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Human chorionic gonadotropin treatment: a viable option for management of secondary hypogonadism and male infertility

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Abstract

Introduction: Low testosterone and its symptoms is a condition affecting many males with severe repercussions on health. Testosterone affects metabolism, bones, joints and ligaments, the cardiovascular system, liver, sexual functions, muscle mass and the nervous system. Nowadays, due to recent research showing the benefits of testosterone replacement therapy, this treatment is gaining in popularity among aging men. However, testosterone replacement can increase the risk of infertility.

Areas covered: Human Chorionic Gonadotropin (HCG) is used in the treatment of male infertility due to its Luteinizing Hormone (LH) -like action triggering testosterone and sperm production. Due to these positive effects on testosterone production, HCG has also been used to treat secondary hypogonadism. In this review, based on a literature review for the years 1977–2020 via Google Scholar, we summarize the current research on HCG as treatment for patients suffering from low testosterone and provide an overview of the pros and contras for HCG therapy as compared to testosterone replacement therapy for the treatment of secondary hypogonadism.

Expert opinion: The testosterone and sperm production triggering effects of HCG without the side effects on fertility seen in testosterone replacement therapy make HCG therapy a prime candidate for patients suffering from secondary hypogonadism.

Keywords: low testosterone, spermatogenesis, luteinizing hormone, follicle stimulating hormone

Article highlights

- When choosing a treatment method for patients with secondary hypogonadism, age and co-morbidities of the patient should be taken into consideration.

- HCG can raise endogenous testosterone while maintaining or even increasing several fertility parameters such as sperm volume and motility.

- As compared to TRT, HCG treatment has been shown to minimize side effects, especially those in hematocrit, estradiol, prostate volume and PSA increases.

- HCG can significantly increase intratesticular testosterone in a dose-dependent manner, with dosages between 250 and 500 IU seeming to be optimal to restore physiological intratesticular testosterone levels.

- A key reason for choosing HCG over TRT in HH men would be the maintenance and or improvement of fertility

1. Introduction

The traditional treatment method for patients suffering from low testosterone symptoms is testosterone replacement therapy (TRT). However, TRT is associated with several side effects, especially the risk of infertility. As alternative treatment, HCG has been introduced to treat low testosterone symptoms without the side effects of exogenous testosterone administration. We reviewed the current body of research in order to assess the pros and contras of both TRT and HCG treatment for the treatment of low testosterone symptoms. TRT has been gaining in popularity after numerous recent studies advocating its many health-related benefits in male patients; i.e., positive effects on glucose metabolism, muscle mass, bone mass density, anti-inflammation, depression and erectile dysfunction have been reported [1-7]. However, TRT is also associated with several potential side effects such as decrease in sperm count and motility leading to infertility, increase of estradiol leading to water retention, increase of red blood cells and high blood pressure, gynecomastia, increase in dihydrotestosterone (DHT) leading to skin problems and hair loss [8,9]. Furthermore, even though the correlation between prostate cancer and testosterone levels has been widely refuted during the last decade [10,11] TRT seems to increase prostate-specific antigen (PSA) [12]. In the light of these side effects, many patients and physicians tend to be reluctant to the use of this treatment. This seems especially true for young patients planning to have children in the future. For this reason, this later group may benefit from a different method to increase testosterone due to the decrease in sperm and the ensuing risk of infertility of TRT.

Human chorionic gonadotropin (HCG) is originally released by the placenta after implantation. However, HCG is also the analog of luteinizing hormone (LH) produced in the pituitary gland. LH activates the testosterone and sperm production mechanism within the testes and HCG is therefore used to treat infertility in males [13,14]. As compared to TRT, HCG treatment has been shown to minimize side effects, especially those in hematocrit, estradiol, prostate volume and PSA increases [15]. In fact, the European Academy of Andrology guidelines on investigation, treatment and monitoring of functional hypogonadism recommend gonadotropin therapy when fertility is desired in patients suffering from secondary hypogonadism [16]. This manuscript, will review potential applications of HCG treatment as a method to restore healthy testosterone levels in men suffering from secondary hypogonadism while comparing benefits and disadvantages of HCG treatment on the one side and TRT on the other.

2. Methods

We performed a literature review for the years 1977–2020 via Google Scholar. Also abstracts from major reproductive conferences were considered. To this end, we searched for words including “testosterone replacement therapy”, “TRT”, “hypogonadism”, “low testosterone”, “human chorionic gonadotropin”, “HCG”, “azoospermia”, “oligospermia” and ‘male infertility’. Exclusion criteria were: studies involving females or children.

