The Effects of Gonadotropin Replacement Therapy on Metabolic Parameters and Body Composition in Men with Idiopathic Hypogonadotropic Hypogonadism

Key words
- idiopathic hypogonadotropic hypogonadism
- metabolic syndrome
- gonadotropin replacement therapy

Abstract

Testosterone replacement therapy (TRT) in idiopathic hypogonadotropic hypogonadism (IHH) slows the process of metabolic syndrome (MetS), diabetes mellitus, and cardiovascular diseases by its inverse effects on insulin resistance, dyslipidemia, and blood pressure. Since there are not enough data regarding the effects of gonadotropin replacement therapy (GRT), we aimed to investigate the impact of GRT on MetS parameters in IHH patients. Sixteen patients with IHH and 20 age and body mass index (BMI)-matched healthy controls were enrolled into the study. Patients were evaluated at baseline and 6 months after the GRT. Sex hormones, insulin like growth factor-1, prolactin, insulin, C-reactive protein (CRP), homocysteine, and lipid levels were measured at baseline and after the treatment. Anthropometric measurements, including BMI, body fat ratio (BFR), fat free mass (FFM), waist circumference, and waist-to-hip ratio (WHR), were also performed. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated. Body fat ratio, triglyceride, HOMA-IR, and CRP levels were higher, whereas bone age, fat free mass, and creatinine levels were lower in the patients with hypogonadism. HOMA-IR indices and basal insulin levels decreased significantly after 6 months of GRT compared with baseline levels. Triglyceride levels, and BFRs diminished significantly by an accompanying decline in WHR. FFM of the patients increased following the GRT. No significant changes were detected in CRP, homocysteine, total and LDL-cholesterol levels. Similar to TRT, hCG treatment decreases HOMA-IR, triglyceride levels, BFR and WHRs, and increases FFM in patients with IHH.

Introduction

Hypogonadotropic hypogonadism (HH) is a state of impaired testosterone secretion, which is due to a malfunction at either hypothalamic or pituitary level. HH is diagnosed in patients with low testosterone levels in the presence of low or normal gonadotropin concentrations [1]. In the absence of an identifiable cause of HH, it is called IHH [2]. The common consequences of male hypogonadism include decreased libido, erectile dysfunction, decreased muscle mass, osteoporosis, increased fat mass, loss of energy, changes in mood, and decreased secondary sex characteristics (especially decreased sexual hair) [3].

Testosterone replacement therapy is the most widely used treatment in patients with hypogonadism for inducing/preserving secondary sexual characteristics and sexual function. In subjects with HH, gonadotropins may be used instead of testosterone therapy, especially to provide fertility by induction of both hormonogenesis and spermatogenesis [4]. Gonadotropin therapy is initiated with human chorionic gonadotropin (hCG) alone, which may be sufficient to stimulate spermatogenesis and fertility, and if fertility cannot be achieved with hCG, FSH is added to hCG therapy. Treatment regimen is switched back to testosterone substitution following successful fertilization [2].

Hypogonadism is suggested to be one of the underlying causes of the metabolic syndrome (MetS) [5]. According to recent studies the association between the low testosterone levels and MetS was independent of BMI, and it was reported as an independent risk factor for type 2 diabetes mellitus (DM) [4,6–8]. Current epidemiological data indicated negative correlations between testosterone, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels, whereas a positive association was found between testosterone and high-density lipoprotein (HDL) cholesterol. This relationship has been attributed to the inverse association between testosterone and visceral fat, the development of oxidative stress and inflammation, and the protective effects of testosterone against insulin resistance, dyslipidemia, and inflammation [4–8].
lipoprotein (HDL) cholesterol levels [8,9]. Because of the relationship with diabetes, MetS, inflammation and dyslipidemia; low testosterone levels is accepted as a novel cardiovascular risk factor, besides the other already-known ones [10]. Low testosterone levels were inversely linked to coronary atherosclerosis [8–11], and associated with increased cardiovascular and all cause mortality [12,13]. TRT was shown not only to improve the symptoms of hypogonadism but also to recover the insulin resistance, dyslipidemia, and hypertension. Therefore, testosterone replacement therapy (TRT) has some potency to slow the process of DM and cardiovascular diseases by its positive effects on MetS components [11,13].

