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# Evidence for a Positive Association Between Serum Carnitine and Free Testosterone Levels in Uremic Men with Hemodialysis

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## Abstract

***Background and Aims:*** Low free testosterone levels are associated with sexual dysfunction and an increased risk of cardiovascular disease in male hemodialysis patients. Carnitine deficiency is frequently observed in hemodialysis patients as well. However, the relationship between carnitine and testosterone levels remains unknown. In this study, we examined whether carnitine deficiency was independently associated with low free testosterone levels in male hemodialysis patients.

***Methods:*** Nineteen male hemodialysis patients underwent determinations of blood chemistries, including serum levels of free testosterone, carnitine, and pentosidine, one of the well-characterized advanced glycation end products.

***Results:*** Mean free testosterone levels in hemodialysis patients were significantly lower than those in healthy controls ($4.67 \pm 2.69$ vs. $9.50 \pm 3.67$ pg/mL, $p < 0.001$). Univariate analysis revealed that carnitine ($p = 0.023$), pentosidine (inversely, $p = 0.027$), blood glucose (inversely, $p = 0.032$), creatinine ($p = 0.026$) levels, and statin use (inversely, $p = 0.034$) were correlated with free testosterone values. Multiple stepwise regression analysis revealed that carnitine ($p = 0.001$) and statin use (inversely, $p = 0.002$) were the independent determinants of age-adjusted free testosterone levels in hemodialysis patients ($r^2 = 0.612$).

***Conclusions:*** The present study gives the first evidence that decreased carnitine levels were independently associated with low free testosterone values in male hemodialysis patients. Our study suggests that decreased carnitine levels may be a novel therapeutic target for uremic men with hemodialysis.

## Introduction

Disturbances in sexual function are a common feature of hemodialysis (HD) patients.[1,2] About 52% of male HD patients were diagnosed as hypogonadism on the basis of low concentration of serum testosterone levels.[1] A large number of studies have indicated that decreased testosterone levels are associated with derangements in sexual drive, libido, and erectile dysfunction (ED) and impairment of muscle mass and strength in these patients.[1,2] Furthermore, low testosterone levels have also been shown to increase the risk of cardiovascular disease (CVD) and could be associated with all-cause and CVD mortality in male HD patients.[1,3] Although several factors such as hypothalamic–pituitary dysfunction, malnutrition, inflammation, anemia, and atherosclerosis have been proposed to contribute to the development and progression of sexual dysfunction in uremic men,[4] the precise underlying mechanism is not fully understood, and therapeutic options for hypogonadism in male HD subjects may be far from satisfactory and limited by considerable side effects.[5,6] Therefore, to identify a novel therapeutic target that could link low testosterone levels to uremia is urgently needed for improving the sexual life and preventing the progression of CVD in male HD patients.

Carnitine is a natural substance that is supplied through the intake of protein-rich foods and synthesized by the liver, kidney, skeletal, cardiac muscles, epididymis, and testis in humans.[7,8] Carnitine is involved in fatty acid $\beta$-oxidation and energy production by transporting long-chain fatty acids from the cytoplasm to mitochondria.[8] It has been reported that serum carnitine levels were significantly decreased in HD patients because about 80% of serum carnitine is

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eliminated from the blood via HD.[9,10] Since carnitine supplementation has been shown to improve aging-related sexual dysfunction assessed by nocturnal penile tumescence and the International Index of Erectile Function Score,[11] carnitine deficiency may be one of the causative factors for the development and progression of low-testosterone-related sexual dysfunction in HD patients.

Reducing sugars can react non-enzymatically with the amino groups of proteins to initiate a complex series of rearrangements and dehydrations, and then to produce a class of irreversibly cross-linked, fluorescent moieties termed advanced glycation end products (AGEs).[12–14] The formation and accumulation of AGEs have been known to progress in a normal aging process and at an accelerated rate under diabetes or end-stage renal failure, thereby playing a role in the development and progression of CVD in HD patients.[15–21] Moreover, there is accumulating evidence to show that AGEs could contribute to diabetes- and/or aging-related ED.[22–25] Indeed, exponential age-related or diabetes-associated increase in penile pentosidine levels was observed, which was linked to ED.[22] Inhibition of AGEs formation or breakdown of pre-formed AGEs has been shown to improve ED in diabetic rats.[23,24] Furthermore, we have recently found that circulating AGEs levels are inversely correlated with serum testosterone levels in un-medicated non-diabetic men.[26] However, it remains unclear which anthropometric, metabolic, clinical, and biochemical variables, including serum carnitine and AGEs levels, are independently correlated with low free testosterone values in HD patients. Therefore, in this study, we examined whether carnitine deficiency and increased levels of pentosidine, one of the well-characterized AGEs were independently associated with decreased free testosterone values in male HD subjects.

