Relationship Between Erectile Dysfunction, Diabetes and Dyslipidemia in Hypertensive-Treated Men

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Purpose: PRESIDEN study is a large study to analyze the erectile dysfunction (ED) incidence in Spanish population. The present study is a pilot sub-analysis from PRESIDEN to determine if ED or plasma testosterone (TST) level in controlled hypertensive patients may be associated with comorbidities and/or plasma nitrite+nitrate and antioxidant capacity.

Materials and Methods: Forty-four hypertensive individuals were aleatory selected from PRESIDEN study, matching by age (28 showing ED and 16 without ED).

Result: Diabetes was present in 28.57% of ED patients and in 18.75% of patients without ED. In patients with and without ED, increasing age showed tendency of higher frequency of an additional comorbidity (diabetes or dyslipemia) (P = .09). Apparently, plasma TST levels were lower in older ED patients compared to younger patients with and without ED, although it did not reach statistical significance (P = .69). Older ED patients also showed lower TST levels than older patients without ED, although it was not statistical significant (16.15 ± 2.84 vs 13.91 ± 2.77; P = .69). Dyslipidemia was showed by 52.17% with lower TST (≤ nmol/L) while 23.80% of patients with plasma TST levels > 15 nmol/L had dyslipidemia. The percentage of ED patients was similar between patients with low and high TST levels.

Conclusion: More ED hypertensive patients seem to show two comorbidities (diabetes and dyslipidemia) than hypertensive patients without ED. Younger patients with ED tended to show more commonly diabetes than older ED patients. Plasma TST levels were not associated with more prevalence of ED but lower plasma TST levels showed tendency to higher prevalence of dyslipidemia.

Keywords: diabetes; dyslipidemia; erectile dysfunction; hypertension; oxidative stress; plasma testosterone.

INTRODUCTION

Erectile dysfunction (ED) has higher prevalence among hypertensive men than in general population.(1) Indeed, hypertension is considered risk factor for ED and often precedes it.(2)

In the hypertensive patients different factors have been associated with ED, including duration and severity of hypertension, non-controlled hypertension, older age, as well as some antihypertensive therapy among others.(3,4) In this regard, thiazides have negative effect on ED.(5)

However, independently of these factors, ED and hypertension shared that endothelial dysfunction seems to be cause of their genesis. Moreover, endothelial dysfunction is also common cause to promoting other vascular co-morbidites including diabetes mellitus.(6,7) In this regard, reduction of nitric oxide (NO) generation and oxidative stress are key players in the pathogenesis of endothelial dysfunction, and therefore, in hypertension and ED.(8-10) The increased oxidative stress associated with hypertension was reported to result not only by increasing oxidative-related molecules but also by diminishing antioxidant capacity.(11)

Hypertension is often associated with metabolic abnormalities, such as diabetes and dyslipidemia.(12) However, although both dyslipidemia and diabetes have also a close relationship with ED, less has been analyzed if the presence of ED may increase the frequency of them in hypertensive men. Indeed, ED was suggested as predictor of cardiovascular diseases and even some authors note that ED symptoms in hypertensive patients would represent more deterioration of endothelial functionality, alerting for a possible progression of the disease.(13,14) If this hypothetical major vascular deterioration can imply an additional worse on either the ability to generate

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Table 1. Erectile dysfunction(ED) in the hypertensive

	Hypertensive patients (n=44)	
	Without ED (n=16)	With ED (n=28)
Age	59.43 ± 2.31	60.85 ± 1.65
Comorbidities		
+0	8/16	13/28
+1	7/16	10/28
+2	1/16	5/28
Diabetes	3/16	8/28
Dyslipidemia	6/16	12/28
Nitrites+nitrates (µmol/L)	4.54 (3.21-7.76)	3.53 (2.41-6.85)
Antioxidant capacity (µmol/L)	1.68 (1.29-1.87)	1.61 (1.33-1.83)
TST (nmol/L)	15.78 ± 1.11 15.44 ±1.05	

The results of continuous variables (age and plasma testosterone (TST) levels) are represented as mean ± SEM. The variables without normal distribution (plasma nitrate +nitrite levels and plasma antioxidant capacity) were represented as medians and 25th-75th percentiles (numbers into brackets). The results of categorical variables are represented as number of cases with respect to the total included patients within each experimental group.

