The triad of erectile dysfunction, testosterone deficiency syndrome and metabolic syndrome: findings from a multi-ethnic Asian men study (The Subang Men’s Health Study)

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The etiology of erectile dysfunction (ED) is multi-factorial. This paper examines the association between ED, testosterone deficiency syndrome (TDS) and metabolic syndrome (MS) in Malaysian men in an urban setting. One thousand and forty-six men aged ≥40 years from Subang Jaya, Malaysia were randomly selected from an electoral-roll list. The men completed questionnaires that included: socio-demographic data, self-reported medical problems and the International Index of erectile function (IIEF-5). Physical examination and the following biochemical tests were performed: lipid profile, fasting blood glucose (FBG) and total testosterone. The response rate was 62.8% and the mean age of men was 55.8 ± 8.4 (41–93) years. Ethnic distribution was Chinese, 48.9%; Malay, 34.5%; Indian, 14.8%. The prevalence of moderate–severe ED was 20.0%, while 16.1% of men had TDS (<10.4 nmol/L) and 31.3% of men had MS. Indian and Malay men were significantly more likely to have ED (p = 0.001), TDS (p < 0.001) and MS (p < 0.001) than the Chinese. Multivariate regression analysis showed that elevated blood pressure, elevated FBG, low high-density lipoprotein and heart disease were predictors of ED while all MS components were independently associated with TDS. Malay and Indian men have a higher disease burden compared to Chinese men and were more likely to suffer with ED, TDS and MS. MS components were closely related to TDS and ED.

Keywords: male sexual dysfunction, testosterone deficiency, metabolic syndrome, Asian men, culture, prevalence, aging male

Introduction

The etiology of erectile dysfunction (ED) is multi-factorial and it includes psychological, neurological, hormonal and vascular causes [1]. The Massachusetts Male Aging Study has shown that the prevalence of ED increases with age [2]. Other risk factors of ED, independent of age, include: heart disease, hypertension, diabetes mellitus, low high-density lipoprotein (HDL) and psychological disorders [2].

The risk factors of ED are similar to metabolic syndrome (MS) components, namely: large waist circumference, elevated blood pressure (BP), elevated triglycerides, elevated fasting blood glucose (FBG) and HDL. The biochemical abnormalities, together with the pro-inflammatory state due to adipocyte-released cytokines, expedite the development of atherosclerosis [3–5]. This may explain the association between ED and MS.

Obesity and MS are prevalent in both developed and developing countries [6]. It is not surprising that the threat to health resulting from the pathogenesis of MS has resulted in escalating prevalence of cardiovascular diseases and diabetes mellitus worldwide, irrespective of socio-economic status.

The association between testosterone deficiency and MS has been previously suggested in the literature. Kaplan et al. previously reported that men with MS had significantly lower serum total testosterone (TT) compared to their metabolically free counterparts [7]. However, Laaksonen et al. have also described the inverse relationship. They reported that low testosterone independently predicted the development of MS in middle-aged men and suggested that it might be an early marker of insulin resistance [8]. The association between testosterone deficiency syndrome (TDS) and ED is slightly more complex. Men with biochemical defined hypogonadism can have normal erectile function although testosterone supplementation might have a role in treating ED in addition to phosphodiesterase-5 (PDE-5) inhibitors [9].

The aim of this study was to investigate the relationship between ED, testosterone deficiency and MS as well as...
its sub-components in Asian men. Although other studies have suggested the link between ED, TDS and MS, there is a void of data in Asian men using the International Diabetes Federation (IDF) Asian criteria of MS [10–12]. The Subang Men’s Health Study is a population-based study comprising randomly selected Asian men from diverse ethnic groups namely Malay, Chinese and Indians. This has allowed us to determine the prevalence of ED in Asian men based on age and ethnicity.

Methods

This was a cross-sectional community based study which was conducted in Subang Jaya, an urban township in Malaysia consisting of a population of 110,000. Men aged 40 years and above were selected randomly from the 2003 electoral-roll list using computer-generated numbers. A total of 1665 men were invited to participate in the study by mail and response rate was optimized by telephone calls, reminder letters and home visits. The response rate was 63% (n = 1046). Ethics approval for this study was obtained from the University of Malaya Medical Center, Kuala Lumpur, Malaysia. Written consent was obtained from all the participants.

