Original Article

Plasma Tissue Inhibitor of Matrix Metalloproteinase-1 Level Is Increased in Normotensive Non-Dippers in Association with Impaired Glucose Metabolism

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Non-dipping (nocturnal blood pressure [BP] decrease<10%) is related to accelerated urinary salt excretion (u-NaCl), and increased risk of left ventricular hypertrophy (LVH) and cardiovascular events. We evaluated whether non-dippers exhibit an advanced extracellular matrix fibrosis, in relation to increased u-NaCl, among normotensive subjects. We measured plasma tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), a marker of collagen fibrosis in extracellular matrix, to evaluate the relationship between non-dipping and u-NaCl in 73 normotensive subjects (no antihypertensive medications, clinic BP<140/90 mmHg and/or 24-h ambulatory BP<125/80 mmHg). Non-dippers had a significantly higher percentage of subjects with impaired fasting glucose (IFG) or diabetes mellitus (DM), and had a greater left ventricular mass index (LVMI), plasma TIMP-1 level and u-NaCl than dippers (IFG or DM: 24.0 *vs.* 6.3%, $p=0.029$; LVMI: 118±31 *vs.* 103±26 g/m^2, $p=0.039$; TIMP-1: 168±35 *vs.* 151±30 pg/mL, $p=0.035$; u-NaCl: 5.1±1.7 *vs.* 3.9±1.7 g/12 h, $p=0.005$). In logistic regression analysis, non-dipping was independently associated with u-NaCl and TIMP-1. u-NaCl was correlated with non-dipping ($r=0.35$, $p=0.003$) and serum glucose level ($r=0.26$, $p=0.027$). On the other hand, TIMP-1 level was significantly correlated with the presence of IFG or DM ($r=0.23$, $p=0.046$), but not with u-NaCl. In conclusion, plasma TIMP-1 level, a measure of cardiovascular fibrosis in extracellular matrix, is greater in normotensive non-dippers than in dippers; however, the increased TIMP-1 level may be related to impaired glucose metabolism, and non-dipping may be related to increased u-NaCl associated with high serum glucose levels in normotensive subjects. (*Hypertens Res* 2008; 31: 2045–2051)

***Key Words*: non-dipper, cardiovascular fibrosis, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), impaired fasting glucose, urinary salt excretion**

Introduction

Nocturnal blood pressure (BP) is the strongest predictor of cardiovascular disease in comparison with awake, 24-h average, home, and clinic BP (*1*). However, the reasons that nocturnal BP offers a higher predictive value remain unclear. Blunted nocturnal BP dipping (non-dipping) (*2*) is also associated with an increased risk of left ventricular (LV) hypertrophy (*3*), silent cerebral infarction (*4*), urinary microalbumin excretion ratio (*5*, *6*), and cardiovascular events (*7–9*). Increased risks associated with non-dippers are seen even in community-dwelling normotensive subjects (*3*, *9*).

Non-dipping may be associated with a risk of cardiovascu-

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lar remodeling independently of BP level. Cardiac remodeling includes cardiomyocyte hypertrophy and fibrosis of the extracellular matrix, and it is hypothesized that pressure overload (hypertension) causes cardiomyocyte hypertrophy (concentric hypertrophy), which then leads to apoptosis and fibrosis of the extracellular matrix (eccentric hypertrophy) in relation to increased angiotensin II level (*10*). Recently, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), procollagen type I C-terminal propeptide (PICP), and collagen type I pyridinoline cross-linked C-terminal telopeptide (ICTP) have been identified as markers of cardiovascular fibrosis and remodeling (*11*). The presence of such collagen markers in the extracellular matrix is reported to be associated with arterial stiffness (*12*), LV hypertrophy (*13*), increased carotid intima media thickness (*14*), and cardiovascular remodeling (*11*). However, the relationships between these collagen markers in the extracellular matrix and non-dipping are not well understood.

