Taurine in 24-h Urine Samples Is Inversely Related to Cardiovascular Risks of Middle Aged Subjects in 50 Populations of the World

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Abbreviations

TAU	Taurine
CHD	Coronary heart diseases
Cre	Creatinine

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BMI	Body mass index
BP	Blood pressure
TC	Total cholesterol
CARDIAC	Cardiovascular Diseases and Alimentary Comparison
SHR	Spontaneously hypertensive rats
Na	Sodium
K	Potassium
Mg	Magnesium
ORs	Odds ratios
CYP7A	Cytochrome P450 7A1
LDL	Low-density lipoprotein

1 Introduction

Taurine (Tau), which is rich in various seafood such as fish, shells, squid, and shrimp, is a ubiquitous sulfur-containing amino acid involved in many important biological functions (Huxtable 1992). The preventive effect of dietary Tau against hypertension and stroke was first proven experimentally in rat models of genetic hypertension, spontaneously hypertensive rats (SHR) and stroke-prone SHR (Nara et al. 1978; Okamoto and Aoki 1963; Okamoto et al. 1974). Further, experimental and clinical studies examining the effect of Tau on hypertension (Fujita and Sato 1986; Fujita et al. 1987; Yamori et al. 2009), dyslipidemia (Murakami et al. 1996; Yamori et al. 2010a; Yokogoshi et al. 1999), atherosclerosis (Murakami 2014; Murakami et al. 1996, 2002a, 2010) and obesity (Fujihira et al. 1970; Tsuboyama-Kasaoka et al. 2006; Zhang et al. 2004) supported a possible role for Tau in reducting cardiometabolic diseases. A world-wide epidemiological survey to investigate the association of nutritional biomarkers in 24-h urine samples, including sodium (Na), potassium (K), Magnesium (Mg), and Tau with cardiovascular risk factors was carried out by WHO-coordinated cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study in over 60 populations of the world (WHO-CARDIAC Study group 1986, 1990; Yamori et al. 1990, 1996, 2001, 2006, 2010b).

This study showed an inverse association between average 24-h urinary Tau excretion and the mortality due to coronary heart disease (CHD) (Yamori et al. 1996, 2001, 2006) and also reported that the group of individuals excreting more than the world average of 24-h urinary taurine (Tau/creatinine (Cre) ratio) had significantly lower cardiovascular disease risks (Yamori et al. 2010b), and therefore Tau/Cre ratios are inversely associated with CHD and stroke (Yamori et al. 2010b). This study confirmed that there was a close relationship between the population averages of cardiovascular disease risks and the dietary habits, established by analyzing various dietary biomarkers in 24-h urine samples (Yamori et al. 1984). However, the population averages are influenced greatly by genetic background of the individuals and environmental factors in the regions examined. Therefore, in the

present study, we investigated the association with and without the adjustment of confounding variables between 24-h urinary Tau/Cre ratio and cardiovascular disease risk factors in individuals, including obesity, hypertension and hypercholesterolemia, among the CARDIAC study populations disregarding genetic background, living conditions and gender.

2 Methods

2.1 Study Population

The WHO-coordinated CARDIAC Study was initiated in 1985 as a multi-center cross-sectional study with a standard research protocol, with a total of 12,335 men and women participating in the study. Details of the study design and methods of the CARDIAC Study have been reported elsewhere (WHO-CARDIAC Study group 1986, 1990; Yamori et al. 1990, 2006). Briefly, in each center, 100 men and 100 women aged 48–56 years were selected randomly from the general population. In the present study, 50 population samples of 22 countries are included. These 22 countries include various ethnic groups and diverse populations: Australia (97 participants), Brazil (244), Belgium (165), Bulgaria (209), Canada (160), China (686), Ecuador (254), France (158), Georgia (65), Greece (35), Israel (50), Italy (82), Japan (920), New Zealand (140), Portugal (115), Russia (31), Spain (274), Sweden (28), Tanzania (51), Nigeria (40), UK (224) and USA (183) (Fig. 1). The study was approved by the CARDIAC Study's institutional review board committee.

