Increased arterial stiffness is closely associated with hyperglycemia and improved by glycemic control in diabetic patients

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ABSTRACT

Aims/Introduction: Although arteriosclerotic diseases have been reported to be frequently complicated by diabetes mellitus (DM), a detailed relationship between hyperglycemia and arterial stiffness has not been fully clarified. We investigated the influence of hyperglycemia on arterial stiffness using the cardio-ankle vascular index (CAVI), which is a new method for estimating arterial stiffness.

Materials and Methods: CAVI values of 52 early-staged DM patients (duration <5 years, no microangiopathies) were compared with those of 43 age-matched non-diabetic (NDM) subjects. The association between CAVI and clinical background factors was evaluated. The effect of glycemic improvement on CAVI was examined in 36 DM patients who were hospitalized for 2 weeks to treat hyperglycemia. CAVI and clinical parameters were measured twice during hospitalization and again after 8 weeks. Additionally, we measured CAVI before and 2 h after breakfast in five DM and five NDM subjects.

Results: The CAVI of DM patients was significantly higher than that of NDM subjects. Multiple regression analysis showed that neither hypertension, obesity nor dyslipidemia, but aging and hemoglobin A1c (HbA1c) were significantly related to CAVI elevation. The CAVI, HbA1c and total cholesterol (TC) had significantly improved. Improvement of CAVI was significantly associated with HbA1c improvement. In contrast, no significant association was observed between the improvements of TC and CAVI. CAVI values before and after breakfast did not change significantly.

Conclusions: CAVI elevation seems to be a sensitive arteriosclerotic marker, which is closely associated with hyperglycemia and improved by glycemic control. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00229.x, 2013)

KEY WORDS: Arterial stiffness, Cardio-ankle vascular index, Glycemic control

INTRODUCTION

The age of death in Japanese patients with diabetes mellitus (DM) is 10 years younger than the general population, and the second most common cause of death is vascular disease. To improve the prognosis of DM patients, early diagnosis of arteriosclerosis is important. Arterial stiffness is recognized as an early arteriosclerotic index in DM patients. The cardio-ankle vascular stiffness index (CAVI) has recently been used as an index that reflects arterial stiffness. We have previously reported that the CAVI measures arterial stiffness independent of blood pressure. Increased arterial stiffness has been reported to be complicated by metabolic syndrome, sleep apnea syndrome and smoking. However, a detailed relationship between hyperglycemia and arterial stiffness has not been fully clarified.

In the present study, we investigated the clinical factors that were related to CAVI in patients with DM of short duration and no microangiopathies. Furthermore, the effect of glycemic control on CAVI was also examined.

MATERIALS AND METHODS

Arterial Stiffness in the Early Stage of Diabetes

We measured CAVI in 52 DM patients (five type 1 and 47 type 2 diabetic) with DN of short duration (<5 years) without microangiopathies and 43 age-matched non-diabetic (NDM) subjects. In DM patients, 15 were outpatients and 37 were inpatients of the Wakayama Medical University Hospital. As many patients had been hospitalized for glycemic control, two-thirds of the patients were under insulin treatment. Then we compared clinical factors, such as sex, age, body mass index (BMI), blood pressure (BP), hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), smoking habit, ankle brachial pressure index (ABI) and CAVI between the two groups (Table 1). Participants with a low ABI <0.9 were excluded. HbA1c (%) was
compared between the two groups. The association between the CAVI and clinical background factors including age, sex, BMI, hypertension and dyslipidemia were evaluated by multiple regression analysis (model 1). Additional analyses that added smoking as an independent variable were also carried out (model 2).

**Effect of Glycemic Control on Arterial Stiffness**

We measured CAVI in 36 DM patients (five type 1 and 31 type 2 diabetic) who were hospitalized for 2 weeks for glycemic control and diabetes education. As many patients had been hospitalized for the improvement of hyperglycemia, 86% (31/36) of the patients had been treated with insulin. After 8 weeks, the CAVI was re-examined to evaluate the influence of glycemic control on CAVI. The association between the change of clinical characteristics and arteriosclerotic indices was also evaluated. Furthermore, we measured the CAVI before and 2 h after breakfast in five DM and five NDM participants to examine the influence of very short-term blood glucose change on CAVI.