Additionally, non-dipping is associated with increased sodium excretion (*15*). A decrease in daytime sodium excretion is a cause of non-dipping (*16*), but the relationship between cardiovascular fibrosis and urinary salt excretion (u-NaCl) remains unclear.

The purpose of this report is to evaluate whether cardiovascular fibrosis, as measured by plasma collagen markers of the extracellular matrix, can be associated with non-dipping in the context of increased u-NaCl even in normotensive subjects.

Methods

Subjects

This cross-sectional study was conducted in 1998 in the Miyori district in the rural community of Kinugawa, Tochigi, Japan. The details of our subject group have been reported previously (*3*). Briefly, a total of 181 adults (33% of the 541 residents aged 20 years or older) participated in this study. After excluding the patients without ambulatory blood pressure monitoring (ABPM) and echocardiography and those with a history of stroke, 74 normotensive subjects satisfied the following criteria (*3*): 1) clinic systolic BP (SBP) <140 mmHg and diastolic BP (DBP) <90 mmHg, 2) 24-h average ambulatory SBP <125 mmHg and DBP <80 mmHg, and 3) no use of antihypertensive drugs, because we wished to focus on pathophysiological mechanisms of non-dipping and to avoid the possible confounding effects of hypertension. After excluding a subject who was unable to measure u-NaCl correctly, we obtained data from a total of 73 subjects.

Impaired fasting glucose (IFG) was defined as a fasting glucose level of 6.2–6.9 mmol/L (111–125 mg/dL) and/or HbA1c 5.9–6.1%. Diabetes mellitus (DM) was defined by a fasting glucose level ≥ 7.0 mmol/L (126 mg/dL), HbA1c $\geq 6.2\%$ or the use of hypoglycemic agents. Hyperlipidemia was defined as a total cholesterol level ≥ 6.2 mmol/L (≥ 240 mg/dL) or by the use of lipid-lowering agents. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Twenty-Four-Hour ABPM

Noninvasive ABPM was carried out on a weekday with an automatic device (TM-2425; A&D Co. Inc., Tokyo, Japan), which recorded BP using the oscillometric method and heart rate every 30 min for 24 h. Sleep BP was defined as the average BP from the time when the subjects went to bed until the time they got up the following day, and waking BP was the average recorded BP during the remainder of the day. We classified the subjects according to their nocturnal SBP decrease as follows: subjects were considered dippers if their nocturnal SBP decrease was $\geq 10\%$ and non-dippers if it was $<10\%$.

Echocardiography

M-mode echocardiography was performed using two-dimensional monitoring. LV chamber recording was acquired at the tip of the mitral valve. The interventricular septal thickness (IVST) and posterior wall thickness (PWT) were measured at end diastole. The LV internal dimensions were measured at end diastole (LVIDd) and end systole (LVIDs), in accordance with the recommendations of the American Society of Echocardiography (*17*). The LV mass (LVM) was calculated using the equation described by Devereux and Reichek (*18*). The relative wall thickness (RWT) was calculated as $2 \times \mathrm{PWT/LVID}$.

Carotid Ultrasonography

Imaging of right and left extracranial carotid arteries was performed using a 7.5-MHz transducer with the subject in a supine position with hyperextension of the neck. Measurement of the intima-media thickness (IMT) of the far wall at the end of diastole was performed in B-mode.

Blood and Urinary Sample Tests

Blood samples were drawn the morning following the aforementioned ABPM. All blood samples were measured in the same laboratory (SRL, Inc., Tokyo, Japan). Serum insulin levels were measured using an enzyme immunoassay (Eiken Chemical Co., Tokyo, Japan). As an index of insulin resistance, HOMA-R was calculated as follows: insulin (μU/mL) $\times$ fasting blood glucose (mg/dL)/405.

