The clinical association between free androgen index and erectile dysfunction in men

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Objectives: *To assess the relation of sex hormone levels in men, as measured by Free Androgen Index (FAI), with severity of erectile dysfunction (ED) and with their response to treatment.*
Methods: *We retrospectively reviewed the medical records of men who consecutively attended the urology clinic with the complaint of ED between March 2004 and October 2007. The Sexual Health Inventory for Men (SHIM) score was used as the main outcome measure in this study, and its variation was tested by certain variables using the Epi Info software.*
Results: *A total of 150 men were studied. The majority of patients (93%) had FAI in the normal range levels, and had shown no relation to the SHIM score even after adjustment for other factors. However, FAI was highly related to patients' response to treatment, with the higher the level the higher was the proportion of patients responded well to treatment. Age of the patient was the only factor influencing the SHIM score they could attain, as shown by the linear regression analyses.*
Conclusion: *The FAI level is not related to the severity of ED. Its role however, is confined to the way patients are going to respond to medical treatment of ED. Further studies are therefore needed to assess the effectiveness of using this parameter as a reliable test of bioactive testosterone for men with ED.*

Key Words:

Testosterone and erectile dysfunction

The role of low testosterone (T) levels in erectile dysfunction (ED) remains unclear. Both organic and psychogenic factors contribute to ED, with vasculogenic causes being the most common etiology. Approximately 10%-20% of patients with ED are diagnosed with hormonal abnormalities.[1] A recent 20 year meta analysis by Isidori revealed that the effects of T on ED, but not libido, were inversely related to the mean baseline T concentration. In addition, in men with an average T level at baseline below 12 nmol/l, T treatment moderately improved the number of nocturnal erections, sexual thoughts and motivation, number of successful intercourses, scores of erectile function and overall sexual satisfaction, whereas T had no effect on erectile function in eugonadal men compared to placebo.[2]

Evidence is strong that, in animal systems, testosterone has direct effects on erectile tissue.[3] However, although testosterone clearly has an impact on libido in humans, its effect on penile function is less clear. Evaluation of ED includes medical, sexual, and psychosocial history assessments, as well as laboratory tests to check for diabetes and hormonal abnormalities.

Historically, the pivotal role that androgens play in maintaining sexual activity was thought to be exerted mainly on sexual interest. In the mid 1990s, animal studies showed that expression of the nitric oxide synthase (NOS) gene inside the penis depends on the presence of adequate androgen levels. In humans, it has been observed that the efficacy of ED therapy with phosphodiesterase 5 inhibitors (PDE5i) may be blunted in patients with subclinical hypogonadism in whom androgen levels have not been previously normalized.[4]

There are several ways to measure testosterone levels. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free: approximately 2%-3%), bound

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TABLE 1. **The normal values for the Free Androgen Index (FAI)[6]:**

Age (years)	Normal values
20-29 years	30-128
30-39 years	24-122
40-49 years	14-126
Older than 49 years	18-82

to specific plasma proteins (sex hormone-binding globulin-SHBG), and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction. Bioavailable testosterone includes free testosterone plus testosterone weakly bound to albumin. Therefore, bioavailable T is a more reliable indicator of the androgen status in patients. However, bioavailable T testing is too time consuming, therefore, it is not suitable for clinical practice.[5-7]

We depend, in this study, on the measurement of the FAI to estimate physiologically active testosterone.[5] This index is calculated as the ratio of total testosterone divided by SHBG (both expressed in the same units) and multiplied by 100 to yield numerical results comparable in free testosterone concentration. The normal range is shown in Table 1. FAI can be simply obtained from the following equation.[8]

$$FAI = \frac{\text{Total T. (nmol/l)}}{\text{SHBG (nmol/l)}} \times 100$$

Objectives

The study aimed to describe ED patients by certain factors and to examine the potential role of these factors, mainly the level of FAI, on the severity of illness. The role of FAI on patients' response to treatment was also examined.

Methods

Study design

A case series of patients who presented for the first time with erectile dysfunction have been investigated by a retrospective review of their hospital medical records.

