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Relationship between changes in haemoglobin A_{1C} and prostate-specific antigen in healthy men

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ABSTRACT

Background: Although many studies have shown an inverse relationship between diabetes and prostate cancer, it still remains unclear why diabetes may reduce the risk of prostate cancer. An inverse association between haemoglobin A_{1C} (HbA_{1C}) and prostate-specific antigen (PSA) also has been reported in previous studies that assessed the association cross-sectionally. To fully understand the relationship between diabetes and prostate cancer, it is essential to examine the association in a longitudinal design. The effect of plasma volume should also be considered in examining the PSA level. The aim of this study was to determine whether changes in HbA_{1C} were associated with PSA levels, independent of plasma volume changes, as indicated by haematocrit and weight.

Methods: We investigated 5917 Japanese men aged 50 and over who visited St. Luke's International Hospital, Tokyo for routine health check-ups in 2006 and 2007. We performed a multiple linear regression analysis to examine any association between changes in HbA_{1C} and PSA over 1 year.

Results: Adjusting for age, body mass index at baseline and changes in weight and haematocrit, the increases in HbA_{1C} and PSA were concordant (5.7% increase per 1-unit HbA_{1C} change; 95% confidence interval, 2.8–8.5%; $p < 0.001$).

Conclusions: In contrast to previous cross-sectional observations showing an inverse association between HbA_{1C} and PSA, longitudinal observations suggest a positive association between the two. Further studies are needed to investigate the association between diabetes and prostate cancer.

1. Introduction

Prostate cancer and diabetes are both very common diseases in the aging male population. The prostate-specific antigen (PSA) and haemoglobin A_{1C} (HbA_{1C}) tests are widely used as population-based screening tools for each. Many studies have shown an inverse relationship between diabetes and prostate cancer.[1–5] The inverse relationship between these endpoints was supported by an inverse association between HbA_{1C} measurements and PSA levels in previous studies.[6,7] In these studies, however, the association between the two values was assessed cross-sectionally.

The mechanism by which diabetes may reduce the risk of prostate cancer remains unclear. To fully understand the relationship between diabetes and prostate cancer, it is essential to observe changes in HbA_{1C} and PSA in a longitudinal

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manner. To our knowledge, no reported study has investigated the relationship between changes in HbA_{1C} and PSA in a longitudinal design.

PSA levels seem to be influenced by several factors that should be taken into account when interpreting test results. Men with a higher body mass index (BMI) have lower PSA levels.[8–13] Increased plasma volume may be responsible for the observed decrease in PSA concentrations in men with a higher BMI.[8,9,12,13] However, because higher BMI is also associated with diabetes, it is important to take the plasma volume effect into account in examining any relationship between HbA_{1C} and PSA. Haematocrit is the most popular indicator of plasma volume.[14] Changes in body weight are widely used to check the body fluid balance, especially in patients on dialysis or those with diabetes insipidus. We previously investigated the effects of changes in plasma volume on PSA using haematocrit and weight, and found that decreased PSA levels were observed in men with haemodilution.[15] Changes in haematocrit and weight could be useful indicators of plasma volume changes, as confounding variables, when assessing the association between HbA_{1C} and PSA.

The aim of this study was to determine whether changes in HbA_{1C} were associated with PSA levels independent of changes in haematocrit and weight in healthy men.

2. Patients and methods

The internal review board of St. Luke's International Hospital approved all procedures performed in this study.

In 2006 and 2007, 9604 and 9892 men aged 50 and over visited the Centre for Preventive Medicine at St. Luke's International Hospital for routine health check-ups, respectively. This hospital is located in the central business district of Tokyo and provides primary to tertiary care to an urban population in the Tokyo metropolitan area. This institution also focuses on preventive medicine and provides health check-ups services.

All men completed a questionnaire that included questions regarding medical history and life style. Prostate cancer diagnoses and history of diabetes were obtained from the data form.