The plasma samples were stored at $-80°C$ in a refrigerator until the measurements were made. TIMP-1, PICP, ICTP, renin, aldosterone, and adiponectin levels were measured using the stored plasma samples. Plasma renin activity was measured by radioimmunoassay (SRL Inc.). Aldosterone concentrations were measured with the use of a commercially available radioimmunoassay (SRL Inc.). The plasma levels of

Table 1. Characteristics of Non-Dippers in the Normotensive Subject

	Dipper (n=48)	Non-dipper (n=25)	p
Age, years	58.4±10.9	60.9±10.9	0.35
Male, %	37.5	52.0	0.23
Body mass index, kg/m^2	23.4±2.5	23.2±2.8	0.68
Current smoker, %	31.9	30.4	0.90
Hyperlipidemia, %	33.3	44.0	0.37
Diabetes or impaired glucose tolerance, %	6.3	24.0	0.029
24-h systolic blood pressure, mmHg	112±7	111±6	0.59
24-h diastolic blood pressure, mmHg	69±5	69±6	0.59
Fasting blood glucose, mg/dL	92±9	101±35	0.19
HbA1c, %	5.3±0.3	5.6±1.1	0.22
Fasting insulin, μg/mL	5.8±2.3	7.5±12.3	0.35
Adiponectin, μg/mL	11.7±5.7	12.0±6.3	0.85
Plasma renin activity, ng/mL/h	1.6±1.3	1.5±1.4	0.92
Aldosterone, pg/mL	91.3±35.8	90.8±44.5	0.95
Creatinine, mg/dL	0.87±0.13	0.91±0.16	0.24
Estimated GFR mL/min/1.73 m^2	57±8	57±10	0.76
Na, mEq/L	141±2	141±2	0.87
K, mEq/L	4.0±0.3	4.1±0.5	0.28
Cl, mEq/L	104±2	104±2	0.76
PICP, ng/mL	104±40	100±30	0.68
ICTP, ng/mL	3.3±1.0	3.5±1.2	0.48
TIMP-1, ng/mL	151±30	168±35	0.035
Left ventricular mass index (LVMI), g/m^2	103±26	118±31	0.039
LVMI (men>114 g/m^2, women>106 g/m^2), %	29.2	56.0	0.025
Relative wall thickness (RWT)	0.39±0.08	0.44±0.12	0.036
RWT>0.42, %	22.9	44.0	0.062
Carotid intima-media thickness, mm	0.6±0.2	0.7±0.1	0.38
Urinary Na excretion, g/12 h	1.6±0.7	2.0±0.6	0.02
Urinary K excretion, g/12 h	0.7±0.3	0.8±0.3	0.09
Urinary Cl excretion, g/12 h	2.3±1.0	3.1±1.1	0.002
Urinary salt excretion, g/12 h	3.9±1.7	5.1±1.7	0.005

Data shown as means±SD or as a percentage. p values were calculated using a non-paired t-test. GFR, glomerular filtration rate; PICP, procollagen type I C-terminal propeptide; ICTP, collagen type I pyridinoline cross-linked C-terminal telopeptide; TIMP-1, tissue inhibitor of matrix metalloproteinase-1.

adiponectin were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) system (adiponectin ELISA kit; Otsuka Pharmaceutical Co., Tokyo, Japan). Plasma PICP and ICTP were measured using radioimmunoassays (Orion Diagnostic, Espoo, Finland). Plasma TIMP-1 level was measured using an enzyme-linked immunosorbent assay (Fuji Chemical Industries, Ltd., Toyama, Japan). The coefficients of variation were 5.0% for plasma PICP, 4.0% for ICTP, 8.1% for MMP-1, and 11.3% for TIMP-1. In our previous report (*3*), we showed data concerning atrial and brain-type natriuretic peptides (ANP, BNP); however, we found that these data were significantly altered by a single subject who exhibited extremely high levels of ANP (330 pg/mL) and BNP (770 pg/mL). Accordingly, we do not show these results in this manuscript.