2.2 Data Collection

After excluding the participants who had missing data or who failed to complete the 24-h urine collection, the remaining 4,211 participants (2,120 men and 2,091 women) were included in data analyses. All participants were invited to a local hospital or health center for a physical examination, and a 15-ml overnight fasting blood sample was obtained. 24-h urine samples were collected using a standard aliquot cup that allowed participants to collect an exact portion of voided urine repeatedly (WHO-CARDIAC Study group 1986, 1990). BP was measured using a standard automated sphygmomanometer (Khi machine, VINE Co., Ltd., Tokyo) and these measurements were repeated three times (Fukuda and Yamori 1987; WHO-CARDIAC Study group 1986, 1990). A structured questionnaire was used for face-to-face interviews during the field survey, and included items on demographic data, lifestyle factors and medical history (WHO-CARDIAC Study group 1986, 1990). The urine and blood samples were frozen at −20 °C and analyzed

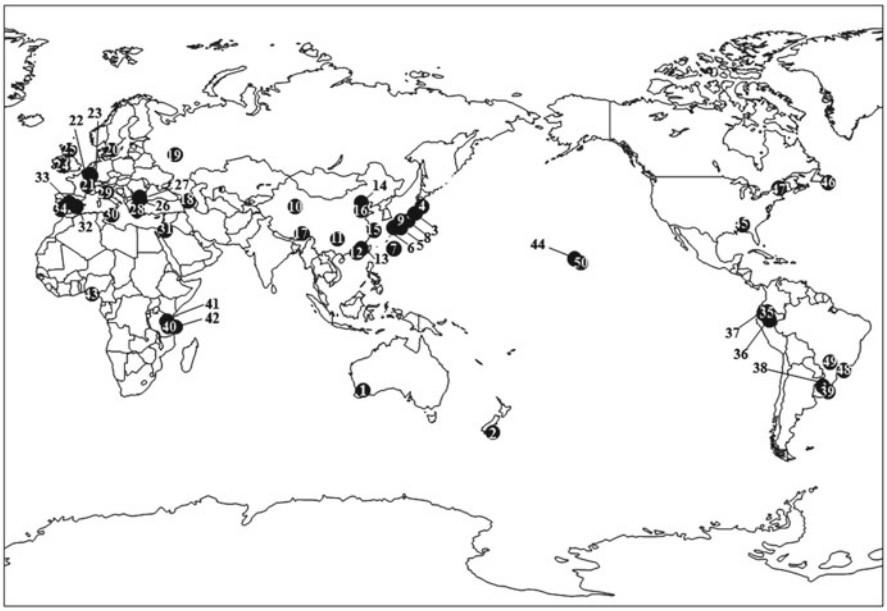

Fig. 1 Geographical distribution of population samples of the Cardiovascular Disease and Alimentary Comparison (CARDIAC) Study (1985–1994). The following are the 50 study sites of 22 countries and their principal investigators. (*1*) Perth: L.J. Beilin, M.S.T. Hobbs, K. Jamrozik. (*2*) Dunedin: F.O. Simpson. (*3*) Toyama: S. Kagamimori. (*4*) Hirosaki: T. Kanazawa. (*5*) Beppu: S. Kodama. (*6*) Kurume: H. Toshima. (*7*) Okinawa: G. Mimura, K. Taira. (*8*) Hiroshima: M. Yamakido. (*9*) Ohda: Y. Yamori. (*10*) Urumqi: B.X. He. (*11*) Guiyang: M.X. Zhang, X.L. Wu. (*12*) Guangzhou: Z.D. Huang. (*13*) Meshen: I. Lee. (*14*) Beijing: L.S. Liu. (*15*) Shanghai: G.S. Zhao. (*16*) Shijiazhuang: H.X. Zhang. (*17*) Lhasa: S.F. Sun. (*18*) Georgia: S.M. Dalakishivili. (*19*) Moscow: R.G. Oganov. (*20*) Gothenburg: L. Wilhelmsen. (*21*) Orleans: A. Marie. (*22*) Leuven: A. Amery. (*23*) Ghent: G. De Backer. (*24*) Belfast: A.E. Evans. (*25*) Stornoway: C.A. Birt. (*26*) Sofia (urban): N. Nicolov, I. Tomov. (*27*) Sofia (rural): N. Nicolov, I. Tomov. (*28*) Athens: A. Ioanidis. (*29*) Milan: G. Cerasola. (*30*) Palermo: G.C. Cesana. (*31*) Tel Aviv: T. Rosenthal. (*32*) Navas: A. Fernandez-Cruz. (*33*) Madrid: A. Fernandez-Cruz. (*34*) Lisbon: M.O. Carrageta. (*35*) Quito: P.D. Dillon. (*36*) Vilcabamba: V. Del Pozo. (*37*) Manta: V. Del Pozo. (*38*) Uruguaiana: Y. Moriguchi, E. Moriguchi. (*39*) Bagé: Y. Moriguchi, E. Moriguchi. (*40*) Handeni: J. Mtabaji, M. Njelekela. (*41*) Shinya: J. Mtabaji, M. Njelekela. (*42*) Dar es Salaam: J. Mtabaji, M. Njelekela. (*43*) Ibadan: O.O. Akinkungbe. (*44*) Honolulu: G. Mimura. (*45*) Jackson: H.G. Langford. (*46*) Newfoundland: G. Fodor, A. Chockalingam. (*47*) Montreal: P. Hamet. (*48*) Sao Paulo: Y. Moriguchi, E. Moriguchi. (*49*) Campo Grande: Y. Moriguchi, E. Moriguchi. (*50*) Hilo: M. Kanahele