The participants attended either the primary care clinic of a nearby tertiary hospital or one of the 30 general practices in Subang Jaya. All general practitioners (GPs) involved were trained to conduct the interview using a structured questionnaire and to perform a standardized physical examination. A fasting blood sample was taken from all the participants between 8.30 AM–11.00 AM. The following physical and blood parameters were measured: weight, height, hip and waist circumference, BP, fasting lipid profile, FBG and total testosterone. Blood samples were collected and sent to a designated central laboratory for analysis. The participants were informed personally of the blood test results and referrals were made when necessary.

The following information was captured in the questionnaire: socio-demographic data, self-reported medical problems (hypertension, diabetes mellitus, heart disease, cholesterol problem, ED, prostate problem), lifestyle (smoking, alcohol consumption) and the use of PDE-5 inhibitors. The questionnaires were available in English, Malay and Chinese. The participants also completed the International Index of erectile function (IIEF-5) questionnaire. The scores were categorized into: no ED (22–25), mild ED (17–21), mild to moderate ED (12–16), moderate ED (8–11) and severe ED (5–7). The IIEF-5 has been translated and validated in the local Malay language [11].

In this study, MS was defined using the IDF 2006 Asia-Pacific criteria. Men who had a waist circumference of >90 cm together with two or more of the following criteria were considered as having MS: (1) elevated triglyceride: >150 mg/dL (1.7 mmol/L); (2) reduced HDL: <40 mg/dL (0.9 mmol/L); (3) elevated systolic BP: >130 mm Hg or diastolic: >85 mm Hg (or on treatment for hypertension); and (4) impaired fasting plasma glucose: >100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes. TDS was defined as total serum testosterone <10.4 nmol/L (300 ng/dL).

The data were managed and analyzed using SPSS version 16 (SPSS Inc, Chicago, IL, USA). Descriptive statistics for socio-demographic and comorbidities data were presented. The Pearson’s chi-square test was used to test associations between categorical variables and t-test used for continuous data. Multiple logistic regression was used to identify variables, which are independently associated with ED and testosterone deficiency. Statistical significance was set at p < 0.05.

Results

Participants’ characteristics

Table I shows the socio-demographic characteristics of the participants. The mean age of men in this study was 55.8 ± 8.4 years (41–93 years) and it was similar across the three ethnic groups. The ethnic distribution was as follows: Chinese, 511 (48.9%); Malay, 361 (34.5%); Indian, 155 (14.8%); and others, 19 (1.8%). Malay and Indian men were found to have a significantly higher disease burden compared to Chinese men as shown in Table I.

Prevalence of ED

The prevalence of self-reported ED was 20.8% (n = 192). However, when IIEF-5 was used to screen for ED, 65% (n = 589) of men were found to have some degree of ED (mild–severe), with 21.8% (n = 198) suffering from moderate–severe ED; 7.9% (n = 82) of men were not sexually active. The mean age of men suffering from moderate–severe ED was significantly older (59.0 ± 8.2) than those with no-mild ED (53.6 ± 6.5) (t = 15.9, df = 905, p < 0.001). Based on IIEF-5, the prevalence of moderate–severe ED in men aged above 70 years was five folds higher than those aged 40–49 years (Figure 1).

By ethnicity, 54.5% (n = 267) of Chinese, 68.1% (n = 231) of Malays and 58.4% (n = 83) of Indians had at least mild ED (Table I). A significant association was found between ethnicity and ED severity with a higher proportion of Malays (23.3%) and Indians (26.1%) suffering from moderate–severe ED compared to Chinese (15.9%) (χ² = 11.2 df = 2, p = 0.004).

Prevalence of MS

This study reported a total of 31.6% (n = 316) of men suffering from MS and the majority had at least one MS component (92.2%). Hypertension (systolic BP ≥ 130 mm Hg or diastolic ≥85 mm Hg) was the most prevalent (56.8%) followed by waist circumference ≥90 cm (56.5%). However, waist circumference was the most common MS component observed in Malay (65.3%) and Indian (74.8%) men while hypertension was the most prevalent MS component among Chinese men (58.2%). There were significantly more Indian men having MS (48.6%) compared to Malay (35.0%) and Chinese (23.8%) men (χ² = 35.1, df = 2, p < 0.001) (Table I).