Although the positive effects of TRT on MetS have already been recognized, the positive or negative impact of GRT on MetS has not been addressed sufficiently, especially in prospective studies. The aim of the present study was to evaluate the effects of hCG treatment on MetS parameters, insulin resistance, and body composition in men with IHH.

Materials and Methods

Study design and patient selection

Sixteen male patients with IHH (mean age 27.5±10.5 years, range 17–48 years) and 20 healthy controls were included in the study. All patients were diagnosed according to clinical findings of hypogonadism (such as low testis volumes, decreased body and facial hair, delayed puberty, eunochoidal stature), subnormal testosterone levels in the presence of low or normal gonadotropins. Patients were excluded if they had any other hormonal and systemic disease, or if they used any medication for hypogonadism in the last 6 months preceding the replacement therapy. The participants of the control group were selected among healthy males who were referred to the Outpatient Clinic of Endocrinology and Metabolism for check-up. All patients and controls gave written informed consent and the local research ethics committee approved the protocol.

Patients

The onset of IHH was before the onset of puberty in all patients. Three patients desired fertility. Only one patient had received fertility treatment with GRT for 6 months and had a child before the start of the study. This patient had not been treated for IHH during the past one year. The remaining 15 patients were naive for GRT. None of the participants had any contraindication to GRT.

Treatment and follow-up procedures

The patients were treated with human chorionic gonadotropin (hCG) as a substitution for LH. Intramuscular injections of hCG 5000 IU were administered 3 times a day for 6 months. Physical examination measurement of height, weight, head-pubis and pubis–heel ratio, body mass index (BMI), pattern of axillary and pubic hair, penis size, and testes volumes were recorded. Thyroid, breast, ophtalmological, and smelling examinations were also performed. Penile size was measured in centimeters of length and testicular size was measured by a Prader orchimetre. The basal (fasting) insulin level, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index, lipid profile, body fat ratio (BFR), body mass index (BMIs), waist circumference, waist-to-hip ratio (WHRs), homocysteine level, and C-reactive protein (CRP) were assessed prior to and following GRT. Their bone ages were also calculated.

Heights and body weights were measured in centimeter (cm) and kilogram (kg) in all patients, respectively. BMI was calculated by using the equation [BMI = weight (kg)/height² (m²)]. Minimum waist (W) circumference (in centimeters; minimum circumference between the lower rib margin and the iliac crest, mid-waist) and maximum hip (H) circumference (in centimeters; the widest diameter over the greater trochanters) were measured while the subjects were standing with their heels together. Waist-to-hip ratio (WHR) was calculated by proportioning-waist circumference (cm) to hip circumference (cm). Body composition including fat-free mass and percentage body fat for each patient were measured in the fasting state by TANITA BF-300 body fat analyzer (TANITA Corporation, Tokyo, Japan). All measurements were repeated after 6 months of hCG treatment.

Laboratory and other measurements

Bone age was determined by radiological examinations of the left hand wrist in all patients and controls before and after hCG treatment. All patients were evaluated by pituitary magnetic resonance imaging (MRI) to exclude any anatomical lesions.

Biochemical tests

All blood samples were obtained in the morning after an overnight fast. Complete blood count, erythrocyte sedimentation rate, fasting blood glucose, blood urea nitrogen, creatinine, uric acid, total protein, albumin, aspartate aminotransferase, and alanine aminotransferase tests were drawn from all patients and control group (data are not shown).

