Relevance of oestradiol-testosterone balance in erectile dysfunction patients' prognosis

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ABSTRACT

Introduction: The ageing process in man is accompanied by a number of endocrine changes including decline in testosterone (T), physiological imbalance between androgen and oestradiol (E2) and changes in the E2-T ratio. In this study, hormone profile data from a group of erectile dysfunction (ED) patients were reviewed to evaluate its impact on ED, with emphasis on oestradiol derangement.

Methods: 30 ED patient case notes with a record of hormone profiles were retrospectively reviewed. Laboratory investigation included levels of total testosterone, total oestradiol, prolactin, luteinising and follicle stimulating hormones, in addition to lipid profile and glucose, based on specific history. These patients were divided into two groups based on the history of presence (Group A) or absence (Group B) of adequate sexual desire.

Results: In Group B patients, the E2-T derangement with increasing age was statistically significant with lower serum T level (2.6 ng/ml; range, 1.6–3.7 ng/ml) and elevated E2 level (60 pg/ml; range, 40–120 pg/ml).

Conclusion: In this preliminary report, although low total testosterone level is seen together with impaired libido and erectile impairment, the accompanying significant increase in E2 indicates the possible role for oestrogen in causation and/or persistence of ED in this group of patients.

Keywords: erectile dysfunction, hormone imbalance, oestradiol, oestradiol-testosterone balance, testosterone

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INTRODUCTION

Although there has been a growing recognition in the last three decades of the various organic causes leading to 75%–80% cases of erectile dysfunction (ED),[1] exact identification of the aetiology for ED in every case is still an essential prerequisite and determinant of successful management outcome. Since normal sexual function is the net consequence of appropriate coordination of neurological, vascular and endocrine signals from the central and peripheral nervous systems to the end organ, inherent pathology in any of these systems can precipitate sexual dysfunction; such organic factors are particularly relevant with regard to ageing-induced erectile impairment.[2] In this context, recent years have also witnessed an increasing interest in the hormonal derangements in ED and loss of libido.[3,4] Secondary hypogonadism with low testosterone (T) accounts for 10%–20% of erectile dysfunction in the elderly,[1,5] and oestrogen, another hormonal risk factor in males,[6] precipitated significant impairment of parameters of sexual behaviour and erectile function (including decreased intracavernous perfusion pressure and nitric oxide mediated cavernosal smooth muscle relaxation) in our basic research.[7,8] Therefore, we believe that the significantly higher oestradiol (E2) levels in the ageing males[9] may be yet another organic risk factor for ED; this pathophysiology is hitherto ill-defined in the clinical causation of erectile impairment. This study represents the first preliminary report on the E2-T data obtained from a retrospective review of case notes from a small ED patient pool from our centre in an attempt to identify the possible determinant role of E2 and its imbalance with testosterone in the clinical management outcomes of ED.

METHODS

The cohort of ED patients were managed at the Andrology Clinic, National University Hospital, National University of Singapore during 2003–2004. Out of this pool of 242 ED patients, 35 patients with specific complaints of declining sexual desire/interest consented for hormone levels estimation. In these patients, a self-reported inability to achieve and/or maintain an erection for sexual intercourse was obtained, using a clinical questionnaire

Table I. Co-existent conditions in 30 erectile dysfunction patients.

Clinical condition	No. (%) of patients	Patients: Group A	Patients: Group B
Multifactorial	9 (30.0%)	5	4
Vascular	5 (16.7%)	1	4
Diabetes mellitus	3 (10.0%)	1	2
Diabetes mellitus/peripheral neuropathy	2 (6.7%)	1	1
Pelvic surgery	1 (3.3%)	1	nil
Psychogenic	4 (13.3%)	2	2
Idiopathic	6 (20.0%)	2	4

based on the 15-item international index of erectile function (IIEF) scale.[10] The history provided information on the onset and duration of ED, average frequency of sexual activity in the past and present, incidences of morning erections, degree of sexual interest, partner's level of interest and presence of comorbid factors such as cigarette smoking and alcohol consumption. In addition, details of intercurrent medical illnesses, surgical history and drug intake (prescription, non-prescription and substance abuse) were also sought and physical examination was conducted to rule out gynaecomastia, testicular atrophy and Peyronie's plaques. The clinical characteristics and risk factors of the patients included in this study are listed in Table I.