The prevalence of MS increased significantly with age (χ² = 10.7, df = 3, p = 0.013) (Figure 2). In addition, the number of MS components was significantly correlated with age (χ² = 43.6, df = 12, p < 0.001). The prevalence of moderate to severe ED was also significantly higher in men with MS compared to their non-MS counterparts independent of age (χ² = 17.2, df = 1, <0.001).
Prevalence of TDS
Using serum TT < 10.4 nmol/L as a criterion, 16.0% (n = 166) of men had biochemical testosterone deficiency. There was no significant difference between age and TDS. However, based on ethnicity, a higher proportion of Malays and Indians had TDS compared to the Chinese ($\chi^2 = 15.8$, df = 2, $p < 0.01$) (Table I). TDS was significantly associated moderate to severe ED ($\chi^2 = 4.04$, df = 1, $p = 0.044$) and BMI–APC ($\chi^2 = 56.7$, df = 3, $p < 0.001$). There is a 2.4-fold increase in the prevalence of TDS from overweight (23.0 to <25.0 kg/m²) to obesity (25.0 to <30.0 kg/m²) and a further 1.8-fold increase from obesity to morbid obesity ($\geq$30).

MS components and ED
We compared the prevalence of men with ED (moderate–severe ED) and without significant ED (no-mild ED) with MS, its individual components and heart disease (self-reported) (Table II). ED was found to be significantly associated with MS, increased waist circumference ($\geq$90 cm), raised BP (≥130/85 mm Hg), elevated FBG (≥5.6 mmol/L), low HDL (≤1.0 mmol/L), coronary heart disease, TDS (≤10.4 nmol/L) and morbid obesity (BMI ≥30). Multiple logistic regression analysis showed that elevated BP ($p = 0.014$), elevated FBG ($p = 0.004$), low HDL ($p = 0.004$) and heart disease ($p < 0.001$) were independent predictors of ED (Table II).
MS components and TDS
Our analysis also revealed that MS and its individual components were significantly associated with TDS (Table III). All men with TDS suffered from at least one or more MS components. Multiple logistic regression analysis showed that MS and all MS components were significant predictors of TDS: MS ($p = 0.05$), increase waist circumference ($p < 0.001$), elevated BP ($p = 0.009$), elevated FBG ($p < 0.001$), elevated triglycerides ($p = 0.006$) and low HDL ($p = 0.002$) (Table III).

Discussion
We found ED, MS and TDS are all prevalent in this urban community. This is consistent with the findings in our preliminary study in 2003 on men aged above 40 years in Petaling Jaya, another urban area in the Klang Valley, Malaysia [14].

Where MS is concern, Tan et al. has shown that applying the western criteria for MS tend to underestimate the prevalence of MS in Asian men [15]. Asians have been shown to have higher prevalence of hypertension and diabetes mellitus compared to Caucasians with corresponding BMI, and this further supports the use Asian MS criteria [16]. Using the IDF Asian criteria, the prevalence of MS in our study was 31.6%. Other epidemiological studies done in Asian men reported MS prevalence rates of between 23.1 and 34.8% depending on age of the population sampled [17–18]. This high prevalence reflects the high chronic disease burden in developing countries, which is projected to increase significantly in the next decades [19].

It is difficult to compare prevalence of TDS between studies because there is no specific cut-off level to diagnose TDS. In general, it is agreed that a total testosterone $\geq 12$ nmol/L is considered to be normal [20]. We defined TDS as men with a total testosterone level $< 10.4$ nmol/L (300 ng/dL), which is recommended by the Food and Drug Administration and the Endocrine Society of the United States [21]. Low testosterone has been associated with increase all-cause mortality even when age, medical morbidity, BMI and race were accounted [22]. In our study, 16.0% of men were found to have biochemically defined hypogonadism.

We reported an independent association between moderate–severe ED and MS components: elevated BP, elevated FBG and low HDL [23]. This is not surprising as all components of MS, except for waist circumference, can lead to endothelial dysfunction [24]. Endothelial dysfunction is a known factor leading to ED via RhoA/Rho-kinase endothelial nitric oxide (NO) synthase suppression [25]. Esposito et al. have found that endothelial dysfunction, high C-reactive protein and ED severity correlated significantly with the number of MS components [23]. This pro-inflammatory state might lead to an increase in free radicals resulting in low NO half-life. Corona et al. has also shown an independent association between elevated BP, fasting glucose and triglyceride with penile blood flow [12]. However, the direction of causality has not been established.

However, we did not find increase waist circumference, the main criterion in the IDF MS criteria, as an independent associate factor of moderate–severe ED. This finding is in contrast to the study by the Asia-Pacific Research Group [26].

