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EFFECT OF A COMBINATION OF OMEGA-3 AND ORAL TESTOSTERONE UNDECANOATE ON SERUM TESTOSTERONE LEVELS IN PATIENTS WITH TESTOSTERONE DEFICIENCY

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ABSTRACT

Background and Objective

Oral testosterone undecanoate (TU) is taken up by the intestinal lymphatic system. Thus, the dietary lipid content affects TU absorption. This study aimed to investigate the effect of combined omega-3 fatty acids (OMG3) and oral TU on serum testosterone levels in patients with testosterone deficiency (TD).

Material and Methods

Sixty consecutive patients with symptomatic TD and low serum total testosterone (TT) levels were enrolled and divided randomly into group 1, oral TU 80 mg twice daily for 30 days, and group 2, OMG3 and oral TU 80 mg twice daily for 30 days. Serum TT concentrations and male function scales were evaluated at baseline and 7 days and 1 month post-treatment. Dietary habits were investigated, and caloric and lipid intakes were measured during the treatment periods.

Results

The groups did not differ in terms of mean age, body mass index, comorbidities, initial serum TT concentrations, and IIEF/AMS scores. After 7 days and 1 month of treatment, serum TT concentrations were only significantly increased in group 2. The degree of increase in TT was higher in group 2 than in group 1 at 7 days and 1 month, although the difference was only significant at 1 month. Both groups

exhibited significant improvements in IIEF and AMS scores at 1 month, with no significant inter-group difference. A diet diary study revealed that 23.3% and 20% of both groups did not eat breakfast and both groups consumed <12 g of lipids and <500 Kcals, without significance differences.

Conclusion

We observed a significant increase in serum TT concentration after 1 month of treatment with the combination of OMG3 and oral TU, compared to with oral TU monotherapy. Therefore, the combination of OMG3 and oral TU can be considered for the treatment of TD in Korean patients with irregular breakfast habits.

Key Words: *lipid; omega-3; testosterone; testosterone deficiency; testosterone undecanoate*

INTRODUCTION

Testosterone deficiency (TD) is a condition associated with a low serum total testosterone (TT) concentration and symptoms of menopause such as sexual dysfunction. Clinically, testosterone treatment (testosterone replacement therapy, TRT) is administered to men with a serum TT concentration <300–350 ng/dL.[1] Several TRT options are currently available.[2] Of these, continuous oral testosterone administration is limited by complications such as liver toxicity problems.[3,4] However, oral testosterone undecanoate (TU) is supplemented with oleic acid to compensate for the disadvantages of alkylated testosterone. This supplementation allows for the absorption of testosterone through the intestinal lymphatics, thus avoiding liver toxicity and drug inactivation.[5]

Although oral TU is used widely as a primary treatment for TD worldwide,[5] the absorption rate of this drug is high only when it is taken with fatty meals, which promote the effective absorption through the intestinal lymphatic vessels.[6] Studies on the bioavailability of drugs with and without meals have demonstrated that taking oral TU with a meal increases the pharmacokinetic effects, compared to drug ingestion while in a fasting state.[7] A Western clinical study that blood TU concentrations according to the dietary lipid content identified that consuming a normal Western meal, rather than a fatty meal, before taking TU is sufficient to enhance its effects.[5] However, that study only investigated Western diets, and it remains uncertain whether the same effect would be observed in Asian populations, which generally have different dietary habits.

In Korea, the lipid content in the breakfast of a typical adult man is likely to be less than a Western meal. Moreover, skipping breakfast or consuming a simple breakfast, which is common in Korea, is also likely to interfere with the absorption of TU.[8] Therefore, Korean men would likely require an additional lipid supplement to ensure proper TU absorption. We have considered supplementing TU with omega-3 (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]; OMG3) to compensate for the insufficient lipid intakes of Korean men. Several studies have demonstrated that OMG3 improves the function of endothelial cells and can prevent cardiovascular diseases.[9] In this study, we aimed to determine whether the combination of OMG3 and TU would improve the absorption of TU and better enable the maintenance of stable high blood testosterone concentrations when compared with TU monotherapy in patients with TD. We further investigated whether this combination therapy would improve the symptoms of TD.

METHODS

This study enrolled 60 consecutive men aged >40 years who had symptomatic TD and a low serum TT concentration (<350 ng/dL). All patients

who agreed to receive TRT were included. Patients who had received TRT for TD within the last 6 months, had been diagnosed with prostate cancer or breast cancer, and had a serum prostate-specific antigen concentration >3.0 ng/mL and hematocrit >52% were excluded from the study.

