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Sexual Dysfunction

Effect of Testosterone Replacement Treatment in Testosterone Deficiency Syndrome Patients with Metabolic Syndrome

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Purpose: This study was conducted to investigate the effect of testosterone replacement treatment (TRT) in testosterone deficiency syndrome (TDS) patients with metabolic syndrome.

Materials and Methods: We reviewed the data of 200 men who were diagnosed with TDS and were undergoing TRT between August 2006 and August 2009. The 200 patients were divided into two groups (group 1: 71 patients with metabolic syndrome, group 2: 129 patients without metabolic syndrome) depending on metabolic syndrome, which was diagnosed according to the NCEP III criteria for Asians. Age, BMI (body mass index), waist circumference, serologic tests, AMS (the Aging Males' Symptoms scale), and IIEF (International Index of Erectile Function) were measured.

Results: In group 1, waist circumference and fasting glucose were significantly decreased; hemoglobin and total testosterone were increased; and the somatovegetative scale score of the AMS, the total AMS score, the erectile function score of the IIEF, the overall satisfaction score of the IIEF, and the total IIEF score were significantly improved after TRT. On the other hand, in group 2, waist circumference, BMI, total cholesterol, LDL, and fasting glucose were significantly decreased; hemoglobin and total testosterone were increased; and the 2 subscale scores of the AMS (psychologic and somatovegetative), the total AMS score, all subscale scores of the IIEF, and the total IIEF score were significantly improved after TRT.

Conclusions: Overall, the patients who had TDS with metabolic syndrome showed less improvement in AMS, IIEF, and serum variables. Therefore, the correction of metabolic syndrome, such as diabetes, obesity, and hypertension, should be considered during TRT.

Key Words: *Hormone replacement therapy; Metabolic syndrome X; Testosterone*

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INTRODUCTION

Recently in Korea, the prevalence rates of cardiovascular diseases, diabetes mellitus, and obesity, which are thought to suggest metabolic syndrome, are increasing, and mortality statistics show that cerebrovascular diseases, cardiac disease, and diabetes mellitus are ranked numbers 2, 3, and 5, respectively, in males [1]. Accordingly, there have been many investigations of the correlation between cardiovascular disease and metabolic syndrome.

In 1988, Reaven suggested the basic characteristics of metabolic syndrome as the group of insulin resistance risk factors, such as hyperinsulinemia, glucose intolerance, dyslipidemia, and hypertension [2]. Afterwards, various research allowed the World Health Organization (WHO) to define the term metabolic syndrome for the first time in 1998 [3]. Since then, on the basis of basic factors such as diabetes mellitus, obesity, dyslipidemia, hypertension, and albuminuria, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, the European

Group for the Study of Insulin Resistance (EGIR), and others have suggested diagnostic criteria for metabolic syndrome [4,5].

In many recent epidemiologic investigations, it has been revealed that there is a close relationship between obesity and low serum testosterone values, and metabolic syndrome and type 2 diabetes mellitus are also known to be related to low serum testosterone levels [6]. Also, it has been reported that low serum testosterone levels can be a risk factor for diabetes mellitus and metabolic syndrome [6].

Whereas many researchers have reported on the correlation between metabolic syndrome and testosterone, none have reported on the effectiveness of testosterone replacement therapy (TRT) in patients with testosterone deficiency syndrome (TDS) accompanied by metabolic syndrome. Thus, in the present study, we tried to determine the effect of TRT in TDS patients with metabolic syndrome.

MATERIALS AND METHODS

1. Subjects

Among TDS patients (testosterone $<$ 3.5 ng/dl) who visited the urology clinic at this hospital from August 2007 to August 2010, 200 males who received TRT for 30 weeks or more were investigated retrospectively.

A total of 71 subjects were assigned to the patient group that met the diagnostic criteria of metabolic syndrome (group 1) and 129 subjects to the patient group that did not meet the diagnostic criteria of metabolic syndrome (group 2).

TABLE 1. Comparisons of BMI, Hb, PSA, glucose, lipid profile, and total testosterone between group I and group II before TRT (independent t-test)

	Group 1	Group 2	p-value
Age (yr)	57.8±9.9	57.6±9.8	0.869
BMI (kg/m^2)	26.35±2.47	24.56±2.39	$<$0.001[a]
Waist (inch)	35.86±1.50	33.81±2.06	$<$0.001[a]
Hb (mg/dl)	14.61±1.42	14.73±1.19	0.541
PSA (ng/dl)	1.02±0.79	1.52±2.57	0.067
Glucose (mg/dl)	121.1±32.1	111.5±30.1	$<$0.001[a]
Total cholesterol (mg/dl)	186.38±39.90	182.93±37.82	0.573
Triglyceride (mg/dl)	192.69±180.80	206.80±213.91	0.677
LDL cholesterol (mg/dl)	113.41±38.90	109.17±29.86	0.485
HDL cholesterol (mg/dl)	42.15±9.57	47.72±21.11	0.004[a]
Total testosterone (ng/ml)	2.31±0.82	2.52±1.12	0.164

