

The Efficacy of Testosterone Ointment on Insulin Resistance in Men with Metabolic Syndrome

Hajime Ueshiba*

Department of Internal Medicine, Toho University School of Medicine, Tokyo, Japan

*Corresponding author: Hajime Ueshiba, Department of Internal Medicine, Toho University School of Medicine, Tokyo, Japan, Tel: 81 3-3762-4151; E-mail: ueshiba@med.toho-u.ac.jp

Received date: April 24, 2017; Accepted date: May 08, 2017; Published date: May 15, 2017

Copyright: © 2017 Ueshiba H. This is an open-access article distributed under the terms of the creative commons attribution license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Low levels of testosterone are related with metabolic syndrome and type 2 diabetes mellitus. Testosterone levels are considered to be negatively correlated with insulin resistance and HbA1c levels. There are also reports that testosterone replacement therapy reduces insulin resistance or improves glycemic control.

Transdermal administration of testosterone ointment (Glowmin) is a method of drug administration that keeps blood concentrations stable and constant. In this study, testosterone ointment (Glowmin) was administrated as a testosterone supplement to male metabolic syndrome with low free testosterone levels. This study included 5 male metabolic syndrome with low free testosterone levels (mean age, 50.6 ± 8.8 years; mean BMI, 29.5 ± 3.1 kg/m²; mean waist circumference, 97 ± 7 cm; free testosterone levels, <8.5 pg/ml; values indicate means ± SD). Glowmin was administrated to the submandibular area at a dose of 0.3 g twice a day for 6 months. Three months after administration, a significant decrease was observed in fasting immunoreactive insulin levels, homeostasis model assessment for insulin resistance, total cholesterol and LDL-C. Six-months after administration, each of these parameter estimates remained steady.

In conclusion, transdermal administration of testosterone ointment (Glowmin) gradually reduced insulin resistance in male metabolic syndrome with low free testosterone levels.

Keywords Metabolic syndrome; Testosterone; Glycemic control

Introduction

Epidemiological studies consistently report that men with metabolic syndrome or type 2 diabetes mellitus frequently have low testosterone levels [1-4]. In addition, longitudinal demographic studies show that low levels of testosterone and sex hormone-binding globulin (SHBG) are predictive markers for the development of metabolic syndrome and type 2 diabetes mellitus [5-8]. Testosterone in the blood exists in 3 forms: free testosterone (FT, 2%), albumin-bound testosterone (20-40%), and SHBG-bound testosterone (60-80%) [9]. Bioavailable testosterone fractions (corresponding to free and albumin-bound testosterone) decreases in states of insulin resistance [1,4,7,10]. However, only FT is a directly measurable parameter.

Testosterone levels are considered to be negatively correlated with insulin resistance and HbA1c levels [11-13]. There are also reports that testosterone replacement therapy reduces insulin resistance or improves glycemic control [13-17]. One report has shown that, in a hypogonadal man with type 2 diabetes mellitus, testosterone replacement therapy reduced insulin resistance and improved glycemic control [13]. At present, testosterone replacement therapy is administered mainly by Enarmon-Depot injection and has an immediate and reliable effect. However, the therapy induces extremely large fluctuations in blood testosterone concentrations; consequently, subjective symptoms may vary and adverse events such as plethora may occur. Because no self-injection kit has been approved, frequent visits to an outpatient clinic for injections are also a problem.

Meanwhile, transdermal administration of testosterone ointment (Glowmin, Daitou Pharma, Japan) is a method of drug administration that keeps blood concentrations stable and constant. However, there are only a few reports that assess whether this mode of administration has an immediate and reliable effect.

In this study, testosterone ointment (Glowmin) was administrated as a testosterone supplement to men with metabolic syndrome who had low FT levels. The effect on insulin resistance was then assessed.