3. Function of HCG

HCG is a member of the glycoprotein hormone family which includes LH, thyroid-stimulating hormone (TSH), and follicle-stimulating hormone (FSH). HCG is a hormone involved in embryonic signaling and is a key element of gestations development during pregnancy. HCG is produced mainly by differentiated syncytiotrophoblasts and activates multiple pathways via binding to the luteinizing hormone/chorionic gonadotropin receptor (LHCGR) among others. HCG regulates angiogenesis in the uterine endothelium, myometrial quiescence and immunomodulation at the maternal-fetal interface [18]. Within the HCG molecule, the αsubunit (comprised of 93-amino acid, 14.5 kD) of HCG has some homologies with TSH, LH, and FSH, and the βsubunit (comprised of 145-amino acid, 22.2kD) homology to LH is over 80% [18]. The βsubunit of LH comprises 121 amino acids. The difference of amino acids 121-145 is called the C-terminal peptide (CTP) and makes HCG antibodies also react to LH as well as the other way round [18]. Due to their homogeneity, HCG binds to the LHCGR and mimics the effects of LH, making it a powerful actor in improving sperm and testosterone production. In fact a recent animal study discovered that HCG is about 10 times more potent than LH in cAMP activation and slightly more potent on cAMP-dependent Erk1/2 phosphorylation [19]. Interestingly though, they could not observe any significant differences between LH and HCG treatments when comparing

the activation of downstream signals involving Creb phosphorylation, *Stard1* gene expression and testosterone synthesis [19].

The testosterone stimulating properties of HCG make it a prime candidate for men suffering from chronically low testosterone levels.

4. Different forms of secondary hypogonadism

Secondary hypogonadism can be organic, that is typically occurring with significant low clinically and biochemically levels of androgens. On the other hand, functional hypogonadism occurs more often, is often curable and shows less severe androgen deficiency. When treating patients with secondary hypogonadism, the age and co-morbidities such as obesity, diabetes or cardiovascular diseases of the patient must be taken into consideration when choosing a treatment. Even in cases of secondary hypogonadism, HCG therapy might not be the optimal choice for some individuals and TRT a better choice. It is therefore crucial to asses all the above parameters for each patient before starting either treatment.

5. HCG treatment as testosterone replacements therapy

HCG can raise endogenous testosterone while maintaining or even increasing several fertility parameters such as sperm volume and motility**,** especially when used in combination with clomiphene citrate, tamoxifen, anastrozole, or recombinant follicle-

stimulating hormone (rFSH) [13], [20]. If fertility is the main purpose of the treatment, sequential administration of HCG and rFSH seem to lead to promising outcomes [21]. It is important, however, to assess the symptomatic improvements of HCG as compared to TRT and not focus solely on the serum testosterone response achieved with the treatment. For example, one recent study investigated the effects of HCG (1500 IU/ 3 times per week) in idiopathic hypogonadotrophic hypogonadism [22]. It is known that TRT improves symptoms of metabolic syndrome, diabetes and cardiovascular diseases in those patients. Six months of HCG treatment led to improvements in homeostasis model assessment of insulin resistance (HOMA-IR), basal insulin levels, triglyceride level, body fat and waist-to-hip ratio. These results indicate similar results as those observed with TRT [22]. Another study showed that HCG treatment (5000 IU, twice per week) in patients with nonorganic erectile failure or lack of sexual desire does improve several sexual parameters as compared with placebo [23]. Interestingly, these effects on sexual behavior did not correlate with serum testosterone levels [23]. Further research with regard to the symptomatic effects of HCG on patients suffering from symptoms due to hypogonadism is important in order to assess the potential of HCG as cure for secondary hypogonadism.

5.1 Effects on intratesticular testosterone

Exogenous testosterone administration suppresses intratesticular testosterone (ITT), which is crucial for the production of sperm [24]. In such patients, ITT has been shown to be suppressed by 94%. However, with every other day injections of HCG at dosages of

125IU, ITT was only 25% less than baseline, with 250IU 7% less and with 500IU 26% greater than baseline [25]. In another study, 37 normal men were treated with GnRH antagonist acyline and attributed to one of the following low dose HCG groups: 0, 15, 60, or 125 IU sc every other day or 7.5 g daily testosterone gel for 10 days. In order to measure ITT, testicular fluid was retrieved via percutaneous aspiration at baseline and after 10 days of treatment. Median baseline ITT was 2508 nmol/liter. ITT improved in a dose-dependent manner: 15 IU HCG group reached an ITT of 136 nmol, 60 IU HCG group reached an ITT of 319 nmol, 125 IU HCG group reached an ITT of 987 nmol/liter. Serum HCG significantly correlated with both ITT and serum testosterone [24,26]. These studies indicate that HCG can significantly increase ITT in a dose-dependent manner and that dosages between 250 and 500 IU might be optimal to restore physiological ITT levels.