NO or the oxidative stress, remains to be established.
Hormonal abnormalities have been also identified as possible cause of ED, particularly associated in older age with low serum testosterone (TST) levels. Indeed, at TST levels as high as 12-15 nmol/L patients may undergo low sexual potency and low libido.[15] Although, it was suggested that TST levels are inversely correlated with severity of erectile dysfunction, controversial results exists about it. Indeed, a recent meta-analysis concluded that TST had positive effects on male sexual function in hypogonadal subjects but its effects on hypogonadal men is uncertain.[16] However, in our knowledge it is not well established the possible relationship between low total plasma TST levels and cardiovascular comorbidities, including ED, in hypertensive patients.
Taken together, the aims of the present study were to analyze if the presence of ED modify the frequency of dyslipidemia and diabetes mellitus in hypertensive treated patients and if there is any relation with modifications in the plasma levels of either nitric oxide or total antioxidant capacity. Moreover, it was analyzed whether low TST levels may be associated with either the frequency of comorbidities in pharmacologically controlled hypertensive patients and/or with the circulating levels of the above-mentioned biochemical parameters.

MATERIAL AND METHODS

Population included

In 2011 the Spanish Andrology Society (ASESA) started the campaign "Men change", where men were invited to participate in a cross-sectional national epidemiologic prevalence study called as PRESIDEN study. Subjects who agreed to participate completed a series of specific questionnaires and blood samples were also taken for determining biochemical parameters. The present work is a retrospective pilot sub-analysis from the PRESIDEN study carried out in pharmacologically controlled arterial hypertensive men who were only recruited in the province of Malaga, Spain. Men recruited in the present work were aleatory selected and matching by age. Inclusion criteria were age ≥ 18 years with arterial hypertension that was defined as previously diagnosed by a physician. All the included hypertensive patients were receiving optimal antihypertensive therapy. Patients with the following conditions were excluded: Non-controlled hypertension, malignant hypertension, secondary forms of hypertension, evidence of myocardial infarction, angina pectoris or heart failure. Patients who had plasma creatinine levels greater than 2.0 mg/dL (176.8 µmol/L) or missing covariates were excluded. Patients with a history of neoplasia, infections or autoimmune disease, or any surgical procedure in the preceding 6 months were excluded.
The abridged five-item version of the 15-item International Index of Erectile Function (IIEF-5)[17] was used to determine presence of ED. On this scale, a score < 21 is indicative of ED.
For the analysis of the cardiovascular co-morbidities, dyslipidemia was defined as previously diagnosed by a physician, receiving lipid lowering drugs, or either total cholesterol > 200 mg/dL, LDL-cholesterol >100 mg/dL or serum triglyceride > 150 mg/dL. Diabetes mellitus as previously diagnosed by a physician and was defined according to the clinical guidelines Task Force from the International Diabetes Federation.[18].
Plasma for total TST, nitrite+nitrate and total antioxidant capacity determinations were obtained from overnight fasting blood samples recollected in tubes containing EDTA. Blood samples were immediately centrifuged and plasma aliquots was made and stored at -80ºC until the biomarker determinations.
The study was blinded for the researches that performed the molecular analysis, was approved by the Ethical Committee of Hospital Clínico San Carlos and informed consent was obtained from all individual participants included in the study.
Determination of nitrite+nitrate, total antioxidant capacity and testosterone plasma levels.
Plasma nitrite/nitrate and total antioxidant capacity were determined using commercial ELISA Kits (Cayman Chemical Company, Ann Arbor, MI, USA) Plasma total TST levels were also determined by using an ELISA commercial kit (ab 108666 Abcam, UK).

