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Relationship between low serum endogenous androgen concentrations and arterial stiffness in men with type 2 diabetes mellitus

Michiaki Fukui[a,*], Hiroyuki Ose[a], Yoshihiro Kitagawa[b], Masahiro Yamazaki[a], Goji Hasegawa[a], Toshikazu Yoshikawa[c], Naoto Nakamura[a]

[a]*Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan*
[b]*Department of Endocrinology and Hematology, Osaka General Hospital of West Japan Railway Company, Osaka 545-0053, Japan*
[c]*Department of Inflammation and Immunology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan*

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Abstract

The aim of this study was to evaluate the relationship between arterial stiffness determined by pulse wave velocity (PWV) and serum endogenous androgen concentrations as well as major cardiovascular risk factors in men with type 2 diabetes mellitus. Serum free testosterone and dehydroepiandrosterone sulfate (DHEA-S) concentrations were measured in 268 men with type 2 diabetes mellitus. Relationships between PWV and serum endogenous androgen concentrations as well as major cardiovascular risk factors, including age, blood pressure, serum lipid concentration, glycemic control (hemoglobin A_{1c}), body mass index, and degree of albuminuria, were evaluated. Positive correlations were found between PWV and age ($r = 0.491$, $P < .0001$), duration of diabetes ($r = 0.320$, $P < .0001$), systolic blood pressure ($r = 0.292$, $P < .0001$), and log (urinary albumin excretion) ($r = 0.269$, $P < .0001$). Inverse correlations were found between serum free testosterone concentration and PWV ($r = -0.228$, $P = .0003$) and between serum DHEA-S concentration and PWV ($r = -0.252$, $P = .0002$) in men with type 2 diabetes mellitus. Pulse wave velocity was significantly greater in patients with lower concentrations of free testosterone (<10 pg/mL) than in patients with higher concentrations of free testosterone (1864 ± 359 vs 1736 ± 327 cm/s; $P = .0053$). Pulse wave velocity also was significantly greater in patients with lower concentrations of DHEA-S (<1000 ng/mL) than in patients with higher concentrations of DHEA-S (1843 ± 371 vs 1686 ± 298 cm/s; $P = .0008$). Multiple regression analysis identified both serum free testosterone concentration ($\beta = -.151$, $P = .0150$) and serum DHEA-S concentration ($\beta = -.200$, $P = .0017$) as independent determinants of PWV. In conclusion, serum endogenous androgen concentrations are inversely associated with arterial stiffness determined by PWV in men with type 2 diabetes mellitus, which is true for men in general based on other works.

1. Introduction

Progression of cardiovascular disease (CVD), the primary cause of mortality and morbidity in patients with type 2 diabetes mellitus, is accelerated by risk factors, including smoking, hypertension, and hyperlipidemia [1]. Low serum concentrations of endogenous androgens have also been linked with increased CVD risk in men [2]. Men with diabetes have significantly lower serum concentrations of endogenous androgens than nondiabetic men [3,4]. We recently demonstrated an inverse association between serum endogenous androgen concentrations and carotid atherosclerosis, determined by ultrasonographically evaluated intima-media thickness (IMT) and plaque score, in men with type 2 diabetes mellitus [5]. Arterial stiffness can be assessed simply, noninvasively, and reproducibly by measuring pulse wave velocity (PWV) along the thoracoabdominal aorta [6,7]. Pulse wave velocity is a marker for both severity of vascular damage and prognosis in atherosclerotic vascular disease [8]. Intima-media thickness and PWV may reflect different aspects of the atherosclerotic process; the former is an assessment of structure and the latter, of function [9].

Few studies have examined associations between serum endogenous androgen concentrations and PWV in men

* Corresponding author. Tel.: +81 75 251 5505; fax: +81 75 252 3721.
E-mail address: sayarinapm@hotmail.com (M. Fukui).