5.2 Effects on serum testosterone

A weekly dosage of 4500IU spread over 3 weekly injections has shown to lead to normal testosterone levels in isolated HH men [27]. Another study showed that single injections of 400IU, 2000IU and 4000IU of HCG led to significant serum testosterone concentrations in hypogonadal as well as eugonadal males without differences among the groups after administration [28]. In hypogonadal men, 400IU, 2000IU and 4000IU of HCG increased testosterone from about 200 to 400 ng/dl. In eugonadal men, 400IU,

2000IU and 4000IU of HCG led to an increase from about 450 to 700 ng/dl in testosterone [28]. Interestingly, higher doses of HCG did not lead to greater testosterone level increases [28]. Another study showed similar results, with no differences in serum testosterone after single injections of 1500, 3000 or 4500IU of HCG, with testosterone increasing 24 hours post-injection and peaking 3-4 days later [29]. Serum testosterone peaked 3 days after injection [28].

From the above information, it can be suggested that low dose HCG (~500IU) injected 3 times per week can restore healthy serum and intratesticular testosterone levels in HH patients. The higher dosages used in infertility treatment to trigger sperm production might not be necessary if the goal is to increase serum testosterone levels. That is, combined treatment with HCG followed by rFSH might also be potent in order to induce fertility [21].

Indeed, HCG dosages used in the treatment of infertility can range from 3,000 to 10,000 IU 2-3 times per week [30]. One study showed that 3-6 months (1000 IU 3 times/week or 2000IU 2 times/week) of HCG treatment in 100 males with hypogonadotropic hypogonadism leads to normal serum testosterone concentrations despite the fact that 81 patients remained azoospermic [31]. These data show that low dose HCG treatment is very effective in restoring normal serum testosterone levels, however spermatogenesis might require higher dosages of HCG. The exact mechanism by which HCG affects sperm production besides testosterone increase is not completely

understood yet and needs further investigation. We summarized studies involving HCG treatment on testosterone and/or fertility parameters in Table 1.

6. Benefits of HCG vs. TRT

HCG has been shown to have minimal side effects as compared to TRT [15]. For example, a recent study directly comparing TRT and HCG treatments showed that Vitamin D levels were higher and estrogen levels lower in the HCG group [15]. Moreover hematocrit, PSA and prostate volume were significantly lower in the HCG group without a reduction of sperm density and motility [15]. However, a key reason for choosing HCG over TRT in HH men would be the maintenance and or improvement of fertility.

With regard to serum testosterone levels, 3 weekly injections of about 500 IU of HCG might lead to steady serum testosterone levels with very few fluctuations. Popular injectable testosterone esters such as enanthate or undecanoate lead to severe fluctuations with possible negative side effects and mood swings. Enanthate is usually administered once every 2 weeks, whereas undecanoate can be injected every 10-14 weeks. Enanthate tends to peak 2-3 days after an injection of 200 mg and steadily decline thereafter reaching baseline levels one week post injection [32]. Undecanoate, which is gaining in popularity due to its more stable levels and minimal injection frequency, needs about 1-2 weeks to peak serum testosterone level after injection of 500 or 1000 mg before steadily decreasing thereafter and reaching baseline levels

around 8-10 weeks post-injection [33]. Daily topical testosterone applications have been shown to lead to more or less steady serum testosterone levels with some intraday fluctuations [34] (Figure 1). With regard to level fluctuations, 3 weekly injections of HCG might maintain more stable serum testosterone levels. However, it is noteworthy to mention that data on HCG are far less in comparison to the different testosterone applications.