The patients were randomly divided into two groups using the block randomization method. Patients in group 1 (n=30) received oral TU (80 mg twice daily, directly after meals). Patients in group 2 (n=30) received a combination of OMG3 (1500 mg [3 tablets] in the morning, 500 mg [1 tablet] in the evening) and oral TU (80 mg twice daily, directly after meals). Both regimens were administered for 1 month.

For each patient, the medical history and underlying comorbidities were investigated, and the body mass index (BMI) was calculated. Radioimmunoassays to determine the serum TT concentrations were performed using blood samples collected in the morning (between 8:00 and 11:00). The International Index of Erectile Function (IIEF) and Aging Males' Symptoms Scale (AMS) scores were administered at baseline and 1 month after treatment to evaluate the symptoms of TD patients. The patients used 3-day diet diaries to record the number of times that breakfast was consumed and the types of foods consumed after 7 days and 1 month of treatment. The recorded contents and amounts of the meals were converted to the amounts of food ingredients before cooking, and the calorie and lipid amounts were calculated using the National Standard Food Ingredients Table.[10]

For the statistical analysis, independent samples and paired *t*-tests were used to compare serum TT levels between the two groups. P-values <0.05 were considered statistically significant.

Ethics Statement

The study protocol was reviewed and approved by the Institutional Review Board of Seoul Paik Hospital. The research conformed to the principles outlined in the Declaration of Helsinki.

RESULTS

Groups 1 and 2 did not differ significantly with respect to the mean age (58.0 vs. 56.4 years, P=0.866), BMI (24.8 vs. 24.1, P=0.723), comorbidities (P=0.376), or initial serum TT concentration (P=0.637) (Table 1).

After 7 days of treatment, the serum TT concentration significantly increased in group 2 (P=0.029), but not in group 1 (P=0.809). At 1 month, the serum TT concentration in group 2 had increased significantly relative to the baseline (P=0.001), whereas no significant increase was observed in group 1 (P=0.115) (Figure 1). When we compared the changes in serum TT concentrations after 7 days of treatment, the degree of increase was higher in group 2 than in group 1, although this difference was not statistically significant (P=0.241). At 1 month, however, the degree of increase in the TT concentration was significantly higher in group 2 than in group 1 (P=0.002) (Figure 2). The number and frequency of patients who did not exhibit an increase in the serum TT concentration were significantly higher in group 1 than in group 2 (5, 16.7% vs. 0, 0%, P<0.001). At 1 month, this difference remained significant (4, 7.5% vs. 0, 0%, P<0.001). The two groups did not differ in terms of the baseline IIEF and AMS scores. Both groups exhibited significant within-group improvements in these scores at 1 month, with no significant inter-group difference. Notably, no serious drug-related adverse events were reported at 1 month in either group.

The 3-day diet diary analysis revealed similar numbers of patients who did not eat breakfast more than once in both groups (group 1 vs. 2: 7, 23.3% vs. 6, 20%, nonsignificant), and this pattern remained at the 1-month analysis. Regarding the lipid contents in breakfast meals, both groups reported consuming <12 g of lipids, and this

TABLE 1 Baseline Characteristics of Both Groups

	Group I (n=30)	Group II (n=30)	*p*-value
Age	58.0 ± 8.3	56.4±7.2	0.866
BMI (Kg/m^2)	24.8 ± 2.5	24.1±2.9	0.723
Comorbidities, N			0.376
None	10/30	8/30	
Hypertension	9/30	10/30	
Diabetes Mellitus	5/30	4/30	
Dyslipidemia	7/30	5/30	
Hepatobiliary disease	2/30	4/30	
Pulmonary disease	2/30	1/30	
IIEF total	25.52 ± 13.58	23.24 ± 13.1	0.213
Erectile function	10.12 ± 6.03	9.60 ± 7.08	0.116
Orgasmic function	3.21 ± 3.19	3.04 ± 2.15	0.347
Sexual desire	4.03 ± 1.50	3.66 ± 1.87	0.153
Intercourse satisfaction	4.12 ± 2.90	4.01 ± 2.03	0.430
Overall satisfaction	3.85 ± 1.88	3.50 ± 1.81	0.219
AMS total	51.53 ± 13.02	52.39 ± 14.28	0.532
Psychogenic	14.49 ± 8.11	14.56 ± 7.08	0.741
Somatic	19.42 ± 6.90	19.42 ± 5.75	0.880
Sexual	17.88 ± 5.80	18.27 ± 6.02	0.230
Total testosterone (ng/dL)	290.40±50.31	268.92±43.22	0.637

BMI, body mass index; IIEF, International Index of Erectile Function; AMS, Aging Males' Symptoms Scale. Group I: oral testosterone undecanoate only, Group II: combination of oral testosterone undecanoate and Omega-3. Data are shown as the mean ± standard deviation.

difference was not significant. Both groups also reported consuming <500 kcal at breakfast, which was nonsignificantly different.