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[10,11]. To our knowledge, the relationship between serum endogenous androgen concentrations and arterial stiffness determined by PWV has never been explored in men with type 2 diabetes mellitus. The number of patients with type 2 diabetes mellitus is progressively increasing all over the world, and CVD is the leading cause of mortality and morbidity in patients with diabetes who have 2 to 5 times the risk of CVD of the general population. This is why we chose to focus on diabetic men. In this study, we evaluated the relationships between arterial stiffness and serum endogenous androgen concentrations as well as major cardiovascular risk factors in men with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Subjects

Serum free testosterone and dehydroepiandrosterone sulfate (DHEA-S) concentrations were measured in 268 consecutive men with type 2 diabetes mellitus recruited from outpatient clinics of the Kyoto Prefectural University of Medicine (Kyoto, Japan) and the Osaka General Hospital of West Japan Railway Company (Osaka, Japan). We then evaluated the relationships of PWV and ankle-brachial index (ABI) to serum endogenous androgen concentrations as well as to major cardiovascular risk factors, including age, blood pressure, serum lipid concentration, glycemic control (hemoglobin A_{1c} [HbA_{1c}]), body mass index (BMI), degree of albuminuria, current treatment of diabetes, and presence of CVD.

Serum free testosterone and DHEA-S concentrations (reference ranges, 14.0-40.0 pg/mL and 150-2400 ng/mL, respectively) were measured by the Coat-A-Count free testosterone and DHEA-S kits (Diagnostic Products, Los Angeles, CA). The intra-assay coefficients of variation (CVs) were 10.0%, 6.0%, and 5.0% for free testosterone concentrations of 1.87, 11.8, and 38.7 pg/mL, respectively. The interassay CVs were 21.0%, 8.0%, and 7.0% for free testosterone concentrations of 1.38, 11.03, and 37.3 pg/mL, respectively. The intra-assay CVs were 9.8%, 7.2%, 6.6%, and 6.0% for DHEA-S concentrations of 173, 430, 1980, and 5680 ng/mL, respectively. The interassay CVs were 9.5%, 8.3%, 4.9%, and 7.3% for DHEA-S concentrations of 200, 480, 2050, and 5490 ng/mL, respectively. Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were assessed using standard enzymatic methods. Hemoglobin A_{1c} was assayed using high-performance liquid chromatography. A mean value for urinary albumin excretion was determined from 3 urine collections.

Type 2 diabetes mellitus was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [12]. Retinopathy was graded as follows: no diabetic retinopathy, simple diabetic retinopathy, and proliferative diabetic retinopathy. Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion less than 30 mg/g of creatinine (Cr); microalbuminuria, 30 to 300 mg/g Cr; or macroalbuminuria, more than 300 mg/g Cr. Mean values for biochemical parameters obtained during the previous year in patients with type 2 diabetes mellitus were used for statistical analysis. Cardiovascular disease was defined as the presence of previous myocardial infarction or cerebral infarction based on the clinical history or physical examination.

Patients were excluded if they had been castrated for treatment of testicular or prostate cancer, or were taking any medications known to affect sex hormone concentrations (eg, antiandrogenic agents for prostate cancer). Approval for the study was obtained from the local research ethics committee, and informed consent was obtained from all participants.

2.2. Measurement of PWV and ABI

Brachial-ankle (ba) PWV and ABI (reference ranges, <1400 cm/s and 0.9-1.3, respectively) were measured using a Colin Waveform Analyzer (form PWV/ABI; Colin Medical Technology, Komaki, Japan), which simultaneously measures pulse volumes in the brachial and posterior tibial arteries using an oscillometric method together with bilateral arm and ankle blood pressure. Both PWV and ABI were measured after allowing the patient to rest in the supine position for at least 5 minutes. For measuring baPWV, pulse volume waveforms of the brachial and tibial arteries were recorded. Details of the method have been described elsewhere [13]. After bilateral determination of baPWV, the higher value was taken as representative for each subject. Ankle-brachial index was calculated bilaterally as the ratio of systolic pressure in the ankle to systolic pressure in the arm, with the lower value considered representative for each subject.