Population and setting

All patients with erectile dysfunction presented to the urology clinic at Sheikh Khalifa Medical City (SKMC) in Abu-Dhabi, UAE, between March 2004 and October 2007 and followed in the same hospital were eligible for inclusion in the study. Only those with stable heterosexual relationships and with no psychological disorders were included in the study. A total of 150 files were finally included in analysis. Patients were divided into three groups according to the FAI level [< 40(n = 11), 40-70 (n = 41) and > 70(n = 48)] according to the UAE health authority guidelines.

Instrument

All files for ED patients were carefully scrutinized, and all relevant data were abstracted into a specially designed form. Such data included information about patient's age, duration of ED, medical history, smoking status, and others. The FAI and the SHIM score[9] that reflects sexual performance were also filled for all patients in their records and abstracted into the same form. All blood samples were collected during the working hours (10:00 am-1:00 pm) after overnight fasting. Results were collected when available. This included results on certain tests such as the fasting blood sugar (FBS), HgA1C, serum cholesterol, triglycerides, low density lipoproteins (LDL) and high density lipoproteins (HDL). Results of hormonal assays such as the folliclular stimulating hormone (FSH), leutinizing hormone (LH), and serum prolactin, were also obtained. The FAI measurement was done using the Immunochemiluminometric assay (ICMA).

All patients received sildenafil 50 mg and 100 mg doses and all patients were followed up in 6 month pattern.

Outcome measures

The average SHIM score attained by different subgroups of patients was the main outcome in this study. Percentage of patients with good response to treatment (as defined in our study by objective improvement in the SHIM score of 21 and above) was the other outcome on which the influence of FAI was tested.

Analysis

Data entry and analysis was parametrically done using the Epi Info software. Percentages were first calculated for patients with certain characteristics. Chi square, t- and F- tests were used to examine significance of differences between proportions, two, and more than two means respectively. The Epi Info 2003 was used to perform multivariate linear regression. In all analyses, the level of significance (α) corresponded to a p value of 0.05.

Ethical concerns

Approval of the study was obtained from the research committee at SKMC. For confidentiality of data, patients' names were not collected from the medical records.

Results

Ages of patients varied between 24 and 67 years old with the mean age of 49 (SD = 10.6) and only one third of the patients aged > 55 years. Patients' medical conditions and smoking history are shown in Table 2. Most of the patients (38.7%) reported having ED for 1-2 years with only 16.7% had it for more than 5 years. On the other hand, the great majority of patients (97.3%) reported a gradual onset for their complaint of sexual dysfunction.

As shown in the same table, the majority of patients (92.6%) had FAI in the normal range levels (14.5-94.5), and only four patients had it below normal.

TABLE 2. **Average SHIM score attained by different subgroups of ED patients and significance of differences as tested by the t- and F tests as needed**

Variable name	Frequency* (%)	Average SHIM score	p value
Age of patient (years)			
< 35 y	14 (9.3)	16	
35-44 y	41 (27.3)	13.2	
45-54 y	45 (30.0)	13.8	
≥ 55 y	50 (33.3)	10.7	0.00
Diabetes mellitus (DM)			
Yes	67 (46.2)	12.7	
No	78 (53.8)	12.8	0.79
Hypertension			
Yes	34 (23.3)	12.8	
No	112 (76.7)	12.8	0.95
Hypercholesterolemia			
Yes	22 (14.7)	13.4	
No	128 (85.3)	12.8	0.33
Currently smoking			
Yes	31 (20.7)	13.1	
No	119 (79.3)	12.8	0.64
Duration of erectile dysfunction ED (years)			
< 1 y	33 (22)		13.2
1-2 y	58 (38.7)	12.6	
3-5 y	34 (22.7)	13.1	
> 5 y	25 (16.7)	12.6	0.78
Onset of ED			
Sudden	4 (2.7)		14.0
Gradual	146 (97.3)	12.8	0.42
Free Androgen Index (FAI)**			
Less than normal range level	4 (2.7)	13.2	
In the normal range level	138 (92.6)	12.8	
Above normal range level	7 (4.7)	12.5	0.53

