酒群で強かった。

Elevated C-Reactive Protein Is a Predictor of the Development of Diabetes in a General Japanese Population

The Hisayama Study

YASUFUMI DOI, MD
YUTAKA KIYOHARA, MD
MICHIAKI KUBO, MD
TOSHIHARU NINOMIYA, MD
YOSHIYUKI WAKUGAWA, MD
KOJI YONEMOTO, PHD
MASANORI IWASE, MD
MITSUO IIDA, MD

OBJECTIVE — We examined the association between high-sensitivity C-reactive protein (CRP) levels and the development of diabetes in a general Japanese population.

RESEARCH DESIGN AND METHODS — A total of 1,759 Japanese subjects, aged 40–79 years and without diabetes (according to American Diabetes Association fasting criteria), were stratified into three groups according to CRP tertiles by sex and followed up prospectively for a mean of 9.0 years.

RESULTS — During the follow-up, 131 subjects (67 men and 64 women) developed diabetes. In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly as the tertiles of CRP levels increased. In multivariate analyses, the risk of developing diabetes was significantly higher in the highest CRP tertile than in the lowest after adjustment for a number of confounding factors (odds ratio 2.63 [95% CI 1.23–5.65] for men and 2.25 [1.01–5.01] for women). In stratified analyses, this CRP-diabetes association was stronger in subjects without obesity or other risk factors related to insulin resistance and in nondrinking subjects.

CONCLUSIONS — Our findings suggest that elevated CRP concentration is a significant predictor of diabetes in the general Japanese population, independent of obesity and insulin resistance.

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In some cohort and nested case-control studies in Western countries, an elevated C-reactive protein (CRP) level has been an independent predictor of diabetes (1–10). Recent cross-sectional studies have also demonstrated clear associations of elevated serum CRP levels with obesity and insulin resistance (11–13). These findings suggest that the inflammatory state illustrated by elevated CRP concentrations is associated with hyperglycemia and diabetes through obesity or increased insulin resistance. However, epidemiological findings concerning this issue are still controversial; several studies have reported a significant positive association between elevation in CRP levels and the future risk of diabetes even after adjustment for BMI (1,2,4,7,9,10), whereas in other studies (3,6) this association disappeared after adjustment for BMI.

Japanese are characterized by low BMI levels and low CRP concentrations in blood compared with Westerners (14). Moreover, there have been no reports on the relationship between CRP levels and the development of diabetes among general populations in Japan. The aim of the present study is to examine the effects of serum CRP levels on the development of diabetes in a prospective study of a defined Japanese population, taking into account comprehensive risk factors.

RESEARCH DESIGN AND METHODS

Study population and follow-up survey

In 1988, a screening survey for the present study was performed in the Town of Hisayama in Japan. A total of 2,587 residents aged 40–79 years (80.2% of the total population of this age-group) participated in the baseline survey. The diabetes classification was based on the fasting criteria of the American Diabetes Association (15), i.e., subjects with fasting plasma glucose levels ≥7.0 mmol/l or those who were taking diabetes medications were considered diabetic.

After the exclusion of 80 subjects who had already eaten breakfast before the examination, 233 subjects with diabetes, and 67 subjects whose CRP concentrations could not be measured due to insufficient quantities of stored sera, the remaining 2,207 subjects (926 men and 1,281 women) were enrolled in the baseline examination. Among those, 1,759 subjects (694 men and 1,065 women) underwent follow-up examinations in 1993–1998 (follow-up rate 79.7%). We considered a subject to have developed diabetes when he/she met the above-mentioned baseline criteria. During this period, 131 subjects (67 men and 64 women) developed diabetes.

Laboratory measurements

Plasma glucose levels were determined by a glucose-oxidase method, and serum insulin was measured by radioimmunoassay. HbA_{1c} levels were measured by high-pressure liquid chromatography. Total cholesterol, HDL cholesterol, and triglycerides were all determined enzymatically. Serum specimens collected at the time of CRP measurement were stored at −20°C until used in 2002. High-sensitivity CRP

From the Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
Address correspondence and reprint requests to Yasufumi Doi, MD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: doi@intmed2.med.kyushu-u.ac.jp.
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Abbreviations: CRP, C-reactive protein.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

concentrations were determined using a modification of the Behring latex-enhanced CRP assay. Sitting blood pressure was obtained three times and the average values used in the analyses. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or current treatment with antihypertensive agents. BMI (kilograms per meters squared) was used as an indicator of obesity.

Diabetes in first- or second-degree relatives indicated a family history of diabetes. Those subjects engaging in sports at least three times a week during their leisure time comprised a regular exercise group. Information on smoking habits and alcohol intake was used to classify subjects as having current habits or not.

Statistical analysis

Because the distributions of CRP, fasting insulin, and triglycerides were skewed, these variables were natural log transformed for statistical analyses. To analyze CRP levels as categorical variables, these levels were divided into tertiles by sex (0.05–0.28, 0.29–0.77, and 0.78–13.5 mg/l for men and 0.05–0.24, 0.25–0.57, and 0.58–5.78 mg/l for women). The age-adjusted cumulative incidence of diabetes was calculated by the direct method and compared by the Mantel-Haenszel χ^2 test using 10-year age-groupings. Age- and multivariate-adjusted odds ratios (ORs) and 95% CIs were calculated by logistic regression analysis. $P < 0.05$ was considered statistically significant in all analyses.

This study was conducted with the approval of the Ethics Committee of Kyushu University, and written informed consent was obtained from all participants.

Table 1—*Characteristics of subjects by sex*

	Men	Women
n	694	1,065
Age (years)	58 ± 10	57 ± 10
High-sensitivity CRP (mg/l)	0.49 (0.07–7.14)	0.36 (0.06–3.22)
Fasting plasma glucose (mmol/l)	5.6 ± 0.5	5.5 ± 0.5
HbA_{1c} (%)	5.5 ± 0.5	5.4 ± 0.5
Family history of diabetes (%)	9.3	7.3
Fasting insulin (pmol/l)	30.0 (18.0–72.0)	36.0 (18.0–72.0)
BMI (kg/m^2)	22.9 ± 2.9	23.0 ± 3.1
Total cholesterol (mmol/l)	5.10 ± 1.04	5.57 ± 1.05
HDL cholesterol (mmol/l)	1.26 ± 0.30	1.35 ± 0.29
Triglycerides (mmol/l)	1.25 (0.58–3.49)	1.02 (0.49–2.33)
Systolic blood pressure (mmHg)	131 ± 19	130 ± 20
Diastolic blood pressure (mmHg)	80 ± 11	75 ± 11
Hypertension (%)	41.5	32.7
Current drinking (%)	61.0	8.5
Current smoking (%)	47.6	5.4
Regular exercise (%)	16.1	4.9

Data are means ± SD or medians (95% CI) unless otherwise indicated.

RESULTS — The clinical characteristics of the subjects by sex are shown in Table 1. The mean age was 58 years for men and 57 years for women.

In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly with elevating tertiles of baseline serum CRP concentrations. The incidences in the 3rd tertile for both sexes and in the 2nd tertile for men were significantly higher than in the 1st tertile (Fig. 1). As shown in Table 2, the risk of future diabetes in either sex was more than threefold higher in the 3rd tertile than in the 1st tertile after adjustment for age. These associations remained substantially unchanged even after adjustment for the other confounding factors, including age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity (adjusted OR 2.63 [95% CI 1.23–5.65], $P = 0.014$, for men and 2.25 [1.01–5.01], $P = 0.049$, for women).