In our data analysis, comparison was made between two sample groups, based on these ED patients' response to the sexual desire domain of the IIEF questionnaire at scores of 3 and above for Q11: "how often the sexual desire was felt" and Q12: "how the patient rated his desire." After dropping the five overlaps (three or above for one question and two or less for the other), the remaining 30 patients were divided into those with adequate sexual desire (Group A, n=13) and those giving a history of loss of libido (Group B, n=17). All men had a completed record of their serum hormone levels with the sampling done in the morning; this included evaluations of total testosterone and total oestradiol, prolactin, luteinising hormone (LH) and follicle stimulating hormone (FSH). The sex hormone levels were estimated by scintillation proximity radioimmunoassays[11] using the respective tracer (Amersham International, Buckinghamshire, UK); this modified in-house method validated and correlated significantly with the WHO RIA for measurement of low serum E2 levels in males. Laboratory estimations also covered lipid profile and glucose levels non-selectively, irrespective of the medical history of risk factors. All investigations were conducted using standard assay protocols and diagnostic kits at the Departments of Obstetrics and Gynaecology and Laboratory Medicine at this centre.

Univariate statistical comparisons of hormone levels were made by non-parametric Mann-Whitney U test using software from the Statistical Package for Social Sciences version 13.0 for Windows (SPSS Inc, Chicago, IL, USA). A multivariate linear regression was also performed to compare the two groups, adjusting for age. A p-value of < 0.05 was considered statistically significant.

RESULTS

Of the 30 subjects included in this retrospective study, 40% were above 50 years of age (53.3% in Group B), 76.7% were married, and the rest were in a steady relationship. About 10% were chronic smokers and/or alcohol users. Sexual history revealed that in most cases, ED was of an insidious onset, accompanied by some degree of decrease in desire in 83.3%, loss of libido in 50% and co-existent premature ejaculation and psychogenic factors (excluded through preservation of erectile capacity during masturbation, quality of morning erections, partner selective erection, etc.) in 16.7% and 13.3%, respectively. Physical examination did not indicate testicular abnormality suggestive of hypogonadism or gynaecomastia in any of these cases. Medical history and clinical investigation revealed a high prevalence of vascular, metabolic and neurological disorders (63.4%; Table I). Statistical comparisons of the hormone levels in group B (history of loss of desire) with Group A (Table II) indicated that Group B patients on an average had lower serum T levels (2.6 ng/ml; range, 1.6–3.7 ng/ml) and higher E2 levels (60 pg/ml; range, 40–120 pg/ml) with some overlapping in the E2 range between the two groups. The decrease in T ($p = 0.004$) and increase in E2 ($p = 0.004$) between the two groups were statistically significant after adjustment for age.

DISCUSSION

The major finding from our case notes review is the higher level of E2 in older patients (Group B) presenting with

Table II. Hormone profile data.

Parameter	Group A (n=13)	Group B (n=17)	Unadjusted p-value#	Adjusted p-value*
Age (years)				
Mean (SD)	41.6 (10.1)	49.7 (12.2)		
Range	28–58	31–69	0.056	–
Median	39	50		
Testosterone (ng/ml)				
Mean (SD)	4.2 (1.6)	2.7 (0.7)		
Range	1.9–6.4	1.6–3.7	0.010	0.004
Median	3.9	2.6		
Oestradiol (pg/ml)				
Mean (SD)	45.1 (13.7)	70.3 (22.4)		
Range	23–69	40–120	0.001	0.004
Median	42	60		
Prolactin (mIU/L)				
Mean (SD)	124.1 (91.4)	133.6 (96.9)		
Range	39–335	2.3–312	0.935	0.648
Median	86	119		
LH (IU/L)				
Mean (SD)	4.2 (2.5)	5.7 (5.6)		
Range	1.6–11.2	1.5–23.5	0.595	0.780
Median	4	4		
FSH (IU/L)				
Mean (SD)	2.2 (1.8)	4.5 (6.8)		
Range	0.6–7.7	0.6–28.3	0.174	0.435
Median	1.5	2.6		

Mann-Whitney U test; *Linear regression adjusting for age

lack of sexual interest and ED, after adjustment for age. Extrapolation of this finding from a small cohort of aged ED subjects indicated that E2-T hormonal balance may be one of the determinants of successful management outcomes for ED. Further studies using larger patient pools and epidemiological data are needed to support this preliminary and interesting clinical observation. Erectile dysfunction is a frequent accompaniment of low desire state or loss of libido in men with hormonal abnormalities such as testosterone deficiency or hyperprolactinaemia.[12] Physical examination for signs of changes in secondary sexual characteristics, presence of atrophic testes and decreased serum levels of testosterone and gonadotropins delineate alterations in hypothalamo-pituitary-testicular function and also aid in determining whether the hypogonadism is of primary or secondary nature.[13]