Statistical analysis

Kolmorov-Smirnov test was used to assess plasma parameters distribution. In this regard, both plasma nitrite+nitrate levels and antioxidant capacity did not follow normal distribution. Therefore, the values of these parameters were represented as medians and 25th and 75th percentiles and their comparison between groups was performed with the non-parametric Mann-Whitney´s test. Age and plasma TST values were normally distributed and were represented as mean ± SEM. Comparisons of age and TST levels were performed using

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Table 2. Influence of aging

	Without ED (n=16)		With ED (n=28)	
	< 65 years old	≥ 65 years old	< 65 years old	≥ 65 years old
Patient´s number	11	5	19	9
Comorbidities				
+0	6/11	2/5	9/19	4/9
+1	4/11	3/5	6/19	5/9
+2	1/11	0/5	4/19	0/9
Diabetes	2/11	1/5	6/19	1/9
Dyslipidemia	4/11	2/5	7/19	4/9
Nitrites+nitrates (µmol/L)	4.85 (3.29-10.45)	3.92 (3.12-4.67)	3.83 (2.54-7.34)	3.34 (2.27-4.40)
Antioxidant capacity (µmol/L)	1.71 (1.29-1.87)	1.65 (1.50-1.84)	1.61 (1.31-1.92)	1.59 (1.43-1.87)
TST (nmol/L)	15.61 ± 1.21	16.15 ± 2.84	16.09 ± 0.98	13.91 ± 2.77

The results of continuous variables (age and plasma testosterone (TST) levels) are represented as mean □ SEM. The variables without normal distribution (plasma nitrate +nitrite levels and plasma antioxidant capacity) were represented as medians and 25th-75th percentiles (numbers into brackets). The results of categorical variables are represented as number of cases with respect to the total included patients within each experimental group. ED: Erectile dysfunction.

unpaired two-sided Student´s t test. Categorical variables were compared by the Fisher's exact test. For statistical significance were assuming a type I error probability of <.05. SPSS statistical software (version 17.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Comparison between hypertensive patients with and without ED

Forty-four pharmacologically controlled arterial hypertensive men were included in the study. Twenty eight of them showed IIEF-5 score < 21, indicative of ED, and 16 had IIEF-5 score □ 21 suggesting erectile functionality (**Table 1**). Mean age was similar between ED patients and patients without ED (Table 1).

Similar number of patients with and without ED had no comorbidities 46.42% and 50% respectively. As shown in Table 1 in absolute number, 43.75% of patients without ED and 35.71% of ED patients had additional comorbidity (P = .70). However, the percentage of patients with ED showing two comorbidities tended to be higher than in the patients without ED (17.85% and 6.26% respectively), although the sample size was probably small enough to achieve statistical significance.

There were not differences in the percentage of patients showing dyslipemia or diabetes between the two groups of patients (**Table 1**).In this regard, dyslipemia was present in 37.5% of patients without ED and 42.85% of the ED patients. Diabetes was more common in patients with ED 28.57% than in patients without ED 18.75%, although it was far of reaching statistical significance (P = .70).

Plasma levels of nitrite+nitrate (as measured of nitric oxide levels), seem to be lower in ED patients as compared with those in patients without ED, although statistically were not different (P = .31, **Table 1**). The plasma antioxidant capacity and TST levels were similar between hypertensive patients with and without ED (**Table 1**).

In the hypertensive patients with and without ED, increased age was associated with tendency to present higher frequency of additional comorbidity, although it did not reach statistical significance (P = .09, **Table 2**). As table 2 shows, diabetes appeared to be more common in the younger (< 65 years) patients with ED than in ED patients with age > 65 years old, (with ED < 65 years: 31.57%; > 65 years: 11.11%), although it was not did not reach statistical significant (P = .37).

No statistical differences were observed in the nitrite+nitrate plasma levels when younger and older patients with and without ED were compared (P = .69 and P = .23 respectively, **Table 2**). However, it should be of interest that older patients without ED and ED patients of any age slightly showed lower nitrite+nitrate plasma levels than younger patients without ED (**Table 2**). However, it did not achieve statistical significance in any case (P = .69).

Total plasma antioxidant capacity was similar in younger and older patients with and without ED (**Table 2**). Total TST plasma levels were also similar between patients with and without ED, although the mean value was lower in older patients with ED as compared with the remaining patients (**Table 2**).

Relationship between total plasma testosterone levels and comorbidities in hypertensive patients

To identify patients with TST deficiency, and due to the small sample size, the statistical analysis was performed considering the cut-off point of total plasma TST levels > 15 nmol/L, since the mean value found in the included individuals was 15.57.