We next estimated the age- and sex-adjusted ORs and 95% CIs for the development of diabetes by an increment of 1 log CRP in men and women together according to the other risk factor levels (Table 3). Analyses were performed by dividing the subjects into three groups according to tertiles of BMI, triglycerides, and HDL cholesterol levels or into two

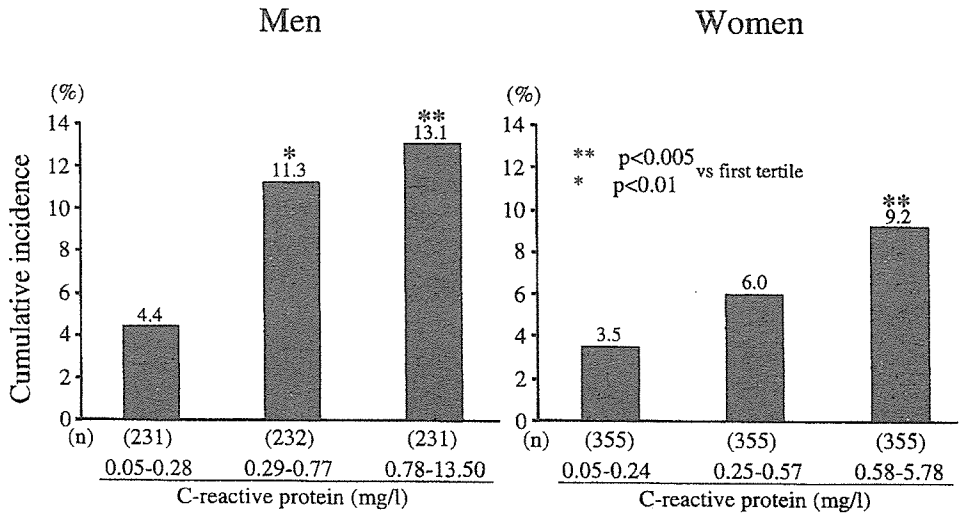

Figure 1—*Age-adjusted cumulative incidence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex.*

Table 2—*Age- or multivariate-adjusted ORs and 95% CIs for occurrence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex*

	High-sensitivity CRP level (mg/l)							
	Men				Women			
	0.05–0.28	0.29–0.77	0.78–13.50	*P* for trend	0.05–0.24	0.25–0.57	0.58–5.78	*P* for trend
Population at risk (*n*)	231	232	231		355	355	355	
Cases of diabetes (*n*)	11	26	30		10	21	33	
Age-adjusted OR (95% CI)	1 (referent)	2.67 (1.28–5.56)	3.23 (1.57–6.70)	0.002	1 (referent)	2.12 (0.98–4.58)	3.35 (1.60–7.03)	0.001
Multivariate-adjusted OR (95% CI)	1 (referent)	1.96 (0.92–4.19)	2.63 (1.23–5.65)	0.014	1 (referent)	1.76 (0.80–3.87)	2.25 (1.01–5.01)	0.049

Multivariate adjustment was made for age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity.

groups by hypertension status, current drinking, and current smoking. Significant positive associations between CRP levels and incident diabetes were observed among subjects in the 1st tertile of BMI, among subjects in the 1st and 2nd tertiles of triglycerides, among subjects of the 2nd and 3rd tertiles of HDL cholesterol, and among subjects without hypertension or current drinking. Significant associations were also observed in both smokers and nonsmokers. However, clear CRP-diabetes associations were not seen in the other categories of any risk factors.

CONCLUSIONS — We demonstrated in a prospective study of a general Japanese population that elevated CRP level is an independent predictor of diabetes for both sexes even after adjustment for comprehensive risk factors. In stratified analyses, the CRP-diabetes association was stronger in subjects without risk factors related to insulin resistance, such as obesity, dyslipidemia, and hypertension, and among nondrinkers, whereas the presence of a current smoking habit did not affect this association.

To our knowledge, this is the first report to indicate that the low-grade inflammatory state illustrated by increased CRP is an independent risk factor for developing diabetes in a general Japanese population. Similar findings were observed in a Japanese-American population (13) as well as in some other Western populations (5–12,14). Since Japanese Americans have a Western lifestyle, their findings cannot be generalized to Japanese living in Japan. Our subjects were thinner than those in previous reports (1–10). Our findings suggest that the subclinical inflammatory process has an important role in the development of diabetes in relatively lean Asian populations, as it does in Western populations.

Recent cross-sectional epidemiological data have demonstrated that elevated serum CRP levels are associated with obesity, insulin resistance, and glucose intolerance (11–13). These findings suggest that the inflammatory state affects glucose levels in blood and increases the risk of diabetes via obesity or insulin resistance. However, our study showed that the association between CRP levels and the development of diabetes is independent of serum insulin levels as well as BMI. These findings are in accord with those of several other cohort studies (1,9). Additionally, our stratified analyses showed that the CRP-diabetes association was stronger particularly in individuals with low levels of risk factors related to insulin resistance. Therefore, a low-grade inflammatory state can be considered a risk factor for diabetes independent of obesity and insulin resistance, and unknown mediators are also thought to be involved in the development of diabetes.

In our subjects, the influence of CRP on the incidence of diabetes was stronger in nondrinkers than in drinkers. Some studies have shown that moderate alcohol

Table 3—*Age- and sex-adjusted ORs and 95% CIs for occurrence of diabetes by an increment of 1 log high-sensitivity CRP in all subjects according to risk-factor levels*

Risk factor	Population at risk (*n*)	Cases of diabetes (*n*)	Age- and sex-adjusted OR (95% CI)	*P*
BMI (kg/m^2)				
≤21.5	586	29	1.36 (1.05–1.75)	0.017
21.6–24.2	587	35	1.20 (0.92–1.57)	NS
≥24.3	586	67	1.25 (0.99–1.59)	NS
Triglycerides (mmol/l)				
≤0.88	587	30	1.30 (1.01–1.67)	0.042
0.89–1.34	582	29	1.50 (1.12–2.01)	0.007
≥1.35	590	72	1.16 (0.94–1.43)	NS
HDL cholesterol (mmol/l)				
≤1.14	572	49	1.04 (0.82–1.31)	NS
1.15–1.40	583	44	1.43 (1.13–1.81)	0.003
≥1.41	604	38	1.57 (1.20–2.07)	0.001
Hypertension				
Without	1,123	54	1.45 (1.18–1.77)	0.0003
With	636	77	1.16 (0.95–1.41)	NS
Current drinking				
Without	1,246	77	1.43 (1.20–1.71)	0.0001
With	513	54	1.14 (0.92–1.42)	NS
Current smoking				
Without	1,372	95	1.29 (1.09–1.53)	0.003
With	387	36	1.34 (1.04–1.72)	0.022

consumption is associated with lower CRP concentrations (16,17). Additionally, recent cohort studies have revealed that moderate alcohol consumption reduced the risk of future type 2 diabetes (18,19). Therefore, the intake of alcohol may attenuate the influence of CRP on the development of diabetes.

A recent cohort study has reported a significant association between inflammation and future diabetes among nonsmokers but not among smokers (8). In our subjects, however, an association between elevated CRP levels and incident diabetes was observed in both nonsmokers and smokers. This suggests that the CRP-diabetes association is independent of current smoking.

Several limitations of our study should be discussed. The primary limitation is that a diagnosis of diabetes was not based on a 75-g oral glucose tolerance test, but on a single reading of fasting glucose level, as was the case in other epidemiological studies (2,8,9). Subjects with diabetes having normal fasting glucose levels were misdiagnosed in our study. Additionally, some of the participants who were classified as having worsening fasting glucose status may not have been so categorized after repeated testing. These misclassifications should weaken the association found in this study. Therefore, the true association may be stronger than that shown in our findings. A secondary limitation is that CRP concentrations were measured in serum conserved for a long period at −20°C. However, the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years was confirmed in the Reykjavik Study (20). The last limitation is that our study lacked information on drug use, which could affect serum CRP levels. It is known that several medications can alter CRP levels, including statins, ACE inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone (21). However, these medications were rarely used in our country in 1988. This suggests that such a bias does not invalidate the present findings.