Table II. Prevalence of comorbidities in ED and non-ED populations.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Insignificant ED (no-mild) N (%)</th>
<th>Insignificant ED (no-mild) N (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (logistic regression) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome (APC):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference ($&gt; 90$ cm)</td>
<td>128 (66.0)</td>
<td>373 (54.6)</td>
<td>$1.6 (1.2, 2.2)$*</td>
<td>$1.2 (0.7, 1.9)$*</td>
</tr>
<tr>
<td>Blood pressure ($\geq 130/85$ mm Hg)</td>
<td>132 (69.8)</td>
<td>383 (56.6)</td>
<td>$1.8 (1.3, 2.5)$*</td>
<td>$1.6 (1.1, 2.5)$*</td>
</tr>
<tr>
<td>Fasting blood glucose ($\geq 5.6$ mmol/L)</td>
<td>79 (40.5)</td>
<td>176 (25.0)</td>
<td>$2.0 (1.5, 2.8)$**</td>
<td>$1.8 (1.2, 2.8)$*</td>
</tr>
<tr>
<td>Triglycerides ($\geq 1.7$ mmol/L)</td>
<td>81 (41.5)</td>
<td>260 (36.9)</td>
<td>$1.2 (0.9, 1.7)$</td>
<td>$N/A$</td>
</tr>
<tr>
<td>HDL ($\leq 1.0$ mmol/L)</td>
<td>43 (22.1)</td>
<td>79 (11.2)</td>
<td>$2.2 (1.5, 3.4)$**</td>
<td>$2.0 (1.3, 3.3)$*</td>
</tr>
<tr>
<td>Coronary heart disease (self-reported)</td>
<td>37 (20.6)</td>
<td>55 (8.3)</td>
<td>$2.9 (1.8, 4.5)$**</td>
<td>$2.6 (1.6, 4.3)$*</td>
</tr>
<tr>
<td>Testosterone ($&lt; 1.4$ mmol/L)</td>
<td>40 (20.4)</td>
<td>102 (14.5)</td>
<td>$1.5 (1.0, 2.3)$*</td>
<td>$1.0 (0.6, 1.6)$</td>
</tr>
<tr>
<td>Morbid obesity (BMI $\geq 30$ kg/m²)</td>
<td>31 (15.8)</td>
<td>68 (9.8)</td>
<td>$1.7 (1.1, 2.7)$*</td>
<td>$1.3 (0.7, 2.2)$</td>
</tr>
</tbody>
</table>

APC, Asia-Pacific criteria; BMI, body mass index; CI, confidence interval; ED, erectile dysfunction; HDL, high-density lipoprotein; OR, odds ratio; $^*$ $p < 0.05$; $^{**} p < 0.01$. 

Figure 1. Prevalence of ED severity based on age groups. ($p < 0.001$).

Figure 2. Prevalence of MS based on age groups ($p = 0.013$).

Table II. Prevalence of comorbidities in ED and non-ED populations.
to other studies, which reported that waist circumference was an independent predictor for ED development [26]. Heidler et al. also found that MS and waist-hip-ratio were independently associated with ED in men above 50 years [11]. However, there studies used a waist circumference cut-off of ≥94 cm. Hence, it is plausible that waist circumference might not be as important a risk factor for ED in the context or Asian men.

We found TDS to be independent predictors of MS and its sub-components. The close association between MS and low testosterone has been well reported and the causality of TDS and ED could be bidirectional. Low testosterone is known to increase visceral fat deposition in men [27]. Furukawa et al. showed that obesity is associated with increase oxidative stress, which promotes obesity-associated MS [28]. Further, longitudinal data by Laaksonen and colleagues showed that men with MS have a 2.6-fold increased risk of developing TDS [8]. In addition, a cross-sectional study by Braga-Basaria et al. found that more than 50% of men with prostate cancer treated with androgen deprivation therapy for a minimum of 12 months developed MS subsequently [29].

We also reported an association between TDS and ED but logistic regression did not show an independent association. TDS can directly and indirectly lead to the development of ED. Recent evidence has suggested that some patients with ED who remain impotent despite trying PDE-5 inhibitors might benefit from the addition of testosterone replacement therapy [30]. In addition, TDS can influence the development of ED via other biological pathways such as the development of MS and diabetes [7].

MS and cardiovascular disease have been known to be associated with ED [31]. We have shown that the presence of ED (moderate–severe) was independently associated with some of the components of MS and coronary artery disease (self-reported). However, TDS (<10.4 nmol/L) was not associated with self-reported cardiovascular disease. This finding is consistent with the review findings by Wu and Eckardstein, which fail to find any relationship between testosterone and cardiovascular disease [32]. However, a recent review by Traish et al. provides evidence to support the view that low testosterone is associated with cardiovascular disease [33]. In addition, there is an increasing evidence to support the role of testosterone replacement therapy in men with preexisting cardiovascular disease [34]. Hence, controlled clinical trial are required to elucidate the role of TDS as a risk factor for cardiovascular disease and whether testosterone replacement therapy is indicated in Asian men with TDS.