Serum total and HDL-cholesterol, and triglyceride levels were measured by enzymatic reactions using Olympus AU 2700 auto analyzer (Olympus Diagnostics, GmbH, Hamburg, Germany). LDL-cholesterol levels were calculated by Friedewald’s formula [14]. Glucose levels were determined by glucose oxidase method (ADVIA 1800, Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). Following a free carbohydrate diet for 3 days, all patients underwent a 75 g oral glucose tolerance test (OGTT) after an overnight fasting at baseline and 6 months after the hCG treatment. Insulin levels at 0, 30, 60, 90, 120 min of OGTT were measured synchronously with the glucose levels. Insulin was measured by an enzyme immunoassay kit (ADVIA Centaur Insulin IRI, Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA).

Homeostasis model assessment of insulin resistance was calculated (fasting plasma glucose level (mmol/l)/fasting insulin level (μIU/ml))/22.5). Subjects with a HOMA-IR score of ≥2.7 were considered as having insulin resistance [12,15].

Homocysteine levels were measured by high-performance liquid chromatography (HPLC) with fluorescence detection (Chromosystems, Germany) and CRP levels were measured by an ultrasensitive method (Human CRP lumELISA Kit, Ultra Sensitive, Calbiotech, Inc., CA, USA).

Basal hormone levels were measured by commercially available kits using a chemiluminescence method for FSH (ACS:180, Bayer, Germany; ref. range for men: 1.4–8.1μIU/ml), LH (ACS:180, Bayer, Germany; ref. range for men: 1.5–9.3μIU/ml), estradiol (ACS:180, Bayer, Germany; ref. range for men: 0–52 pg/ml), prolactin (PRL) [ACS:180, Bayer, Germany; ref. range for men: 2–18 ng/ml] and a radioimmunoassay method for free testosterone (Biosource, Nivelles, Belgium; ref. range for men: 8.9–42.5 ng/dl), total testosterone (Biosource, Nivelles, Belgium; ref. range for men: 134–595 ng/dl), TSH (Biosource, Nivelles, Belgium; ref. range for men: 0.2–4.5μIU/ml), and IGF-1 (Biosource, Nivelles, Belgium; ref. range: 107–310 ng/ml).

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Patients were evaluated with hCG (Pregnyl-Organon) stimulation test before and after GRT. An amount of 1 500 IU hCG was given via intramuscular injection once a day for 3 consecutive days. On the 4th day, blood samples were drawn to measure serum levels of free and total testosterone. If the increments in free and total testosterone levels were more than 50% from the baseline it was accepted as gonadotropin deficiency [16].

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences version 16.0 for Windows® system (SPSS® Inc., Chicago, IL, USA). The normality of distribution of continuous variables was evaluated using the Shapiro-Wilk test. In case of significant deviation from normality, and categorical variables were expressed as numbers. All statistical tests were 2-sided and statistical significance was set at p-value less than 0.05.

Results

Baseline characteristics

The demographic, body composition and biochemical parameters of patients (n=16) and healthy controls (n=20) are displayed in Table 1. The 2 groups were similar with regard to age and BMI, but the bone age of the patients was significantly lower. Waist circumference and body fat ratio of the patients were significantly higher, but there was no significant difference in terms of waist-to-hip ratio. Basal insulin, HOMA-IR, AUC insulin, triglyceride, total cholesterol and CRP levels were significantly higher in patients with IHH (p<0.05, for each one), whereas fasting plasma glucose, LDL cholesterol, and HDL cholesterol were similar between the groups (Table 2). Total testosterone, free testosterone, prolactin and estradiol levels were significantly lower in the patient group, however there was no difference in IGF1 levels (Table 3). There was no significant difference in total body fat free mass in hypogonadal patients compared with healthy controls.