Group 1: TDS patients with metabolic syndrome, Group 2: TDS patients without metabolic syndrome, BMI: body mass index, PSA: prostate-specific antigen, LDL: low-density lipoprotein, HDL: high-density lipoprotein, [a]: statistical significance, $p<0.05$ in independent t-test between group 1 and group 2

2. Methods

Testosterone undecanoate 1 g was used for TRT and was injected intramuscularly at an interval of 10 to 14 weeks.

The criteria for metabolic syndrome were based on the NCEP III criteria for Asians. Among the five standards of systolic blood pressure $\geq$130 or diastolic blood pressure $\geq$ 85 mmHg or taking hypertension medication, fasting blood glucose (FBG) $\geq$110 mg/dl or taking hypoglycemic medication, fasting triglyceride $\geq$150 mg/dl, fasting HDL cholesterol $\leq$40 mg/dl, and waist circumference $\geq$90 cm (35.4 inches), those patients who met three or more criteria were determined to have metabolic syndrome. The evaluation of erectile dysfunction used the International Index of Erectile Function (IIEF) survey, and the evaluation of TDS symptoms used the AMS (Aging Males' Symptoms) survey.

Blood pressure maintained at a stable state for 10 minutes or more was measured by a single investigator with a mercury hemomanometer at the right upper arm, and waist circumference was measured with a tape measure at the thinnest part in the middle between below the ribs and the iliac crest while the patient had his or her breath comfortably released. Serum tests involved taking blood between 0800 and 1100 after 8 hours or more of fasting, and hemoglobin, prostate-specific antigen (PSA), glucose, triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, and serum testosterone were measured.

3. Statistical analysis

Using independent T-tests and paired T-tests, differences between the two groups and the differences between before and after treatment of each group were compared and analyzed. All statistical analysis used the statistical software SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA), and $p<0.05$ was considered to be statistically significant.

TABLE 2. Comparisons of IIEF and AMS scores between group 1 and group 2 before TRT (independent t-test)

	Group 1	Group 2	p-value
IIEF (erectile function)	15.03±8.72	14.96±8.59	0.970
IIEF (orgasm)	5.07±3.43	5.30±3.69	0.751
IIEF (sexual desire)	5.79±2.40	5.68±2.39	0.815
IIEF (sexual satisfaction)	5.87±4.12	6.15±4.08	0.736
IIEF (overall satisfaction)	5.31±2.98	5.37±2.65	0.912
IIEF (total)	37.08±18.49	37.46±18.32	0.916
AMS (psychologic)	10.19±17.09	7.13±4.82	0.085
AMS (somatovegetative)	18.92±16.53	14.10±6.20	0.030[a]
AMS (sexual)	14.50±16.94	11.60±6.51	0.118
AMS (total)	37.23±20.21	32.89±15.01	0.116

Group 1: TDS patients with metabolic syndrome, Group 2: TDS patients without metabolic syndrome, IIEF: International Index of Erectile Function, AMS: The Aging Males' Symptoms scale, [a]: statistical significance, $p<0.05$ in independent t-test between group 1 and group 2

RESULTS

1. Differences between TDS patients with and without metabolic syndrome before TRT

In the pretreatment comparison of the patient group with metabolic syndrome (group 1) and the patient group without metabolic syndrome (group 2), BMI, waist circumference, FBG, and HDL cholesterol showed statistically significant differences. In the survey results, the pretreatment somatovegetative subscale of the AMS showed a significant difference (Table 1, 2).

2. Effect of TRT in TDS patients with metabolic syndrome (group 1)

In group 1, after TRT, there was a statistically significant reduction in waist circumference, an increase in serum hemoglobin and testosterone, and a reduction in FBG. In the survey results, 2 detailed items (erectile function, overall satisfaction) and the overall score of the IIEF and 1 detailed item (somatovegetative subscale) and the overall score of the AMS showed statistically significant increases (Table 3, 4).

3. Effect of TRT in TDS patients without metabolic syndrome (group 2)

In group 2, there was a statistically significant reduction in BMI and waist circumference, an increase in serum hemoglobin and testosterone, and a reduction in FBG, total cholesterol, and LDL cholesterol. In the survey results, all detailed items and the overall score of the IIEF and 2 detailed items (psychologic, somatovegetative subscale) and the overall score of the AMS showed statistically significant increases (Table 3, 4).

