Patient-reported outcomes and biochemical alterations during hormonal therapy in men with hypogonadotropic hypogonadism who have finished infertility treatment

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Abstract. Male hypogonadotropic hypogonadism (MHH) is effectively treated by gonadotropins with a high rate of ejaculate sperm and paternity; however, there is no information regarding the appropriate management, including patient-reported outcomes (PROs), of men with MHH who have finished infertility treatment. To compare health-related quality of life, erectile function and biochemical alterations in men with MHH who were treated with testosterone replacement therapy (TRT) or human chorionic gonadotropin (hCG). Twenty-six MHH patients (mean age: 34 years) who needed to improve their androgen deficiency symptoms underwent either hCG therapy (n = 16, started with self-injection of 2,000–7,500 IU per week) or TRT (n = 10, testosterone enanthate 250 mg every 3 weeks). The 36-item Short Form Health Survey (SF-36) questionnaire, five-item International Index of Erectile Function (IIEF-5) and hormonal and biochemical analyses were assessed every 3 months. Changes and comparison of each treatment regarding these parameters were analyzed. Both hCG and TRT significantly improved all domains of the SF-36, except for bodily pain and social functioning. hCG significantly improved the general and mental health domains compared with TRT. Significant improvements in IIEF-5 were observed with both treatments, showing significant improvement with hCG compared to TRT. TRT caused progressive testicular atrophy. There were significant decreases in waist circumference and triglycerides in both treatment groups and significant elevations in prostate-specific antigen and hematocrit. Both hCG and TRT are effective and safe, with preferable PROs by hCG, for treating androgen deficiency in men with MHH who do not need infertility treatment.

Key words: Male hypogonadotropic hypogonadism, Gonadotropin, Testosterone replacement therapy, Quality of life, Erectile function

THE PURPOSES of treatment for male hypogonadotropic hypogonadism (MHH) are often heterogeneous based on each patient’s age and needs, and paternity is often debated as an issue of the ultimate goal of treatment [1]; MHH is a medically treatable male factor infertility, and the combination of human chorionic gonadotropin (hCG) and recombinant human follicle-stimulating hormone (rhFSH) results in a high appearance rate of ejaculate sperm [2]. However, the majority of men with MHH should be treated properly by lifelong testosterone maintenance to avoid androgen deficiency-related clinical and biochemical symptoms that detrimentally affect multiple organs and health-related quality of life (HRQOL) [3, 4]. In situations in which fertility is not an issue, testosterone replacement therapy (TRT) using various types of testosterone injections can be used [5], but these men can temporally lose the ability to produce endogenous testosterone and experience defects in spermatogenesis [6].

Androgen deficiency in MHH can be equally treated by TRT or hCG. HRQOL is also an important aspect of managing MHH patients, and gonadotropin treatment has been shown to improve HRQOL during the adolescent period [4, 7, 8], but information regarding appropriate management after infertility treatment is completely lacking. Investigating patient-reported outcomes (PROs), including HRQOL and erectile function, as well as biochemical/endocrinological alterations during this period is important in terms of transition to middle age, a time when a variety of comorbidities may occur. The purpose of this study was to elucidate the appropriate treatment of MHH (TRT or hCG) after infertility treatment from the standpoint of PROs and biochemical/endocrinological analyses.
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Materials and Methods

A retrospective clinical study between April 2008 and March 2020 was conducted at the Department of Urology, Yamaguchi University and was approved by the ethics committees of the institutions. A total of 34 men with MHH who required infertility treatment and had completed gonadotropin treatment with hCG and rhFSH were included. Of these patients, 32 (94%) could retrieve sperm by ejaculation or microdissection testicular sperm extraction, and 28 men (88%) who had at least one child (Fig. 1). After pregnancy was confirmed, gonadotropin treatment was stopped, and the patients were asked to return to us if they felt androgen deficiency symptoms, such as general fatigue or erectile dysfunction. None of the patients had any psychiatric disorders or any metabolic, malignant or inflammatory diseases. Patients who could not retrieve sperm or who had not had a child were excluded because HRQOL would be expected to decrease.