2.3. Statistical analysis

Means and frequencies of potential confounding variables were calculated. Unpaired Student *t* tests or analyses of variance were conducted to assess statistical significance of differences between groups, using StatView software (version 5.0; SAS Institute, Cary, NC). Relationships between PWV or ABI and serum endogenous androgen concentrations; or age, glycemic control, and other variables were examined by linear regression analysis. All continuous variables are presented as mean ± SD. Multiple regression analysis was performed to assess the combined influence of variables on PWV or ABI. To examine the effects of various factors on PWV or ABI, we considered serum free testosterone (or DHEA-S) concentration, duration of diabetes, BMI, HbA_{1c}, systolic blood pressure, diastolic blood pressure, plasma total cholesterol, HDL cholesterol, triglyceride concentrations, and smoking status as independent variables. A *P* value of less than .05 was considered statistically significant.

3. Results

Clinical characteristics of the 268 men with type 2 diabetes mellitus enrolled in this study are shown in Table 1. Mean serum concentrations of free testosterone and DHEA-S were 9.4 ± 3.0 pg/mL and 1149 ± 735 ng/mL, respectively. Mean PWV and ABI were 1802 ± 353 cm/s and 1.07 ± 0.18, respectively.

Relationships between PWV or ABI and other variables are shown in Table 2. Positive correlations were found between PWV and age, duration of diabetes, systolic blood pressure, and log (urinary albumin excretion). Inverse correlations were found between ABI and age, plasma triglyceride concentration, and log (urinary albumin excretion). No significant correlations were found between PWV and HbA_{1c} or between ABI and HbA_{1c}. Neither PWV nor ABI differed between patients treated with and without insulin (1873 ± 352 vs 1779 ± 351 cm/s or 1.05 ± 0.19 vs 1.08 ± 0.17, respectively). Ankle-brachial index was significantly lower in patients with CVD than in those without CVD (0.95 ± 0.24 vs 1.09 ± 0.15, $P < .0001$), although PWV did not differ between patients with and without CVD (1859 ± 360 vs 1788 ± 352 cm/s).

Inverse correlations were found between serum free testosterone concentration and PWV ($r = -0.228$, $P = .0003$) and between serum DHEA-S concentration and PWV ($r = -0.252$, $P = .0002$) in men with type 2 diabetes mellitus (Fig. 1). No significant correlations were found between serum free testosterone concentration and ABI ($r = 0.030$, $P = .6338$) or between serum DHEA-S concentration and ABI ($r = 0.051$, $P = .4362$) in men with type 2 diabetes mellitus. Pulse wave velocity was significantly greater in patients with lower concentrations of free testosterone (<10 pg/mL) than in patients with higher concentrations of free testosterone (1864 ± 359 vs 1736 ± 327 cm/s; $P = .0053$). Similarly, PWV was significantly greater in patients with lower concentrations of DHEA-S (<1000 ng/mL) than in patients with higher concentrations of DHEA-S (1843 ± 371 vs 1686 ± 298 cm/s; $P = .0008$).

Multiple regression analysis demonstrated that serum free testosterone concentration ($\beta = -.151$, $P = .0150$), duration

Table 1
Clinical characteristics of patients with diabetes

	Mean ± SD
n	268
Age (y)	64.4 ± 10.8
Age at onset (y)	50.5 ± 11.9
Duration of diabetes (y)	13.7 ± 11.0
BMI (kg/m^2)	23.2 ± 3.2
HbA_{1c} (%)	7.1 ± 1.1
Systolic blood pressure (mm Hg)	133 ± 15
Diastolic blood pressure (mm Hg)	77 ± 11
Total cholesterol (mg/dL)	194 ± 31
Triglyceride (mg/dL)	137 ± 87
HDL cholesterol (mg/dL)	52 ± 13
Retinopathy (NDR/SDR/PDR)	189/42/37
Nephropathy (normo-/micro-/macroalbuminuria)	162/84/22
Current treatment (diet/OHA/insulin)	29/173/66
Smoking (none/past/current)	54/116/98
PWV (cm/s)	1802 ± 353
ABI	1.07 ± 0.18
Free testosterone (pg/mL)	9.4 ± 3.0
DHEA-S (ng/mL)	1149 ± 735

NDR indicates no diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy; OHA, oral hypoglycemic agent.