**Methods of Measuring Arteriosclerotic Indices**

CAVI and ABI were measured using a pulse wave analyzer, VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan). ABI and CAVI represent the degree of vascular stenosis and the stiffness of the arterial wall in one examination, respectively. The arteries measured for arterial stiffness included both elastic and muscular arteries. Details were described previously. Left, right and mean (the average of left and right) values were evaluated.

To evaluate IMT and plaque, ultrasonography was carried out with a Power Vision 7000 TM (Toshiba, Tokyo, Japan). IMT of the carotid artery was measured at three sites, and an average was used for analysis. Plaque was defined as a circumscribed elevated lesion ≥1.1 mm in thickness.

**Statistical Analyses**

Data are shown as mean ± standard deviation (SD). Differences in the average data and the prevalence of clinical background factors between non-diabetic and diabetic participants were statistically analyzed by an unpaired t-test and a chi-square test, respectively. Serial changes of the data were statistically analyzed by a paired t-test. The associations between the CAVI and clinical background factors were evaluated by multiple regression analyses. Statistical analyses were carried out using statistical software (Statview-J5.0TM; Hulinks, Tokyo, Japan). $P < 0.05$ was accepted as statistically significant.

**RESULTS**

**Arterial Stiffness in the Early Stage of Diabetes**

In the DM group, HbA1c and TG were significantly higher, and HDL was lower compared with the NDM group. Although ABI, IMT and prevalence of plaque did not show a significant difference between the DM and NDM groups, right, left and mean CAVI of the DM group were significantly higher than

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### Table 1 | Comparison of clinical characteristics and arteriosclerotic indices between non-diabetic and diabetic participants

| Clinical background | NDM | DM | P-value |
|---------------------|-----|----|---------|
| n                   | 43  | 52 |         |
| Sex (male/female)   | 35/8| 26/26 | 0.002 |
| Age (years)         | 43.0 ± 6.4 | 44.5 ± 10.0 | 0.403 |
| Duration of diabetes mellitus (years) | 24 ± 1.7 | |
| Therapy (diet and exercise/OHA/insulin) | 5/12/35 | |
| Body mass index (kg/m²) | 24.2 ± 3.6 | 24.4 ± 4.0 | 0.784 |
| Systolic BP (mmHg)  | 124 ± 15 | 121 ± 14 | 0.283 |
| Diastolic BP (mmHg) | 79 ± 9  | 78 ± 9  | 0.494 |
| Hypertension (%)    | 37.2 | 28.8 | 0.387 |
| HbA1c (%)           | 5.3 ± 0.3 | 9.6 ± 2.3 | <0.001 |
| Total cholesterol (mg/dL) | 200 ± 30 | 193 ± 74 | 0.572 |
| Triglyceride (TG: mg/dL) | 138 ± 101 | 195 ± 156 | 0.049 |
| HDL-C (mg/dL)       | 61 ± 15 | 48 ± 11 | <0.001 |
| Dyslipidemia (%)    | 53.5 | 61.5 | 0.429 |
| Smoking, %          | 35.5 (11/31) | 36.0 (18/50) | 0.962 |

Values are presented as mean ± SD. Mean indicates the average of left and right. Hemoglobin A1c (HbA1c %) was estimated as a National Glycohemoglobin Standardization Program equivalent value. ABI, ankle brachial pressure index; BP, blood pressure; CAVI, cardio-ankle vascular index; DM, diabetes mellitus group; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media complex thickness; NDM, non-diabetes mellitus group; OHA, oral hypoglycemic agents.

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Table 2 | Relationships between cardio-ankle vascular index and clinical characteristics in 95 diabetic and non-diabetic participants evaluated by multiple regression analysis

| Case number | Decision coefficient ($R^2$) | Independent variables | $P$-value | Mean CAVI | Higher CAVI | Mean CAVI | Higher CAVI |
|-------------|-----------------------------|-----------------------|-----------|---------|-----------|---------|-----------|
| 95          | 0.337                       | Age (years)           | <0.0001   | 0.544 (0.0001) | 0.536 (0.0001) | 0.578 (0.0001) | 0.568 (0.0001) |
| 81          | 0.049                       | Sex (male: 0, female: 1) | 0.001     | 0.173 (0.067) | 0.177 (0.060) | 0.275 (0.012) | 0.281 (0.010) |
| 81          | 0.049                       | Body mass index (kg/m²) | 0.001     | 0.182 (0.123) | 0.192 (0.213) | 0.010 (0.298) | 0.012 (0.291) |
| 81          | 0.049                       | Hypertension (no: 0, yes: 1) | 0.001     | 0.002 (0.0049) | 0.002 (0.036) | 0.019 (0.046) | 0.020 (0.039) |
| 81          | 0.049                       | Dyslipidemia (no: 0, yes: 1) | 0.001     | 0.013 (0.0619) | 0.024 (0.0809) | 0.010 (0.319) | 0.007 (0.062) |
| 81          | 0.049                       | Smoking (no: 0, yes: 1) | 0.001     | 0.020 (0.888) | 0.032 (0.383) | 0.045 (0.0665) | 0.052 (0.0621) |