## Methods

### Patients

Nineteen male patients receiving chronic HD (mean age, 66.3 ± 11.2 years old; mean duration of HD, 127.8 ± 94.5 months) and age- and sex-matched 11 healthy controls (mean age, 60.0 ± 7.1 years old) underwent a complete history, physical examination, and determinations of blood chemistries, including serum carnitine, pentosidine, and free testosterone. Patients were dialyzed for 4–5 hr with high-flux dialyzers three times a week. Fourteen patients had diabetes mellitus, 9 patients received inhibitors of the renin–angiotensin system (RAS), and 6 received statins for the treatment of dyslipidemia.

### Data collection

The medical history was ascertained by a questionnare. Blood pressure was measured in the sitting position using an upright standard sphygmomanometer just before starting HD. Vigorous physical activity and smoking were avoided for at least 30 min before blood pressure measurement.

Table 1. Clinical Characteristics of Healthy Controls and Hemodialysis Patients

| *Values* | *Healthy controls* | *HD patients* | p *value* |
|---|---|---|---|
| Number of patients | 11 | 19 | |
| Age (years old) | 60.0 ± 7.1 | 66.3 ± 11.2 | 0.100 |
| Body mass index (kg/m$^2$) | 22.2 ± 2.5 | 22.8 ± 3.6 | 0.621 |
| SBP (mmHg) | 131.6 ± 22.3 | 157.8 ± 24.5 | 0.007 |
| Hemoglobin (g/dL) | 15.6 ± 0.9 | 11.0 ± 0.8 | < 0.001 |
| Albumin (g/dL) | 4.64 ± 0.13 | 3.73 ± 0.25 | < 0.001 |
| Plasma glucose (mg/dL) | 104.0 ± 14.6 | 122.4 ± 34.4 | 0.105 |
| LDL-C (mg/dL) | 139.0 ± 38.3 | 65.1 ± 22.8 | < 0.001 |
| Triglycerides[a] (mg/dL) (range) | 116.4 (41-200) | 97.6 (46-261) | 0.287 |
| BUN (mg/dL) | 15.3 ± 3.7 | 55.0 ± 13.0 | < 0.001 |
| Creatinine (mg/dL) | 0.77 ± 0.10 | 10.8 ± 2.2 | < 0.001 |
| Uric acid (mg/dL) | 5.26 ± 1.33 | 6.75 ± 0.84 | 0.001 |
| Corrected Ca (mg/dL) | 8.61 ± 0.25 | 9.09 ± 0.43 | 0.002 |
| P (mg/dL) | 3.27 ± 0.42 | 4.34 ± 0.87 | 0.001 |
| Whole PTH (pg/mL) | 28.7 ± 10.9 | 45.7 ± 24.1 | 0.007 |
| CRP (mg/dL) | 0.18 ± 0.34 | 0.43 ± 0.80 | 0.335 |
| $\beta_2$-MG (mg/L) | 1.7 ± 0.4 | 31.6 ± 5.7 | < 0.001 |
| Serum carnitine ($\mu$mol/L) | 60.1 ± 6.3 | 35.9 ± 8.7 | < 0.001 |
| Total testosterone (ng/mL) | 5.56 ± 2.38 | 3.79 ± 2.29 | 0.055 |
| Free testosterone (pg/mL) | 9.50 ± 3.67 | 4.67 ± 2.69 | < 0.001 |
| Pentosidine ($\mu$g/mL) | 0.042 ± 0.009 | 0.325 ± 0.114 | < 0.001 |
| HD duration (months) | 0 | 127.8 ± 94.5 | |
| Kt/V | — | 1.52 ± 0.19 | |
| Diabetes (number) | 0 | 14 | |
| Medication | | | |
| RAS inhibitors (number) | 0 | 10 | |
| Statins (number) | 0 | 13 | |

Data are shown as mean ± standard deviation or range

[a]Log-transformed values were used.

SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; Ca, calcium; P, phosphate; PTH, parathyroid hormone; CRP, C-reactive protein; $\beta_2$-MG, $\beta_2$-microglobulin; HD, hemodialysis; RAS, renin angiotensin system.