Height, weight and body fat were all measured using a digital electronic scale (BF-220, Tanita). Height was measured to the last complete 0.1 cm, weight to the last complete 0.1 kg and body fat to the last complete 0.1%. BMI was calculated by dividing the weight in kilograms by the square of the height in meters. Waist circumference was also measured. Participants had fasted since 9:00 pm on the previous evening, and blood samples were drawn by venipuncture. PSA, HbA_{1C} and haematocrit were measured in the hospital laboratory on the day of blood collection. Serum PSA levels were measured using a chemiluminescent enzyme immunoassay kit (Fujirebio, Tokyo, Japan).

From the participants, 7023 men aged 50 and over at baseline who had health check-ups in both 2006 and 2007 were identified. These included 6962 men who had undergone serum PSA, HbA_{1C} and haematocrit determination and anthropometric measurements, including height, weight, body fat and waist circumference, and who were eligible for this study. During the study period, men who had a PSA exceeding 4 ng/mL either in 2006 or 2007 ($n = 458$) or had a prior diagnosis of prostate cancer before the examination in 2007 ($n = 156$) were excluded from the analysis. We also excluded 431 men who had undergone any treatment for diabetes between 2006 and 2007. Thus, in total, 5917 men were included in the analysis.

The subjects were divided into three subgroups by age: 50–59, 60–69 and $\geqslant 70$ years. We calculated the increased rate of PSA (the difference divided by the value at baseline). Based on changes in weight, body fat, waist circumference, haematocrit and HbA_{1C} over 1 year, we categorised each variable into two groups (no change or decrease, and increase). We used Wilcoxon's rank sum test to examine differences in the rate of increase in PSA between the two groups for each variable, stratifying by age.

We performed a multiple linear regression analysis to examine the association between PSA changes and the changes in HbA_{1C} (difference between measurements) over 1 year using age, BMI at baseline and changes in weight and haematocrit as confounding variables. Because PSA change data were not normally distributed, log-transformed PSA changes were used and the values were back-transformed to interpret the results. In order to avoid log-transforming negative PSA changes, we used PSA change relative to baseline (PSA in 2007 divided by PSA in 2006) as the outcome variable in the regression analysis. We also used changes in body fat or waist circumference, instead of weight gain.

A p-value < 0.05 was deemed to indicate statistical significance (two-tailed). All statistical analyses were performed using the Statistical Analysis System (SAS Institute, Cary, NC).

3. Results

Table 1 shows the distribution of the clinical parameters at baseline. Only 2% of the participants were obese (BMI $\geqslant$ 30 kg/m^2) and 28% were overweight (BMI 25–30 kg/m^2).

Relationships between the increase rate of PSA and changes in clinical factors according to age are presented in Table 2. Men with increased weight had significantly decreased PSA in the 50–59 and 60–69 age groups ($p = 0.024$ and 0.015, respectively). Compared with men with no change or decreased HbA_{1C}, the PSA increase rate was significantly higher in those with increased HbA_{1C} ($p < 0.001$ for participants 50–59 years, $p = 0.004$ for 60–69 years and $p = 0.025$ for $\geqslant 70$ years).

We performed a multiple regression analysis to assess any association of changes in HbA_{1C} with PSA changes. Adjusting for age, BMI at baseline and changes in weight and haematocrit, annual change in HbA_{1C} was positively associated with PSA changes (5.7% increase per 1-unit HbA_{1C} change; 95% confidence interval [95% CI], 2.8–8.5%; $p < 0.001$), as shown in Table 3.

We also performed analyses with multiple regression models using indicators of adiposity other than weight: changes in body fat or waist circumference. Again, the levels of increase of HbA_{1C} were significantly associated with PSA changes, adjusted by body fat (4.5% increase per unit HbA_{1C} change; 95% CI, 1.8–7.4%; $p = 0.001$) or waist circumference (4.6% increase per unit HbA_{1C} change; 95% CI, 1.8–7.4%; $p = 0.001$).