centrally in the laboratory of WHO-collaborating Center for Research on Primary Prevention of Cardiovascular Disease, Izumo, Japan (in 1993, this center was transferred to the Graduate School of Human and Environmental Studies, Kyoto University, Japan). Standardized laboratory methods were used (WHO-CARDIAC Study group 1986, 1990). Quality controls were carefully maintained by internal and external quality surveillance procedures. Measurements included in the present report are BMI, BP, serum total cholesterol (TC), urinary Na, K, Mg, Ca, Cre and Tau excretion levels.

2.3 Statistical Analysis

Subjects with obesity were defined as those with BMI ≥ 30 kg/m^2. Patients with hypertension were defined as those with systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or those who were receiving anti-hypertensive drug therapy. Hypercholesterolemic subjects were defined as those with serum TC ≥ 220 mg/dl. The markers in 24-h urine are expressed as the ratio of each parameter relative to Cre. We categorized 24-h urinary Tau/Cre ratio in quintiles. The distributions of 24-h urinary Na/Cre, K/Cre, Ca/Cre and Mg/Cre ratio were highly skewed, and thus log transformations were performed to achieve a normal distribution. In all analyses, the log-transformed values were then used. For easy interpretation, nontransformed values are reported in the tables.

Differences between baseline characteristics of participants within each quintile were analyzed using the Cochrane-Armitage test for trends for proportions and the Jonckheere-Terpstra trend test for continuous measures. General linear models were used to estimate adjusted means of BMI, systolic BP, diastolic BP and TC across quintiles of 24-h urinary Tau/Cre ratio after adjustment for potential confounding variables. Models were initially adjusted for potential confounders by traditional cardiac risk factors (age, sex and use of anti-hypertensive medication). Final multivariable models were additionally adjusted for natural logarithm-transformed 24-h urinary Na/Cre, K/Cre, Ca/Cre, Mg/Cre ratios and survey years (1985–1989 or 1990–1994, which represent participants who had an average age of 52 years old and were born in the years 1933–1937 and 1938–1942, in order to adjust potential cohort effects on the study outcomes).

To evaluate the association between the Tau/Cre ratio and cardiovascular disease risk factors, we estimated adjusted odds ratios (ORs) for obesity, hypertension and hypercholesterolemia in relation to quintiles of the Tau/Cre ratio using logistic regression models, including variables for age, sex, anti-hypertensive medication use, natural logarithm-transformed Na/Cre, K/Cre, Ca/Cre, Mg/Cre ratios and survey year (1985–1989 or 1990–1994). Adjustments were made in two stages the same as the analyses of multiple linear regression models described above. Anti-hypertensive medication use was not included in the adjusted variables for the estimation of ORs for hypertension.