In conclusion, we showed that subclinical elevation in CRP concentrations is an independent predictor of diabetes in a general Japanese population. CRP was an effective predictor of diabetes in individuals with the lowest BMI as well as in individuals without other risk factors related to insulin resistance. These findings add to the notion that low-grade inflammation is an important factor in the pathogenesis of type 2 diabetes. Further study is necessary to clarify the role of inflammation in the cascade to the development of diabetes.

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3) 今後の研究計画

本研究は、様々な危険因子と生活習慣病との関係を検討し、久山町住民のみならず、国民全体の健康増進に有用なエビデンスを構築することを目的とする。例えば、現在メタボリックシンドロームが心血管病や糖尿病の発症の危険因子として注目されている。しかし、日本人においてメタボリックシンドロームが心血管病や糖尿病の発症に与える影響を検討した前向き追跡研究はまれである。その理由の一つとして、メタボリックシンドロームの診断基準には腹囲の測定が必須であるが、既存コホート研究において追跡開始時に腹囲の測定がなされていないことが挙げられるであろう。また、日本人における慢性炎症と心血管病の関係についてもメタボリックシンドロームと同様に日本人でのエビデンスが乏しい。これも既存コホート研究では、追跡開始時に慢性炎症の指標として高感度 CRP が測定できていないためであると思われる。幸運なことに、久山町研究では 1988 年の第 3 集団で腹囲と高感度 CRP の測定がなされている。

今後久山町研究では 1988 年の第 3 集団において、欧米のメタボリックシンドロームの診断基準や 2005 年にメタボリックシンドローム診断基準検討委員会から発表されたわが国のメタボリックシンドロームの診断基準が日本人において適切であるかを心血管病や糖尿病の発症予防の観点から検証していきたい。また、高感度 CRP についても、日本人における心血管病の危険因子としての意義を検討する必要があると思われる。

今回の大規模コホート共同研究では、既存の危険因子と心血管病や悪性新生物との関係を日本人において検証していくことを 3 本柱の 1 本目としている。これに対しては可能な限りデータ提供を行うと同時に、積極的に分析にも参加していきたい。さらに、3 本柱の 2 本目である前向きコホート共同研究においては、新しい危険因子を検証することを目的としている。その目的から、メタボリックシンドロームや高感度 CRP と心血管病の関係の検証は最優先課題であると思われる。今後、久山町研究の追跡対象集団では、腹囲や高感度 CRP などの新しい危険因子の測定も健診項目に加えていく予定である。

６．放射線影響研究所成人健康調査コホート

分担研究者　児玉 和紀　　財団法人 放射線影響研究所 疫学部・部長
研究協力者　笠置 文善　　財団法人 放射線影響研究所 疫学部・副部長
研究協力者　山田 美智子　財団法人 放射線影響研究所 臨床研究部・副部長

(1)成人健康調査の概要

1)目的と調査対象

放射線影響研究所(放影研)は 1947 年設立された原爆傷害調査委員会を引き継ぎ、放射線の人体に及ぼす医学的影響を調査研究し、被爆者の健康維持および福祉に貢献することを目的としている。放影研では約 12 万人の寿命調査集団について被曝線量と死亡率および癌の罹患率の関係を解析しているが、成人健康調査集団は寿命調査集団の中から 2 万人を選んで設定され、2 年に 1 度の包括的な健康診断を実施する事により疾病の発生率と測定値等の情報を収集することを目的として、追跡調査を継続している。オリジナル集団の 1/4 を占める広島・長崎市外在住者の追跡は 1976 年に中止され、その後 3400 人が新たに集団に追加された。

2)調査方法と調査項目

健診は基本的に放影研外来で実施される。高齢者や重症で外来受診が困難な対象者に対しては訪問による健診も実施している。1958 年より全期間を通じて実施されている項目は既往歴等に関する問診、身体計測（体重、身長）、血圧（水銀計）、内科診察、臨床検査（血液一般、総ｺﾚｽﾃﾛｰﾙ値）、心電図、胸部 X 線検査、尿検査、便検査である。1986 年からは自動生化学検査測定器の導入に伴い 肝機能検査、中性脂肪、血糖、尿酸、腎機能検査を毎回実施しており、HDL ｺﾚｽﾃﾛｰﾙは 1990 年、HbA1c 値は 1998 年、CRP は 2001 年から追加測定されている。また、1965 年、1978 年、1986 年のサイクルに受診した対象者については喫煙、飲酒、学歴、食習慣等の情報が問診調査で得られている。対象者 1 人あたり 1 回の健診に付き 1986 年 6 月までは最高 6 種類の診断が、それ以降は最高 12 種類の診断が国際疾病分類（ICD）コードでコードされている。成人健康調査コホートは放影研の寿命調査集団のサブグループであり、厚生省・法務省の公式許可を得て、死因に関する情報が入手されている。

3)結果の要約

成人健康調査の主たる目的は放射線の医学的影響の調査である。放射線は癌の死亡、罹患のリスクを増加させている。循環器疾患の死亡ならびに罹患に関する解析で放射線の影響が示唆されている疾患もあるが、その影響は喫煙、血圧等の影響に比べ小さいものであった。

成人健康調査集団の男性の内、1965年時年齢が45-69歳の対象者は、「日本に居住する日本人とハワイならびにカリフォルニアに移住した日系人における冠動脈性心疾患と脳卒中の疫学的特性を調べる調査：Ni-Hon-San Study」の調査対象者であった。Ni-Hon-San Studyは1965年に調査が開始された循環器疾患に関する疫学研究であり、遺伝的に同種の人口集団が非常に異なる環境下に居住した場合、同一のリスク要因がどのように作用し、冠動脈性心疾患および脳血管疾患の死亡と罹病にどのような差が生じるかについての貴重な知見を報告してきた。この調査では3地域のプログラムが協力して比較可能な情報を収集できるよう画一的な研究計画書が作成され、測定法の標準化や問診内容の評価の統一など、複数の異なるコホート研究を統合して実施する疫学研究の方法を発展させる事にも貢献した。

(2)最新の研究成果

（公表論文）

日本人集団におけるﾍﾓｸﾞﾛﾋﾞﾝA1c値と死亡率の関係

白人ではﾍﾓｸﾞﾛﾋﾞﾝA1c濃度（HbA1c）があらゆる死因の死亡率と関連を持つことが知られている。しかし、この関係は日本人では明らかではない。また、ﾍﾓｸﾞﾛﾋﾞﾝA1cと悪性新生物による死亡率の関係に関する研究も乏しい。この研究では1986-1994年に放射線影響研究所の成人健康調査を受診した原爆被爆者とその対照からなる3710人のHbA1cを測定し、ベースラインのHbA1cで5グループ（HbA1c <5.5%の正常ﾍﾓｸﾞﾛﾋﾞﾝA1c群は1341人、5.5%≤ HbA1c <6.0%の正常高値群は1341人、6.0%≤ HbA1c <6.5%の軽度高値群は589人、6.5%≤ HbA1cの高値群は259人、タイプ2糖尿病と診断されていた群378人）に分けた。ベースライン時の平均年齢は67.6±10.1歳、死亡は2000年12月まで追跡し、平均追跡期間は8.83±3.44年であった。Coxの比例ハザードモデルにより、正常群と比較したハザード比を求めた。追跡期間中の総死亡数は754人、循環器疾患死亡253人、悪性新生物死亡249人であった。年齢、性、収縮期血圧、総ｺﾚｽﾃﾛｰﾙ値、喫煙、飲酒、被爆線量を調整後、総死亡ならびに循環器疾患死亡では軽度高値群以上でハザード比の有意な増加が認められた。悪性新生物死亡は高値群と糖尿病群でハザード比の有意な増加が認められた。この研究の結果は日本人でもHbA1c値が6%以上であれば、死亡率の増加が認められ、糖尿病と診断されていない人でもHbA1cの測定が重要であることを示唆している。