Blood was drawn from arteriovenous shunt just before starting HD sessions for the determinations of hemoglobin, albumin, lipids (low-density lipoprotein cholesterol and triglycerides), blood urea nitrogen, creatinine, uric acid, calcium, and phosphate. Whole parathyroid hormone was evaluated by an immunoradiometric assay (IRMA; Allegro I-PTH, Nichols Institute, San Juan Capistrano, CA). $\beta_2$-Microglobulin ($\beta_2$-MG) was measured by a Latex immunoagglutination assay (Eiken Chemical Co.,Ltd. Tokyo, Japan). Serum carnitine levels were determined as described previously.[27] Total and free testosterone levels measured by electro-chemiluminescence immunoassay and radioimmunoassay, respectively (SRL Inc., Tokyo Japan). Pentosidine levels were evaluated by an enzyme-linked immunosorbent assay (ELISA; Fushimi Pharmaceutical Co., Ltd., Kagawa, Japan).[28] Other blood chemistries were measured at a commercially available laboratory (Wako Pure Chemical Industries, Ltd., Osaka, Japan) as described previously.[29] Efficacy of HD was also evaluated by a single-pool fractional clearance of body water for urea (Kt/V) as described previously.[30]

Informed consent was obtained from all patients, and the study protocol was approved by the Institutional Ethics Committees of Kurume University School of Medicine and Sugi Cardiovascular Hospital, Japan.

### *Statistical analysis*

Data are presented as mean ± standard deviation. Use of RAS inhibitors and statins and the presence or absence of diabetes mellitus were coded as dummy variables. Because triglycerides levels were not normally distributed, log-transformed values were used for analysis. To compare clinical values between healthy controls and HD patients, an unpaired *t*-test was performed. To determine independent correlates of age-adjusted free testosterone, multiple stepwise regression analysis was performed. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed with SPSS 19 system.

## Results

### *Demographic data*

Demographic data are shown in Table 1. Serum carnitine and free testosterone levels in HD patients were significantly lower than those in healthy controls (serum carnitine, 60.1 ± 6.3 vs. 35.9 ± 8.7 μmol/L, $p < 0.001$; free testosterone, 9.50 ± 3.67 vs. 4.67 ± 2.69 pg/mL, $p < 0.001$). Serum pentosidine levels in HD patients were significantly elevated compared with healthy controls (0.325 ± 0.114 vs. 0.042 ± 0.009 μg/mL, $p < 0.001$). There was no significant difference of total testosterone levels between the two groups (healthy controls vs. HD patients, 5.56 ± 2.38 vs. 3.79 ± 2.29 ng/mL, $p = 0.055$).

### *Correlation with free testosterone levels*

Univariate analyses revealed that plasma glucose (inversely, $p = 0.032$), creatinine ($p = 0.026$), serum carnitine ($p = 0.023$, Fig. 1A), pentosidine levels (inversely, $p = 0.027$, Fig. 1B), and statin use (inversely, $p = 0.034$) were significantly associated with free testosterone values (Table 2). Because these significant parameters could be closely correlated with each other, multiple regression analysis was performed. Multiple stepwise regression analysis showed that serum carnitine ($\beta = 0.620$, $p = 0.001$) and statin use ($\beta = -0.595$, $p = 0.002$) were independent correlates of age-adjusted free testosterone levels ($r^2 = 0.612$, Table 2). When we analyzed the data of patients ($n = 7$) whose free testosterone levels within the normal range (5.4–16.7 pg/mL; provided by a clinical laboratory testing company, SRL, Inc., Japan), mean serum carnitine levels in these patients were significantly higher than those with lower than normal free testosterone levels (40.0 ± 7.4 vs. 33.6 ± 8.7 μmol/L). No significant correlation of total testosterone with carnitine or pentosidine levels was observed in HD patients. There was no significant correlation between serum carnitine and free testosterone levels in healthy controls ($p = 0.631$). Serum free and total testosterone, carnitine, and pentosidine levels did not differ between diabetic and nondiabetic HD subjects (data not shown).