Subjects and Methods

This study included 5 men with metabolic syndrome who had low FT levels (mean age, 50.6 ± 8.8 years; mean body mass index [BMI], 29.5 ± 3.1; mean waist circumference [WC], 97 ± 7 cm; values indicate means ± standard deviation [SD]). This sample included 3 men receiving oral antihypertensive agents and 2 men receiving oral antihyperlipidemic agents. A low FT level was defined as less than 8.5 pg/ml, which is the level recommended by the diagnostic algorithm for late-onset hypogonadism (LOH) syndrome [18]. Metabolic syndrome was defined as a case meeting the Japanese diagnostic criteria [19]. Specifically, men with metabolic syndrome included those with a WC ≥ 85 cm and who met at least 2 of the following 3 criteria: 1) hypertriglyceridemia (≥ 150 mg/dl) and/or low levels of high-density lipoprotein (HDL) cholesterolemia (<40 mg/dl); 2) systolic blood pressure ± 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg; and 3) fasting plasma glucose (FPG) level ≥ 110 mg/dl. All subjects provided informed consent, and Glowmin was administrated to the submandibular area at a dose of 0.3 g twice a day for 6 months. The

following parameters were measured before administration of Glowmin and 1, 3, and 6 months after administration, and their fluctuations were analyzed: BMI, WC, FPG, fasting immunoreactive insulin (F-IRI), HbA1c, homeostasis model assessment for insulin resistance (HOMA-R), total cholesterol (TCHO), triglycerides (TG), HDL-cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C, calculated by the Friedewald equation), and FT. HOMA-R was calculated from FPG and F-IRI as follows: $HOMA-R \pm FPG [mg/dl] \times F-IRI [\mu IU/ml] / 405$. Free testosterone level was measured by free testosterone RIA kit (Sceti Medicalabo, Sakura city, Chiba, Japan).

The results were expressed as means \pm SD. Paired t-tests were performed to compare parameters before and after the administration

of Glowmin. A p-value of less than 0.05 was considered to indicate statistical significance.

This study was conducted with the approval of the Ethics Committee of Toho University Omori Medical Center (No. 25-104).

Results

The parameter estimates before administration of Glowmin were as follows: BMI, 29.5 ± 3.1 ; WC, 97 ± 7 cm; FPG, 112 ± 6 mg/dl; F-IRI, 25.1 ± 8.5 μ IU/ml; HOMA-R, 7.0 ± 2.7 ; HbA1c, $5.8 \pm 0.3\%$; TCHO, 227 ± 31 mg/dl, TG, 185 ± 64 mg/dl; HDL-C, 43 ± 9 mg/dl; LDL-C, 147 ± 36 mg/dl; and FT, 5.9 ± 1.0 pg/ml (Table 1).

	Before	After 1M	After 3M	After 6M	
BMI (kg/m)	29.5 3.1	29.2 3.2	29.0 3.1	29.0 3.1	
WC (cm)	97 7	97 7	96 6	96 6	
FPG (mg/dl)	112 6	112 6	109 4	107 5	
F-IRI (μ IU/ml)	25.1 8.5	22.0 7.3	17.4 4.2	16.3 4.0	P<0.01
HbA1c (%)	5.8 0.3	5.8 0.4	5.8 0.2	5.5 0.3	
HOMA-R	7.0 2.7	6.1 2.3	4.7 1.2	4.2 1.2	P<0.01
TCHO (mg/dl)	227 31	221 36	203 26	201 25	P<0.05
TG (mg/dl)	185 64	181 24	178 30	177 31	
HDL-C (mg/dl)	43 9	43 7	46 12	46 11	
LDL-C (mg/dl)	147 36	142 43	121 36	119 34	P<0.05
Free-Testo (pg/ml)	5.9 1.0	6.6 1.2	7.7 0.6	7.7 0.6	P<0.05

Table 1: Changes of each parameter before and after administration of testosterone ointment.

One month after administration, FT increased significantly to 6.6 ± 1.2 pg/ml ($p < 0.05$), but no significant changes were observed in any of the other parameters (Table 1). Three months after administration, a significant decrease was observed in F-IRI (to 17.4 ± 4.2 μ IU/ml, $p < 0.01$), HOMA-R (to 4.7 ± 1.2 , $p < 0.01$), TCHO (to 203 ± 26 mg/dl, $p < 0.05$), and LDL-C (to 121 ± 36 mg/dl, $p < 0.05$) (Table 1). FT increased significantly to 7.7 ± 0.6 pg/ml, $p < 0.05$ (Table 1). Six-months after administration, each of these parameter estimates remained steady (Table 1). There were no significant fluctuations in the other parameters (Table 1). The fluctuations in F-IRI, HOMA-R, TCHO, LDL-C, and FT for each subject are shown in (Figures 1-5), respectively. All men showed decreases in F-IRI and HOMA-R. FT increased in all patients. For TCHO and LDL-C, the extent of decrease appeared to vary among individuals.