Fig. 1 Cohort inclusion flow chart.

Endocrinological treatments

As hormonal therapies, all patients finished TRT (intramuscular administration of 250 mg testosterone enanthate every 3 weeks for 3 months). Self-administration of testosterone is not approved in Japan. The patients were asked to continue TRT or switch to hCG, starting with subcutaneous self-injection of 3,000 IU × 2 per week according to patients’ preference. The hCG dose was increased by increments of 500 IU per injection every 3 months until the achievement of serum testosterone levels ≥400 mg/dL. hCG dose reduction was recommended if erythrocytosis, gynecomastia or severe acne was occurred.

Measurements of PROs

The patients were asked to visit every 3 months, and physical and biochemical/endocrinological examinations were performed as follows. Testicular volume was measured using a punched-out orchidometer, and the development of external genitalia was categorized by Tanner’s classification. Waist circumference, body mass index (BMI), and blood pressure were measured. Luteinizing hormone (LH), FSH, estradiol, total testosterone, and prostate-specific antigen (PSA) levels and biochemical analyses, including hemoglobin, blood sugar, total cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), creatinine, albumin and testosterone levels, were measured in the morning. Semen examination was monitored to evaluate ejaculatory and remnant spermatogenic functions at 12 months of treatment. The 36-item Short Form Health Survey (SF-36) questionnaire, which has been standardized for the Japanese population by Fukuhara et al. and has been widely applied as a general outcome measurement [9], was used to evaluate HRQOL. Erectile function was assessed with the five-item International Index of Erectile Function (IIEF-5) questionnaire. To investigate the effects of testosterone concentration on PROs, the hCG group was subdivided into two groups based on testosterone levels greater than 350 ng/dL or less and SF-36 domain scores; IIEF-5 was compared between the groups.

Statistical analysis

Differences in each SF-36 domain and IIEF-5 between the pretreatment and posttreatment values were analyzed using a paired t-test. Differences between the hCG and TRT groups, and the high and low testosterone groups during hCG treatment were analyzed using an unpaired t-test. For comparisons of discrete variables, chi-square and Fisher’s exact tests were employed. All of the tests were two-tailed, and a 5% significance level was used for statistical significance. Statistical data were processed with InStat, version 3 (GraphPad, San Diego, CA).
**Results**

**Patients’ backgrounds**

Of the 28 patients who successfully had at least one child, 26 (93%), with a mean age of 34 years old, returned to us requiring TRT after 8.8 months of the non-treatment period (Fig. 1). The other two patients who did not visit us were contacted by telephone and had no symptoms but were advised to receive TRT in the future. After TRT was administered for 3 months, 16 patients (62%) chose to switch to hCG, whereas 10 patients (38%) continued TRT. Reasons to choose hCG were familiarity to self-administration in 10 (63%) and every three months visit to the hospital in 6 (37%). Reasons to choose TRT were reluctance to self-administration in 8 (80%) and preferable effect after initial TRT in 2 (20%). Table 1 shows the patients’ backgrounds subdivided by each treatment, including the wives’ infertility treatment and the outcome. Conceptions were achieved either spontaneously or by intrauterine insemination, in vitro fertilization or intracytoplasmic sperm injection, and the mean number of children obtained was 1.5, ranging from 1 to 3. Except for the distance of residence from the hospital, there was no difference between the groups (Table 1).

### Changes of testosterone

Changes in serum testosterone levels are shown in Supplementary Fig. 1. In the hCG group, the basal testosterone level at 257.7 ng/dL was the effect of previous TRT and the mean testosterone concentrations were 411.9, 439.4, 429.4 and 408.2 ng/dL at 6, 12, 18 and 24 months, respectively, which were significantly higher than the basal levels ($p < 0.001$). In the TRT group, the mean nadir level of testosterone was 256 ng/dL with high individual differences (56 to 356 ng/dL).