Table 2
Correlation between PWV or ABI and other variables

	PWV		ABI	
	r	*P*	*r*	*P*
Age	0.491	<.0001	−0.196	.0013
Age at onset	0.173	.0068	−0.073	.2459
Duration of diabetes	0.320	<.0001	−0.080	.1989
BMI	−0.145	.0224	0.065	.2953
HbA_{1c}	−0.034	.5941	−0.060	.3290
Systolic blood pressure	0.292	<.0001	0.094	.1269
Diastolic blood pressure	0.042	.5123	0.262	<.0001
Total cholesterol	−0.121	.0567	−0.008	.8922
Triglyceride	−0.122	.0540	−0.122	.0460
HDL cholesterol	−0.010	.8732	0.228	.0002
Log (urinary albumin excretion)	0.269	<.0001	−0.132	.0443

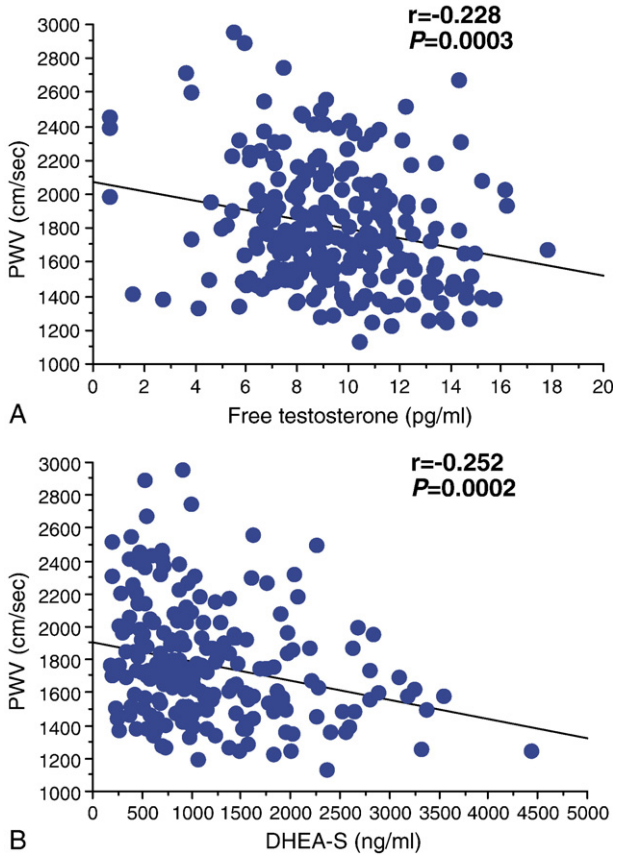

Fig. 1. Correlation between serum free testosterone concentration and PWV (A) and between DHEA-S concentration and PWV (B) in men with type 2 diabetes mellitus.

Table 3
Multiple regression analysis on PWV or ABI

	PWV				ABI			
	β	P	β	P	β	P	β	P
Free testosterone	−.151	.0150	–	–	−.105	.1004	–	–
DHEA-S	–	–	−.200	.0017	–	–	−.031	.6413
Duration of diabetes	.228	.0010	.261	.0002	.010	.8922	−.012	.8693
BMI	−.167	.0168	−.150	.0389	.047	.5126	.022	.7717
HbA_{1c}	−.037	.5509	−.101	.1127	−.026	.6926	−.006	.9355
Systolic blood pressure	.445	<.0001	.410	<.0001	−.187	.0484	−.176	.0795
Diastolic blood pressure	−.152	.1245	−.080	.4351	.421	<.0001	.391	.0003
Total cholesterol	.036	.6098	−.009	.8938	−.068	.3567	−.078	.3042
Triglyceride	−.078	.2742	−.064	.3757	−.069	.3463	−.077	.3170
HDL cholesterol	−.056	.4281	−.018	.8022	.169	.0202	.182	.0159
Smoking	−.104	.0877	−.099	.1166	−.193	.0024	−.199	.0033

of diabetes (β = .228, P = .0010), BMI (β = −.167, P = .0168), and systolic blood pressure (β = .445, P < .0001) were independent determinants of PWV (Table 3). Furthermore, serum DHEA-S concentration (β = −.200, P = .0017), duration of diabetes (β = .261, P = .0002), BMI (β = −.150, P = .0389), and systolic blood pressure (β = .410, P < .0001) were independent determinants of PWV. Neither serum free testosterone nor DHEA-S concentrations were an independent determinant of ABI.

