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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

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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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