To minimize the confounding influence of daily physical activity, as well as for operational simplicity, the subjects collected urine from 19:00 to 07:00 (12 h) during ABPM.

Statistical Analysis

Data are shown as means±SD or as a percentage. The differences in means between non-dippers and dippers and in subjects with and without IFG or DM were calculated using a non-paired t-test. The differences in percentage between non-dippers and dippers and between subjects with and without IFG or DM were calculated using the χ^2 test. Because non-dippers were associated with multiple variables, a logistic regression analysis was used to evaluate the significant factors related to non-dipping after adjustment for confounding factors. The relationships between dipping status and continuous or dichotomous variables (*i.e.*, TIMP-1, u-NaCl, and

Table 2. Logistic Regression Analysis for Non-Dippers

	Model 1			Model 2 (adjusted for hypertensive TOD)			Model 3 (adjusted for IFG or DM)		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Urinary salt excretion, g/12 h	1.58	1.11–1.63	0.012	1.63	1.11–2.40	0.013	1.60	1.07–2.38	0.022
TIMP-1, SD (32.2) ng/mL	2.11	1.09–4.07	0.026	2.35	1.13–4.89	0.022	2.09	0.998–4.38	0.051
LVMI: men>114 g/m^2, women>106 g/m^2				3.92	0.94–16.41	0.06	4.40	0.99–19.54	0.051
RWT>0.42				1.41	0.33–5.98	0.64	1.48	0.34–6.52	0.61
Carotid IMT, SD (0.15) mm				0.96	0.47–1.96	0.91	0.95	0.46–1.95	0.88
IFG or DM							5.22	0.76–36.03	0.094

OR, odds ratio; CI, confidence interval; IFG, impaired fasting glucose; DM, diabetes mellitus; LVMI, left ventricular mass index; RWT, relative wall thickness; IMT, intima-media thickness; TIMP-1, tissue inhibitor of matrix metalloproteinase-1; TOD, target organ damage. Data were calculated using logistic regression analysis. Model 1 was also adjusted for age, gender, body mass index, presence of hyperlipidemia, current smoker status, and 24-h systolic blood pressure level. Model 2 was adjusted for hypertensive target organ damage in addition to all those adjustment factors incorporated in model 1. Model 3 was adjusted for the presence of IFG or DM in addition to all those adjustment factors incorporated in model 2. Probability <0.05 was considered statistically significant.

glucose levels) were evaluated using Spearman's test. Because fasting glucose level and u-NaCl were related to other variables, multiple regression analysis between u-NaCl and fasting glucose level was performed to exclude the effects of confounding factors. Similarly, after excluding for confounding factors the determinants of TIMP-1 were analyzed using multiple regression analysis. A probability of <0.05 was considered statistically significant. SPSS 16.0 software (SPSS, Inc., Chicago, USA) was used for the analysis.

Results

Subjects

The mean age was 59.2±10.2 years, and 42.5% of the subjects was male. Nine subjects exhibited IFG or DM (6 subjects had IFG and 3 subjects exhibited DM). There were 25 subjects (34.2%) with non-dipping (*3*). There were 11 subjects with sleep BP≥120/70 mmHg in this study.

Non-Dippers *vs.* Dippers in Normotensive Subjects

Characteristics of non-dippers and dippers are shown in Table 1, and a subset of the results has been previously reported (data from non-dippers) (*3*). Non-dippers had a significantly higher prevalence of IFG or DM and u-NaCl and exhibited higher LVMI and TIMP-1 levels than dippers. In logistic regression analysis, non-dipping was independently related to the u-NaCl and TIMP-1 levels after adjustment for confounding factors of age, gender, BMI, presence of hyperlipidemia, current smoking status, and 24-h SBP (Table 2, model 1). Even after adjustment for parameters associated with cardiovascular remodeling (*i.e.*, LVM index [LVMI], RWT, and carotid IMT), TIMP-1 level and u-NaCl remained significant variables for non-dipping (model 2, Table 2). However, the significance of TIMP-1 disappeared after the presence of IFG or DM was added to model 2, and the significance of u-NaCl remained (model 3, Table 2).