With regard to the cost of HCG vs. TRT therapy, one vial of HCG containing 10,000 IUs is sold for about $370 USD. If the patient takes 500 IU of HCG three times a week, the vial will last for 6.5 weeks, with a monthly cost of about $230. Injectable depo-testosterone costs about $20 per month. On the other hand, nasal testosterone seems to cost about $700, transdermal gel about $300 and oral undecanoate testosterone about $800 per month . From this example it is obvious that HCG therapy is more expensive as compared to injectable depo based TRT. However, nasal, transdermal and oral testosterone can be more expensive as compared to HCG. Besides its use for the treatment of female infertility, HCG is FDA-approved for hormone treatment in men. FDA-approved HCG medication is only available as injectable and requires a prescription from a licensed medical professional. Furthermore, HCG treatment for men is often not covered by insurances leading to high treatment costs. (Fig. 1)

7. Intramuscular vs. Subcutaneous injections

The bioavailability (plasma concentration area under the curve and maximum concentration) of HCG has been shown to be higher after intramuscular injection as compared to subcutaneous injection in women [35]. On the other hand, another study showed higher serum HCG concentrations after subcutaneous injection as compared to intramuscular injection in women [36]. In male patients, one study compared the steroidogenesis in response to either intramuscular or subcutaneous HCG administration up to 144 hours post injection [37]. As compared to intramuscular injection, subcutaneous injection led to a delayed peak in serum HCG levels, however, interestingly testosterone, LH and FSH did not show any significant differences in either form of administration [37]. Evidence would suggest that in order to maintain steady testosterone levels, frequent subcutaneous HCG might be easier and minimize scar tissue at the injection sites.

8. Side effects of HCG treatment

Since HCG treatment raises serum testosterone levels, it can lead to similar side effects as seen in direct TRT, including gynecomastia, high blood pressure, acne and hair loss and raises in estrogen potentially leading to gynecomastia. However, unlike supplementation with supraphysiological doses of testosterone as seen in doping, physiological serum testosterone increases triggered by HCG supplementation only

rarely results in side effects (Table 2). Moreover, as compared to TRT, HCG treatment seems to have less side effects with regard to effecting hematocrit, estradiol, prostate volume and PSA increases [15]. Interestingly, serum testosterone seems to peak 72 hours post HCG injection and significantly correlates with estradiol peaks observed 24 hours after injection [38]. Therefore similar to TRT, even though not in line with guidelines, ancillary drugs such as aromataze inhibitors, selective estrogen receptor modulators or 5α-reductase inhibitors are used off-label in some rare cases of severe side effects due to increased serum estradiol or DHT levels. However, as opposed to TRT, HCG does not increase the risk of infertility but rather improves fertility. It is currently unknown if long term administration of HCG can lead to side effects such as gonadotropin resistance. (Table 2)

9. Choosing the right treatment (HCG vs. TRT)

For men, the appropriate method of testosterone restoration should be done in consultation with a medical professional and assessed depending on several factors (Figure 2):

1) The type of hypogonadism: Primary vs. Secondary, patients suffering from primary hypogonadism will not benefit from HCG since testosterone production in the testes is impaired. Only men suffering from secondary hypogonadism, which is an impaired hypothalamus or pituitary function, might benefit from HCG treatment to

restore their testosterone level.

2) Does the patient desire to maintain or improve his fertility? If yes, TRT alone is not recommended. HCG alone or combined with TRT is recommended. When used with TRT, HCG can be used either during TRT to maintain fertility while on TRT or after a cycle of several months on TRT to restore fertility.
3) Does the patient dislikes frequent injections? HCG treatment might require more frequent injections as compared to TRT, which can be administered less frequently or topically.
4) What is the desired level of testosterone for the patient? Each individual will respond differently to HCG, in some individuals the elevation in serum testosterone will be very weak and not lead to the desired level. In such situations concomitant use of TRT or TRT alone might allow to target more precisely serum testosterone levels. (Fig.2)

10. Conclusion

HCG therapy is an effective treatment for patients suffering from infertility, often restoring healthy sperm production. However, HCG also increases serum and intratesticular testosterone levels, making it a prime candidate to treat patients with secondary hypogonadism. Even though the cost and injection frequency might be slightly higher as compared to TRT, HCG alone or used with TRT might be the best option for patients who desire to have children in the future. Depending on the response to HCG alone,

concomitant TRT might be necessary to bring serum testosterone levels to the desired levels. Responses of serum testosterone levels seem to be independent of the dose of HCG and to peak 3 days post injection. Therefore, low doses of ~400 IU HCG injected every 3 days intramuscularly or subcutaneously might lead to a significant increase of serum and intratesticular testosterone with few daily fluctuations in levels. Indeed, high dosages commonly seen in the treatment of male infertility going as high as 5000 IU several times per week might be unnecessary if the goal is not to increase sperm production but rather to increase testosterone only. In summary, HCG might be a safe, affordable and effective method to restore healthy testosterone levels in males suffering from secondary hypogonadism. Nonetheless, further clinical trials should be carried out to demonstrate and elucidate the benefits of HCG therapy.