### PROs

Fig. 2 shows the changes in each SF-36 domain during hCG or TRT. The baseline norm-based scores of each domain were similar to those of the healthy Japanese men. Both treatments significantly improved all domains, except for bodily pain and social functioning. TRT failed to improve role-emotional. In the general and mental health domains, there was significant improvement with hCG compared with TRT (Fig. 1 D and H). All patients were sexually active. Significant improvements in IIEF-5 were observed during hCG or TRT, and there was significant improvement with hCG compared with TRT after 12 months of treatment (Fig. 3). None of the patients required phosphodiesterase 5 inhibitors.

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**Table 1** Patients’ background at re-admission after infertility treatment

|                      | hCG (n = 16) | TRT (n = 10) | p-value |
|----------------------|-------------|-------------|---------|
| Age                  | 34.2 ± 5.2  | 34.7 ± 4.1  | n.s.    |
| BMI                  | 21.5 ± 2.4  | 21.0 ± 1.4  | n.s.    |
| Reason of MHH (Primary/Secondary) | 10/6       | 6/4        | n.s.    |
| Education level (University/High school) | 6/10       | 4/6        | n.s.    |
| Residence (distance from hospital, km) | 21.4 ± 21.8 | 6.7 ± 5.8  | $p < 0.05$ |
| Testicular volume (mL) | 15.6 ± 3.0  | 14.8 ± 1.9  | n.s.    |
| Pubic hair stage     | 4.1 ± 0.8   | 3.9 ± 0.7   | n.s.    |
| Genital stage        | 4.3 ± 0.6   | 4.3 ± 0.5   | n.s.    |
| LH (IU/L)            | 0.6 ± 0.2   | 0.6 ± 0.2   | n.s.    |
| FSH (IU/L)           | 0.7 ± 0.2   | 0.8 ± 0.1   | n.s.    |
| Testosterone (ng/dL) | 69.8 ± 22.9 | 63.3 ± 18.9 | n.s.    |
| Number of patients who underwent micro-TESE to retrieve sperms | 2 (13%)  | 0 (0%)     | n.s.    |
| Number of children obtained | 1.5 ± 0.6  | 1.4 ± 0.7  | n.s.    |

**BMI, body mass index; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; MHH, male hypogonadotropic hypogonadism; micro-TESE, microdissection testicular sperm extraction**
patients in the TRT group completed treatment as planned. The mean weekly dose of hCG was 4,031 ± 1,564 IU per week, ranging from 2,000 to 7,500 IU. Moderate acne occurred for 1 patient each of the treatment groups and was treated by antibiotic ointment. None of the patients had to change the treatment dose or interval because of elevated hematocrit and other biochemical alterations. Supplementary Figs. 2 and 3 illustrate the changes in each SF-36 domain and IIEF-5, respectively, during hCG treatment subdivided by the level of serum testosterone (more than 350 ng/dL or less). There was no significant difference in any SF-36 domain or IIEF-5 between the groups at any follow-up period. As a study design, we did not evaluate the effect of initial TRT for three months prior to start hCG or continuous TRT.

**Spermatogenesis and biochemical changes**

Testicular volume and semen examination at 12 months after treatment revealed significantly decreased testicular volume, semen volume and sperm concentration and the incidence of azoospermia in the men treated with TRT (Table 2). At 24 months after treatment, there were significant decreases in waist circumference and triglycerides in both groups and a significant decrease in total cholesterol in the TRT group (Table 3). Significant elevations in PSA and hematocrit were observed in both groups but not to the extent to which the treatment was stopped.

**Discussion**

This study showed that hCG and TRT are effective and safe for men with MHH who have completed infertility treatment. Importantly, 93% of the patients returned to us within a year (Fig. 1) after stopping gonadotropin treatment, requiring treatment for sexual function, general fatigue, anxiety, depression and distress [4, 7, 10]. Based on PROs, including SF-36 (Fig. 2) and IIEF-5 (Fig. 3), hCG rather than TRT significantly improved HRQOL and erectile function. As a limitation of clinical study, adjustment of testosterone concentration between the groups is potentially impossible because the pharmacokinetics of testosterone differ completely between hCG and TRT, whereas PROs are independent of testosterone concentration (Supplementary Figs. 2 and 3). These findings suggest that hCG or TRT should be recommended for the lifelong management of MHH, and we must pay attention to patients’ general well-being and HRQOL during the transition from adulthood to middle age.