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ARTICLE

S. Nakanishi · M. Yamada · N. Hattori · G. Suzuki

Relationship between HbA_1c and mortality in a Japanese population

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Abstract *Aim/hypothesis:* HbA_1c concentrations are known to be associated with all-cause excess mortality risk in Caucasians. However, the relationship has not been clarified well in the Japanese. In addition, studies of the relationship between HbA_1c and mortality from malignant neoplasms are scarce. *Methods:* HbA_1c was measured for 3,710 people of a cohort composed of A-bomb survivors and controls. At baseline they were divided into five groups: a normal HbA_1c group of 1,143 individuals with HbA_1c of <5.5%, a slightly high but normal HbA_1c group of 1,341 individuals with HbA_1c ≥5.5% to <6.0%, a slightly high HbA_1c group of 589 individuals with HbA_1c ≥6.0% to <6.5%, a high HbA_1c group of 259 individuals with HbA_1c ≥6.5%, and a group of 378 individuals known to have type 2 diabetes. Using a Cox proportional hazards model, hazard ratios based on comparisons with the normal HbA_1c group were obtained. *Results:* During the observation period there were 754 deaths. For all-cause and cardiovascular disease mortality, a significant increase of the hazard ratio was observed for the slightly high HbA_1c group. A similar increase in malignant neoplasm-related mortality was observed for both the high HbA_1c group and the diabetes group. *Conclusions/interpretation:* Our results suggest that individuals in the Japanese population with HbA_1c levels of 6% or more might have increased mortality risk. The results indicate that HbA_1c measurements should be sought even for people who have not been diagnosed with diabetes.

S. Nakanishi (✉) · M. Yamada · N. Hattori · G. Suzuki
Radiation Effects Research Foundation,
5-2 Hijiyama Park, Minami-ku,
Hiroshima, 732-0815, Japan
e-mail: nshuhei@rerf.or.jp
Tel.: +81-82-2613131
Fax: +81-82-2637279

S. Nakanishi
Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Keywords Cardiovascular disease · Cohort study · HbA_1c · Japanese population · Malignant neoplasms · Mortality

Abbreviations AHS: Adult Health Study · RERF: Radiation Effects Research Foundation · ICD: International Classification of Diseases

Introduction

HbA_1c has been reported to be a convenient marker for diabetes screening [1, 2] and as a surrogate marker for metabolic syndrome [3]. There have also been many reports on the relationship in Europeans and Americans between death from cardiovascular disease and diabetes [4, 5] or obesity [6], which are determinants of metabolic syndrome [7]. Furthermore, several large-scale prospective studies have indicated that high levels of HbA_1c increase all-cause mortality risk and cardiovascular disease mortality risk [8–11]. This indicates a possible use of HbA_1c as a marker for prediction of the prognosis of subjects both with and without diabetes. A recent report suggested an increase of cancer mortality risk among those diagnosed as having impaired glucose tolerance based on 75-g OGTT [12]. A report on the involvement of obesity in increased cancer mortality risk has also appeared [13]. There may, therefore, be a relationship between HbA_1c and malignant neoplasms.

Association of obesity with all-cause mortality in a Japanese population has been reported [14], but possible associations of HbA_1c and mortality have not been investigated. We therefore studied whether HbA_1c is related to all-cause death and death from cardiovascular disease or malignant neoplasms in a Japanese population.

Subjects and methods

Study design The Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki established the Adult

Health Study (AHS) cohort. Under the AHS project, health information (both from clinical examinations and from biological tests) was collected from a total of about 20,000 individuals including A-bomb survivors and controls in Hiroshima and Nagasaki, in 2-year cycles since July 1958, to investigate disease onset. The study cohort is composed of about 10,000 individuals proximally exposed to moderate to large doses of A-bomb radiation, about 5,000 individuals distally exposed to low doses and matched by sex and age with the proximal group, and about 5,000 non-exposed individuals. Since 1984 we have obtained HbA_1c measurements for these cohort populations and followed their prognosis. Participants in this study were 3,710 individuals in the AHS in Hiroshima who underwent examinations from July 1986 to June 1994 (from the 15th to 18th examinations) and were followed until death or until December 2000. The AHS population in Nagasaki was excluded because the HbA_1c measurement method employed at the time of initiation of the follow-up was different from the method employed in Hiroshima. The programme of the AHS has already been described in detail elsewhere [15].

The AHS biennial health examinations, conducted with informed consent, consist of history-taking, physical examination and laboratory tests. At baseline examination all participants were interviewed by trained nurses who administered a structured questionnaire that included information about personal medical history, smoking and drinking status, and medications. The physical examinations performed included blood pressure and measurement of standing height without socks and body weight without outer clothing. Blood samples were obtained to measure serum total cholesterol, HbA_1c, and other data. For all individuals, HbA_1c was measured by means of high-performance liquid chromatography using an automated analyser (interassay coefficient of variation about 2%). For total and HDL cholesterol our laboratory has demonstrated the ability to meet the National Cholesterol Education Program's performance criteria for accuracy. All these examinations were approved by the responsible ethics committee (RERF's Human Investigation Committee). Coding of present diagnoses and past medical history at baseline examination was performed according to the International Classification of Diseases (ICD), 9th revision, by the examining physicians. Type 2 diabetes mellitus was diagnosed according to 1985 WHO criteria [16]. A total of 378 individuals who were administered oral anti-glycaemic drugs, or who were using insulin, or who were already diagnosed as having type 2 diabetes by a physician, on the basis of medical history at the time of the initiation of the follow-up or previous examinations, were categorised as the "known diabetes" group. The HbA_1c range of the known diabetes group was from 4.2 to 11.9%, depending on the efficacy of treatment. The remaining individuals were divided into a "normal" group with HbA_1c less than 5.5%, a "slightly high but normal HbA_1c" group with HbA_1c of 5.5% or more and less than 6.0%, a "slightly high HbA_1c" group with HbA_1c of 6.0% or more and less than 6.5%, and a "high HbA_1c" group with HbA_1c of 6.5% or more. The numbers of subjects in these HbA_1c categories were 1,143, 1,341, 589, and 259 respectively.

Coding of death Deaths were identified by routine surveillance of information obtained from the obligatory household registries (koseki) in Japan, and ascertainment of vital status is essentially complete. The underlying cause of death was based on the death certificate and classified on the basis of the ICD. Cardiovascular diseases were defined by ICD-9 codes 401 through 438, and ICD-10 codes I00 through I99, I60.0 through I69.8, and G45. Malignant neoplasms were defined by ICD-9 codes 140.0 through 208.9 and ICD-10 codes C00 through C97.

Statistical analysis All data were expressed as mean ± standard deviation. Factors of metabolic syndrome that might be potential confounders were investigated for each of the five categories. We conducted analysis of covariance and, when significance was obtained, we used the Tukey–Kramer method to assess the relationship between the five categories and other factors. Using the DS86 dosimetry system [17], individual radiation dose (A-bomb kerma dose) was calculated as the sum of the γ-ray and neutron kerma. Because kerma dose and BMI, which was calculated as body weight (kg) divided by the square of standing height (m), did not show normal distribution, analysis was made after logarithmic transformation.