11. Expert opinion

Many men suffering from hypogonadism are seeking medical assistance to improve their condition. However, the harsh side effects of TRT on male fertility can be deal breakers in many patients. Nonetheless, low serum testosterone can have several severe implications if it remains untreated; such as, increased risk for cardiovascular and metabolic diseases. Therefore, it is crucial to find a viable treatment method for patients suffering from low testosterone without endangering the sperm production function. HCG can stimulate endogenous testosterone as well as sperm production due to its analog function to that of luteinizing hormone and may therefore offer novel treatment

possibilities without jeopardizing male fertility in many cases of secondary hypogonadism. Furthermore, HCG treatment seems to stimulate endogenous testosterone production in a balanced way without leading to an overproduction, hence minimizing the risks of potential side effects associated with supraphysiological testosterone levels which are sometimes encountered in TRT patients. The HPG axis seems responsive HCG in a similar fashion as LH, and self-regulates the testosterone production within the testes in an amount independent manner. Doses of HCH as low as 400 IU seem to significantly increase serum testosterone levels and even with dosages 10 times that amount (4000 IU), the serum testosterone elevations seem similar to that of a 400 IU dosage (i.e., remaining within the physiological range). Rather than sensing the amount of HCG and accordingly producing testosterone, even small amounts of HCG seem to maximize the response for testosterone production within the testes probably due to receptor sensitivity. With TRT, when testosterone is injected bound to an ester, the hormone is slowly released into the system at a pace that cannot be controlled. Therefore fluctuations and periods of very high and low serum testosterone can occur. Furthermore, oil-based testosterone preparations have to be injected intramuscularly, whereas HCG can be injected subcutaneously, making the administration process easier and potentially reducing the number of hospital visits for the patients. Even though HCG is already approved and produced in many countries for the induction of ovulation in women, the implementation of HCG therapy as a hypogonadism treatment for men faces obstacles such as regulations and a lack of clear information. In fact, injectable

HCG is not available nor produced in several countries and many physicians are not entirely aware of the testosterone stimulating effects of HCG treatment.

Further studies showing the effects of HCG therapy in hypogonadal men aiming to maintain fertility need to be conducted and compared with the outcomes reached by TRT. Furthermore, longitude studies investigating the testosterone production stimulating effects of HCG therapy need to be conducted in order to see if a resistance to HCG develops with time. Once a strong body of evidence is available, regulatory bodies, pharmaceutical companies and physicians might potentially adopt HCG as treatment for secondary hypogonadism. Despite the fact that new forms of testosterone esters such as undecanoate have been developed, allowing fewer injections and facilitating the treatment, the standard procedures of TRT prescription for secondary hypogonadism might experience a switch to HCG treatment. Indeed, the minimization of side effects especially with regard to sperm parameters and fertility, the easy handling (subcutaneous injection vs. intramuscular injection for testosterone) and the stable serum testosterone levels achievable with HCG treatment are advantages of HCG treatment. HCG treatment seems to be a viable option to treat secondary hypogonadism especially in patients concerned about fertility issues.

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Declaration of interest

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Figure Legends

Figure 1. Representation of serum testosterone fluctuations. After several different administration methods.

Figure 2. Several methods of restoring testosterone levels for different kinds of hypogonadal conditions.

Abbreviations

TE: Testosterone Enanthate, TU: Testosterone Undecanoate, T gel: Testosterone gel.

Table 1. Studies on HCG on testosterone and fertility parameters

Title	Author	Year	Patients	Treatment	Outcome
Clomiphene citrate (CC) and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study	Habous et al.	2018	282 men with hypogonadism, wishing to preserve their fertility	one of three treatment groups: CC 50 mg (n = 95); 5000 IU HCG injections twice weekly (n = 94); or a combination of both therapies (CC + HCG; n = 94).	Testosterone levels increased in all groups at all time points with no statistically significant difference among the groups. qADAM scores improved in all groups at 1 month (CC group: 6.36; HCG group: 5.08; CC + HCG group: 7.26) and at 3 months (CC group: 12.73; HCG group: 11.82; CC + HCG group: 15.13) with a significant difference in intergroup analysis for the CC + HCG group as compared with the CC or HCG group..
Testicular responses to hCG stimulation at varying doses in men with spinal cord injury	Bauman et al.	2017	30 men with chronic SCI 16 eugonadal and 14 or able-bodied men (11	Single dose of hCG was administered at three dose concentrations (that is, 400, 2000	All patients , in all groups responded with an adequate increase in serum testosterone concentration to one or more of the three doses of