*Totals less than 150 are due to missing data
**Refer to Table 1 for the normal values of FAI
***Test at baseline: fasting blood sugar (FBS), HgA1C, serum cholesterol, triglycerides, low density lipoproteins (LDL) and high density lipoproteins (HDL) and hormonal assays such as the follicular stimulating hormone (FSH), leutinizing hormone (LH), serum prolactin ,serum testosterone and SHBG

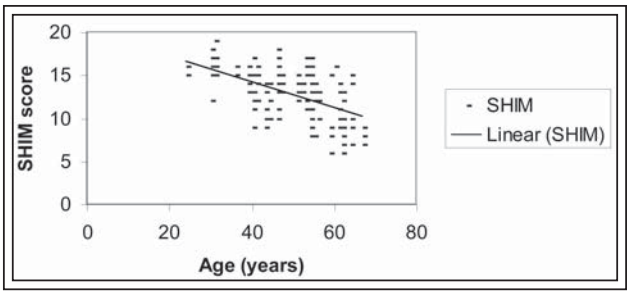

Figure 1. The relation between age and SHIM.

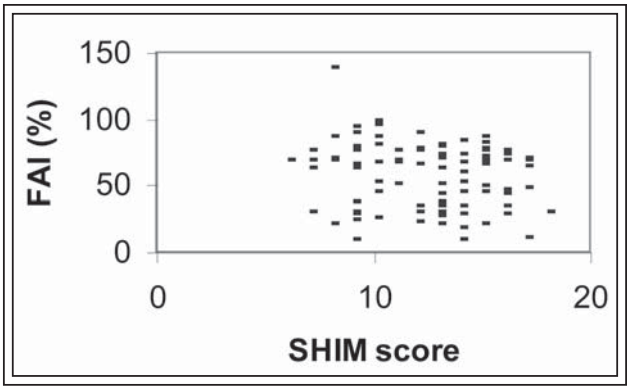

Figure 2. The relation between FAI and SHIM.

All patients included in the study were tested for levels of FSH, LH, and prolactin in their blood, only very few patients had them abnormal (9%, 4%, and 5% respectively). In addition, testing patients for HbA1c could define further 6.7% of the patients to be diabetic while they were unknown previously to have the disease.

Our findings showed that the average SHIM score obtained by the study patients was 12.8 (SD = 2.9); 6 was the minimum and 19 was the maximum scores attained. Results of examining the potential association between certain factors and severity of ED (as reflected by SHIM score) are shown in Table 2.

As can be seen, only age of patients had a significant association with severity of sexual dysfunction, Figure 1,

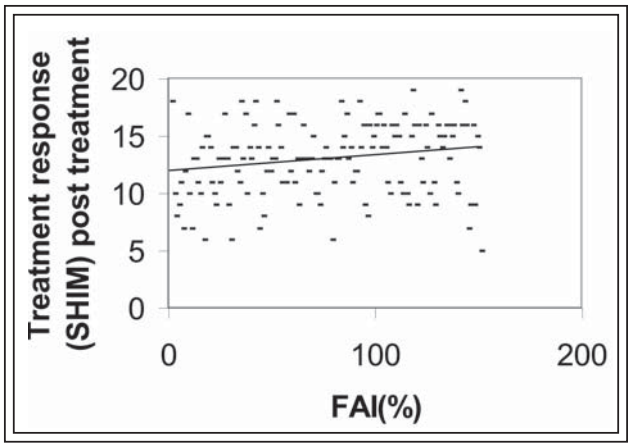

Figure 3. The relation between the FAI and response to treatment (SHIM).

with the highest average SHIM score (16) was attained by patients < 35 years old and the lowest one (10.7) by patients aged 55 years or more (p = 0.00). However, patients with different FAI levels showed no significant differences in the average SHIM scores they attained (13.2, 12.8, and 12.5, p = 0.53), Figure 2. Similarly, we found that none of the other tested factors (DM, blood pressure, hypercholesterolemia, smoking duration and the onset of the complaint whether was sudden or gradual) holds any significant association with the severity of ED.