DISCUSSION

Several previous studies have demonstrated the significant effects of foods on drug pharmacokinetics by increasing, decreasing, and delaying drug absorption.[11,12] Studies of oral TU have shown that the drug molecules are encased in chylomicrons when consumed with a meal, thus allowing TU to bypass the liver and enter the peripheral circulation through the intestinal lymphatic system. Consequently, the TT concentration in the blood increases.[5] In a single-dose randomized crossover study, Bagchus et al.[8] demonstrated that only a small amount of TU was absorbed when taken in a fasting state, whereas ingestion with food dramatically improved the bioavailability. Despite these observations, the amount of food that would enhance the absorption of TU is unclear. Particularly, clinical recommendations to consume fatty meals to increase the absorption rate of TU may be ambiguous from the patient's perspective.[13]

To address this ambiguity, Schnabel et al.[5] studied the pharmacodynamics of TU absorption when taken with meals containing varying

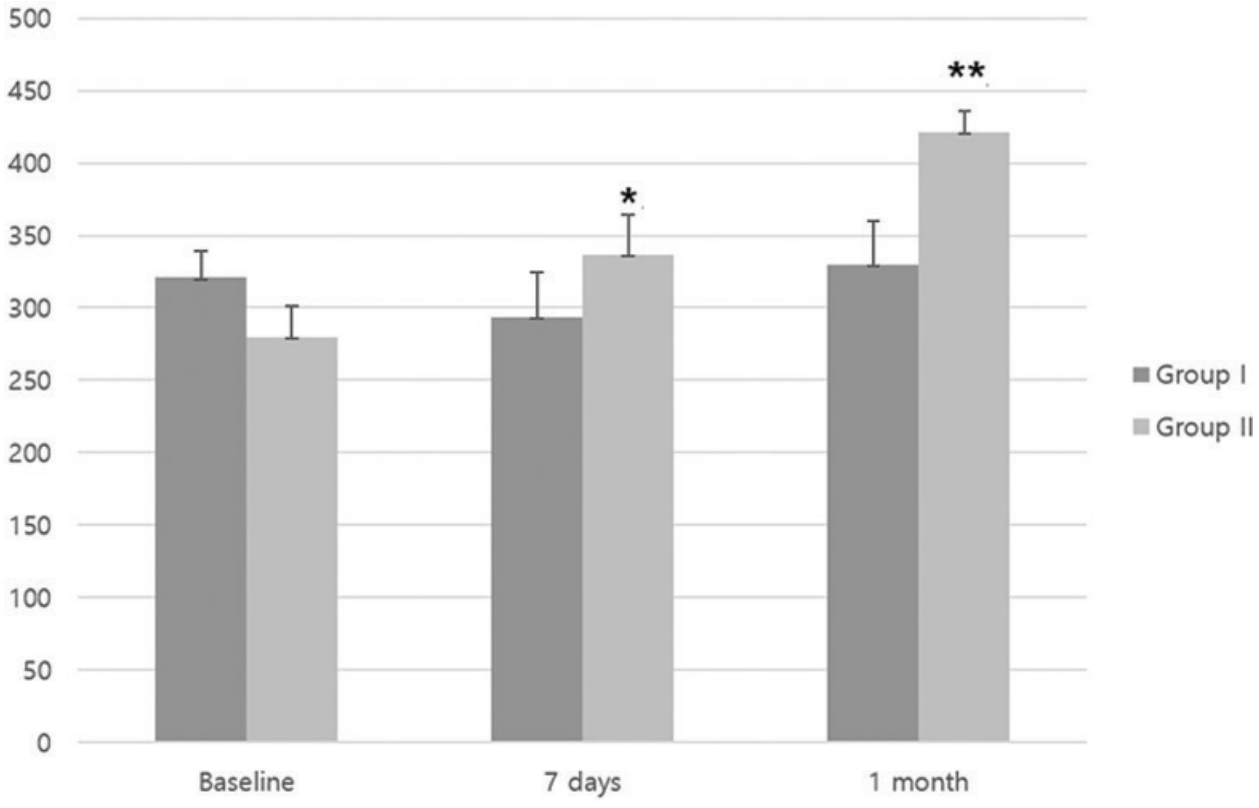

FIG. 1 Total testosterone (TT) concentrations (ng/dL) at baseline and after 7 days and 1 month of treatment in both groups. Only group II exhibited significant increases in TT levels at 7 days and 1 month after treatment. *, P<0.05 and **, P<0.01 (compared with baseline; paired *t*-test). Group I: oral TU monotherapy, Group II: combination of OMG3 and TU. OMG3, omega-3 fatty acids; TU, testosterone undecanoate.