TABLE 3. Comparisons of BMI, waist circumference, Hb, PSA, lipid profile, and total testosterone between before and after TRT in groups 1 and 2 (paired t-test)

	Group 1			Group 2		
	Before TRT	After TRT	p-value	Before TRT	After TRT	p-value
BMI (kg/m^2)	26.35±2.47	26.19±2.63	0.174	24.56±2.39	24.26±2.44	<0.001[a]
Waist (inch)	35.86±1.50	35.56±1.76	0.008[a]	33.81±2.06	33.67±1.94	0.046[a]
Hb (mg/dl)	14.61±1.42	15.54±1.51	<0.001[a]	14.73±1.19	15.29±1.38	<0.001[a]
PSA (ng/dl)	1.00±0.77	1.17±1.01	0.061	1.44±2.77	1.32±1.27	0.627
Glucose (mg/dl)	121.1±32.1	116.6±28.1	0.016[a]	111.5±30.1	107.3±26.1	0.045[a]
Total cholesterol (mg/dl)	187.30±40.52	184.06±39.94	0.602	183.37±38.06	165.65±32.03	<0.001[a]
Triglyceride (mg/dl)	196.55±203.69	160.85±75.73	0.193	186.39±172.13	150.15±93.11	0.094
LDL (mg/dl)	113.42±35.82	110.50±34.74	0.633	105.59±28.65	97.92±32.66	0.034[a]
HDL (mg/dl)	42.09±10.11	43.02±11.61	0.479	46.82±12.91	44.67±11.83	0.094
Total testosterone (ng/ml)	2.31±0.82	4.17±2.62	<0.001[a]	2.52±1.12	4.12±1.92	<0.001[a]

Group 1: TDS patients with metabolic syndrome, Group 2: TDS patients without metabolic syndrome, BMI: body mass index, PSA: prostate-specific antigen, LDL: low-density lipoprotein, HDL high-density lipoprotein, [a]: statistical significance, $p < 0.05$ in paired t-test between before and after TRT

TABLE 4. Comparisons of IIEF and AMS scores between before and after TRT in groups 1 and 2 (paired t-test)

	Group 1			Group 2		
	Before TRT	After TRT	p-value	Before TRT	After TRT	p-value
IIEF (erectile function)	10.95±7.81	15.40±8.32	0.045[a]	11.98±6.96	18.35±6.81	<0.001[a]
IIEF (orgasm)	4.15±3.56	5.70±3.33	0.057	4.33±3.41	6.47±2.76	<0.001[a]
IIEF (sexual desire)	4.95±2.01	5.25±1.77	0.651	4.61±1.69	5.76±1.59	<0.001[a]
IIEF (sexual satisfaction)	4.30±3.84	6.05±3.50	0.061	4.78±3.22	7.41±3.17	<0.001[a]
IIEF (overall satisfaction)	3.85±2.08	5.35±1.13	0.014[a]	4.04±1.76	5.88±1.92	<0.001[a]
IIEF (total)	28.20±18.01	37.75±17.31	0.049[a]	29.73±14.89	43.86±14.74	<0.001[a]
AMS (psychologic)	10.19±17.09	10.48±5.96	0.902	7.20±4.78	9.57±5.16	<0.001[a]
AMS (somatovegetative)	18.92±16.53	25.47±18.06	0.028[a]	14.10±6.20	21.28±14.60	<0.001[a]
AMS (sexual)	14.50±16.94	15.09±16.35	0.463	11.60±6.50	12.40±5.27	0.233
AMS (total)	37.23±20.21	47.48±24.34	0.007[a]	32.89±15.01	43.67±21.43	<0.001[a]

Group 1: TDS patients with metabolic syndrome, Group 2: TDS patients without metabolic syndrome, IIEF: International Index of Erectile Function, AMS: The Aging Males' Symptoms scale, [a]: statistical significance, $p < 0.05$ in paired t-test between before and after TRT

DISCUSSION

TDS was officially jointly defined as late-onset hypogonadism (LOH) by the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), and the European Association of Urology (EAU) in 2005 [7]. On the basis of that definition, the Korean Society for Aging Male Research (KOSAR) and the Korean Society for Sexual Medicine and Andrology suggested a Korean recommendation appropriate for domestic circumstances in 2006 [8]. Since then, in 2008, ISA, ISSAM, EAU, EAA (European Academy of Andrologya), and ASA (American Society of Andrology) jointly announced the second amendment recommendation for the diagnosis, treatment, and monitoring of patients with testosterone deficiency. Although the definition of LOH remained the same as in the original recommendation, LOH and TDS are recommended to be used together [9].