4. Discussion

We evaluated relationships between arterial stiffness determined by PWV and serum endogenous androgen concentrations as well as major cardiovascular risk factors in men with type 2 diabetes mellitus. Serum free testosterone and DHEA-S concentrations correlated inversely with PWV. Patients with low concentrations of free testosterone (<10 pg/mL) or DHEA-S (<1000 ng/mL) had greater PWV than in those with high concentrations of free testosterone or DHEA-S. We divided our patients into subgroups based on a free testosterone concentration of 10 pg/mL or a DHEA-S concentration of 1000 ng/mL, which could be the threshold value for initiating hormone replacement therapy in hypogonadism, although thresholds that have been used to define hypogonadism varied between studies [14]. Our results suggested that alterations in arterial stiffness might explain the known association between lower androgenicity and increased cardiovascular risk in men.

We recently reported an inverse association between serum concentration of free testosterone or DHEA-S and carotid atherosclerosis, determined by ultrasonographically evaluated carotid IMT and plaque score, in men with type 2 diabetes mellitus [5,15]. In addition, IMT and plaque score were significantly greater in patients with lower concentrations of free testosterone (<10 pg/mL) or DHEA-S (<1000 ng/mL) than in a group of patients with higher concentrations of free testosterone or DHEA-S. Intima-media thickness and PWV may assess different aspects of atherosclerosis because IMT is a structural characteristic, whereas PWV is a functional characteristic [9]. Pulse wave velocity, a simple, noninvasive way to quantitate atherosclerosis, measures arterial stiffness to serve as an indicator of both severity of vascular damage and future outcome of atherosclerotic vascular disease. Aortic (carotid-femoral) PWV is a well-established index of central arterial stiffness that has been directly linked with cardiovascular mortality and morbidity [16]. Although aortic PWV is accurate, reproducible, and relatively simple to use, it may not be ideal for routine use in clinics because the use of pressure transducers or Doppler probes on target arteries may be perceived as somewhat difficult to clinical staff. Brachial-ankle PWV is a simpler method of measuring PWV, which requires simply placing blood pressure cuffs on the 4 extremities, and an increasing number of reports have been published using this method [13,17]. Sugawara et al [18] demonstrated that baPWV may provide qualitatively similar information to those derived from central arterial stiffness. Yamashina et al [13] also reported that baPWV correlated well with aortic PWV, and the validity and reproducibility of baPWV measurements are considerably high, and baPWV measured by this simple, noninvasive method is suitable for screening vascular damages in a large population. Ankle-brachial index also is a simple, noninvasive measurement with a proven role both in the diagnosis of peripheral arterial disease and baseline assessment of individuals at risk for CVD. In this study, ABI was significantly lower in patients with CVD than in those without CVD. To our knowledge, the relationship between serum endogenous androgen concentrations and ABI has not been explored either in men with type 2 diabetes mellitus or in the general population. No significant correlations were found between serum endogenous androgen concentration and ABI in the present study. Ankle-brachial index may be less sensitive as a marker for early detection of atherosclerosis than PWV or carotid atherosclerosis determined by ultrasonographically evaluated carotid IMT and plaque score.

Studies examining associations between low serum testosterone concentrations and CVD mortality have been

inconclusive. In disagreement with several reports suggesting that low serum testosterone concentrations in men may be associated with increased risk of CVD, some investigators have found no significant association between total testosterone concentration and prevalence of CVD [19]. However, in the present study, serum free testosterone or DHEA-S concentrations correlated significantly with PWV, which is an early preclinical marker of atherosclerosis.