Mean cardio-ankle vascular index (CAVI) indicates the average of left and right CAVI. Higher CAVI means the higher one in the right and left CAVI. $\beta$, standard regression coefficient.

decreased and those with no change/increase was significantly reduced by hospitalization ($8.0 \pm 1.4$ → $7.3 \pm 1.4$, $P = 0.011$ vs $8.9 \pm 1.0$ → $8.4 \pm 1.2$, $P = 0.036$). HbA1c in the TC decreased group was not different from that in the TC no change/increase group ($-1.51 \pm 1.30$ vs $-1.97 \pm 2.07$, $P = 0.416$).

Changes of plasma glucose and CAVI from fasting to 2 h after breakfast are shown in Figure 2. Plasma glucose levels (mg/dL) at 2 h after breakfast were significantly elevated in the DM group ($143 \pm 20$ → $224 \pm 15$, $P = 0.003$) and the NDM group ($78 \pm 6$ → $111 \pm 14$, $P = 0.002$). However, mean CAVI did not change in the DM group ($10.4 \pm 2.6$ → $10.4 \pm 2.5$, $P = 0.836$) or the NDM group ($6.6 \pm 0.3$ → $6.6 \pm 0.3$, $P = 1.000$).

**DISCUSSION**

The main results were as follows: (i) although ABI and IMT were not different between the DM and NDM groups, only CAVI of DM was elevated significantly compared with NDM; (ii) CAVI elevation was closely associated with HbA1c and aging; (iii) CAVI improved significantly as a result of the glycemic control associated with HbA1c improvement; and (iv) CAVI did not change before or after breakfast.

The initial two results show that the rise of CAVI is an earlier sign of arteriosclerosis than carotid ultrasonographic findings, and it is closely related to hyperglycemia. Sex differences in CAVI has been reported in a large-scale survey of healthy subjects. As CAVI has been reported to be lower for females than for males, the possibility that high CAVI in DM is related to the low proportion of female DM patients cannot be fully ruled out. However, as sex was not selected as a risk factor of high CAVI by multivariate
analyses, the contribution of sex to the high CAVI in diabetes might be low. Increased brachial-ankle pulse wave velocity (baPWV) was also reported as an early marker of arteriosclerosis in mild hyperglycemic patients. We and other investigators reported that baPWV was blood pressure dependent and was not optimal for longitudinal observation compared with CAVI. Furthermore, several studies reported that CAVI is better than baPWV for predicting the presence of coronary

Table 3 | Serial changes of clinical characteristics and arteriosclerotic indices before and after hospitalization in 36 diabetic patients