TIMP-1 Level in Subjects with IFG or DM

Characteristics of subjects with and without IFG or DM are shown in Table 3. The subjects with IFG or DM had a significantly higher TIMP-1 level than those without IFG or DM following adjustment for a significant covariate of age (178 *vs*. 154 pg/mL, $p=0.038$). The subjects with IFG or DM tended to have a higher TIMP-1 level than subjects without IFG or DM, even after adjustment for known covariates; age, gender, BMI, presence of hyperlipidemia, current smoking status, 24-h SBP, and u-NaCl (178 *vs*. 155 pg/mL, $p=0.066$).

Relationships between Waking and Sleep BPs and TIMP-1, Glucose and u-NaCl

High u-NaCl was significantly correlated with sleep SBP level ($r=0.30$, $p=0.010$) and sleep SBP/waking SBP ratio ($r=0.31$, $p=0.007$), but not with age ($r=0.10$, $p=0.41$), gender ($r=-0.05$, $p=0.69$) or waking SBP ($r=0.10$, $p=0.39$). On the other hand, factors related to glucose metabolism (*i.e.*, BMI, glucose level, HOMA-R) had a tendency to positively correlate with waking SBP (BMI, $r=0.22$, $p=0.056$; glucose, $r=0.22$, $p=0.058$; HOMA-R, $r=0.22$, $p=0.060$), but not with sleep SBP. TIMP-1 was not correlated with waking or sleep SBPs (waking SBP, $r=-0.07$, $p=0.56$; sleep SBP, $r=0.06$, $p=0.61$).

Determinants of TIMP-1 Level

TIMP-1 level was positively correlated with the presence of IFG or DM ($r=0.23$, $p=0.046$) and carotid IMT ($r=0.31$, $p=0.008$), but not with u-NaCl ($r=0.11$, $p=0.34$). In multiple

Table 3. Characteristics of Subjects with IFG or DM

	IFG or DM		
	No (n=64)	Yes (n=9)	p
Age, years	58.4±11.1	64.8±7.5	0.044
Male, %	42.2	44.4	0.90
Body mass index, kg/m^2	23.4±2.7	22.7±1.6	0.25
Current smokers, %	29.5	44.4	0.37
Hyperlipidemia, %	34.4	55.6	0.22
Left ventricular mass index (LVMI), g/m^2	109±28	106±30	0.75
LVMI (men>114 g/m^2, women>106 g/m^2), %	37.5	44.4	0.69
Relative wall thickness (RWT)	0.40±0.10	0.43±0.09	0.45
RWT>0.42, %	34.4	33.3	0.95
Carotid intima-media thickness, mm	0.64±0.14	0.68±0.19	0.51
Office SBP, mmHg	123±13	120±10	0.47
Office DBP, mmHg	78±8	79±6	0.81
24-h SBP, mmHg	112±7	112±7	0.94
24-h DBP, mmHg	69±5	69±6	0.80
Daytime SBP, mmHg	116±8	115±9	0.68
Daytime DBP, mmHg	72±6	70±6	0.41
Nighttime SBP, mmHg	101±8	105±8	0.23
Nighttime DBP, mmHg	62±6	64±7	0.29
Non-dippers, %	29.7	66.7	0.029
Fasting blood sugar, mg/dL	91±9	123±52	0.10
HbA1c, %	5.3±0.3	6.5±1.6	0.053
Fasting insulin, μg/mL	5.6±2.2	11.9±20.4	0.38
PICP, ng/mL	103±38	96±28	0.60
ICTP, ng/mL	3.3±1.1	3.9±0.9	0.16
TIMP-1, ng/mL	154±31	179±38	0.031
Creatinine, mg/dL	0.87±0.14	0.94±0.17	0.15
Estimated GFR, mL/min/1.73 m^2	58±8	52±11	0.093
Urinary salt excretion, g/12 h	4.2±1.7	4.8±2.4	0.36