Discussion

Low testosterone level is thought to impair insulin sensitivity and increase body fat percentage, and is associated with truncal obesity, dyslipidemia, hypertension, and cerebrovascular diseases [20]. An epidemiological study has shown that the prevalence of testosterone deficiency is as high as 40% in men with type 2 diabetes mellitus [4]. Furthermore, it has been reported that individuals with metabolic syndrome have lower levels of endogenous total testosterone and FT than those without metabolic syndrome [21]. In addition, low

testosterone level is a predictive factor for the development of insulin resistance, metabolic syndrome, and type 2 diabetes mellitus [22].

In 2006, Kapoor et al. [1] reported that testosterone replacement therapy reduced insulin resistance in hypogonadal men with type 2 diabetes mellitus [13]. After testosterone ester was intramuscularly injected at a dose of 200 mg once every 2 weeks for 3 months, insulin resistance (-1.73 , HOMA-R) and HbA1c levels (-0.37%) reduced. In addition, improvements in WC, leptin, and TCHO were also observed. Even with transdermal supplementation of testosterone (2% testosterone gel), insulin resistance reduced by 15% after 6 months and 16% after 12 months in hypogonadal men with type 2 diabetes mellitus or metabolic syndrome [17].

In this study, testosterone ointment (Glowmin) was administered to men with metabolic syndrome who had low FT levels to supplement testosterone, and the effects on glucose and lipid metabolism were assessed. The improvement of insulin resistance and serum lipid level was maintained even 6 months after administration. The FT levels significantly increased 1 month after administration, and the metabolic parameters were assumed to have improved gradually. In this study, Glowmin was administered to the submandibular area at a dose of 0.3 g twice a day. Studies on the effects of Glowmin on metabolic parameters and the incidence of adverse events might need to be conducted with administration to the abdomen at a dose of 0.6 g per day, and improved administration methods would facilitate long-term

use. The mechanism that testosterone improves HOMA-R and LDL-C without changing BMI, glycemia and HbA1c levels is uncertain at present. We speculate that the decrease of visceral fat will become deeply involved. In this study, the improvement of BMI and waist circumference were not demonstrated. However, if we have more longer period of observation, waist circumference may be reduced, because waist circumference has tendency to be decreased compared with values before treatment.

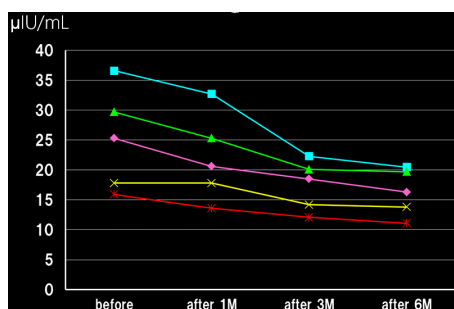


Figure 1: F-IRI.

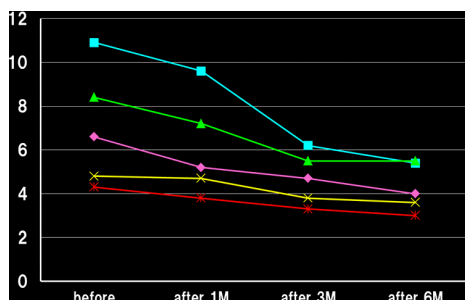


Figure 2: HOMA-R.

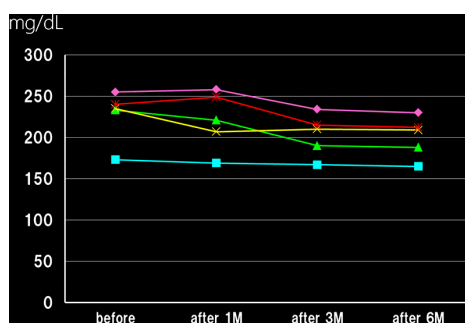


Figure 3: TCHO.