amounts of lipids. In that study, the group that consumed a normal diet containing 19 g of lipids achieved significantly higher blood TT concentrations than the group that consumed very little lipids (5 g). However, consumption of a fatty meal (≥44 g) did not yield further significant improvements.[5,10] Therefore, the authors concluded that a normal Western diet would not interfere with the proper absorption of TU. However, with respect to the serum testosterone levels, differences between this study results and clinical findings were existed. Some patients might not have taken their drugs twice daily and immediately after meals. In some patients, the blood TT concentrations did not remain in the normal range even when oral TU was taken correctly. In our previous retrospective study, published in 2010,[14] we compared testosterone (T)-gel and oral TU. Although T-gel was fixed at the initial dose and oral TU was increased according to the TT concentration in the clinical protocol, the oral TU group required a significantly longer time to reach the highest TT concentration, which was significantly lower than the highest concentration in the T-gel group. Ultimately, there was no significant difference between the two groups in the final TT level after dose elevation was performed in TU group.[14] However,

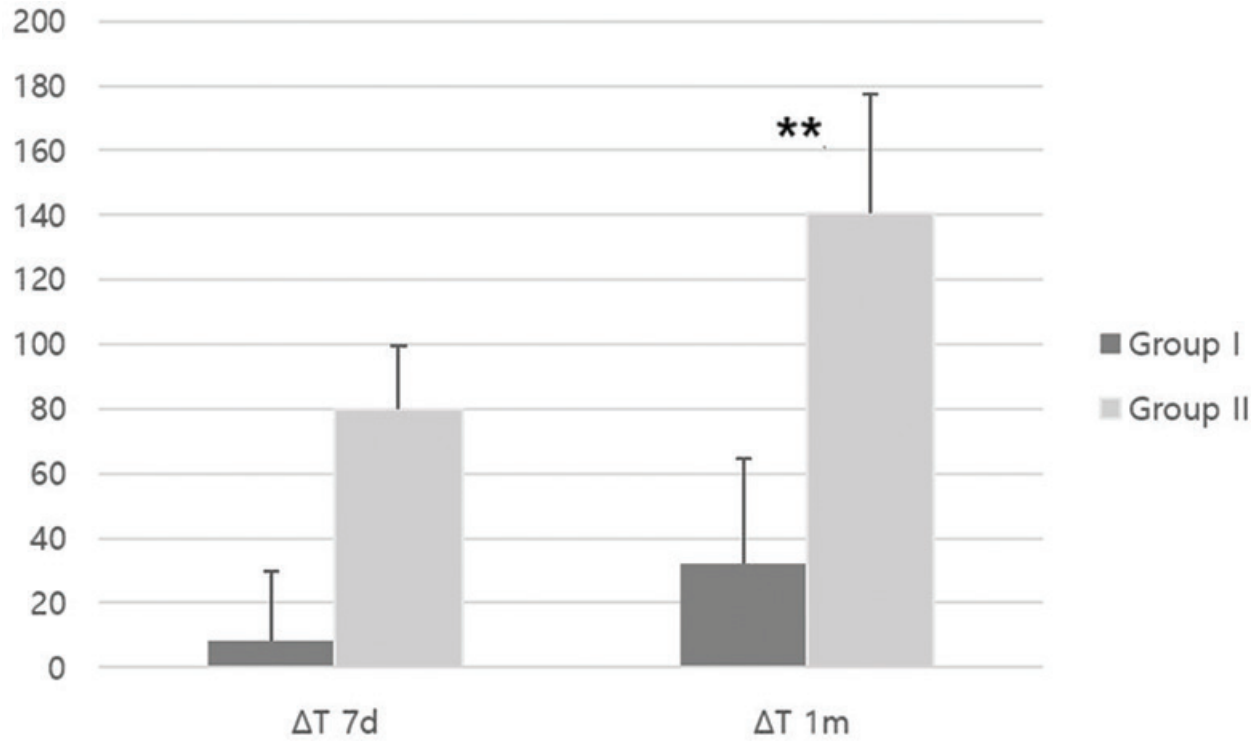

FIG. 2 Between-group comparison of the changes in the serum total testosterone (TT) concentration (ng/dL) from baseline to 7 days and 1 month after treatment. The difference between the two groups was significant at 1 month (**, P=0.002). ΔT 7d: the change in TT from baseline to 7 days; ΔT 1m: the change in TT from baseline to 1 month. Group I, oral TU monotherapy; Group II, combination of OMG3 and TU. OMG3, omega-3 fatty acids; TU, testosterone undecanoate.