We used a Cox proportional hazards model, making it possible to assign death hazard ratios and 95% confidence intervals to the four categories adjusted for potential confounders. As potential confounders we used age, systolic blood pressure, total cholesterol, A-bomb kerma dose and BMI as continuous values. Adjustment was also made for sex as one categorical value. Smoking and drinking status was divided into three categories: "never," "ever" (or data missing), or "current". Hazard ratio was estimated by adjustment for two sets of potential confounders: the first set, age, sex and A-bomb kerma dose, and the second set, age, sex, kerma dose and other potential confounders, namely, smoking and drinking status, body-mass index, total cholesterol, and systolic blood pressure. For the Cox proportional hazards model, proportional hazard assumptions for the five categories were verified by inspection of log–log survival curves. In all analyses no interaction was observed between sex and each category of HbA_1c (data not shown). Therefore, analysis was conducted for both sexes combined. For all data analysis Statistical Analysis System (SAS) procedures were used.

Results

Individuals were followed for an average of 8.83±3.44 years. Mean age at the time of initiation of the follow-up was 67.6±10.1 years. Clinical characteristics of this study and numbers of all deaths, deaths due to cardiovascular disease, and deaths due to malignant neoplasms during the observation period are shown in Table 1. Compared with the normal HbA_1c group, the four other groups had

Table 1 Clinical characteristics at baseline

	HbA_1c				Known diabetes
	<5.5	5.5 to <6.0	6.0 to <6.5	6.5 or more	
Numbers of subjects	1,143	1,341	589	259	378
Men (%)	303 (26.5)	380 (28.3)	211 (35.8)	100 (38.6)	148 (39.2)
Age (years)	67.0±10.5	68.2±9.8[a]	68.1±10.1	66.7±10.4	67.6±10.1
Death (%)	190 (16.6)	237 (17.7)	119 (20.2)	66 (25.5)	142 (37.6)
Cardiovascular disease (%)	66 (5.8)	76 (5.7)	50 (8.5)	22 (8.5)	39 (10.3)
Malignant neoplasm (%)	59 (5.2)	80 (6.0)	39 (6.6)	24 (9.3)	47 (12.4)
Current smoker (%)	193 (16.9)	243 (18.1)	140 (23.8)	61 (23.6)	81 (21.4)
Current drinker (%)	357 (31.2)	449 (33.5)	238 (40.4)	95 (36.7)	142 (37.6)
A-bomb kerma dose	5.38±0.93	5.39±0.93	5.39±1.00	5.40±0.98	5.46±0.88
Body-mass index (kg/m^{-2})	22.3±3.3	22.8±3.4[a]	23.3±3.4[a]	24.1±4.0[a]	23.4±3.8[a]
HbA_1c (%)	5.16±0.25	5.69±0.14[a]	6.15±0.13[a]	7.35±1.22[a]	6.94±1.51[a]
Systolic BP[b] (mmHg)	132±22	133±22	134±21	136±21	137±22[a]
Diastolic BP (mmHg)	79±12	79±12	80±11	80±12	78±12
Total cholesterol (mmoL/L)	5.53±1.02	5.78±1.00[a]	5.82±1.01[a]	5.76±1.17[a]	5.66±1.16
HDL cholesterol (mmoL/L)	1.45±0.39	1.41±0.40	1.36±0.37[a]	1.30±0.37[a]	1.34±0.37[a]

Data are expressed as means ± SD. A-bomb kerma dose data are log-transformed
[a] $p<0.05$ toward the normal HbA_1c group ($HbA_1c<5.5\%$) by the Tukey–Kramer method after adjustment for age and sex. The percentage is expressed as the rate of the numbers of each category
[b] Blood pressure

significantly higher BMI even after adjustment for sex. In comparison with the normal HbA_1c group, those known to have diabetes had significantly higher BMI, systolic blood pressure, and HDL cholesterol. A positive trend ($p<0.0001$) was observed for mean BMI, systolic blood pressure, and total cholesterol, which increased as HbA_1c increased; a negative trend ($p<0.0001$) was observed for mean HDL cholesterol, which decreased as HbA_1c increased.

With a Cox proportional hazards model that used all-cause mortality as a dependent variable and HbA_1c categories, sex, age, and kerma dose as independent variables, significant elevation of mortality risk for the high HbA_1c group and the diabetes group compared with the normal group was obtained. The hazard ratios for all-cause mortality were 0.96 (95% confidence interval: 0.79–1.16) for the slightly high but normal HbA_1c group, 1.13 (0.90–1.42) for the slightly high HbA_1c group, 1.47 (1.11–1.95) ($p=0.007$) for the high HbA_1c group, and 1.68 (1.33–2.11) ($p<0.0001$) for the diabetes group. For cardiovascular disease mortality, no significant increase was observed in the hazard ratio whereas a significant increase was observed in the ratio for mortality from malignant neoplasms among the high HbA_1c group and the diabetes group. The hazard ratios for mortality from malignant neoplasms were 1.05 (0.75–1.48) for the slightly high but normal HbA_1c group, 1.16 (0.77–1.74) for the slightly high HbA_1c group, 1.62 (1.00–2.61) ($p=0.048$) for the high HbA_1c group, and 1.76 (1.18–2.62) ($p=0.006$) for the diabetes group. Hazard ratios after further adjustment for systolic blood pressure, BMI, total cholesterol, and smoking and drinking status are shown in Table 2. The hazard ratios for all-cause mortality were significantly

Table 2 Adjusted hazards ratio of death from a Cox proportional hazards model

	HbA_1c				Known diabetes	p value for trend
	<5.5	5.5 to <6.0	6.0 to <6.5	6.5 or more		
All causes of death						
Adjusted for age, sex, and A-bomb kerma dose (A)						
Hazard ratio (95% CI)	1	0.96 (0.79–1.16)	1.13 (0.90–1.42)	1.47 (1.11–1.95)	1.68 (1.33–2.11)	<0.0001
Adjusted for (A), BMI, systolic BP, total cholesterol, smoking and drinking status (B)						
Hazard ratio (95% CI)	1	1.06 (0.85–1.31)	1.36 (1.05–1.76)	1.63 (1.19–2.24)	1.89 (1.46–2.44)	<0.0001
Death from cardiovascular disease						
Adjusted for (A)						
Hazard ratio (95% CI)	1	0.88 (0.63–1.22)	1.37 (0.95–1.98)	1.45 (0.89–2.35)	1.28 (0.84–1.96)	0.0341
Adjusted for (A) and (B)						
Hazard ratio (95% CI)	1	0.99 (0.67–1.47)	1.63 (1.06–2.52)	1.83 (1.07–3.15)	1.58 (0.97–2.56)	0.0049
Death from malignant neoplasms						
Adjusted for (A)						
Hazard ratio (95% CI)	1	1.05 (0.75–1.48)	1.16 (0.77–1.74)	1.62 (1.00–2.61)	1.76 (1.18–2.62)	0.0015
Adjusted for (A) and (B)						
Hazard ratio (95% CI)	1	1.10 (0.77–1.56)	1.30 (0.85–2.00)	1.70 (1.02–2.82)	1.82 (1.20–2.76)	0.0012

Hazard ratio (95% CIs) of Cox proportional hazards model as independent variables accounting for death

higher for the slightly high HbA_1c group, the high HbA_1c group, and the diabetes group ($p<0.0001$ for trend). The hazard ratios for death from cardiovascular disease were significantly higher for the slightly high HbA_1c group and the high HbA_1c group ($p=0.005$ for trend). The hazard ratios for death from malignant neoplasms were significantly higher for the high HbA_1c group and the diabetes group ($p=0.001$ for trend). The adjusted hazard ratios for all-cause mortality, for cardiovascular disease mortality, and for mortality from malignant neoplasms per unit HbA_1c were 1.32 (1.22–1.43) ($p<0.0001$), 1.25 (1.09–1.46) ($p=0.0022$) and 1.31 (1.16–1.48) ($p<0.0001$), respectively.