Testosterone exerts a favorable effect upon vascular reactivity, inflammation, cytokine production, adhesion molecule expression, insulin resistance, serum lipid concentrations, and hemostatic factors [20]. The antiatherogenic properties of DHEA may involve several mechanisms, including decreased insulin resistance [21], inhibition of differentiation and proliferation of smooth muscle cells and fibroblasts [22], a hypolipidemic effect [23], decreased platelet aggregation [24] and plasminogen activator inhibitor [21], enhanced endothelial function [21], and increased vascular contractility [25]. Dehydroepiandrosterone also reduces atherogenic cytokines such as interleukin 6 [26] and tumor necrosis factor α [27]. Considering that DHEA is metabolized enzymatically to androgens and estrogens, DHEA may exert its effects either directly or after these conversions. However, DHEA has been reported to inhibit human vascular smooth muscle cell proliferation by mechanisms independent of either androgen or estrogen receptors [28].

Generalized vascular damage may serve as a common pathogenetic mechanism linking microalbuminuria with premature atherosclerosis [29,30]. In a recent study, microalbuminuria was found to be related independently to carotid IMT in patients with type 2 diabetes mellitus [31]. In the present study, PWV was also significantly associated with the degree of albuminuria.

The number of patients with type 2 diabetes mellitus is progressively increasing all over the world, and CVD is the leading cause of mortality and morbidity in patients with diabetes, who have 2 to 5 times the risk of CVD of the general population. This is why we chose to focus on diabetic men. Men with diabetes have significantly lower plasma concentrations of endogenous androgen than nondiabetic men [3,4]. Increased risk for CVD in diabetic men, thus, could be mediated partly by low concentrations of endogenous androgen. Advanced age is one of the strongest predictors for coronary artery disease; the decline in endogenous androgen concentration with age may help to explain age-related rise in the risk of CVD. Because decreased concentrations of endogenous androgen are responsible for aging, adjusting for age to assess the relationship between serum endogenous androgen concentrations and PWV or ABI might result in an overadjustment. To address this, we performed multiple regression analysis to assess the combined influence of variables on PWV or ABI using the following factors: serum free testosterone (or DHEA-S) concentration, duration of diabetes, BMI, blood pressure, plasma lipid concentration, HbA_{1c}, and smoking status. Pulse wave velocity showed an independent inverse association with serum endogenous androgen concentrations.

In this study, no significant correlations were found between PWV and HbA_{1c} or between ABI and HbA_{1c}. Certainly, the presence of diabetes is an important risk factor for the development and progression of atherosclerosis [32]. Mechanisms for the deleterious impact of diabetes on arterial stiffness include increased insulin resistance, advanced glycation end products, and reactive oxidative stress as well as hyperglycemia [33,34]. The United Kingdom Prospective Diabetes Study showed that strict blood pressure control decreases the risk of macrovascular complications as well as the risk of microvascular complications; however, strict blood glucose control could not decrease the risk of macrovascular complications in diabetic patients [35]. Furthermore, some previous studies also demonstrated no significant associations between diabetic control and PWV [32,36]. Postprandial glucose instead of HbA_{1c} may be associated with PWV because postprandial glucose has been recently reported to be associated with atherosclerosis [37].

Few studies have examined associations between serum endogenous androgen concentrations and PWV in men [10,11]. Furthermore, testosterone suppression in nondiabetic men with prostate cancer has been reported to be associated with increased arterial stiffness [38]. Ishihara et al [39] reported that serum DHEA-S concentration was inversely associated with PWV in either nondiabetic men or women. Effects of estradiol on PWV in postmenopausal women are inconclusive [40,41]. To our knowledge, this is the first study to investigate the relationship between serum endogenous androgen concentrations and arterial stiffness determined by PWV in men with type 2 diabetes.

Limitations of our study include a cross-sectional design and effects of treatment of diabetes, hypertension, and hyperlipidemia on the results. However, ongoing treatments necessarily complicate analyses of patients with type 2 diabetes mellitus. Moreover, we could not compare the effect of endogenous androgen on arterial stiffness with that in nondiabetic patients in this study. A few prospective clinical trials [42], some cross-sectional studies [43], and also experimental studies [44] suggest that endogenous androgen has a beneficial effect in men against development of atherosclerosis or its clinical manifestations. Large prospective trials and intervention studies are needed to better assess metabolic and cardiovascular benefits of androgen in men with type 2 diabetes mellitus.

In conclusion, serum endogenous androgen concentrations are inversely associated with arterial stiffness determined by PWV in men with type 2 diabetes mellitus, which is true for men in general based on other works.

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