A majority of adolescents with MHH feel anxiety and may have an impaired emotional state and depression concerning future reproductive function, and anxiety has been shown to be a strong predictor of decreased physical and mental health [8, 11]. In general, the HRQOL of MHH men who have finished infertility treatment is supposed to be quite different from that of adolescents. The SF-36 questionnaire, which has been standardized worldwide and for the Japanese population [9], is a validated measurement of the different dimensions of HRQOL. Aydogan et al. reported that in addition to recovering sexual function and QOL, TRT improved anxiety and depression scores in MHH [4]. In this study, all the domains, except for bodily pain and social functioning, improved significantly irrespective of the treatment, and the domains for general and mental health (Fig. 2) and erectile function (Fig. 3) were significantly higher with hCG than with TRT.

Several reasons to explain these findings are proposed. First, testicular atrophy per se has no functional role; nevertheless, it is always accompanied by scrotal atrophy and atrophy of the other external genitalia, which affects physical appearance and is indirectly associated with erectile function. Rohayem et al. also observed a similar finding that self-reported satisfaction concerning testicular volume was considerably high after gonadotropin treatment [8]. The psychosocial impact of small testes is considerable, particularly if the patient becomes sexually active [1]. Second, a smaller semen volume in TRT patients (Table 2) may be associated with ejaculatory and erectile function. According to the results for patients with MHH due to nonfunctioning pituitary macroadenoma with a mean age of 49 years, TRT improved the IIEF-5 score from 15.5 to 17.8 [12], and it may be improved to a greater extent by using hCG (Fig. 3). In addition, a close association between sexual dysfunction and vitality via the SF-36 questionnaire has been reported in adults [13], indicating that improvement in both SF-36 domains (Fig. 2) and IIEF-5 (Fig. 3) is bidirectionally related. Third, our primary purpose of semen examination was to evaluate ejaculatory function by measuring semen volume. As expected, sperm concentration was significantly higher and the incidence of azoospermia significantly lower in patients treated with hCG than in those treated with TRT (Table 2). These findings are not important for follow-up of MHH patients who had finished infertility treatment and still unable to conceive. In contrast, a number of men treated with hCG had higher self-esteem, as they still had the potential to be biologically reproductive. Fourth, subcutaneous injection of hCG can be readily restarted because the MHH patients used the injection for a long time and they had to understand the appropriate dose of hCG to maintain their masculinization and regulate their androgen deficiency-related symptoms.

According to the literature [14], TRT every three
weeks is not optimal and leads to pronounced fluctuations in testosterone levels, whereas administration of TRT every 10 days is recommended to avoid subphysiological levels. As shown in Supplementary Fig. 1, testosterone levels in hCG treatment were arbitrarily maintained just above 400 ng/dL whereas nadir testosterone levels in TRT were approximately 250 ng/dL; this means that the bioavailability of testosterone is not extremely lower than that of the hCG group. Furthermore, optimal testosterone levels greater than 300 or 350

Fig. 2 The changes of SF-36 subdomains in patients treated with hCG (closed circle) or TRT (closed square).

a, \( p < 0.05 \) compared with baseline; b, \( p < 0.01 \) compared with baseline; c, \( p < 0.0001 \) compared with baseline; d, \( p < 0.001 \) compared with baseline; e, \( p < 0.05 \) compared with TRT; f, \( p < 0.01 \) compared with TRT. TRT, testosterone replacement therapy
ng/dL were data obtained mainly from investigations of late-onset hypogonadism. In MHH, there is no optimal standard of testosterone level; in fact, there was no significant difference in the SF-36 domain (Supplementary Fig. 2) and IIEF-5 (Supplementary Fig. 3) between the hCG and TRT groups. These results indicate that a lower testosterone concentration is sufficient to maintain preferable PROs in MHH because the patients had been exposed to extremely low serum testosterone levels for a long time.