Discussion

We studied the relationship between HbA_1c and mortality in a Japanese population. The study showed that high levels of HbA_1c increased the risk of all-cause mortality and death from cardiovascular or malignant neoplasms. This suggested that even a relatively minor level of glucose intolerance, as indicated by HbA_1c of 6% or more, might induce mortality in Japanese people.

A study conducted on Europeans and Americans suggested that HbA_1c has potential for use as a surrogate marker for metabolic syndrome [3]. In the current study population, as HbA_1c increased even those not diagnosed as having diabetes showed a tendency to manifest common characteristics of metabolic syndrome, including obesity, increase of systolic blood pressure, and decrease of HDL cholesterol (Table 1). Therefore, in a Japanese population also it is suggested that an increase of HbA_1c might indicate the presence of a prodromal state of metabolic syndrome, irrespective of whether or not diabetes has been diagnosed.

It is considered that an increase of HbA_1c is related to glucose intolerance [1, 2]. Previous reports [5, 6] were indicative of an increase in both all-cause mortality and cardiovascular disease mortality in type 2 diabetes patients. In the current study, results involving all-cause mortality did not contradict previous results. For cardiovascular disease mortality, however, no significant increase of the hazard ratio was observed in those already diagnosed as having diabetes (Table 2). One reason for this, although a positive trend was ascertained, was a consequence of weak statistical power, because coronary heart disease mortality among Japanese people is less than half that of Europeans and Americans [18, 19]. This lack of statistical power prompted Yano et al. [20] to report that systolic blood pressure was the only risk factor for death from cardiovascular disease in the Japanese population. In addition, most of the individuals known to have diabetes in the current study have been followed at medical institutions and are most probably under the modifying effect of drug and other treatments, which may have affected the results of the current study. After all, based on the results of this study, those with HbA_1c of 6% or more might be considered a group at high risk of cardiovascular disease and be followed carefully even among people without type 2 diabetes.

Even now, opinions are divided on the relationship between type 2 diabetes and malignant neoplasm mortality [4, 12, 21–25]. A positive relationship with type 2 diabetes has been reported for specific malignant neoplasms, such as pancreatic cancer [21, 22], colorectal cancer [23, 24], and prostatic cancer [25]. In the current study a significant increase of malignant neoplasm mortality was observed both in the high HbA_1c group (6.5% or more) and the diabetes patients but, because of the small number of cases, it was impossible to study the correlation between diabetes and specific malignant neoplasms. A previous report [12] showed an increase of cancer mortality risk among those with impaired glucose tolerance, suggesting that hyperglycaemic status, as reflected in the increase of HbA_1c, may increase not only all-cause and cardiovascular disease mortality but also malignant neoplasm mortality.

HbA_1c was a risk factor for mortality from malignant neoplasms, even adjusted for BMI, systolic blood pressure, and total cholesterol in this study. This result suggests the possibility that high HbA_1c levels might affect malignant neoplasms through the pathophysiology of hyperglycaemia, rather than that of obesity, hypertension or hyperlipidaemia. However, the mechanism involved between glucose intolerance and malignant neoplasms is not clear. One possibility may be the effect of oxidative stress enhanced by glucose intolerance. It has been demonstrated that in type 2 diabetes oxidative stress is increased, seemingly via three independent biochemical pathways [26]. One of the three pathways involves AGE, which are increased in diabetes. A report indicated that an increase of AGE enhanced oxidative stress through a receptor for AGE and contributed to the formation of vascular lesions in diabetes patients [27]. Because HbA_1c is one kind of Amadori compound observed in the process of AGE production [28], an increase of HbA_1c in the pre-diabetes stage suggests the possibility of increased AGE production. It has also been shown that oxidative stress is increased even in the stage of impaired glucose tolerance, which occurs before the onset of type 2 diabetes [29]. In other words, there may be a pathway by which an increase of oxidative stress incidentally reduces glucose tolerance and increases HbA_1c. The above mechanism indicates a possibility that an increase of HbA_1c implies the presence of enhanced oxidative stress. Because oxidative stress is suspected to be a cancer risk factor, because it can damage DNA [30, 31], the relationship between HbA_1c and malignant neoplasm mortality may be partly explained by the enhancement of oxidative stress.

However, this study has some limitations. First, some medications might have affected this study, especially the results of the diabetes group. We could not provide differences between results stratified by diabetes treatment because of the lack of statistical power. Second, the duration of follow-up in this study is too short to investigate the relationship between HbA_1c and death from malignant neoplasms. Accordingly, it is difficult to con-

clude that high HbA_1c itself is a risk factor for death from malignant neoplasms or is an epiphenomenon associated with the premalignant state. Further investigation is needed.

We studied the relationship between HbA_1c and mortality in a Japanese population. As in those with diabetes, an increase of all-cause mortality, cardiovascular disease mortality, and malignant neoplasm mortality was observed as HbA_1c increased. Our study suggests that HbA_1c might be effective as a marker for mortality risk.

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循環器疾患死亡のリスク因子としての血清尿酸値：原爆被爆生存者における長期コホート研究

この研究の目的は血清尿酸値と循環器疾患死亡の関係を明らかにする事である。1966-1970 年に放射線影響研究所の成人健康調査を受診した原爆被爆者とその対照からなる 10,615 人について Cox の比例ハザードモデルにより、ベースラインの血清尿酸値と循環器疾患死亡ならびに総死亡との関連を解析した。ベースライン時の平均年齢は 49 歳、死亡の追跡は 1999 年まで行い、平均追跡期間は 24.9 年であった。追跡期間中の総死亡数は 5225 人、その内 1984 人が循環器疾患死亡であった。Cox の比例ハザードモデルにより、男女各々5 群に分けた血清尿酸値群の最低位群と比較したハザード比を求めた。男性のベースライン時血清尿酸値区分は 5.0、6.0、7.0、8.0mg/dl（297.4、356.9、416.4、475.8mmol/l）、女性の区分は 4.0、5.0、6.0、7.0mg/dl（237.9、297.4、356.9、416.4mmol/l）とした。男性では年齢調整後の循環器疾患死亡と総死亡に尿酸値との関連を認めた。年齢、肥満度（BMI）、収縮期血圧、総ｺﾚｽﾃﾛｰﾙ値、喫煙、飲酒、高血圧既往、糖尿病既往、循環器疾患既往調整後も、総死亡との関連は認められたが循環器疾患死亡では有意差がなくなった。女性では同様な調整を行った後も、総死亡と循環器疾患死亡の両方に有意な増加を認めた。血清尿酸値は女性では循環器疾患死亡のリスク因子であった。また男女共に、血清尿酸値と総死亡のリスク増加の関係が認められた。

Serum Uric Acid Concentration as a Risk Factor for Cardiovascular Mortality: A Longterm Cohort Study of Atomic Bomb Survivors

MASAYUKI HAKODA, NAOMI MASUNARI, MICHIKO YAMADA, SAEKO FUJIWARA, GEN SUZUKI, KAZUNORI KODAMA, and FUMIYOSHI KASAGI

ABSTRACT. ***Objective.*** To elucidate the association of serum uric acid concentration with cardiovascular mortality risk.

Methods. Serum uric acid level measured from 1966 through 1970 in 10,615 Japanese individuals from a cohort of atomic bomb survivors was analyzed for association with subsequent cardiovascular and all-cause mortality until 1999 using the Cox proportional hazard model.

