

Testosterone deficiency syndrome among males with type 2 diabetes mellitus in East Malaysia

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ABSTRACT

Type 2 diabetes mellitus (T2DM) may be independently associated with testosterone deficiency syndrome (TDS). Both conditions are linked with reduced quality of life and cardiovascular comorbidities. The magnitude of TDS among T2DM men and its predictors has still not been well established in Malaysia. This study aimed to determine the prevalence of TDS and its predictors among men with T2DM attending a government health clinic in Kuching, Sarawak. TDS severity and level of serum total testosterone were also explored. A cross-sectional study was conducted involving 360 respondents. Aging Males Symptoms Scale (AMS) score > 26 and serum total testosterone ≤ 12 nmol/L were used to diagnose TDS. The prevalence of TDS in current study was 19.7%. Multivariate analysis showed that determinants for TDS included age (Adjusted OR 1.061; 95% CI 1.020; 1.103), Iban ethnicity (Adjusted OR 2.469; 95% CI 1.154; 5.283) and a waist circumference equal or greater than 90 cm (Adjusted OR 3.655; 95% CI 1.472; 9.081). However, there was no significant association between TDS and the level of serum total testosterone ($p = 0.581$). We concluded that the prevalence of TDS in this study was relatively low. The severity of this condition may not be influenced by testosterone level. Physicians might consider a diagnosis of TDS if elder diabetic men with abdominal obesity present to primary care clinics with clinical features of hypogonadism. Health care providers also might consider lowering their threshold to screen for TDS among Iban men with T2DM.

Keywords: diabetes mellitus, testosterone deficiency syndrome, Malaysia

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INTRODUCTION

Testosterone deficiency syndrome (TDS) is defined as the presence of both clinical symptoms (i.e. low libido, loss of concentration, erectile dysfunction, depression, increased fat mass, decrease muscle mass and decreased bone mineral density) and biochemically deficiency in serum testosterone levels which associated with advancing age.¹ Recent consensus has identified type 2 diabetes mellitus (T2DM) as a risk factor for hypogonadism. Low testosterone concentrations in men with T2DM have been associated with insulin resistance, which leads to multiple complications and poor quality of life.²

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The overall prevalence of TDS varies from 6% to 9.5% in men aged 40–70 and rises to 15–30% among diabetic or obese men.¹ It is estimated that in the United States in 2025, as many as 6.5 million of the male population age between 30 to 79 years old will have symptomatic testosterone deficiency.³ Early recognition and detection of TDS are very important since this condition can be treated if diagnosed early. It is accepted by most of the consensus that total serum testosterone above 12 nmol/l (350 ng/dl) does not require treatment.^{2,4,5} Testosterone replacement therapy in patients with diabetes may improve glycaemic control.⁶

There is limited epidemiological information in Malaysia regarding TDS among diabetes patients. The figures may be underestimated due to under-diagnosed. The present study aims to identify the magnitude of this problem among male diabetes patients and its determinants. Thus, the findings of this study could help in identifying patients with increased risk of developing TDS and will indirectly increase awareness among clinicians and patients on the importance of screening for TDS in T2DM.

MATERIALS AND METHODS

This cross-sectional study was conducted at a government health clinic located in the Kuching District of Sarawak, East Malaysia. This study was conducted among 360 T2DM men aged 40 to 70 years old who were randomly selected from the clinic's diabetes registry. The data collection was done within three months of June 2016. Patients who were on testosterone replacement therapy, opiates or oral steroid were excluded as it may interfere with serum total testosterone level. Patients who presented with an acute illness and arrived in the afternoon for blood taking were excluded, as these may cause a transient reduction in serum total testosterone. As the questionnaire was self-administered, patients who had cognitive impairment, mentally unfit or did not understand Malay language or English were excluded. The sample size for this study was calculated using the formula to estimate prevalence. It was gauged based on the prevalence of androgen deficiency in Taiwanese men with T2DM which was 32.5%.⁷ Assuming a non-respondent rate of 10 %, the sample size needed for this study was 360 patients.

The sociodemographic data of the respondents were collected using a standardised form. The sociodemographic data collected were age, race, marital status and alcoholic status. Information on comorbidities was obtained by direct questioning the patients themselves and by checking patients' medical record. Both English and validated Malay Versions of Aging Males Symptoms (AMS) Questionnaire were used in this study to assess symptoms of TDS. This self-administered questionnaire consists of 17 items. Each item was rated using a Likert scale and was divided into three domains: psychological, somatic and sexual. Based on the AMS score, TDS was interpreted clinically as follows: normal (score of < 27), mild (score of 27–36), moderate (score of 37–49) and severe (score of > 49). A pilot study involving 36 respondents was done to test the reliability of the Malay version of AMS. The Cronbach's Alpha of this questionnaire was 0.819, reflecting good internal consistency.