Examining the adjusted effect of FAI on SHIM score after controlling all other factors in the multivariate linear regression model has also shown no role for FAI level on the sexual performance of patients. On the other hand, re-evaluation of patients after receiving their treatments, in the form of sildenafil citrate (50 mg and 100 mg), by 6 to18 months showed that patients with different FAI levels did respond differently to treatment, Figure 3. Only 25% of those having FAI < 40 showed good response to management compared to 72% and 100% among patients with FAI levels equal to 40-70 and > 70 respectively (p for trend = 0.00), Table 3.

TABLE 3. **The relationship between level of FAI and patients response to treatment as tested by Chi square test**

Level of Free Androgen Index (FAI)	**Patients with good response to treatment n (%)**	**p value**
< 40	11 (25.0)	
40-70	41 (71.9)	
> 70	48 (100.0)	0.00 *

*p value for trend = 0.00

Discussion

The findings of this study that most of the ED patients had FAI levels in the normal range, and that the level of FAI had no relation to severity of sexual dysfunction is inconsistent with most of the current literature. However, Davis et al[10] concluded that the FAI levels are unreliable if they are measured in patients with abnormally low levels of SHBG. Therefore, it would have been prudent in our study to compare the levels of the FAI and SHBG levels. Rhoden et al,[11] on the other hand, showed that the total testosterone (TT) serum levels were not different for individuals with and without ED and similar concentrations of TT were observed in the different severity degrees of ED. On the other hand, Becker studied the cavernous and systemic testosterone plasma levels during different penile conditions in healthy males and patients with erectile dysfunction. He found that there was a significant rise in the cavernous levels of the testosterone in healthy individuals, as opposed to those with ED.[12] Interestingly, Carani et al[13] studied the nightsleep related erections and the penile response to visual erotic stimuli (VES) in 44 men: 13 with severe hypogonadism, and others with mild hypogonadism. A third group with severe hyperprolactinaemia and mild hypogonadism. A fourth group were control. They found that night erections are androgen dependent, in addition, there are two thresholds for serum testosterone: one below which sexual behavior is impaired with normal night erections, and a lower threshold below which night erections are also impaired. The penile response to visual evoked sexual stimulation being only partially androgen independent.

Similarly, in support with other studies, this study clearly shows a significant influence of level of FAI on patients' response to treatment. It has been cited in the literature that decreased testosterone levels in patients with both ED and type II DM may be responsible for the failure of such patients to respond to PDE5 therapy and it was found that combination with oral testosterone undecanoate restores sexual function in these patients.[14] Other recent publications have also supported the success of combination therapy with sildenafil and testosterone.[4,15] The consistency of the finding that testosterone level does have an influential effect on the way patients would respond to treatment, as shown by the above mentioned studies and adding sildenafil was more useful in patients with high FAI, should open the way in front of trialing adding testosterone to other treatments of ED. Blind clinical trials are supposed to provide the most powerful evidence based decisions to make in this regard. Exploiting multiple pathways in the physiologic processes leading to erection may help improve therapy for ED.[16]

Furthermore, it is the number of patients found with diabetes mellitus was unsurprisingly high. Diabetes mellitus is a major public health problem in the Middle Eastern Arab countries. Type 2 DM prevalence has reached epidemic proportions among the adult population of many Arabian Gulf countries. The prevalence of Type 2 DM in the UAE is ~20% of the adult population.[17] Understanding the fact that ED is not an uncommon finding in patients with DM, one can understand the high percentage of patients presenting to our clinic with DM.

The main limitation in this study lies in that fact that with using the FAI, its calculation assumes normal serum albumin levels. Therefore, it must be interpreted with caution in patients with decreased albumin levels (e.g. nephrotic syndrome, liver cirrhosis, etc).[18]

The time frame for collecting the blood samples was not optimal in the sense of the timing (being later than the recommended time) and the wide gap of the collection time and this is attributed to the long travel distance to the hospital and the fact that the FAI test is only available at our labs and finally is the sample size.

Conclusion

The FAI level has no role on measuring the severity of erectile dysfunction in Middle East men, but it does influence the way patients are going to respond to medical treatment of ED. Further studies are therefore needed to assess the effectiveness of using FAI as a reliable test of bioactive testosterone for men presenting with erectile dysfunction and to identify patients who may get benefit from adding testosterone in their treatment. □

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