Results. During an average followup of 24.9 years, 5225 deaths occurred, of which 1984 were ascribed to cardiovascular disease. In men, after adjustment for age, elevated serum uric acid level was associated with both cardiovascular and all-cause mortality. After additional adjustment for potential cardiovascular disease risk factors including body mass index, smoking status, alcohol consumption, systolic blood pressure, cholesterol level, and histories of hypertension, diabetes and cardiovascular disease, elevated serum uric acid level in men was associated with all-cause mortality but not with cardiovascular mortality. In women, even after these adjustments, elevated serum uric acid level was significantly associated with cardiovascular and all-cause mortality.

Conclusion. Increased serum uric acid level is a significant and independent risk factor for cardiovascular mortality in women and for all-cause mortality in both men and women. (J Rheumatol 2005;32:906–12)

Key Indexing Terms:
URIC ACID CARDIOVASCULAR DISEASE MORTALITY COHORT

Besides the well known causal relationship between uric acid and clinical manifestations of gout, an association of increased serum uric acid concentration with cardiovascular disease was first suggested about 50 years ago[1]. Since serum uric acid level is closely linked to other cardiovascular disease risk factors such as hypertension, hyperlipidemia, and obesity, numerous studies have debated whether the suggested association is independent from these other risk factors[2-14]. Among recent large-scale prospective studies, a report from the Framingham Heart Study noted that the apparent relationship of uric acid to cardiovascular or all-cause mortality did not remain significant after adjustments for other cardiovascular disease risk factors[9]. On the other hand, a report from the First National Health and Nutrition Examination Survey (NHANES I) showed a significant and independent association of uric acid concentration with cardiovascular and all-cause mortality in both men and women[11]. These 2 studies had similar population sizes and followup periods and therefore the source of the discrepancy in the results is unclear. Among individuals at higher risk for cardiovascular events, such as those with hypertension[15-17], prevalent cardiovascular disease[18], and diabetes[19], more consistent results have been obtained for the association of serum uric acid level with future risk for cardiovascular event and cardiovascular mortality.

To investigate this unresolved relationship between serum uric acid level and cardiovascular disease, we utilized a Japanese cohort that has been followed over many years. The Adult Health Study cohort was established in 1958 in the cities of Hiroshima and Nagasaki, Japan, to explore the longterm effects of ionizing radiation from the atomic bombs[20,21]. The participants of this cohort are invited to receive clinical examinations every 2 years, and nearly complete death information has been continuously obtained for this population. We analyzed the relationship between serum uric acid level, measured in more than 10,000 individuals from 1966 through 1970, and subsequent death until 1999, making it the longest and the largest of the studies on the association of uric acid level with subsequent risk for

From the Department of Clinical Studies and the Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan.

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M. Hakoda, MD, PhD, Chief, Division of Clinical Laboratories; N. Masunari, BSc, Pharmacist; M. Yamada, MD, PhD, Chief, Division of Health Examinations; S. Fujiwara, MD, PhD, Chief, Department of Clinical Studies; F. Kasagi, PhD, Assistant Chief, Department of Epidemiology; G. Suzuki, MD, PhD, Chief Scientist, Radiation Effects Research Foundation; K. Kodama, MD, PhD, Chief Scientist, Radiation Effects Research Foundation.

Address reprint requests to Dr. M. Hakoda, Department of Clinical Studies, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan. E-mail: hakoda@rerf.or.jp

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cardiovascular and all-cause mortality. We show here that serum uric acid level is significantly and independently associated with cardiovascular mortality in women and with all-cause mortality in both men and women.

MATERIALS AND METHODS

Subjects. The study population comprised the participants of biennial clinical examinations in the Adult Health Study, conducted since 1958 at the Radiation Effects Research Foundation in Hiroshima and Nagasaki, Japan, to evaluate the longterm effects of ionizing radiation from the atomic bombs on human health[20,21]. The original Adult Health Study cohort consisted of 19,961 individuals, about half of whom were exposed to the bomb proximally (< 2000 m from the hypocenter) and the other half who either were exposed distally (≥ 3000 m from the hypocenter) or were not in the city at the time of the bombings. The people making up this latter half were not substantially exposed to radiation from the bombs. The detailed study design of the Adult Health Study has been described[21]. Those persons selected underwent clinical examination at our institute only if they accepted our invitation to do so. The participation rate of subjects was actually about 75%. Serum uric acid level was measured in the examinations conducted from 1966 through 1970 (examination cycles 5–6). The number of participants during this period was 13,591, and the number of those who underwent serum uric acid measurement in this period was 13,559. Among this total, 10,615 participants (3860 men, 6755 women; mean age 48.6 yrs; age range 20–89 yrs) with available lifestyle information (smoking status and drinking habits), disease history, blood pressure, body mass index (BMI), and serum cholesterol level were the subjects for this analysis.

Baseline measurements. Participants were interviewed by nurses to obtain disease histories and lifestyle information including smoking status and drinking habits. Serum uric acid level was measured by a phosphotungstic acid procedure using an autoanalyzer (Technicon Instruments, Tarrytown, NY, USA). Total cholesterol and blood glucose were determined by the Abell-Kendall method and the Folin-Malmros microtechnique, respectively, with an autoanalyzer. Diagnosis of hypertension was based on a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or current treatment with antihypertensive drugs. Diabetes was defined on the basis of a fasting blood glucose level ≥ 140 mg/dl, a blood glucose level ≥ 180 mg/dl at the 2 h point of the 50 g glucose tolerance test, or the use of oral hypoglycemic agents or insulin.

Outcome measures. Primary outcome measures were death from cardiovascular disease (coronary heart disease, stroke, or other cardiovascular disease) and death from all causes. Deaths were identified through checks on the status of all surviving cohort members, using the Japanese family registration system (*koseki*). No individual was lost during the followup. Information on the underlying cause of death was obtained from death certificates, and was coded according to the *International Classification of Diseases* (ICD). Four ICD revisions were used depending on the time of death. Thus, ICD 7, ICD 8, ICD 9, and ICD 10 were used for deaths during 1966-67, 1968-78, 1979-97, and 1998-99, respectively (Table 1).

Table 1. International Classification of Diseases (ICD) codes for cause of death.

		ICD Codes		
Period of Death	ICD Revision	Total Cardiovascular Disease	Coronary Heart Disease	Stroke
1966–67	7th	400–468 330–334	420	330–334
1968–78	8th	390–458	410–414	430–438
1979–97	9th	390–459	410–414	430–438
1998–99	10th	100–199	120–125	160–169

Statistical analysis. Since uric acid level differs substantially between men and women, results of the 2 sex groups were analyzed separately. To evaluate uric acid level as a risk factor for cardiovascular and all-cause mortality, the subjects were stratified into 5 groups by sex depending on baseline serum uric acid level. For men, the dividing points were 5.0, 6.0, 7.0, and 8.0 mg/dl (297.4, 356.9, 416.4, 475.8 mmol/l, respectively), and for women, the points were 4.0, 5.0, 6.0, and 7.0 mg/dl (237.9, 297.4, 356.9, 416.4 mmol/l, respectively). Cox proportional hazard regression models were used to examine the relationship of serum uric acid level to death from all causes, total cardiovascular disease, coronary heart disease, or stroke. Mortality hazard ratio for each uric acid category was calculated using as reference the lowest uric acid categories, < 5.0 mg/dl (297.4 mmol/l) in men and < 4.0 mg/dl (237.9 mmol/l) in women. These analyses were adjusted for baseline characteristics, including age, BMI (kg/m^2), systolic blood pressure (mm Hg), total cholesterol level (mg/dl), smoking status (non-smoker, ex-smoker, or current smoker), alcohol consumption (g/week), histories (yes/no) of hypertension, coronary heart disease, stroke, diabetes, kidney disease and malignant tumor, and radiation dose (Gray) from the atomic bombings.