Table 1 – Subject characteristics at baseline.

Age, in years, mean ± SD	60 ± 7
50–59	3356 (57)
60–69	1872 (32)
70⩽	689 (12)
Body mass index (BMI), kg/m^2, mean ± SD	23.7 ± 2.7
<18.5	132 (2)
18.5–22	1356 (23)
22–25	2657 (45)
25–30	1642 (28)
⩾30	130 (2)
Weight, kg, mean ± SD	67.5 ± 9.1
Average change over 1 year	–0.4
Body fat, %, mean ± SD	21.2 ± 4.7
Average change over 1 year	–0.4
Waist circumference, cm, mean ± SD	85.4 ± 7.4
Average change over 1 year	–0.4
Haematocrit, %, median, interquartile range	42.2, 40.4–44.0
Average change over 1 year	0.1
Haemoglobin A_{1C}, %, median, interquartile range	5.2, 5.0–5.5
Average change over 1 year	0.0
Prostate-specific antigen (PSA), ng/mL, median, interquartile range	0.9, 0.6–1.3
Average change over 1 year	0.0

Values are *n* (%) unless otherwise stated.

4. Discussion

In the present study, we investigated the association between changes in HbA_{1C} and PSA over 1 year. By multiple regression analysis, including age and BMI at baseline and changes in weight and haematocrit, we found a positive association between changes in HbA_{1C} and PSA, as opposed to the inverse association between the two values reported in previous cross-sectional studies.

We also analysed the data in a cross-sectional manner. In multiple regression analysis, after adjusting for age and BMI at baseline (which are commonly considered to be potential confounders), HbA_{1C} was not associated with PSA in both 2006 (0.4% decrease per 1-unit HbA_{1C}; 95% CI, –3.3–2.7%; $p = 0.814$) and 2007 (0.8% decrease per 1-unit HbA_{1C}; 95% CI, –4.0–2.4%; $p = 0.607$). Unlike the previous cross-sectional studies that found the significant inverse association between HbA_{1C} and PSA,[6,7] we did not find such an association. This discrepancy may be, in part, due to differences in the statistical analyses or the characteristics of subjects. In the study by Müller and colleagues,[6] for example, HbA_{1C} was used as a categorical variable and many people with obese and diabetes were included; 53% of the participants were overweight (BMI 25–30 kg/m^2) and 25% were obese (BMI ⩾ 30 kg/m^2) and 18% had a high HbA_{1C} (6.1–6.9%) and 8% had a very high HbA_{1C} (⩾7%). In our study, 28% were overweight and 2% were obese and 5% had a high HbA_{1C} and 1% had a very high HbA_{1C}.

Studies have suggested that the protective effect of diabetes on prostate cancer incidence is greater in men with long-standing diabetes; meanwhile men with newly diagnosed diabetes, up to 5 years after diagnosis have an increased risk of prostate cancer.[2,16–18] Although the mechanism underlying this association remains unclear, the observed positive association between changes in HbA_{1C} and PSA in our study may provide support for those findings in previous studies. Most of the subjects in our study (70%) had a BMI < 25 kg/m^2. One recent study showed that diabetes was inversely associated with early stage prostate cancer, but the subgroup of men with BMI < 25 kg/m^2 with diabetes had an increased risk of aggressive prostate cancer.[4] It is unclear whether this finding may be, in part, due to a positive association between changes in HbA_{1C} and PSA. Further studies are needed to

Table 2 – Relationship between prostate-specific antigen increase rate (%) and changes in clinical factors according to age.