Metabolic syndrome refers to the expression of risk factors of cardiovascular diseases such as obesity, hypertension, dyslipidemia, and glycometabolic abnormality, in addition to which the insulin resistance observed in type 2 diabetes is also characteristic [10,11]. Such metabolic defects occur at the same time and influence the overall body from the cardiovascular system to the nervous system to the endocrine system [11]. In particular, the relationship between metabolic syndrome and TDS has been the subject of consistent research. In 1977, Phillips reported that male patients with myocardial infarction exhibited insulin resistance and dyslipidemia along with a trend for reduced testosterone, and since then, there have been many reports studying the relationship between TDS and each risk factor of metabolic syndrome [12].

Among the risk factors for metabolic syndrome, insulin resistance is an important characteristic of type 2 diabetes mellitus, and the hyperinsulinemia caused by it is an important risk factor for the occurrence of cardiovascular disease. In a study conducted of healthy male adults, an inverse proportional relationship of testosterone value and blood insulin concentration was reported [13]. Also, in the NHANES (National Health and Nutrition Examination Survey) conducted for 1,413 male adults, it was reported that free testosterone and bioavailable testosterone are related to diabetes and that low testosterone can be a risk factor for diabetes mellitus [14]. Also, in reverse, many researchers have reported that compared to patients without diabetes mellitus, diabetes mellitus patients have lower testosterone values [15,16]. Dhindsa et al stated that 33% of 103 patients with type 2 diabetes mellitus showed a reduction in free testosterone [17]. In addition, other research has shown that type 2 diabetes mellitus patients have a reduction in total testosterone [18]. In the present study, in the TDS patients, the FBG value dropped after TRT, and it was indirectly shown that diabetes mellitus and testosterone values were related. Simply FBG alone, however, lacks the determinative evidence to explain the interrelationship between diabetes and testosterone, and it appears that further tests such as HbA1c, glucose tolerance test, and insulin value, are needed.

Obesity, which is an important definitive factor of metabolic syndrome, is independently related to each of the different components of metabolic syndrome. As the level of obesity increases, evidence has shown that the testosterone value drops [19,20]. In addition, visceral obesity is reported to have a greater interrelationship with the testosterone value than other forms of obesity [21,22]. Vermeulen et al, in a study targeting 57 elderly men in their 70s, reported that the lower the testosterone value, the higher the obesity and insulin values [23]. Also, studies have reported that when TRT was performed on those with obesity, visceral fat was reduced [24]. In this study, both group 1 (with metabolic syndrome) and group 2 (without metabolic syndrome) showed statistically significant reductions in BMI and waist circumference.

Dyslipidemia increases the risk of cardiovascular diseases. The increased total cholesterol and LDL cholesterol and triglyceride are atherogenic factors, and HDL cholesterol is an atherogenesis-preventive factor. In various studies, it has been reported that when the testosterone value is decreased, the HDL cholesterol value is decreased as well [25], whereas on the other hand, total cholesterol, LDL cholesterol, and triglyceride are increased [26,27]. In a large-scale study with monitoring observation for 13 years (the Multiple Risk Factor Intervention Trial), as the testosterone value decreased in elderly patients, triglyceride increased, whereas HDL cholesterol decreased [28]. Whitsel et al, through meta-research, reported that in TDS patients after TRT, total cholesterol and LDL cholesterol decreased, whereas HDL cholesterol significantly increased [29]. There are also studies that report that HDL cholesterol decreased after TRT [30], but not all studies are consistent. In this study, after TRT, total cholesterol and LDL cholesterol significantly decreased in group 2 (without metabolic syndrome), and, although not statistically significant, total cholesterol, LDL cholesterol, and triglyceride decreased in group 1 (with metabolic syndrome).

To date, there have been many studies on the interrelationship of metabolic syndrome and TDS, but none reporting the effectiveness of TRT for TDS patients according to the existence of metabolic syndrome. In this study, when we compared the treatment effectiveness after TRT, we found that the group without metabolic syndrome showed improvements in more serum variables and greater improvements in the subjective assessments. If metabolic syndrome and testosterone reduction are interrelated, it is likely that the testosterone reduction had been ongoing for a longer period in group 1 regardless of the onset of the symptoms. Because the TRT period was the same for both groups, it is possible that the effect of treatment response may have appeared late. Thus, it appears necessary to conduct a comparative study on the point at which the treatment effect appears after TRT by extending the study period in the future. Moreover, it is unknown whether metabolic syndrome patients had been receiving proper treatment

for their metabolic syndrome. Thus, it is necessary to categorize the patients according to the existence of treatment for metabolic syndrome during the TRT period and to compare the differences. Despite these limitations, however, it is significant that we were able to compare TRT treatment effectiveness in TDS patients according to the presence of metabolic syndrome.

CONCLUSIONS

When TRT is performed on patients with TDS, those also with metabolic syndrome showed improvements in fewer of the serum variables and survey results than did those without metabolic syndrome. Thus, the correction of metabolic syndrome, such as diabetes, obesity, and hypertension, should be considered during TRT.

Conflicts of Interest

The authors have nothing to disclose.

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