Data are shown as means±SD or as a percentage. p values were calculated using a non-paired t-test or χ^2 test. IFG, impaired fasting glucose; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; PICP, procollagen type I C-terminal propeptide; ICTP, collagen type I pyridinoline cross-linked C-terminal telopeptide; TIMP-1, tissue inhibitor of matrix metalloproteinase-1; GFR, glomerular filtration rate.

linear regression analysis, TIMP-1 level tended to be correlated only with the presence of IFG or DM (β=0.24, p=0.066) when controlling for age, gender, BMI, current smoking status, presence of hyperlipidemia, 24-h SBP level and u-NaCl.

Determinants of u-NaCl

u-NaCl was correlated with fasting glucose level (Fig. 1A). The correlation between u-NaCl and fasting glucose was significant even after excluding 3 subjects with DM (outlying data) (n=70, r=0.27, p=0.025) (Fig. 1B). In multiple regression analysis of the 70 subjects without DM, high u-NaCl was significantly related to fasting glucose level and non-dipping even after adjustment for the confounding factors of age, gender, BMI, current smoking status, presence of hyperlipidemia, and 24-h SBP (fasting glucose level, β=0.35, p=0.008; non-dipping, β=0.39, p=0.002). However, the relationship between u-NaCl and non-dipping remained (β=0.32, p=0.013) and that between u-NaCl and fasting glucose level disappeared (p=0.88) when we performed the multiple regression analysis for u-NaCl in all subjects, including the DM patients (n=73).

Discussion

The main findings of this study were as follows. Cardiovascular fibrosis in the extracellular matrix, as identified using TIMP-1 measurements, and u-NaCl were increased in normotensive non-dippers. Such an increase in TIMP-1 level might be related to the presence of impaired glucose metabolism (*i.e.*, IFG or DM), but not to the u-NaCl or to BP levels. Non-dipping was related to high u-NaCl, and the increased u-NaCl might be positively correlated with high serum fasting glu-

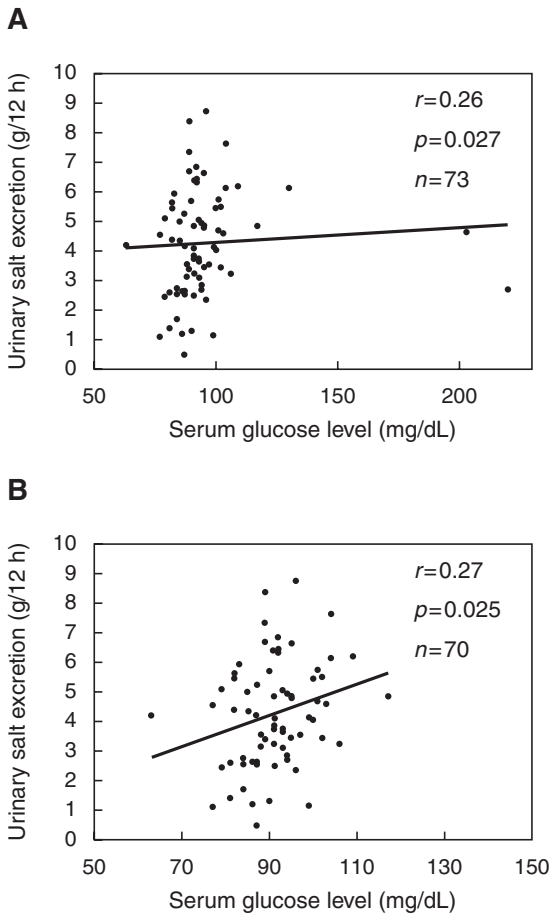

Fig. 1. *Scatter plot of serum glucose level and urinary sodium excretion. r indicates simple correlation coefficient. r and p values were calculated using Spearman's test. A: Includes data from all subjects. B: Excludes three subjects who had diabetes (outlying data).*

cose levels. These results suggested that impaired glucose metabolism contributed to both increased u-NaCl and cardiovascular fibrosis in the extracellular matrix, and that non-dipping might be a consequence of increased salt, together with high fasting glucose levels in normotensive subjects.