Baseline vs. post-treatment demographics, biochemical parameters, Tanner stages and testicular volume

The mean chronological age of the patients was 27.5 ± 10.5 years, whereas their mean bone ages were significantly retarded with

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>Before therapy</th>
<th>After therapy</th>
<th>p1-Values</th>
<th>p2-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.6 ± 2.0</td>
<td>27.5 ± 10.5</td>
<td>–</td>
<td>0.225</td>
<td>–</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.9 ± 5.2</td>
<td>175.3 ± 12.8</td>
<td>176.2 ± 11.5</td>
<td>0.422</td>
<td>0.008</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.7 ± 7.9</td>
<td>79.3 ± 19.5</td>
<td>80.6 ± 17.4</td>
<td>0.211</td>
<td>0.220</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 ± 3.1</td>
<td>25.7 ± 4.6</td>
<td>25.7 ± 4.7</td>
<td>0.404</td>
<td>0.920</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>78.3 ± 5.8</td>
<td>93.3 ± 16.1</td>
<td>92.3 ± 15.5</td>
<td>0.004</td>
<td>0.119</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.82 (0.75–0.90)</td>
<td>0.84 (0.68–1.09)</td>
<td>0.81 (0.68–0.81)</td>
<td>0.417</td>
<td>0.004</td>
</tr>
<tr>
<td>Body fat ratio (%)</td>
<td>17.6 ± 5.8</td>
<td>23.5 ± 8.6</td>
<td>20.2 ± 8.4</td>
<td>0.033</td>
<td>0.019</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>62.2 ± 6.3</td>
<td>60.6 ± 12.1</td>
<td>63.4 ± 10.3</td>
<td>0.042</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone age (years)</td>
<td>20 ± 0.0</td>
<td>16.3 ± 2.1</td>
<td>17.1 ± 1.5</td>
<td>0.0001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

p1: Patients vs. controls; p2: Pretreatment vs. post-treatment

* Statistically significant (p<0.05)
Table 3  Basal hormone levels and testosterone response to LH stimulation test at baseline and after GRT.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>Before therapy</th>
<th>After therapy</th>
<th>p1-Values</th>
<th>p2-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal testosterone (ng/dl)</td>
<td>550 (387–982)</td>
<td>39 (8–158)</td>
<td>512 (207–1209)</td>
<td>&lt;0.001 *</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>17.8 ± 5.8</td>
<td>2.5 ± 1.5</td>
<td>18.2 ± 8.6</td>
<td>&lt;0.001 *</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Testosterone on 4th day after LH stimulation test (ng/dl)</td>
<td>140.5 (14.0–427.0)</td>
<td>512 (372–1273)</td>
<td>&lt;0.001 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>7.6 ± 6.3</td>
<td>21.4 ± 11.4</td>
<td>&lt;0.001 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone on 5th day after LH stimulation test (ng/dl)</td>
<td>170.5 (12–1474)</td>
<td>558 (401–1273)</td>
<td>0.002 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>10.6 ± 12.9</td>
<td>24.3 ± 14.0</td>
<td>0.002 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (ng/dl)</td>
<td>6.2 (3–12)</td>
<td>3.6 (1.1–11.0)</td>
<td>5.4 (0.6–15.8)</td>
<td>0.043 *</td>
<td>0.008 *</td>
</tr>
<tr>
<td>IGF-1 (ng/dl)</td>
<td>437 ± 79.7</td>
<td>370.1 ± 176.4</td>
<td>474.5 ± 200.8</td>
<td>0.111</td>
<td>0.019 *</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>32.7 ± 14.4</td>
<td>22.9 ± 15.5</td>
<td>42.3 ± 27.5</td>
<td>0.045 *</td>
<td>0.013 *</td>
</tr>
</tbody>
</table>

p1: Patients vs. controls; p2: Pretreatment vs. post-treatment. LH: Luteinizing hormone; IGF-1: Insulin like growth factor 1
* Statistically significant (p<0.05)

![Glucose tolerance test curves for glucose before and after treatment with hCG.](image1)

![Glucose tolerance test curves for insulin before and after treatment with hCG.](image2)