As **Table 3** shows, age was not different between hypertensive patients with low and normal total plasma TST levels. In addition, there were no statistical differences in the comorbidities number between patients with low total TST level (≤ 15 nmol/L) and those with higher plasma TST levels (> 15 nmol/L) (**Table 3**) (P = .29). However, apparently more patients having two and three comorbidities were present in the patients with lower TST levels (≤ 15 nmol/L) as compared with patients with TST levels higher than 15 nmol/L (**Table 3**). Indeed, nine of the patients with lower TST levels 39.13% showed two or three comorbidities while in the group of patients with TST levels over 15 nmol/L only five patients showed two or three comorbidities 23.80%.

Dyslipidemia was present in 52.17% of patients with lower plasma TST levels while 23.80% of patients with total plasma TST levels >15 nmol/L showed dyslipidemia as comorbidity (P = .04, **Table 3**). Similar percentage of patients with low and high TST levels showed diabetes as comorbidity (21.73% vs 23.80%,

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Table 3. Influence of plasma testosterone (TST) levels .

		TST≤ 15 nmol/L (n=23)	TST> 15 nmol/L (n=21)
Age		60.22 ± 1.82	60.48 ± 2.12
Comorbidities			
	+0	4/23	4/21
	+1	10/23	12/21
	+2	6/23	4/21
	+3	3/23	1/21
Dyslipidemia		12/23	5/21*
Diabetes		5/23	5/21
IIEF-5 (< 21)		15/23	13/21
Nitrites+nitrates (µmol/L)		4.67 (3.07-7.43)	3.43 (2.54-6.36)
Antioxidant capacity (µmol/L)		1.51 (1.30-1.87)	1.65 (1.36-1.97)

The results of continuous variables (plasma testosterone (TST) levels and age) are represented as mean ± SEM. The variables without normal distribution (plasma nitrate +nitrite levels and plasma antioxidant capacity) were represented as medians and 25th-75th percentiles (numbers into brackets). The results of categorical variables are represented as number of cases with respect to the total included patients within each experimental group. * $p < 0.05$ with respect to TST ≤ 15 nmol/L.

Table 3). Moreover, the percentage of patients showing erectile dysfunction (IIEF-5 <21) was similar between patients with low and high TST levels (65.21% vs 61.90%; $P = .82$).

Patients showing lower TST levels (≤15 nmol/L) had no statistical differences in plasma nitrite+nitrate, although it tended to be diminished in patients with TST values above 15 nmol/L ($P = .15$). Total plasma antioxidant capacity levels were similar between patients with total plasma TST levels > 15 nmol/L and those with TST levels ≤ 15 nmol/L (**Table 3**).

DISCUSSION

In the present study was evaluated if the presence of ED may modify the frequency of dyslipidemia and diabetes as comorbidities in patients under hypotensive treatment. The results showed that ED was associated with tendency to show more commonly two comorbidities (dyslipidemia and diabetes). Moreover, more patients with ED showed diabetes, as comorbidity, although probably the small sample size made that the differences did not achieve statistical significance when it was compared with patients without ED. In this regard, an apparent paradoxical observation was that in older patients with ED (≥ 65 years old) only 1 from 9 patients showed diabetes as comorbidity suggesting lesser frequency of diabetes as comorbidity than in younger hypertensive patients with ED. It may suggest that hypertension and diabetes may be independent risk factors for ED. Indeed, it was reported that diabetic patients have ED at early age and with higher prevalence that non-diabetic patients.[19] Moreover, it could be plausible that patients with ED and diabetes has worse outcome than those without ED, promoting higher mortality. Indeed, in the ED group only 9 patients with age older than 65 years old were recruited while 19 patients with age younger than 65 years old were recruited in the study. In this regard, ED was reported as additional risk factor for 10-years coronary risk.[20]

Although it is commonly assumed that hypertension predisposes somehow men to impotence, precise consequences associated with the presence of ED in hypertensive patients has not been sufficiently established. In this regard, vascular disease is commonly implicated in the pathogenesis of ED. Therefore, ED in hypertensive men could be indicative of higher vascular damage, which may favour an increased frequency of cardiovascular comorbidities. In the present study, the percentage of patients with ED showing two comorbidities tended to be higher than in the patients without ED although it did not reach statistical significance probably due to the small sample size.