RESULTS

Mean (SD) age of the subjects at the time of uric acid measurement was 49.0 (14.8) years for men and 48.6 (13.5) years for women. Mean (SD) uric acid concentration was 5.4 (1.5) mg/dl [321.2 (89.2) μmol/l] in men and 4.2 (1.1) mg/dl [249.8 (65.4) μmol/l] in women, a statistically significant difference ($p < 0.001$). The 90th and 95th percentiles for uric acid distribution were 7.6 and 8.4 mg/dl for men and 5.6 and 6.3 mg/dl for women, respectively. Uric acid level was significantly and positively associated with other cardiovascular disease risk factors in both sexes including BMI, total cholesterol level, and presence of hypertension (Table 2). Uric acid level was also associated with alcohol use in both sexes (Table 2).

During an average followup of 24.9 years (22.9 yrs for men, 26.0 yrs for women), 5225 subjects (49.2%) of a total of 10,615 subjects died [2266 (58.7%) of 3860 men, 2959 (43.8%) of 6755 women]. Among these deaths, 1984 (38.0%) were attributed to cardiovascular disease (coronary heart disease, 427; stroke, 931; other cardiovascular disease, 626). Crude all-cause and cardiovascular mortality rates were 19.8 (25.6 for men, 16.8 for women) and 7.5 (8.5 for men, 7.0 for women) per 1000 person-years, respectively.

In men, age-adjusted hazard ratio for all-cause mortality was significantly increased in subjects with uric acid level ≥ 8.0 mg/dl compared with those in the lowest uric acid category (< 5.0 mg/dl; Table 3). This increase in risk for all-cause mortality remained significant after adjustment for other cardiovascular disease risk factors. In women, age-adjusted hazard ratio for all-cause mortality increased significantly in all uric acid categories compared with the lowest uric acid category (Table 3). After full adjustment, the hazard ratio for all-cause mortality remained significant in the uric acid categories 6.0–6.9 and ≥ 7.0 mg/dl, and a higher hazard ratio was observed for uric acid category ≥ 7.0 mg/dl compared with the 6.0–6.9 mg/dl category (Table 3).

The hazard ratio for cardiovascular mortality in men was

Table 2. Baseline characteristics by sex and uric acid level. Values are mean (SD).

Uric Acid Level, mg/dl	No. of Subjects	Age, yrs	Body Mass Index, kg/m^2	Total Cholesterol, mg/dl	Hypertension, %	Diabetes, %	Current Smoking, %	Alcohol Use, g†/wk	Radiation Dose, Gy
Men									
Total	3860	49.0 (14.8)	21.1 (2.8)	181.8 (38.7)	30.4	13.0	74.1	107 (140)	0.39 (0.82)
< 5.0	1184	51.8 (14.4)	20.5 (2.6)	178.1 (36.7)	27.8	14.4	75.4	92 (126)	0.38 (0.78)
5.0–5.9	1127	48.4 (14.5)	20.8 (2.8)	180.6 (37.0)	25.9	12.6	75.3	101 (144)	0.40 (0.83)
6.0–6.9	866	46.8 (14.8)	21.3 (2.8)	183.1 (39.7)	30.4	11.1	73.7	116 (141)	0.39 (0.85)
7.0–7.9	390	46.6 (15.1)	22.1 (3.1)	187.5 (41.8)	36.9	12.8	73.3	119 (143)	0.36 (0.77)
≥ 8.0	293	49.0 (15.2)	22.5 (3.0)	189.5 (43.3)	49.5	15.0	66.9	141 (156)	0.39 (0.84)
p for trend		< 0.001	< 0.001	< 0.001	< 0.001	> 0.5	0.007	< 0.001	> 0.5
Women									
Total	6755	48.6 (13.5)	22.1 (3.4)	191.8 (41.2)	26.4	6.6	14.4	8 (41)	0.36 (0.75)
< 4.0	3015	47.2 (13.0)	21.7 (3.0)	185.1 (39.6)	19.4	5.1	12.6	5 (26)	0.35 (0.70)
4.0–4.9	2261	48.6 (13.5)	22.1 (3.4)	191.9 (39.6)	27.1	5.9	14.6	9 (42)	0.36 (0.76)
5.0–5.9	1005	50.5 (14.0)	23.1 (3.7)	202.6 (42.3)	34.5	9.4	16.2	11 (50)	0.40 (0.86)
6.0–6.9	339	52.8 (14.1)	23.9 (4.0)	209.2 (46.2)	46.0	12.7	21.2	20 (78)	0.37 (0.78)
≥ 7.0	135	56.9 (13.8)	23.9 (4.0)	212.3 (45.1)	60.0	15.6	21.5	20 (60)	0.40 (0.76)
p for trend		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.07

† Ethanol weight.

Table 3. Relation of serum uric acid level to all-cause mortality.

Uric Acid Level, mg/dl	Person-yrs	No. of Deaths	Mortality Rate*	Age Adjusted Hazard Ratio	Age Adjusted 95% CI	Fully Adjusted† Hazard Ratio	Fully Adjusted† 95% CI
Men							
< 5.0	25,811	754	29.2	1.0		1.0	
5.0–5.9	26,259	649	24.7	1.00	0.90, 1.11	0.99	0.89, 1.10
6.0–6.9	20,871	461	22.1	0.95	0.85, 1.07	0.94	0.83, 1.06
7.0–7.9	9243	214	23.2	1.05	0.90, 1.22	1.05	0.90, 1.23
≥ 8.0	6182	188	30.4	1.38	1.17, 1.61	1.22	1.03, 1.44
Women							
< 4.0	81,405	1130	13.9	1.0		1.0	
4.0–4.9	58,786	980	16.7	1.10	1.01, 1.20	1.07	0.98, 1.16
5.0–5.9	25,226	525	21.0	1.14	1.02, 1.26	1.08	0.97, 1.20
6.0–6.9	7458	221	29.6	1.59	1.37, 1.84	1.44	1.24, 1.67
≥ 7.0	2538	103	40.6	1.90	1.54, 2.31	1.63	1.32, 2.00

* Values are expressed per 1000 person-years. † In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs.

significantly increased in the highest uric acid category (≥ 8.0 mg/dl) compared with subjects in the lowest uric acid category when adjustment was made only for age. However, this hazard ratio increase did not remain significant after full adjustment (Table 4). When cardiovascular disease was restricted to coronary heart disease, age-adjusted hazard ratio for mortality was significantly increased in the uric acid category ≥ 8.0 mg/dl, but it was no longer significant after full adjustment (Table 4). For stroke mortality, no significant increase in hazard ratio was observed in any of the uric acid categories in men.

In women, a significant increase in the hazard ratio for cardiovascular mortality was observed in the uric acid categories 6.0–6.9 and ≥ 7.0 mg/dl compared with the lowest uric acid category (< 4.0 mg/dl) even after full adjustment, and a higher hazard ratio was observed in the uric acid category ≥ 7.0 mg/dl compared with the 6.0–6.9 mg/dl category (Table 4). A significant increase in coronary heart disease mortality was observed for the 6.0–6.9 mg/dl category, but the increase was not significant in the ≥ 7.0 mg/dl category (Table 4). This may result from the small number of cases in this category (n = 12). For stroke mortality, a significant increase in hazard ratio was found for the ≥ 7.0 mg/dl category (Table 4).

Since menopausal status has substantial effects on both uric acid level and cardiovascular disease occurrence, the relation between uric acid level and mortality risk was examined in different age groups in women. Thus, women