A mean of 16.3±2.1 years (p=0.0001). The anthropometric measurements are shown in Table 1. The mean height, bone age (16.3±2.1 vs. 17.1±2.5, p=0.03), testis volumes (3.6±0.7 vs. 9.1±3.4, p=0.0001) and penile lengths (3.6±0.7 vs. 7.9±1.5, p=0.0001) of the patients increased significantly following the treatment. The BFRs significantly decreased in the patient group. Although the mean waist circumference tended to decrease after GRT, it was not statistically significant. However, GRT resulted in a significant reduction in the WHR and in a significant increase in the total body fat-free mass. Basal and free testosterone and LH-stimulated total testosterone levels were elevated significantly following GRT. PRL, estradiol, and IGF-1 levels also increased significantly after the therapy (Table 3). Two of the 3 patients achieved their desired fertility. Eleven (69%) patients had gynecomastia at baseline, which continued after the GRT. The remaining 5 patients developed no gynecomastia during the treatment period. Basal insulin and AUC of insulin responses to OGTT declined after the GRT. Although basal fasting glucose levels unchanged, a significant decrease was detected in the 120th minute of OGTT, besides improved HOMA-IR indices (Table 3). Although pre-treatment HOMA-IR index did not correlated with homocysteine, post-treatment HOMA-IR index was positively correlated (r: 0.76, p: 0.001). HOMA-IR, basal insulin, 2-h OGTT glucose, AUC insulin, triglyceride levels decreased significantly, whereas there were no significant differences in glucose, AUC glucose, total LDL, HDL-cholesterol, CRP, and homocysteine levels after the hCG replacement (Table 2) (Fig. 1, 2). Pretreatment HDL-cholesterol levels negatively correlated with WHR and waist circumference (r: –0.52, p: 0.039, and r: –0.50, p: 0.047, respectively). Pretreatment HDL-cholesterol levels also negatively (r: –0.716, p: 0.002) correlated with pretreatment BFR. Post-treatment HDL-cholesterol levels were negatively correlated with post-treatment waist circumference (r: –0.54, p: 0.03) and post-treatment BFR (r: –0.73, p: 0.01), but not with WHR (p=0.07).
Discussion

Current data indicate that insulin resistance is more frequent among men with IHH compared with the general population and TRT improves life expectancy, reduces risk of developing MetS, other cardiovascular risk factors and type 2 DM [6,9,17–20] in patients with hypogonadism. There are some contradictory studies in the literature about the benefits of TRT on glucose metabolism and insulin resistance. Although testosterone administration was not shown to be effective on insulin resistance in men who had testosterone levels within physiological limits [21], TRT was found to increase glucose uptake in muscles and to be associated with decreased fasting plasma insulin levels, insulin resistance and improved A1c levels in patients with hypogonadism [19,20,22]. On the contrary, androgen deprivation therapy, which is used for prostate cancer, has been shown to increase plasma insulin levels [23]. Testosterone is thought to act on insulin resistance through specific pathways involved in hormone secretion from adipose tissue [24]. In the present study, GRT resulted in significant decreases in HOMA-IR indices, basal insulin levels and glucose concentrations in the 120th minute of OGTT. The improved insulin sensitivity following GRT is presumably due to increased testosterone levels.

Testosterone replacement therapy was shown to have some positive effects on lipid profile. Kapoor et al. have found that TRT decreases total cholesterol and increases HDL-cholesterol levels significantly in 24 type 2 diabetic patients with IHH [17]. In contrast, androgen deprivation therapy has been shown to increase plasma total, LDL, HDL-cholesterol and triglyceride levels [23]. Although we could not find any difference in total and LDL-cholesterol, triglyceride levels significantly decreased after the replacement therapy. Similar to our results, in a previous study, treatment with hCG for 6 months caused no significant difference in total, LDL, HDL-cholesterol levels, whereas a significant decrease was reported in triglyceride levels [25]. We found significant decreases in both WHR and BFR after hCG treatment. Improvement in body composition after GRT occurs presumably via elevated testosterone levels. Androgens inhibit adipogenesis and lead to myogenic differentiation of mesenchymal pleuripotent cells through androgen receptor-mediated pathway. Sex steroid hormones act on adipose tissue by both genomic and nongenomic mechanisms. Sex hormones activate the cAMP cascade and subsequently the activation of hormone-sensitive lipase leads to lipolysis in adipose tissue [26]. Although fat tissue decreased there was no difference in body weight after testosterone treatment. We noticed an increase in fat-free mass (lean body mass) in patients with hypogonadism after GRT. The TANITA BF-300® body fat analyzer is known to calculate the muscle tissue as the component free from the adipose tissue. In the previous studies it was shown that hCG treatment increases muscle tissue [27]. The increase in muscle tissue mass was supposed to be related to the androgen augmentation [28].