| Clinical characteristics | First examination | Second examination after 8 weeks | P-value |
|--------------------------|------------------|----------------------------------|---------|
| n                        | 36               | 36                               |         |
| Sex (male/female)        | 17/19            | –                                |         |
| Age (years)              | 58.7 ± 13.1      | –                                |         |
| Duration of diabetes mellitus (years) | 91 ± 9.1 | – |
| Therapy (diet and exercise/OHA/insulin) | 0/5/31 | 0/9/27 |
| Smoking, % (n/total number) | 51.5 (17/33) | – |
| Retinopathy, n (NDR/SDR/PDR) | 28/5/3 | – |
| Nephropathy, n (non/micro/macro) | 30/4/2 | – |
| Bodyweight (kg)          | 603 ± 109        | 598 ± 109                        | 0.341   |
| Body mass (kg/m²)        | 23.3 ± 4.0       | 23.2 ± 3.9                       | 0.378   |
| Systolic BP (mmHg)       | 126 ± 18         | 132 ± 17                         | 0.097   |
| Diastolic BP (mmHg)      | 80 ± 11          | 82 ± 10                          | 0.339   |
| HbA1c (%)                | 91 ± 18          | 7.4 ± 1.2                        | <0.001  |
| Total cholesterol (mg/dL)| 205 ± 43         | 185 ± 36                         | 0.007   |
| Triglyceride (mg/dL)     | 142 ± 82         | 145 ± 107                        | 0.896   |
| HDL-C (mg/dL)            | 48 ± 11          | 51 ± 14                          | 0.256   |
| Arteriosclerotic indices |                   |                                  |         |
| Right ABI                | 1.12 ± 0.09      | 1.12 ± 0.10                      | 0.846   |
| Left ABI                 | 1.12 ± 0.10      | 1.11 ± 0.09                      | 0.524   |
| Mean ABI                 | 1.12 ± 0.09      | 1.11 ± 0.09                      | 0.788   |
| Right CAVI               | 8.31 ± 1.33      | 7.84 ± 1.42                      | 0.003   |
| Left CAVI                | 8.29 ± 1.25      | 7.76 ± 1.44                      | 0.001   |
| Mean CAVI                | 8.30 ± 1.28      | 7.80 ± 1.40                      | 0.001   |

Values are presented as mean ± SD. Hemoglobin A1c (HbA1c, %) was estimated as a National Glycohemoglobin Standardization Program equivalent value. ABI, ankle brachial pressure index; BP, blood pressure; CAVI, cardio-ankle vascular index; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media complex thickness; NDR, no diabetic retinopathy; OHA, oral hypoglycemic agents; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.

Figure 1 | Changes of cardio-ankle vascular index (CAVI) in subdivided groups by the (a) improvement of hemoglobin A1c (HbA1c) or (b) change of total cholesterol are shown. 1st, first measurement of CAVI during hospitalization; 2nd, second measurement of CAVI after glycemic improvement.
Therefore, early detection of an increased arterial stiffness in the early stage of DM by CAVI might be effective for the prevention of coronary artery disease. The mechanism of CAVI elevation in association with hyperglycemia remains to be elucidated. As CAVI is an index calculated by a formula including blood density, one possible mechanism might be an increase of blood density as a result of high blood glucose.

A third result suggests that CAVI is partially reversible by 2 months of glycemic control, mainly by insulin treatment. The present study is the first report in which CAVI improvement was closely associated with HbA1c improvement. When the DM patient is told that arterial stiffness is improved by strict glycemic control, the DM patient will be encouraged to self-manage good glycemic control. In contrast, a fourth result showed that a very short-term (2 h) glycemic change has no influence on CAVI. These findings might suggest that an ameliorating effect on CAVI by glycemic control is an indirect effect through changes in vascular endothelial or autonomic function, rather than a direct effect of glucose concentration.

There are a few reports in which the effect of treatment for DM on CAVI was examined. Nagayama et al. reported that not glibenclamide, but glimepiride, improved CAVI. In that report, the change in CAVI was significantly correlated with the change in urinary 8-hydroxy-2′-deoxyguanosine, so the authors speculated that reduced oxidative stress might contribute to the improvement of CAVI. Ohira et al. reported the amelioration of CAVI by the switching of premixed human insulin containing rapid-acting insulin to premixed insulin analog containing ultrarapid-acting insulin. Although HbA1c did not change during the observation period, a significant negative correlation was observed between the change in CAVI and the change in 1,5-anhydroglucitol. Therefore, the report noted, the improvement of CAVI was supposed to be elicited by the improvement of postprandial hyperglycemia.

The mechanism in which CAVI is improved by glycemic control in the present study is unknown, but the vascular endothelial and/or sympathetic nerve dysfunctions are supposed to be related to these findings. Hyperglycemia could cause endothelial dysfunction through oxidative stress, and sympathetic hyperactivity by hyperinsulinemia and dehydration. Associations between CAVI and endothelial function or alpha-adrenergic function have also been reported. Another possible mechanism might be a decrease in blood density by glycemic control. In the present study, total cholesterol had also significantly decreased after 8 weeks of glycemic control. Although CAVI change was not closely related to the change of total cholesterol, an influence of total cholesterol could not be completely excluded from the possible mechanism of CAVI improvement. A more detailed investigation and longitudinal observation will be necessary to clarify the relationship between CAVI and diabetes mellitus.

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