Although many cross-sectional and longitudinal studies[14,15] have indicated an age-dependent decline in serum total T levels from the fourth decade, with a wide range given to represent the normal values for testosterone in men (320–950 ng/dL), most of the reductions could still be within "normal levels". Other age-related changes such as gradual loss of the diurnal variation in total T[16] and increases in gonadotropin and sex hormone-binding globulin (SHBG) make the decrease in free testosterone (unbound) somewhat more relevant for clinical interpretations.[17] Furthermore, the imbalance may be compounded by general ill health, concomitant diseases and several prescription medications which also decrease serum T levels.[15] Morley et al[17] showed a significant decline in bioavailable T levels (unbound + albumin-bound fractions), even in healthy elderly men who were carefully screened for pre-existent medical problems. Therefore, it would appear that while ED co-exists with the complexities of T deficiency and loss of libido that sets in a majority of the aged males, the likelihood of the impact of E2 on T balance and its independent effect in such a situation have not been evaluated so far. This is particularly relevant with the present understanding that androgen and oestrogen are physiological antagonists in many systemic functions and their quantitative balance determines the target tissue effects.[18] A non-specific contributing factor for this hormonal imbalance in the elderly may be the enhanced adiposity (aromatisation) mediated hyperoestrogenism. Therefore, in addition to the association of metabolic syndrome including obesity, body mass index and lipid fractions with ED,[19] proper understanding of the negative correlation of leptin levels with obesity, ageing and androgen receptoral insensitivity[20] may also be considered as important research needs in the clinical management of andropausal ED patients.

In this study, both FSH and LH levels were closer to the upper limits of the normal range in all patients, more so in Group B. This increase in gonadotropins may be taken as a positive trigger by low T levels, probably representing an initial stage prior to final gonadotropin suppression by unopposed oestradiol increase and its more efficient effect on the negative feedback loop.[21,22] Normal prolactin levels in these patients, however, ruled out the possibility of hyperprolactinaemia-related hypogonadism and ED. Unlike the critical needs in testosterone estimation discussed earlier, there is minimal difference between total and free E2 values in view of the limited binding of the circulating oestradiol to albumin/SHBG.[23] Therefore, although confirmations by evaluating the non-SHBG oestradiol[24] may be interesting, the presently observed age-independent increase in total E2 levels in Group B ED patients (who had significantly lower T levels correlating with the history of loss of libido) needs further understanding. The clinically pertinent E2-T imbalance seen in this data review indicates that elevated oestradiol may play a role in the causation and perpetuation of ED and may determine limited therapeutic responsiveness to T supplements, if they are prescribed for simple correction of loss of libido. It is known that testosterone supplements improve sexual function only in a small group of patients diagnosed with hypogonadism. Given the physiological antagonism of E2 with T,[21] the value of administration of T preparations that may be aromatised to E2 in men with the existent state of relative hyperoestrogenism is further questionable.

It seems likely that together with the use of currently available oral phosphodiesterase type 5 inhibitors, inclusion of an antioestrogen such as clomiphene citrate and aromatase inhibitors in the standard ED regimen in these patients may provide considerable improvement of the presenting complaints of loss of libido and ED. According to Guay et al,[25] empirical clomiphene citrate improved sexual function in a group of ED patients with hypogonadism and low T levels. However, there was no estimation of E2 levels in that study. Although the aromatase inhibitor, anastrozole, increased both bioavailable and total testosterone (and reduced oestradiol) in a small group of elderly patients in another study,[26] there was no concurrent improvement in the IIEF scores, indicating the importance of other compounding/coexistent factors. Therefore, taken together, we believe at this stage that further studies with a larger sample size are necessary to substantiate our preliminary clinical hypothesis of the role of E2 in ED and to translate our experimental evidence of hyperoestrogenism-mediated erectile impairment[7,8] to ED patients. Furthermore, presence of concurrent organic conditions that predispose to similar hormonal derangements such as non-insulin dependent diabetes mellitus[9,27] and hypercholesterolaemia,[28] which are known causes of hyperoestrogenism, and hypertension and coronary heart disease which precipitate low T levels,[29] may affect the degree of successful management outcomes in these patients to end organ approaches; these comorbidities require special attention.

In conclusion, our preliminary hormonal correlation in a small pool of ED patients emphasises the need for a critical evaluation of E2-T balance/imbalance in erectile pathophysiology. Testosterone assay is currently included in the first-line diagnostic tests for ED.[30] Similarly, we believe that oestradiol assay may eventually find a place as an important, albeit routine clinical investigation for a subgroup of ED patients. The E2-T increase concurrent with such imbalance may also be useful as a suitable diagnostic marker for hormonal adjustments through appropriate therapeutic titration.

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