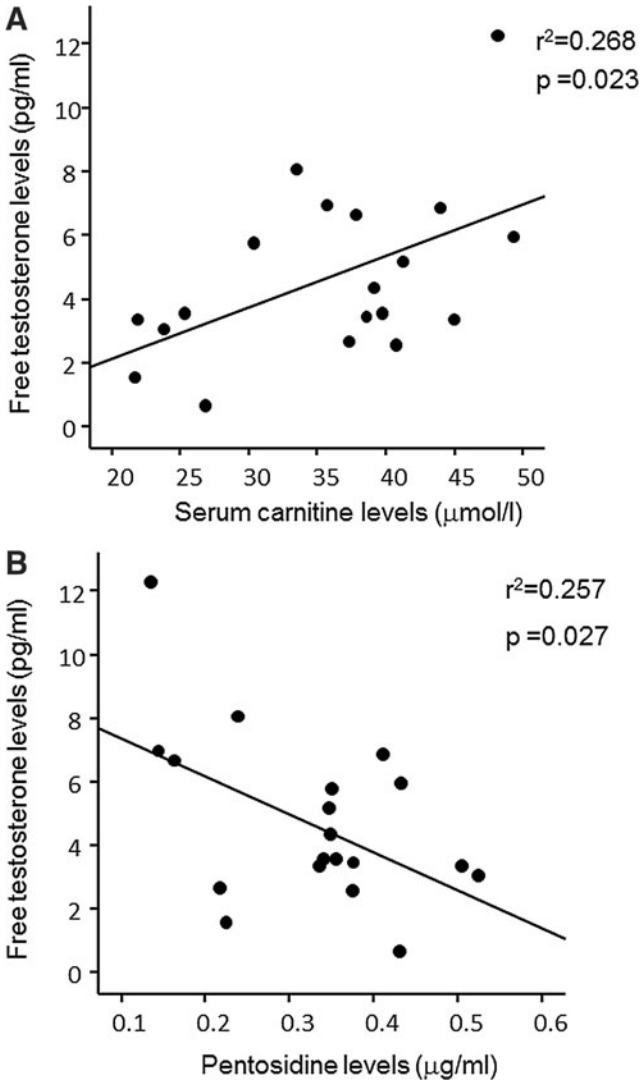


**FIG. 1.** (**A**) Correlation between serum free testosterone and carnitine levels in patients with hemodialysis (HD) ($n = 19$). (**B**) Correlation between serum free testosterone and pentosidine levels in patients with HD ($n = 19$).

## Discussion

We demonstrated here that: (1) Serum free testosterone and carnitine levels were decreased, whereas pentosidine

Table 2. Univariate and Multiple Stepwise Regression Analysis for the Correlates of Age-Adjusted Free Testosterone Levels

| | *Univariate*[a] | | | *Multiple stepwise regression*[a] | | |
|---|---|---|---|---|---|---|
| *Variables* | *β* | *SE* | p *value* | *β* | *SE* | p *value* |
| Age | 0.328 | 0.055 | 0.171 | | | |
| SBP | 0.176 | 0.026 | 0.471 | | | |
| Body mass index | 0.058 | 0.181 | 0.814 | | | |
| Hemoglobin | 0.359 | 0.737 | 0.131 | | | |
| Albumin | 0.383 | 2.414 | 0.106 | | | |
| **Plasma glucose** | **−0.492** | **0.017** | **0.032** | | | |
| LDL-C | 0.005 | 0.029 | 0.985 | | | |
| **Creatinine** | **0.509** | **0.261** | **0.026** | | | |
| Uric acid | −0.426 | 0.704 | 0.069 | | | |
| Corrected Ca | 0.169 | 1.494 | 0.489 | | | |
| P | −0.319 | 0.713 | 0.183 | | | |
| Whole PTH | −0.145 | 0.027 | 0.554 | | | |
| CRP | −0.447 | 0.729 | 0.055 | | | |
| $\beta_2$-MG | 0.104 | −0.413 | 0.079 | | | |
| **Serum carnitine** | **0.517** | **0.065** | **0.023** | **0.620** | **0.049** | **0.001** |
| **Pentosidine** | **−0.507** | **4.937** | **0.027** | | | |
| HD duration | 0.028 | 0.007 | 0.910 | | | |
| Kt/V | 0.181 | 3.331 | 0.459 | | | |
| Diabetes | −0.262 | 1.393 | 0.279 | | | |
| RAS inhibitors | −0.202 | 1.246 | 0.407 | | | |
| **Statins** | **−0.489** | **1.193** | **0.034** | **−0.595** | **0.891** | **0.002** |

[a] $\beta$, standardized regression coefficients; $r^2 = 0.612$. Stain non-use = 0, Stain use = 1.

SE, standard error; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; Ca, calcium; P, phosphate; PTH, parathyroid hormone; CRP, C-reactive protein; $\beta_2$-MG, $\beta_2$-microglobulin; HD, hemodialysis; RAS, renin angiotensin system.

values were dramatically increased in men with HD; (2) low free testosterone levels were significantly correlated with decreased carnitine as well as increased pentosidine levels in HD patients; (3) serum carnitine was one of the independent correlates of free testosterone values in male HD patients; and (4) there was no significant association between total testosterone and carnitine or pentosidine levels.