All statistical analyses except for the Cochrane-Armitage test for trends were conducted using SPSS 15.0J for Windows (IBM Japan, Tokyo, Japan). The Cochrane-Armitage test for trends was performed using EXCEL 2003 (Microsoft, Tokyo, Japan). A two-sided P value ≤0.05 was considered statistically significant.

3 Results

Mean values and proportions of each characteristic by quintiles of 24-h urinary Tau/Cre ratio are shown in Table 1. There was a 14.8-fold difference in the Tau/Cre ratio between the highest and lowest quintiles of the study population (medians:

Table 1 Baseline characteristics by quintiles of 24-h urinary taurine/creatinine ratio in the CARDIAC Study, 1985–1994

	Quintile of taurine/creatinine ratio (μmol/mmol)					
	1 (lowest) (n=842, Median, 16.0; Range, 0.8–<28.8)	2 (n=842, Median, 41.9; Range, 28.8–<55.7)	3 (n=843, Median, 72.7; Range, 55.7–<93.7)	4 (n=842, Median, 121.7; Range, 93.7–<161.9)	5 (high) (n=842, Median, 236.5; Range, ≥162.0)	*P* for trend[a]
Male (%)	42.8	56.2	57.4	49.8	45.6	<0.001
Age (years)	51.9(1.7)	51.8 (1.7)	51.8(1.6)	51.9 (1.7)	52.2 (1.7)	<0.01
Body mass index (kg/m^2)	26.1 (4.3)	25.5 (4.0)	24.5 (3.9)	24.3 (4.1)	23.9 (3.8)	<0.001
Systolic blood pressure (mmHg)	125.5 (19.3)	125.7 (19.8)	123.8 (19.0)	123.8 (19.5)	123.6 (20.2)	<0.01
Diastolic blood pressure (mmHg)	75.1 (12.1)	75.9 (12.5)	74.9 (12.5)	73.6 (12.2)	74.1 (13.1)	<0.001
Serum total cholesterol (mg/dl)	194.5 (48.6)	197.1 (45.8)	189.2 (49.5)	183.3 (40.8)	181.5 (41.6)	<0.001
Antihypertensive treatment (%)	5.6	4.4	4.4	4.5	3.3	<0.001
Obesity[b] (%)	12.8	11.5	9.9	10.2	6.5	<0.001
Hypertension[c] (%)	27.7	26.2	23.7	22.8	24.2	<0.001
Hypercholesterolemia[d] (%)	28.4	28.9	23.1	17.7	15.2	<0.001
Nutrient marker in 24-h urine						
Magnesium/creatinine (mg/mg)	77.9 (39.4)	74.5 (39.4)	78.1 (44.0)	80.4 (37.5)	81.3 (41.4)	<0.001
Calcium creatinine (mg/mg)	135.2 (76.5)	136.1 (87.6)	145.8 (82.7)	162.3 (92.6)	180.5 (94.0)	<0.001
Sodium/creatinine (mmol/mmol)	16.1 (7.8)	15.7(7.3)	17.1 (8.0)	18.3 (8.2)	21.0 (8.9)	<0.001
Potassium/creatinine (mmol/mmol)	5.4 (2.1)	5.0 (2.0)	4.8 (2.0)	4.9 (2.2)	5.4 (2.4)	<0.05
Taurine/creatinine (μmol/mmol)	15.7(7.7)	42.1 (7.7)	73.6 (11.2)	123.3 (19.7)	299.4 (188.7)	<0.001

Values are expressed as mean (standard deviation) or percentage

[a]P values were determined by the Cochrane-Armitage test for trend for proportions and the Jonckheere-Terpstra trend test for continuous measures

[b]Obesity was defined as body mass index ≥30 kg/m^2

[c]Hypertension was defined as an anti-hypertensive treatment or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg

[d]Hypercholesterolemia was defined as serum total cholesterol ≥220 mg/dl

236.5 μmol/mmol/day in the highest quintile, 16.0 μmol/mmol/day in the lowest). There was a weak association between the Tau/Cre ratio and mean age, while higher Tau/Cre ratio was significantly associated with a lower percentage of obesity, hypertension and hypercholesterolemia and with higher Na/Cre, K/Cre, Ca/Cre and Mg/Cre ratios. Participants with the lower Tau/Cre ratio were more likely to be female, obese, hypertensive or hypercholesterolemic than participants with a higher Tau/Cre ratio.