	n	Age 50–59 Mean ± SD	*p*-Value	*n*	Age 60–69 Mean ± SD	*p*-Value	*n*	Age ⩾ 70 Mean ± SD	*p*-Value
Weight change			0.024			0.015			0.154
⩽0	1870	1.5 ± 36.4		1136	1.8 ± 30.6		428	4.6 ± 37.6	
>0	1486	–0.5 ± 39.8		736	–0.6 ± 28.9		261	–1.6 ± 25.9	
Body fat change			0.454			0.404			0.516
⩽0	1967	0.7 ± 34.4		1147	0.3 ± 30.5		400	3.0 ± 32.4	
>0	1389	0.4 ± 42.5		725	1.8 ± 29.2		289	1.1 ± 35.6	
Waist circumference change			0.886			0.300			0.812
⩽0	1911	0.2 ± 33.2		1107	1.3 ± 31.2		407	2.1 ± 32.9	
>0	1445	1.1 ± 43.4		765	0.2 ± 28.0		282	2.4 ± 35.0	
Haematocrit change			0.008			0.108			0.329
⩽0	1591	–0.6 ± 39.8		892	–0.2 ± 29.2		347	2.1 ± 28.4	
>0	1765	1.7 ± 36.2		980	1.8 ± 30.7		342	2.4 ± 38.5	
Haemoglobin A_{1C} change			<0.001			0.004			0.025
⩽0	1818	–0.9 ± 35.3		1105	–0.6 ± 28.6		401	0.5 ± 34.1	
>0	1538	2.4 ± 40.8		767	3.0 ± 31.8		288	4.6 ± 33.2	

Table 3 – Results of multiple regression analysis predicting ln(prostate-specific antigen change relative to baseline).

	Exponentiated regression coefficient	95% Confidence interval	*p*-Value
Intercept	1.017	0.926–1.116	0.731
Age, per year	1.001	1.000–1.002	0.199
Body mass index, per kg/m^2	0.996	0.993–0.999	0.004
Weight change, per kg	0.989	0.985–0.993	<0.001
Haematocrit change, per 1-unit	1.003	0.999–1.007	0.139
Haemoglobin A_{1C} change, per 1-unit	1.057	1.028–1.085	<0.001

investigate the relationship between diabetes and prostate cancer incidence in men with lower BMI.

We investigated the relationship between PSA changes and changes in body fat and waist circumference as well as weight changes (Table 2). These associations were not statistically significant in any age group. This may reflect the difference between fat and lean body mass or plasma volume. We also performed regression analysis using changes in body fat or waist circumference instead of weight gain. Again, we confirmed a significant association between an increase in HbA_{1C} and greater PSA changes.

This study has some limitations. We investigated a limited population who visited one hospital for routine health check-ups. The participants were all Japanese and may have tended to be more health-conscious. However, it seems unlikely that any association between changes in PSA and HbA_{1C} would be observed only in this population.

We acknowledge that the effect of an increase in HbA_{1C} on PSA changes in our study was small. However, our findings may provide useful information in clarifying the association between diabetes and prostate cancer. Obesity is less common in Japan than in Western countries; indeed, only 2% of the participants in this study were obese. Studies with a more obese population are required to further assess this association.

We did not perform further examinations for diseases related to changes in PSA concentration, although we excluded men with PSA levels > 4 ng/mL from our analysis. Latent prostate tumours could still have been overlooked. However, it is unlikely that such a small number of patients would affect the results. We were not able to control for benign prostatic hyperplasia, which may also affect PSA values. PSA concentrations increase with prostate volume,[19,20] and obese men have larger prostates than do non-obese men.[19,21,22] Although we did not measure prostate volume, it is unlikely that weight change over a short period affected prostate volume.

Despite these limitations, we consider our findings valid. To clarify the association between diabetes and prostate cancer, we investigated the association between their indicators, HbA_{1C} levels and PSA concentrations, using changes in both measurements in relatively healthy men. We found that HbA_{1C} increased in accordance with the increase of PSA over 1 year. We need to investigate the mechanism of the linked increase of HbA_{1C} and PSA, which may be associated directly or indirectly.

Conflict of interest statement

None declared.

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