these results suggest a problem with the absorption rate of oral TU, and we suspected that the difference might be attributable to the lower lipid content in the Korean diet relative to the Western diet and/or the tendency to skip or consume only a small breakfast. According to several studies on the fasting rate and breakfast consumption habits of 59-year-old adults in Korea,[15] 34.6% of the participants habitually skipped breakfast or consumed irregular meals, consistent with the results of the current study. Accordingly, in this study, the amount of OMG3 taken in the morning was designed to be greater than that in the evening considering the lower amount of lipids consumed at breakfast. In present study, 20% of subjects in both groups skipped breakfast, which led to the poor absorption of TU in group 1.

The recommended daily nutritional intake for a Korean adult man is 2000–2500 kcal, and the recommended lipid intake should account for approximately 20% of the total energy.[8] According to the National Health and Nutrition Survey of the Ministry of Health and Welfare, the total lipid intake per day in the Korean population is 40–42 g. The total lipid intake per meal can thus be estimated by dividing this intake into three equal parts of 13–14 g. This already does not satisfy the lipid intake per meal of 19 g identified in a previous study,[5] and the amount would decrease further in the morning relative to lunch

and dinner for those who skipped breakfast or consumed a simple breakfast. In this study, the subjects reported a caloric intake at breakfast that would account for only 20% of the total caloric intake per day. Consequently, an additional intake of lipids would likely be required to ensure that Korean men could absorb TU properly.

The lipid intake guideline of the 7th revision of the Korean Nutritional Recommendations[16] suggests that oils rich in monounsaturated fatty acids such as olive oil and canola oil and fish, which are high in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) OMG3, as well as legumes, perilla oil, sesame oil, and walnuts, which are high in linolenic acid (the precursor to EPA and DHA with a low risk of lipid peroxidation), be consumed as the primary sources of lipids. To satisfy the above recommendations, we considered administering an OMG3 supplement with TU, as the previously observed beneficial properties[9] might also help to improve erectile dysfunction, a common symptom of TD. There are few clinical studies about OMG3 investigating male hypogonadism or erectile dysfunction except several animal studies.[17,18] Here, we combined OMG3 with TU to increase the absorption rate of oral TU and demonstrated statistically significant increases in TT concentrations after 7 days and 1 month of treatment relative to the baseline measurement, but only in the group that received the combination therapy. In addition, changes in the TT level from the baseline after 1 month were significantly higher in the OMG3 and TU combination group than the oral TU only group. Moreover, a significantly higher frequency of patients in the TU monotherapy group did not experience an increase in the TT concentration. This was expected, as a lack of proper TU absorption may prevent the serum TT concentration from increasing above the baseline. Taken together, our results demonstrate that supplementation with OMG3 improved the absorption of oral TU. Still, both groups achieved similar improvements in the AMS and IIEF scores relative to the baseline. We would have expected a significant difference in the IIEF scores and better TD symptom scores in the group receiving combined treatment if OMG3 had improved the endothelial function. However, it may be unrealistic to expect a sufficient treatment effect within a short study period such as 1 month. Therefore, we believe that a longer term study is required in the future.

This study had some limitations of note. First, this was a preliminary study with a small sample size, and there may not have been sufficient power to determine statistical significance. Moreover, the dietary patterns and caloric and lipid analyses were based on the patients' self-reported 3-day diet diaries and were therefore subject to reporting bias and error. We did not perform an assessment of the metabolic parameters that are closely related to TD and did not administer treatment for a substantially long duration. Consequently, it was difficult to identify meaningful improvements in symptoms due to TRT or OMG3. Finally, symptom severity was assessed only according to the results of subjective surveys; an objective evaluation was not performed.

CONCLUSIONS

In this study, we observed a significant increase in the serum TT concentration in patients receiving a combination of OMG3 and oral TU compared with those receiving oral TU monotherapy. In particular, the combination therapy significantly decreased the number of patients who did not achieve an increase in the serum TT concentration after treatment. Moreover, we confirmed that many patients in both groups skipped breakfast or did not consume sufficient amounts of calories and lipids at breakfast to promote the absorption of TU in the intestine. These findings suggest that adding

OMG3 to oral TU is beneficial for increasing serum TT levels. Therefore, combined OMG3 and oral TU treatment can be considered in Korean TD patients. Additional large and well-designed studies are needed to confirm and expand upon our findings.

CONFLICT OF INTEREST

The authors have no other conflicts of interest with regard to the content of this article.

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