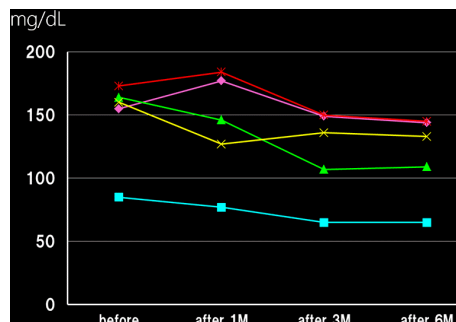


Figure 4: LDL-C.

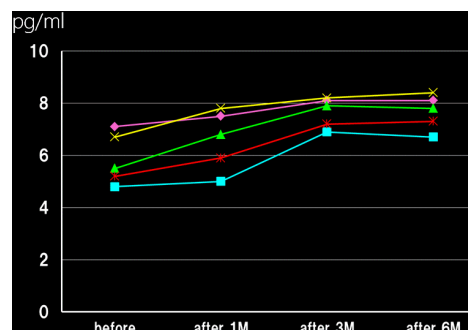


Figure 5: Free-testosterone.

Conclusion

Transdermal administration of testosterone ointment (Glowmin) gradually reduced insulin resistance in men with metabolic syndrome who had low FT levels.

References

1. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH (2007) Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlation with bioavailable testosterone and visceral adiposity. *Diabetes Care* 30: 911-917.
2. Ding EL, Song Y, Malik VS, Liu S (2006) Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 295: 1288-1299.
3. Hofstra J, Loves S, Van Wageningen B, Ruinemans-Koerts J, Jansen I, et al. (2008) High prevalence of hypogonadotropic hypogonadism in men referred for obesity treatment. *Neth J Med* 66: 103-109.
4. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, et al. (2004) Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab* 89: 5462-5468.
5. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB (2000) Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care* 23: 490-494.
6. Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L (1996) Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus predict the development of non-insulin-dependent diabetes mellitus in men. *Am J Epidemiol* 143: 889-897.

7. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL (2002) Rancho Bernardo Study Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. *Diabetes Care* 25: 55-60.
8. Laaksonen DE, Niskanen L, Punnonen K, Nyssönen K, Tuomainen TP, et al. (2004) Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 27:1036-1041.
9. Vermeulen A, Verdonck L, Kaufman JM (1999) A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 84: 3666-3672.
10. Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, et al. (2007) Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES?). *Diabetes Care* 30:234-238.
11. Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, et al. (2005) Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care* 28:1636-1642.
12. Marin P, Holmång S, Jönsson L, Sjöström L, Kvist H, et al. (1992) The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord* 16:91.
13. Kapoor D, Goodwin E, Channer KS, Jones TH (2006) Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol* 154:899-906.
14. Mårin P (1995) Testosterone and regional fat distribution. *Obes Res Suppl* 4: 609S-612S.
15. Simon D, Charles MA, Lahlou N, Nahoul K, Oppert JM, et al. (2001) Androgen therapy improves insulin sensitivity and decreases leptin levels in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. *Diabetes Care* 24:2149-2151.
16. Naharci MI, Pinar M, Bolu E, Olgun A (2007) Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism. *Endocr Pract* 13: 629-635.
17. Sonmez A, Taslipinar A, Tapan S, Serdar MA (2011) Comment on: Jones et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 Study). *Diabetes Care* 2011;34:828-837. *Diabetes Care* 34: e172.
18. The Japanese Society of Urology/ The Japanese Society of Men's Health? The clinical guideline of LOH syndrome?working group:Late-onset hypogonadism syndrome(LOH syndrome) clinical guideline.Jihou Corporation,Tokyo,2007
19. Seino Y, Daida H, Teramoto T, Nakao K, Makino H, et al. (2005) The definition and diagnostic standard of metabolic syndrome. *J Jpn Soc Inter Med* 94: 794-809.
20. Wang C, Jackson G, Jones TH, Matsumoto AM, Nehra A, et al. (2011) Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. *Diabetes Care* 34:1669-1675.
21. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT (2010) Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systemic review and meta-analysis of observation studies. *Int J Epidemiol* 40: 189-207.
22. Haring R, Volzke H, Felix SB, Schipf S, Dorr M, et al. (2009) Prediction of metabolic syndrome by low serum testosterone levels in men: results from the study of health in Pomerania. *Diabetes* 58: 2027-2031.