Testosterone plays pivotal roles in hematopoiesis, muscle strength, lean body mass, bone density, mood states and cognition, and low testosterone is closely associated with the onset of diabetes and other medical comorbidities [15]. There is no report describing the general health status in MHH adults, but we can readily suspect that general health will be severely damaged if left untreated because of extremely low serum testosterone levels. As shown in Table 3, both hCG and TRT significantly decreased waist circumference and triglycerides during the 2-year follow-up, which may contribute to preventing the occurrence of medical comorbidities during middle age. Two main concerns are risks of prostate cancer and thrombosis due to elevated hematocrit (Table 3). In the case of LOH, Conaglen et al. showed that PSA and hematocrit significantly increased with TRT at some point during treatment in 13% and 14% of patients, respectively [16]. Similarly, Tan et al. investigated the safety and efficacy of TRT and reported that significant elevations in PSA and hematocrit were within clinically safe limits [17]. No data have been reported for MHH, and we have to follow up our patients longer to address this issue.

There are several limitations in this study. First, the study design was nonrandomized and retrospective and there was a small sample size without a nontreatment control group. A total of 26 patients appears to be enough to be sufficient for investigation because MHH is not a common cause of male infertility; hence, men who have undergone infertility treatment are rare, and no investigation has focused on this topic, perhaps due to patient recruitment. Second, the causes of MHH are heterogeneous and include congenital causes such as Kallmann syndrome as well as acquired hypogonadism such as pituitary surgery. Regardless, all the patients were married, had at least one child and regularly engaged in sexual intercourse, indicating that they were a specified and reasonable patient group to investigate, enabling a high-quality analysis of erectile function and HRQOL. Last, SF-36 is not specified for hypogonadism. Based on this study, a detailed questionnaire to assess MHH should be established, and further investigations should seek the best long-term management for MHH by including a variety of testosterone formulations, hCG and even clomiphene and aromatase inhibitors.

In conclusion, the efficacy and safety of the self-administration of hCG or TRT for the management of MHH patients who have finished infertility treatment are reported. PROs are important measures to manage these patients in the long-term, and prospective studies with a larger number of participants focusing on hypogonadism and its relationship to HRQOL and sexual functions are needed and may identify appropriate lifelong follow-up methods for these individuals. Longer follow-up data,

| Table 2 Testicular volume and semen parameters during the followup |
|---------------------------------------------------------------|
|                  | hCG (n = 16) | TRT (n = 10) | p-value |
| Testicular volume (mL)          | 17.7 ± 1.9   | 9.4 ± 2.3   | <0.0001 |
| Semen volume (mL)                | 2.9 ± 0.7    | 1.5 ± 0.7   | <0.001  |
| Sperm concentration (<10⁶/mL)   | 6.8 ± 6.2    | 0.8 ± 1.6   | <0.01   |
| Azoospermia                     | 3 (19%)      | 7 (70%)     | <0.01   |
| Sperm motility (%)†‡            | 48.1 ± 14.2  | 41.7 ± 12.6 | n.s.    |
| †, Data were obtained from non-azoospermia cases.            |

Fig. 3 The changes of IIEF-5 in patients treated with hCG (closed circle) or TRT (closed square).

a, p < 0.05 compared with baseline; b, p < 0.01 compared with baseline; c, p < 0.001 compared with baseline; d, p < 0.05 compared with TRT. IIEF-5, five-item International Index of Erectile Function; TRT, testosterone replacement therapy.
including appropriate testosterone concentrations, should be addressed to properly manage MHH patients for long period.

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**Disclosure**

The authors have no conflict of interest in relation to this work.

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**Table 3** Comparisons of changes in physical and blood examinations