Table 2 shows the adjusted mean values of cardiovascular disease risk factors by the quintiles of the 24-h urinary Tau/Cre ratio. The Tau/Cre ratio was inversely associated with BMI, diastolic BP and TC. Adjustment of the analysis of age, sex and anti-hypertensive drug use in Model 1 did not markedly attenuate the associations of Tau/Cre ratio with BMI and TC, and enhanced the association of the ratio with systolic BP and diastolic BP. Upon further adjustment for Na/Cre, K/Cre, Ca/Cre, Mg/Cre ratios and survey year relative to BMI, SBP, DBP and TC in Model 2, the inverse trends remained significant for all the parameters (P for linear trend <0.001 for all comparisons across quintiles).

ORs for obesity, hypertension and hypercholesterolemia are presented in Table 3 for each quintile of the 24-h urinary Tau/Cre ratio. Tau/Cre ratio was significantly associated with obesity and hypercholesterolemia in the crude analysis. The prevalence of obesity and hypercholesterolemia increased in a dose-dependent manner from the highest quintile to the lowest quintile of the Tau/Cre ratio. Participants with the lowest Tau/Cre ratio were 2.91 and 2.21 times more likely to be obese and hypercholesterolemic, respectively, than those within the highest quintile of the Tau/Cre ratio. After adjusting for age, sex and antihypertensive drug use in Model 1, inverse association between Tau/Cre and the prevalence of hypertension became significant. Further adjustment for the confounding variables of other urinary biomarkers and survey years in Model 2 did not markedly change these inverse associations. In the analyses of the prevalence of hypertension, participants with the lowest Tau/Cre ratio were 1.22 and 1.29 times more likely to have hypertension than those within the highest quintile of the Tau/Cre ratio in the analysis of Model 1 and 2. However, the risk of hypertension among the subjects within the second to fourth quintiles was not significantly high compared with that in the subjects in the highest quintile.

4 Discussion

In this multi-center cross-sectional study, the quintile analysis of the 24-h urinary Tau/Cre ratios indicated that the ratios were inversely associated with obesity, hypertension, hypercholesterolemia and nutrient markers in 24-h urine, such as Mg/Cre, Ca/Cre, Na/Cre, K/Cre and Tau/Cre. In linear regression analyses, the Tau/Cre ratios were inversely associated with BMI, diastolic BP and TC. After adjustment for age, sex and antihypertensive drug use, the inverse association of Tau/Cre with systolic BP became significant. The further adjustment for all available 24-h urinary biomarkers did not markedly change these associations.

Table 2 Adjusted means and 95 % confidence intervals of body mass index, blood pressure, serum total cholesterol according to the levels of 24-h urinary taurine/creatinine ratio in the CARDIAC Study, 1985–1994