Endothelial dysfunction has been identified as one of the major pathophysiological mechanisms for ED.[21] Patients with ED of any age and older patients (> 65 years) without ED also tended to show reduction of circulating nitrite+nitrate levels (as measured of NO) when they were compared with younger hypertensive patients without ED. In this regard, reduction of the ability of the vascular cells to produce NO has been linked to both ED and aging.[21,22]

Plasma testosterone levels and comorbidities in hypertensive patients

Total plasma TST levels in ED patients older than 65 years tended to be reduced as compared with younger ED patients and patients without ED. Therefore, it was analysed whether total plasma TST levels may influence cardiovascular comorbidities in the hypertensive patients. In this regard, exogenous TST therapy has been associated with improvement of cardiac risk factors, especially in those patients with hypertension.[23] Probably, the more relevant observation of this analysis was that in the patients with higher plasma TST levels (> 15 nmol/L) dyslipidemia was less common than in the patients with lower plasma TST levels (≤ 15 nmol/L). However, diabetes was equally frequent between patients with high and low plasma TST levels. Accordingly, it was reported that in hypertensive patients low TST levels was associated with impaired lipids management and pro-atherogenic lipid profile.[24]

There are several evidences that men with marked hypogonadism have ED. However, the level of hypogonadism required to induce this ED is questionable.[25] Indeed, in the present study hypertensive patients with total plasma TST levels below 15 nmol/L showed similar prevalence of ED than those with total plasma TST levels higher than 15 nmol/L. However, as above mentioned in older patients with ED was where circulating total TST levels tended to be reduced. In this regard, it was suggested that reduction of TST could contribute to enhance the severity of atherosclerosis contributing to increase arterial stiffness and, therefore, ED.[26]

Paradoxically, in the present study, plasma nitrite+nitrate levels tended to be diminished in patients with the higher TST levels. Indeed, initially we may expect

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that NO levels should be positively associated with TST levels. However, in experimental animals it was reported inverse NO-gonadal relationship and even it was postulated that modulation of NO activity may affect gonadal activity.[27] In addition, intertesticular treatment with NO-donors decreased serum and interstitial fluid TST concentration.[28] Taken together, the fact that nitrite+nitrate plasma levels tended to be higher in patients with lower TST levels while dyslipidemia was more commonly found in them diminished the involvement of NO in the possible relationship between TST levels and the frequency of this comorbidity. In this regard, other factors could be involved in the observed tendency to show higher dyslipidemia frequency by in the hypertensive patients with lower total TST levels. As example, there are evidences supporting a role of TST on inflammatory-related mechanisms. In this regard, TST increases the in vitro production of the anti-atherogenic cytokine IL-10, and TST therapy reduced circulating levels of several pro-inflammatory cytokines in men with low TST levels, most of them with coronary disease.[29,30]

Study limitations

There are several limitations in the study that deserve comment. The first of them is that the very small sample size probably limited the possibility to achieve statistical significance in the parameters in which were observed a tendency to be different. Another limitation of the present study is that due to the transversal nature of the study it is not possible to determinate strictly dependence of variables but simply of association among variables. A longitudinal study (cohort or case-control) would have been necessary to establish the dependency relationship.

Another important limitation was that in the experimental design of the PRESIDEN study was not contemplated collecting the drugs that the patients were taking at inclusion. However, at inclusion physicians declared that the patients were taken optimal clinical medication by their morbidities.

CONSLUSIONS

As conclusions, the percentage of hypertensive patients with ED showing two comorbidities (diabetes and dyslipidemia) tended to be higher than that in hypertensive patients without ED. Moreover, the younger hypertensive patients with ED tended to show more commonly diabetes as additional comorbidity than older patients with ED. Older hypertensive patients with ED tended to show lower levels of total plasma TST than the younger ED patients and that patients without ED of all age. However, TST levels were not associated with higher presence of ED but lower TST levels were associated with higher prevalence of dyslipidemia. It was accompanied of a tendency to show lower nitrite+nitrate plasma levels in patients with lower TST levels than in those hypertensive patients with higher TST levels.

Taken together, although clarification of the physiological and clinical significance of the relationship between hypertension, ED and TST require further investigations; these open the possibility that in hypertensive patients, ED and low total TST levels may be independently associated with cardiovascular comorbidities.

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CONFLICT OF INTEREST

The authors declare that they have not conflict of interest.

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