TRT was shown to decrease leptin and adiponectin levels in hypogonadal men with type 2 diabetes, without having a significant effect on CRP levels [24]. Another study revealed a reduction in CRP levels in men with hypogonadism treated with TRT [29]. In the present study, GRT resulted in a mild, but nonsignificant decrease in homocysteine and CRP, which is a proinflammatory cytokine. TRT alone was previously shown to decrease homocysteine levels more prominently than testosterone plus phosphodiesterase inhibitor combination therapy [30]. In contrast Oktenli et al., showed an increase in homocysteine levels after 6 months of TRT in 35 men with IHH, which was independent from androgen levels [31]. The nonsignificant difference in CRP and homocysteine levels after GRT in our study may be related to the duration of GRT and the relatively low levels of endogenous testosterone after the hCG replacement, when compared to treatment with testosterone.

Although some improvement in the bone ages of the patients were observed after treatment, their bone ages were still retarded compared to their chronological ages, which can be explained by the short duration of GRT. Serum IGF-1 levels significantly increased following GRT. The increase was more striking in patients younger than 21 years. Former studies have indicated that both androgens and estrogens are able to increase IGF-1 levels [32,33]. It was thought that the elevation of IGF-1 levels was due to the effects of sex steroids on growth hormone, which were induced by the activation of hypothalamo-pituitary-gonadal axis in puberty. Sex steroids also were shown to stimulate IGF-1 levels by acting on the liver [34]. Even if GRT is continued for a longer duration after the physiological pubertal age, the elevated IGF-1 levels are found to correlate with height and bone age. Therefore, elevation of the IGF-1 levels might be related to androgenization at tissue level.

We detected a significant, but clinically irrelevant increase in PRL levels following GRT. Likewise, some case reports, which pointed out an elevation of serum PRL levels following TRT, may be probably through aromatization of testosterone to estrogen and stimulation of PRL secretion by estrogens [35,36]. TRT may have some potential side effects including elevation of liver enzymes, progression of congestive heart failure, and elevation of hematocrit levels. And also it is contraindicated in patients with benign prostate hyperplasia and prostate carcinoma [37]. Previously, testosterone treatment was reported to cause a significant increase in hematocrit levels in patients with hypogonadism, however hCG treatment had no such effects. The same study showed that the testicular growth was predominant with hCG treatment [25]. Thanks to these beneficial effects, hCG treatment seems to be more physiological and safer.

This study has several limitations. Low patient number seems to be the main limitation in the present study. However, narrow selection criteria caused such a small number of patients. Accordingly, most of the previous studies on hypogonadism included small cohorts. Lack of a patient group treated with testosterone is another limitation of this study. Also, a 6-month follow-up period may not be sufficient to observe the long-term effects of hCG treatment. To our knowledge this is the first prospective study demonstrating the favorable effects of GRT on glucose metabolism and BFR in male patients with IHH, so our study gives important knowledge about the topic.

In conclusion, GRT plays important roles not only in sex differentiation and development, but also in glucose and fat metabolism. GRT decreases HOMA-IR, BFR, and WHRs in patients with IHH more physiologically than the TRT.

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Conflict of Interest

The authors declare no conflict of interest.

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