	Quintile of taurine/creatinine ratio (μmol/mmol)					
	1 (lowest) (n=842, Median, 16.0; Range, 0.8–<28.8)	2 (n=842, Median, 41.9; Range, 28.8–<55.7)	3 (n=843, Median, 72.7; Range, 55.7–<93.7)	4 (n=842, Median, 121.7; Range, 93.7–<161.9)	5 (high) (n=842, Median, 236.5; Range, ≥162.0)	P for linear trend[a]
Body mass index (kg/m^2)						
Crude	26.1 (25.4, 26.7)	25.5 (24.9, 26.2)	24.5 (23.9, 25.2)	24.3 (23.6, 24.9)	23.9 (23.6, 24.2)	<0.001
Model 1[b]	26.0 (25.4, 26.7)	25.5 (24.9, 26.2)	24.6 (23.9, 25.2)	24.3 (23.6, 24.9)	23.9 (23.7, 24.2)	<0.001
Model 2[c]	26.0 (25.3, 26.6)	25.4(24.8, 26.1)	24.6 (24.0, 25.3)	24.3 (23.7, 25.0)	24.0 (23.7, 24.2)	<0.001
Systolic blood pressure (mmHg)						
Crude	125.5 (122.3, 128.7)	125.7 (122.5, 128.9)	123.8 (120.6, 127.0)	123.8 (120.6, 127.0)	123.6 (122.3, 124.9)	NS
Model 1[b]	125.5 (122.4, 128.6)	125.7 (122.6, 128.9)	123.8 (120.6, 126.9)	123.8 (120.7, 127.0)	123.6 (122.3, 124.9)	<0.001
Model 2[c]	126.1 (122.8, 129.4)	126.0 (122.7, 129.2)	123.8 (120.6, 127.0)	123.6 (120.5, 126.8)	123.0 (121.6, 124.3)	<0.001
Diastolic blood pressure (mmHg)						
Crude	75.1 (73.1, 77.2)	75.9 (73.9, 78.0)	74.9 (72.8, 76.9)	73.6 (71.6, 75.7)	74.1 (73.3, 75.0)	<0.01
Model 1[b]	75.3 (73.3, 77.3)	75.8 (73.8, 77.8)	74.7 (72.7, 76.7)	73.6 (71.6, 75.6)	74.3 (73.5, 75.1)	<0.001
Model 2[c]	75.4 (73.3, 77.5)	75.8 (73.7, 77.8)	74.7 (72.7, 76.8)	73.7 (71.7, 75.7)	74.1 (73.3, 75.0)	<0.001
Serum total cholesterol (mg/dl)						
Crude	194.5 (187.0, 201.9)	197.1 (189.7, 204.5)	189.2 (181.8, 196.6)	183.3 (175.9, 190.7)	181.5 (178.4, 184.6)	<0.001
Model 1[b]	194.0 (186.6, 201.4)	197.5 (190.1, 204.9)	189.7 (182.2, 197.1)	183.3 (175.9, 190.7)	181.1 (178.1, 184.2)	<0.001
Model 2[c]	192.6 (185.2, 199.9)	196.1 (188.8, 203.4)	190.8 (183.6, 198.1)	184.7 (177.5, 191.8)	181.4 (178.4, 184.4)	<0.001

[a]From multiple linear regression models for the relation between 24-h urinary magnesium/creatinine ratio and the risk factors of cardiovascular diseases
[b]Model 1 was adjusted for age, sex and use of anti-hypertensive drugs
[c]Model 2 additionally adjusted for 24-h urinary sodium/creatinine, potassium/creatinine, calcium/creatinine, magnesium/creatinine and survey year

Table 3 ORs (and 95 % CIs) for the prevalence of cardiovascular disease risk factors according to the levels of 24-h urinary Tau/Cre ratio in the CARDIAC Study, 1985–1994

	Quintile of taurine/creatinine ratio (Tau/Cre)									P for linear trend[a]
	1 (lowest)		2		3		4		5 (highest)	
Obesity[b]										
Crude	2.91	(2.09, 4.04)[c]	1.83	(1.29, 2.60)	1.14	(0.78, 1.66)	1.53	(1.07, 2.19)	1.00	<0.001
Model 1[d]	2.84	(2.04, 3.96)	1.87	(1.32, 2.66)	1.16	(0.80, 1.71)	1.52	(1.07, 2.20)	1.00	<0.001
Model 2[e]	2.91	(2.05, 4.12)	1.83	(1.27, 2.63)	1.15	(0.78, 1.70)	1.52	(1.06, 2.19)	1.00	<0.001
Hypertension[b]										
Crude	1.19	(0.96, 1.49)	1.11	(0.89, 1.38)	0.97	(0.78, 1.21)	0.92	(0.74, 1.16)	1.00	NS
Model 1[d]	1.22	(0.98, 1.51)	1.11	(0.89, 1.39)	0.97	(0.78, 1.22)	0.93	(0.74, 1.17)	1.00	<0.05
Model 2[e]	1.29	(1.02, 1.62)	1.15	(0.91, 1.44)	0.99	(0.79, 1.25)	0.94	(0.75, 1.18)	1.00	<0.01
Hypercholesterolemia[b]										
Crude	2.21	(1.74, 2.81)	2.26	(1.78, 2.87)	1.68	(1.31, 2.15)	1.20	(0.93, 1.55)	1.00	<0.001
Model 1[d]	2.20	(1.73, 2.80)	2.36	(1.85, 3.01)	1.76	(1.37, 2.25)	1.22	(0.94. 1.58)	1.00	<0.001
Model 2[e]	1.94	(1.49, 2.53)	2.12	(1.64, 2.75)	1.74	(1.34, 2.26)	1.22	(0.93, 1.60)	1.00	<0.001