Hypogonadism is defined as serum total testosterone levels of 12 nmol/l and below (350 ng/dl). Blood samples were taken between 7–12 noon to minimise diurnal variation.⁴ The results were classified as normal or abnormal. About 2 ml of blood was taken from each patient and the specimens were kept in plain tubes and stored in a polystyrene box prepared by the laboratory at room temperature until the specimens were collected by the dispatcher at noon. The reagents used were Abbott Architect and Generation Testosterone Reagent kits, and the samples were analysed using Abbott Architect CI 8200 machine. Diagnosis of TDS was made per the literature as a combination of AMS score of > 26 with serum total testosterone of \leq 12 nmol/L.² Patients with

only one abnormal result for either AMS score or total serum testosterone were not diagnosed as having TDS and did not benefit from testosterone replacement therapy.^{4,5,2}

Data collected in this study were analysed using SPSS version 22 for Windows. Independent t-test was performed to assess whether there was any significant difference between the mean level of total serum testosterone of two groups of the severity of TDS. Simple logistic regression was used in the bivariate analysis to determine the association between TDS and sociodemographic characteristics of respondents, anthropometric and comorbidities. Variables with a p-value of less than 0.25 or clinically important were chosen for multivariate analysis. Binary logistic regression was performed to determine the independent association between TDS and selected sociodemographic factors and anthropometric factors. In this study, the significant level was set at $p < 0.05$, with a confidence interval of 95%.

This study was approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia (UKM) (UKMREC Approval Number: UKM 1.5.3.5/244/FF - 2015 - 193), Medical Research & Ethics Committee of Ministry of Health Malaysia (NMRR - 15 - 1117 - 24977) and Kuching District Health Office. This study was conducted voluntarily, and written consent was taken from all the respondents before participating in the study with no compulsion to join the study. All respondents were briefed regarding the duration and procedures involved in this study, including blood taking, in the Patient Information Sheet. Participants with TDS were referred to the Urology Clinic for further management.

RESULTS

The response rate for this study was 96%. The main reason patients declined was due to time constraints. About four-fifths (80%) of the participants were between 51 to 70 years old, while another two-fifths (18.6%) were 40 to 50 years old. A majority were married (89.4%), and 27.5% of them reported consuming alcohol. Based on the AMS scoring, nearly half (49.7%) had a mild score, followed by a normal score (33.3%), moderate score (16.4%) and severe score (0.6%). In terms of the three subscales of somatic (score ≥ 9), psychological (score ≥ 6) and sexual (score ≥ 6), about 91.1% of all the samples had somatic complaints, 63.9% had psychological complaints and 90% had sexual complaints. Table 1 shows the characteristics of the respondents.

Prevalence of TDS

The prevalence of TDS in this study was 19.7% (71/360). About 8 out of 10 men with TDS (56/71, 78.9%) had mild severity based on AMS scoring. Another fifth (15/71, 21.1%) had moderate symptoms of TDS. When the scores were further grouped into three the somatic, psychological and sexual categories, all respondents had an abnormal scores for somatic, 73.2% had an abnormal score for psychological, and 97.2% had an abnormal score for sexual.

Associated Factors for TDS

Age, Iban ethnicity, BMI and waist circumference ≥ 90 cm were significantly associated with TDS from bivariate analysis (Table 2). In this analysis, BMI was grouped into two categories; no obese (BMI < 27.5 kg/m²) and obese (BMI ≥ 27.5 kg/m²). The significant level was set at $p < 0.25$ as confounding factors were not controlled for in this simple binary logistic regression. The usual value of $p < 0.05$ was not used in this statistic, as it may cause potential factors with a significant association to be excluded.

Multiple Binary Logistic Regression was performed to assess the impact of several factors on developing TDS. The model has four independent variables (age, Iban ethnicity, BMI (no obese

Table 1 Characteristics of the respondents (N = 316)

Characteristics	n	%
Age (years), mean (SD)	57.7 (7.78)	
Ethnicity		
Malay	161	44.7
Chinese	111	30.8
Iban	48	13.3
Others	40	11.1
Waist Circumference (cm), mean (SD)	96.2 (10.93)	
< 90	94	26.1
≥ 90	266	73.9
BMI Categories (kg/m ²), mean (SD)	27.8 (4.71)	
Normal/underweight (<18.5–22.9)	49	13.6
Obese (23–>40)	311	86.4
Hypertension	317	88.1
Dyslipidemia	345	95.8
AMS score		
Normal (<27)	120	33.3
Mild (27–36)	179	49.7
Moderate (37–49)	59	16.4
Severe (>49)	2	0.6
Serum Total Testosterone (umol/l)		
≤12	98	27.2
>12	262	72.8