Impaired glucose metabolism may directly contribute to cardiovascular fibrosis (as measured by TIMP-1 level) in normotensive subjects. DM increases the risk of LV hypertrophy and cardiovascular events independent of BP level (*19*, *20*), and advanced glycosylation end-products and cross-linked collagen deposits induced by hyperglycemia may be related to the pathophysiological mechanisms of DM-associated cardiovascular damage (*21*). Patients with DM tend to exhibit a LV concentric remodeling pattern (*22*) (probably due to collagen deposits). Relative wall thickness is a stronger risk factor for cardiovascular events than LVMI (*23*). The significance of differences in our results among TIMP-1, PICP, and ICTP remain unclear. TIMP-1 is related to the metabolism of many types of collagen (*24*), and glucose-related cardiovascular fibrosis may not be specific for type I collagen. Diabetic chronic renal insufficiency might be one of the mechanisms that causes non-dipping. However, in our study, there were no significant differences in estimated glomerular filtration rate (GFR) level between non-dippers and dippers.

Decreased capacity for daytime sodium excretion is reported to be a cause of non-dipping (*16*), and our study showed that parameters related to insulin resistance were correlated with daytime SBP. Therefore, the pathophysiological mechanisms linking impaired glucose metabolism to non-dipping might involve sodium retention during the day, a phenomenon that must be compensated for at night to maintain the net diurnal sodium balance (*15*). In our study, fasting glucose level was an independent determinant of u-NaCl in the multiple regression analysis of those subgroup subjects without DM. It is unclear whether the increased u-NaCl was a result of high salt intake or of sodium retention. Subtle increases in glucose level both before and after eating may enhance sodium retention. Pistrosch *et al*. (*25*) reported in patients with type 2 DM that non-dippers exhibit postprandial blood glucose excursions, but this transition does not impact fasting glucose level or HbA1c levels. Kuroda *et al*. (*26*) reported that the involvement of insulin resistance might relate to enhanced tubular sodium reabsorption (as reflected in decreased fractional excretion of sodium). The connection between increased u-NaCl and non-dipping might be related to salt sensitivity, and Uzu *et al*. (*27*) have demonstrated that high sodium intake is related to non-dipping in salt-sensitive subjects. Additionally, Uzu *et al*. (*28*) observed that upright postural change decreased the rate of sodium excretion, especially in non-dippers.

Study Limitations

This study was a cross-sectional design and we could not clarify causal relationships among impaired glucose metabolism, u-NaCl, non-dipping status and TIMP-1. The number of subjects in this study was small, and more detailed studies that examine a larger number of subjects are required. We selected normotensive subjects in order to focus on mechanisms of non-dipping, but it is unclear whether the results of our study can be applied to non-dipping in hypertensive subjects because our data on TIMP-1 and u-NaCl did not reach statistical significance when we performed the parallel analyses using only hypertensive subjects in this study (data not shown). We plan to perform an additional study to confirm these relationships in hypertensive subjects. Finally, our study featured no data related to non-dipping, such as sleep apnea syndrome and sympathetic nerve activation.

Conclusion

Plasma TIMP-1 level, a measure of cardiovascular fibrosis in

the extracellular matrix, is increased in normotensive non-dippers. The increased TIMP-1 level may be related to impaired glucose metabolism, and non-dipping may be related to the increased urinary sodium excretion associated with a high serum glucose level in normotensive subjects.

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