There are a couple of studies suggesting that carnitine is involved in sexual dysfunction.[7,11,31] Indeed, carnitine is expressed in the epididymis and testis in humans, and its levels in the seminal plasma were associated with sperm motility.[7] Furthermore, carnitine supplementation has been shown to not only ameliorate aging-related sexual dysfunction in aged men,[11] but also augment the efficacy of sildenafil, an inhibitor of phosphodiesterase-5, which could restore sexual potency after bilateral nerve-sparing radical retropubic prostatectomy.[32] Carnitine plus sildenafil therapy was also found to be more effective for the treatment of ED in diabetic patients compared with sildenafil monotherapy.[31] Given the present findings that serum carnitine levels were decreased in male HD patients and one of the independent associates of low free testosterone values, low carnitine levels may be a therapeutic target for sexual dysfunction in uremic men. Decreased testosterone levels were associated with the increased risk of CVD in aged and uremic men.[1,3] Supplementation of carnitine has been reported to inhibit the development and progression of CVD in animal models,[33] free fatty acid–induced endothelial dysfunction,[34] and decline in mental performances[35] in humans as well. Therefore, although the present study was cross-sectional and therefore did not elucidate the causal relationships between low carnitine and free testosterone levels, carnitine supplementation may improve hypogonadism and ED and reduce the risk of CVD in male HD patients via the restoration of free testosterone levels.

We did not know the underlying mechanisms for the correlation between carnitine and free testosterone in our HD patients. However, carnitine has been shown to stimulate testosterone production in oligoasthenospermic rats.[36] It also prevents the decrease in plasma testosterone levels after the chronic swimming stress in rats.[37] These findings suggest that carnitine may directly act on the hypothalamus and/or epididymis, thereby stimulating the production of testosterone in humans. Furthermore, we, along with others, have found that: (1) Carnitine inhibits the formation of AGEs both *in vitro* and in an animal model,[38] (2) serum carnitine values are one of the independent correlates of tissue accumulation levels of AGEs in HD subjects,[10] and (3) serum AGEs levels were inversely correlated with testosterone levels in non-medicated men.[26] Accordingly, although an inverse association between pentosidine and free testosterone levels was lost in multivariate analysis, increased accumulation of AGEs may partly explain the link between carnitine and free testosterone levels in our HD patients.

In contrast to the case with free testosterone, total testosterone levels were not associated with serum carnitine or pentosidine values in our patients. Total testosterone is composed of free testosterone, albumin-bound testosterone, and sex hormone-binding globulin-bound testosterone.[39] Only free and albumin-bound testosterone is bioavailable,[39] so total testosterone levels may not reflect the exact gonadal function in our subjects. This is one possible reason why there was no significant association between total testosterone and carnitine or pentosidine levels. Measurement of free

rather than total testosterone levels may be useful for evaluating the clinical efficacy of carnitine supplementation in male HD patients.

In our study, statin use was independently associated with decreased free testosterone levels. Corona et al. have recently reported that free testosterone levels are significantly lower in ED patients taking statins compared with those without stains.[40] They also reported that statin use was associated with reduced testis volume, thus suggesting that statin therapy might induce an overt primary hypogonadism in patients with ED.[40] These observations suggest that statin use may contribute to decreased free testosterone levels in HD patients.

In conclusion, the present study suggests that low carnitine levels and statin use are associated with decreased free testosterone values in male HD patients.

### *Limitations*

Several limitations of this study bear mention. First, our study was limited by a small sample size. Second, it was a cross-sectional one and could not assess the questions of whether deficiency of serum carnitine levels was a cause or consequence of the decrease of free testosterone levels. In this regard, it would be interesting to examine whether intravenous administration of carnitine at the end of the HD session increased serum free testosterone levels in our patients. If we could obtain the positive effects of carnitine supplementation on free testosterone levels, it would strengthen our assumption based on the present findings. However, intravenous carnitine supplementation therapy is not approved for HD patients in Japan. So, unfortunately, we cannot address the issue. Therefore, further longitudinal and/or interventional studies, such as oral supplementation of carnitine, are needed to clarify whether decreased carnitine levels may be a novel therapeutic target for sexual dysfunction in uremic men with hemodialysis. Third, because results on statin use were from 6 patients only, the data should be interpreted with more caution.

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## Author Disclosure Statement

The authors have no conflicts of interest to declare.

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