and obese) and waist circumference ≥ 90). The model was statistically significant at χ^2 (4, N = 360) = 31.09, $p < 0.001$). The Hosmer and Lemeshow test showed that the model was a good fit ($p = 0.551$). The model as a whole explained between 8.3% (Cox and Snell R square) and 13.1% (Nagelkerke R square) of the variance in TDS and correctly classified 79.4% of cases. As shown in Table 3, only three of the independent variables made a unique statistically significant contribution to the model. The factors which were significantly associated with increased risk for TDS were age (Adjusted OR 1.061, 95% CI = 1.020; 1.103), Iban ethnicity (Adjusted OR 2.469, 95% CI = 1.154; 5.283) and waist circumference ≥ 90 cm (Adjusted OR 3.655, 95% CI = 1.472; 9.081). This indicates that by increase one year of age, the chance of developing TDS is 1.06 times higher. Iban ethnicity is about 2.5 times higher odds of developing the syndrome, whereas those with waist circumference ≥ 90 cm are 3.7 times more likely to develop TDS.

An independent t-test was conducted to compare the level of serum total testosterone and severity of TDS. There were no significant differences in serum total testosterone for mild and moderate TDS {mean (SD) = 9.0 (2.678) vs 9.4 (2.14), $p = 0.581$ }. This may indicate that there is no association between the severity of TDS and the level of serum total testosterone in the current study.

Table 2 Bivariate analysis of the association for TDS among diabetes males (N = 316)

List of Variables	Crude OR	(95% CI)	χ^2 (df)	P Value
Age (year)	1.032	(0.997; 1.069)	0.031 (1)	0.077
Ethnicity				
Malay	1.000			
Chinese	0.812	(0.428; 1.538)	-0.209 (1)	0.522
Iban	2.097	(1.024; 4.293)	0.740 (1)	0.043
Others	0.740	(0.286; 1.918)	-0.301 (1)	0.535
Marital Status				
Single/ divorced	1.000			
Married	0.768	(0.346; 1.706)	-0.263 (1)	0.517
Alcohol				
No	1.000			
Yes	1.136	(0.641; 2.013)	0.128 (1)	0.662
Hypertension				
No	1.000			
Yes	1.591	(0.644; 3.931)	0.464 (1)	0.315
Dyslipidaemia				
No	1.000			
Yes	1.625	(0.358; 7.370)	0.486 (1)	0.529
BMI				
No Obese	1.000			
Obese	1.966	(1.154; 3.348)	0.676 (1)	0.013
Waist Circumference (cm)				
< 90	1.000			
≥ 90	4.135	(1.823; 9.379)	1.419 (1)	0.001

Table 3 Multiple binary regression model for the association between TDS among diabetes males with age, race, BMI and waist circumference (N = 316)

List of Variables	Adjusted OR	(95% CI)	B	Wald (df)	P Value
Age (year)	1.061	(1.020; 1.103)	0.059	8.597 (1)	0.003
Ethnicity					
Malay	1.000				
Chinese	0.836	(0.426; 1.641)	- 0.179	0.271 (1)	0.603
Iban	2.469	(1.154; 5.283)	0.904	5.422 (1)	0.020
Others	0.757	(0.281; 2.037)	- 0.278	0.304 (1)	0.581
BMI					
No Obese	1.000				
Obese	1.625	(0.832; 3.173)	0.485	2.017 (1)	0.156
Waist Circumference (cm)					
< 90	1.000				
≥ 90	3.655	(1.472; 9.081)	1.296	7.796 (1)	0.005

DISCUSSION

Studies on TDS among diabetic men are relatively recent and progressively conducted outside Malaysia.^{7,8,9} Therefore, little is known regarding TDS among Malaysian men with diabetes. Recent reviews have recognised T2DM is associated with hypogonadism which may lead worsening of comorbidity and mortality. Testosterone therapy among diabetic men with hypogonadism may improve sexual life, glycaemic level and quality of life.¹⁰ Therefore, this study was conducted to determine the prevalence and associated factors of TDS among men with T2DM, as well as to study the association between the severity of TDS with testosterone level. Diagnosis of TDS was made based on a combination of AMS score of > 26 and serum total testosterone of ≤ 12 nmol/L.

This study has found that the prevalence of TDS among men with T2DM was relatively low (19.7%) compared to studies done in other parts of the world. A study was performed to assess hypogonadism by using a combination of serum total testosterone of ≤ 12 nmol/L and clinical features of hypogonadism as the operational definition for the diagnosis of TDS in India reported that 34.7% of their diabetes patients had TDS.¹¹ Four other studies were done between 2007 to 2012 in different parts of UK and Australia to assess hypogonadism among men with T2DM that also using total serum testosterone of ≤ 12 nmol/L as their cut off point had found that their prevalence was ranging between 25 to 45%.^{8,9,12,13} However, these studies did not take clinical symptoms into consideration. We found that about 27.2% of our current study population had serum total testosterone ≤ 12 nmol/L.