Another aspect of our study relates to the differences in the disease burden of comorbidities among the three ethnic groups: Malay, Chinese and Indians. Malay and Indian men were found to have higher prevalence of MS and its individual components and were more likely to have ED and TDS. The three ethnic groups have distinct cultural and social practices, attitudes and dietary habits, which may affect their health as well as their health seeking behavior. This is evident in a study by Ford et al., which showed that the prevalence of MS varies between different ethnic groups in the US with the highest prevalence reported in Mexican Americans [35]. The Institute of Medicine describes ethnicity as a useful concept that distinguishes people who share a culture and way of life, language, folkways, religion and material culture such as food, music, clothing, literature and art [36]. All these elements have an impact on health resulting in disparities in health status.

Therefore, in countries with multi-ethnic population like Malaysia, research and policy in health promotion should take into consideration of not just gender differences but also ethnic differences [37]. A study conducted in Singapore, a neighboring country, reported ethnic differences exist with regards to BMI, diabetic control, family history of diabetes, presence of associated hypertension and severity of albuminuria. Indians appear to have poorer diabetic control but are also less likely to develop hypertension and renal complications than Chinese [38]. Another study done in the United Kingdom highlighted the problems of integrating Asian patients into western lifestyle and culture in optimizing diabetic control [39].

There are a few limitations in this study. As our study was conducted in an urban setting, the findings may not be extrapolated to represent all Malaysian men. Further, our random sample list was obtained from the Electoral Board of Malaysia. Not all men are required to register as a voter and some registered men might not have changed their contact details if they have moved. The prevalence of comorbidities including coronary artery disease was based on self-report, which is usually underreported. In addition, TDS was defined using total testosterone level and free testosterone level was not calculated. Finally, as this is a cross-sectional study, we cannot to determine causality and the relationship between variables analyzed.

Conclusion

This study confirmed the close link between ED, biochemical hypogonadism and MS in an Asian multi-ethnic com-

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Table III. Prevalence of comorbidities in TDS and non-TDS populations.

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>TDS (TT&lt;10.4 nmol/L) N (%)</th>
<th>Non-TDS (TT ≥ 10.4 nmol/L) N (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (logistic regression) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome (APC)</td>
<td>83 (51.8)</td>
<td>233 (27.9)</td>
<td>2.7 (1.9,3.9)**</td>
<td>1.9 (1.0,3.8)*</td>
</tr>
<tr>
<td>Waist circumference (≥90 cm)</td>
<td>120 (77.4)</td>
<td>435 (52.5)</td>
<td>3.1 (2.1,4.6)**</td>
<td>2.6 (1.5,4.6)*</td>
</tr>
<tr>
<td>Blood pressure (≥130/85 mm Hg)</td>
<td>112 (71.8)</td>
<td>478 (58.4)</td>
<td>1.8 (1.2,2.6)*</td>
<td>1.8 (1.2,2.8)*</td>
</tr>
<tr>
<td>Blood glucose (≥5.6 mmol/L)</td>
<td>74 (44.6)</td>
<td>222 (25.8)</td>
<td>2.3 (1.6,3.3)**</td>
<td>2.4 (1.5,3.7)**</td>
</tr>
<tr>
<td>Triglycerides (≥1.7 mmol/L)</td>
<td>80 (48.2)</td>
<td>312 (36.2)</td>
<td>1.6 (1.2,2.3)*</td>
<td>1.8 (1.2,2.8)*</td>
</tr>
<tr>
<td>HDL (≤1.0 mmol/L)</td>
<td>39 (23.5)</td>
<td>104 (12.1)</td>
<td>2.3 (1.5,3.4)**</td>
<td>2.2 (1.3,3.6)*</td>
</tr>
<tr>
<td>Overweight (BMI &gt; 30)</td>
<td>38 (24.2)</td>
<td>69 (8.1)</td>
<td>3.6 (2.3,5.6)**</td>
<td>2.3 (1.4,3.8)*</td>
</tr>
</tbody>
</table>

APC, Asia-Pacific criteria; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; TDS, testosterone deficiency syndrome; TT, total testosterone; p < 0.01; p < 0.05.
community. Ethnicity is a major determinant of the prevalence of ED, TDS and MS. Elevated BP, impaired FBG and low HDL are independent predictors of ED while all MS components are independently associated with TDS. These risk factors, therefore, should be given particular emphasis, as they are key parameters in the pathogenesis of ED and TDS.

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**Declaration of interest:** The authors report no conflicts of interest.

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