|                         | hCG (n = 16) Baseline | 24-month visit | p-value | TRT (n = 10) Baseline | 24-month visit | p-value |
|-------------------------|-----------------------|----------------|---------|-----------------------|----------------|---------|
| Waist circumstance (cm) | 74.3 ± 4.6            | 72.5 ± 2.4     | 0.0422  | 74.9 ± 4.9            | 73.2 ± 3.3     | 0.0446  |
| BMI                     | 21.5 ± 2.4            | 21.7 ± 1.5     | 0.2525  | 21.0 ± 1.4            | 21.6 ± 1.4     | 0.7548  |
| Systolic blood pressure (mmHg) | 118 ± 10             | 115 ± 9       | 0.3093  | 116 ± 11              | 118 ± 10       | 0.1091  |
| Diastolic blood pressure (mmHg) | 75 ± 6              | 74 ± 4        | 0.7835  | 72 ± 3                | 73 ± 3         | 0.5450  |
| PSA (ng/mL)             | 0.28 ± 0.15           | 0.41 ± 0.11    | 0.0073  | 0.32 ± 0.18           | 0.46 ± 0.17    | 0.0026  |
| Fasting blood sugar (mg/dL) | 75.6 ± 10.4          | 71.9 ± 8.4    | 0.0854  | 78.7 ± 8.0            | 77.0 ± 6.7     | 0.2745  |
| Total cholesterol (mg/dL) | 140.1 ± 29.8         | 129.8 ± 19.5  | 0.0537  | 145.7 ± 29.1          | 129.6 ± 21.3   | 0.0068  |
| Triglycerides (mg/dL)   | 56.4 ± 11.5           | 53.4 ± 8.9     | 0.0339  | 59.2 ± 11.9           | 54.0 ± 11.6    | 0.0304  |
| Hemoglobin (g/dL)       | 14.2 ± 0.6            | 15.6 ± 0.8     | <0.0001 | 14.6 ± 0.6            | 16.3 ± 0.5†    | <0.0001 |
| AST (U/L)               | 24.4 ± 7.0            | 25.8 ± 7.0     | 0.1125  | 26.0 ± 4.4            | 25.8 ± 4.6     | 0.5554  |
| ALT (U/L)               | 22.1 ± 3.1            | 24.4 ± 5.3     | 0.0927  | 22.5 ± 3.4            | 23.2 ± 3.3     | 0.2091  |
| γ-GTP (U/L)             | 21.3 ± 3.4            | 22.8 ± 5.3     | 0.1229  | 23.2 ± 3.2            | 24.1 ± 2.6     | 0.1212  |
| ALP (U/L)               | 177.6 ± 31.2          | 181.6 ± 30.0   | 0.1754  | 185.0 ± 23.2          | 194.5 ± 36.4   | 0.4687  |
| Creatinine (mg/dL)      | 0.76 ± 0.20           | 0.78 ± 0.20    | 0.3332  | 0.81 ± 0.19           | 0.80 ± 0.15    | 0.9526  |
| Albumin (g/dL)          | 4.7 ± 0.4             | 4.8 ± 0.3      | 0.0780  | 4.6 ± 0.5             | 4.8 ± 0.5      | 0.0985  |

BMI, body mass index; PSA, prostate-specific antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase

†, p < 0.05 compared with the value at 24-month visit of TRT→hCG group

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![Supplementary Fig. 1](image-url) The changes of serum testosterone in patients treated with hCG (closed circle) or TRT (closed square). Note that the level of TRT group was nadir level.

a, p < 0.01 compared with baseline
Supplementary Fig. 2  The changes of SF-36 subdomains in patients treated with hCG. Closed bar indicates the group with serum testosterone level more than 350 ng/dL and the mean levels are 468.1, 515.7, 506.7 and 473.8 ng/dL at 6, 12, 18 and 24 months after hCG treatment, respectively. Open bar indicates the group with serum testosterone level less than 350 ng/dL and the mean levels are 318.2, 312.3, 330.0 and 323.9 ng/dL at 6, 12, 18 and 24 months after hCG treatment, respectively.
Supplementary Fig. 3  The changes of IIEF-5 in patients treated with hCG. Closed bar indicates the group with serum testosterone level more than 350 ng/dL and the mean levels are 468.1, 515.7, 506.7 and 473.8 ng/dL at 6, 12, 18 and 24 months after hCG treatment, respectively. Open bar indicates the group with serum testosterone level less than 350 ng/dL and the mean levels are 318.2, 312.3, 330.0 and 323.9 ng/dL at 6, 12, 18 and 24 months after hCG treatment, respectively. IIEF-5, five-item International Index of Erectile Function

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