To date, there was no similar study done in Malaysia to assess the prevalence of TDS among men with T2DM for a comparison. There is a community - based study done in Subang Jaya, Malaysia involving 1046 men aged ≥ 40 years who are randomly selected from an electoral-roll list shows a lower proportion of TDS (16.1%). However, the researcher defines TDS as low early morning testosterone level of less than 14.4 nmol/L.¹⁴ In general, diabetic populations have a higher prevalence of TDS compared to the population without comorbidity. Variation in prevalence may result from the operational definitions that are being used to diagnose TDS.¹⁵

In this study, age, Iban ethnicity and central obesity were independently associated with TDS.

Prevalence of TDS is increased markedly with advancing age as it is well known that physiologically, hormone testosterone will progressively decline with advancing age and some studies had reported that level of testosterone declines by about 1% every year.¹⁶ Surprisingly, Iban ethnicity which represents only 14% of the total study population has a higher risk to develop TDS. There is no previous study to assess the association of Iban ethnicity with TDS for a comparison. What leads this ethnicity preponderance towards TDS is difficult to be explained. Perhaps proper assessment on their lifestyle or future biomolecular research focusing on Iban ethnicity may provide a better understanding of this finding. In a genetic study to assess the origin of Iban ethnicity, the findings have shown that Iban ethnicity is most similar to the population that reside in mainland Southeast Asia and Indonesia.¹⁷ There was a study done in Malaysia to assess the prevalence of TDS by ethnicity among men in the community, and it shows that TDS has a significant association with ethnicity, where Malay and Indian have the highest proportion.¹⁴ Apart from that, it may have related to Iban culture where alcohol and “tuak” (Sarawakian term for rice wine) use are very common in the Iban community.

Waist circumference was found to have a strong association with TDS in the current study. This is in keeping with many previous studies that showed waist circumference has a significant association with TDS and also as a predictor of the level of serum testosterone.^{7,9,11} There are several other confounding factors which need to be considered such as dietary habits, duration of exercise, medications, alcohol consumption and the number of cigarettes and duration of smoking, as these factors decisively affect the outcome of lipid levels and hypertension.¹⁸ Levels of serum testosterone were not a predictor of severity of TDS among men with type 2 diabetes mellitus. The current finding is consistent with a previous study which found no correlation between the levels of testosterone with symptoms of hypogonadism.¹⁹ Out of 71 men diagnosed with TDS in the present study, 78.9% (56/71) had mild severity based on AMS scoring. Another 21.1% had moderate symptoms and none of them had severe symptoms. We hypothesised that these men might have underestimated their symptoms due to optimistic bias or to protect their perception of masculinity. Perhaps good qualitative studies may explain further this complex relationship. While another study had demonstrated that the severity of symptoms had a significant inverse association with the level of testosterone, age was found to be the confounding effect.¹⁰

The definition of TDS is not without flaws. There is no standard guideline to diagnose TDS. Different researchers may use a different level of serum testosterone to diagnose it. This consequently causes different results from one study to another, even though the studies are almost similar. Therefore, a head to head comparison is sometimes not possible.¹⁵ There is also a limited study of TDS with T2DM conducted in Malaysia. As this study was conducted in one primary care clinic in East Malaysia, the results cannot be generalised to the general population in this country.

CONCLUSION

The prevalence of TDS among men with T2DM in this study is low (19.7%) compared to studies in other parts of the world. This might be due to the difference in operational definition in diagnosing TDS used and methodology. Iban ethnicity, older age and waist circumference \geq 90 cm are the independent risks factors for developing TDS among men with T2DM. Level of serum testosterone may not be an ideal indicator to reflect the severity of TDS.

RECOMMENDATION

Physicians may consider the diagnosis of TDS in older diabetic men with abdominal obesity approach at primary care clinics with clinical features of hypogonadism. Health care providers also might consider lowering their threshold to screen for TDS among Iban men with T2DM. Testosterone may have a role and protective effects in the evolution of metabolic syndrome as it is strongly associated with waist circumference as observed in this study. It is well known that high waist circumference is one of the components of metabolic syndrome. This finding sounds promising, but further study and clinical trials are required to prove this postulation. A multi-centred study with random sampling might be a feasible alternative in future to improve the representation of respondents and allow generalisation of the findings. Other areas can be explored in the future, such as determining the association between TDS and diabetic control among the multi-ethnic population of Malaysia.

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CONFLICT OF INTEREST

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