[a]Logistic regression analysis evaluating the linear relations between 24-h urinary taurine/creatinine ratio and cardiovascular diseases risk factors

[b]Obesity, hypertension and hypercholesterolemia were defined as body mass index ≥30 kg/m^2, any anti-hypertensive medication use or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and serum total cholesterol ≥220 mg/dl, respectively

[c]Odds ratio; 95 % CI in parentheses (all such values)

[d]Model 1 was adjusted for age and sex as to hypertension and additionally adjusted for anti-hypertensive medication use as to obesity and hypercholesterolemia

[e]Model 2 additionally adjusted for log-transformed 24-h urinary sodium/creatinine, potassium/creatinine, calcium/creatinine, magnesium/creatinine and survey year

Previous studies using data from the WHO-CARDIAC study demonstrated that the population averages of Tau in the 24-h urine samples were inversely related with CHD mortality rates (Yamori et al. 1996, 2001, 2006). Further analysis of individual 24-h urine samples from 41 populations of the WHO-CARDIAC Study revealed that individuals with 24-h Tau/Cre and Mg/Cre ratios more than the average of all the CARDIAC samples had significantly lower BMI, systolic and diastolic BP and TC than those with the ratios below the average, despite differences in ethnicity and genetic background (Yamori et al. 2010a, b). The present study confirmed and extends our previous findings by testing the associations of quintile scales of the Tau/Cre ratio with three key CVD risk factors and with or without the adjustment for more confounding variables, including Mg/Cre in multivariate analyses.

The role of Tau in BP regulation was first noted by its antihypertensive effect in SHR and stroke-prone SHR (Nara et al. 1978; Yamori 1984a, b, 1989), with the antihypertensive mechanism being due to sympathetic modulation in rat models (Li et al. 1996) and humans (Mizushima et al. 1996). Clinically, Tau administration decreased BP in borderline hypertensive young patients (Fujita et al. 1987) and in Tibetans, which exhibited nearly the lowest 24-h urinary Tau excretion among CARDIAC Study populations in the world because of their religious discipline not to eat fish (Yamori et al. 2009). CARDIAC Study demonstrated populations with greater 24-h Tau excretion in man had significantly lower BP and slower heart rates (HR) than those with lower Tau excretion (Yamori et al. 2009). Further analysis of CARDIAC data world-wide revealed salt-induced BP rise, that is the salt sensitivity was observed in individuals excreting higher Na accompanied by higher HR, among whom higher 24-h urinary Tau excretion was associated with lower BP. These data indicate possible neural involvement in salt-sensitive hypertension and suggest enough Tau intake attenuates salt-induced BP rise.

Quintile analyses of this study indicated an association between obesity in the lowest Tau excretion group, which was 2.9 times more than in subjects with the highest taurine excretion rates, with or without adjustment for confounding variables. Tau supplementation decreased body weight and abdominal fat experimentally in obese KK mice (Fujihira et al. 1970) and body weight clinically in over weight subjects (Zhang et al. 2004). Tau synthesis was reported to be decreased in white adipose tissue of obese mice due to a reduction in cysteine deoxygenate expression, a rate limiting enzyme of Tau synthesis (Tsuboyama-Kasaoka et al. 2006), and Tau supplementation was prone to prevent obesity in both diet-induced and genetically obese mice supposedly by activating energy expenditure including fatty acid β-oxidation in white adipose tissue.

Recently a randomized double-blind placebo-controlled study reported 8 week Tau supplementation with nutritional counselling increased adiponectin levels and decreased markers of inflammation (high-sensitive C-reactive protein) and lipid peroxidation in obese women without any significant reduction in body weight from the control (Rasa et al. 2014). Since obesity-induced inflammatory reactions cause endothelial dysfunction by reducing nitric oxide (NO) bioavailability through oxidative stress (Iantorno et al. 2014), Tau, known to form Tau chloramine to modulate

oxidative stress resulting from inflammatory reactions (Kim and Cha 2014), is expected to prevent cardiovascular complications caused by obesity, even if Tau's short term effect on obesity is not marked.

This study showed that hypercholesterolemia in the lowest quintile of Tau/Cre is 1.9–2.2 times more than in the highest quintel, with and without the adjustment of confounding variables. Tau supplementation decreases high-fat diet induced hyperlipidemia in stroke-prone SHR (Murakami et al. 1996), hamsters (Murakami et al. 2002b) and Japanese quail (Murakami et al. 2010) supposedly by mechanisms involving conjugation with bile acids and alterations in bile acid synthesis. Tau activates mRNA expression and enzymatic activity of cytochrome P450 7A1 (CYP7A), a rate-limiting enzyme of bile acid synthesis (Murakami et al. 1996; Yokogoshi et al. 1999). Bile acids then conjugate with Tau, which lowers blood TC as observed in the inverse association between Tau and TC, reported by the previous and the present CARDIAC data analyses (Yamori et al. 2009, 2010a, b).

Moreover, Tau exerts anti-atherosclerotic effects in addition to its hypocholesterolemic effects (Murakami 2014). As indicated by an experiment on Watanabe heritable hypercholesterolemic rabbits (Murakami et al. 2002b), Tau prevented atherosclerotic lesions, with a reduction in the marker of lipid peroxidation, but without a significant effect on lipidemia. The mechanism is supposed to be due to the reduction of the major receptor for oxidized low-density lipoprotein (LDL), the lectin-like oxidized LDL receptor by Tau treatment (Gokce et al. 2011).

The present study indicates that increased Tau intake reduces hypertension, obesity and hypercholesterolemia, the major risks of CHD and therefore, contributes to the prevention of CHD, as we first reported the inverse association of 24-h urinary Tau with the mortality rates of CHD (Yamori et al. 1996, 2001).

There are some limitations to our study. First, a cause-effect association cannot be determined from the present analysis because of the cross-sectional study design. Second, we did not examine other related serum biomarkers, such as triglycerides, because of the difficulty of asking the participants to fast for more than 12 h in a worldwide cross-country study. LDL and HDL-cholesterol was not analyzed as well because frozen serum samples had to be sent to a standardized analysis center in accordance with the CARDIAC multicenter study protocol (WHO-CARDIAC Study group 1986, 1990). Apolipoproteins, coronary heart disease risk factors (McQueen et al. 2008), were not analyzed because of the difficulty of setting up a standardized method of analysis at the time of designing the CARDIAC Study in 1985 (WHO-CARDIAC Study group 1986). Our study also lacks data on blood glucose levels and HbA1c, biomarkers of diabetes and key components of the metabolic syndrome.

However, this study also has several strengths. First, the Tau/Cre ratio of the 24-h urine samples varied widely because the CARDIAC Study was a worldwide, multicenter study including participants with various dietary customs, and thus we could detect a significant inverse association between the Tau/Cre ratio and cardiovascular disease risk factors. Second, we assessed the dietary intake of nutrients using the 24-h urine sample, which enabled an objective evaluation of dietary intake.

5 Conclusion

Higher 24-h urinary Tau/Cre ratio was associated with lower cardiovascular disease risk factors, including BMI, BP, TC, obesity, hypertension and hypercholesterolemia. Tau deficiency was related to increased susceptibility to hypertension among the participants in the CARDIAC study, irrespective of ethnic differences, living conditions and gender.

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