			eugonadal and 27 hypogonadal)	and 4000 IU on 2 consecutive days and serum T measured on day 1,2 and 3.	HCG. Serum T levels were not significantly different within the Eugonadal and Hypogonadal groups for each dosage. all subjects in the Hypogonadal groups exceeded the lower limit of normal for the response of serum testosterone concentration at each one of the three doses of HCG.
The Use of HCG-Based Combination Therapy for Recovery of Spermatogenesis after Testosterone Use	Wenker et al.	2015	49 men with azoospermia or severe oligospermia due to TRT	HCG 3,000 IU EOD + clomiphene citrate (71.4%), tamoxifen (57.1%), anastrozole (20.4%), or recombinant follicle-stimulating hormone (2%)(or combination)	95.9% return of spermatogenesis or improved sperm count after 3.4-5.7 months. T levels were similar during TRT and HCG treatment.
Concomitant intramuscular Human Chorionic Gonadotropin	Hsieh et al.	2013	26 men undergoing TRT	HCG 500 IU EOD	None of the patients became azoospermic during TRT. Nine out of

Preserves Spermatogenesis in Men					26 men achieved pregnancy with the partner during followup.
Dose-Dependent Increase in Intratesticular Testosterone by Very Low-Dose Human Chorionic Gonadotropin in Normal Men with Experimental Gonadotropin Deficiency	Roth et al.	2010	37 normal men with induced experimental gonadotropin deficiency	HCG: 0, 15, 60, or 125 IU sc every other day or 7.5 g daily testosterone gel for 10 days	0 IU: ITT 77 nmol/liter 15 IU: ITT 136 nmol/liter 60 IU: ITT 319 nmol/liter 125 IU: ITT 987 nmol/liter
Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression	Coviello et al.	2005	29 men with normal reproductive physiology	200 mg T enanthate weekly + either saline placebo or 125, 250, or 500 IU HCG EOD for 3 weeks	LH and FSH were suppressed to 5% and 3% of baseline and ITT was suppressed by 94% in the T enanthate/placebo group. ITT was 25% less than baseline in the 125 IU HCG group, 7% less than baseline in the 250 IU HCG group, and 26% greater than baseline in the 500 IU HCG group
Therapy with human chorionic gonadotrophin	Vicari et al.	1992	17 male patients with	14-120 months of HCG treatment at	Mean testicular volume increased from 3.8 +/- 0.2

alone induces spermatogenesis in men with isolated hypogonadotrophic hypogonadism--long-term follow-up			isolated hypogonadotrophic hypogonadism	1500 IU three times per week	(Mean +/- SEM) ml to a maximal of 14.9 +/- 1.1 ml after 22.2 +/- 2.3 months of hCG treatment. T was significantly higher than baseline after 15 and 24 months. 6 patients became sperm-positive at the 12-month follow-up, 4 at the 24-months follow-up and 3 at the time when their testicular volume was maximal.
Human chorionic gonadotropin treatment of nonorganic erectile failure and lack of sexual desire: a double-blind study	Buvat et al.	1987	45 men with nonorganic erectile failure or sexual desire	HCG, 5,000 IU I.M. twice per week	HCG led to better outcomes than placebo (47% vs 12%, $p < 0.05$) and improved more sexual parameters (67) than placebo (27). The effect on sexual behavior was not associated with the increase in plasma testosterone level
Plasma testosterone response to HCG in normal men without and after administration of anabolic drug	Repcekova et al.	1977	Young, adult males	Acute i.m.administration of 1500, 3000 or 4500 IU of HCG	No difference among T responses between any of the three dosages. The first significant rise in T was observed 24 h after its first application. T was

	higher at day 3 and 4 without differences between doses.

Table 2. Comparison between side effects of TRT vs. HCG treatment

	Red blood cells increase	Estradiol increase	Acne	Hair loss	Infertility	Prostate enlargement	PSA increase
TRT	○□	○□	△	△	○□	○□	○□
HCG	△	△	△	△	×	△	△

PSA: Prostate-specific antigen, ○□: occurs often, △: mild side effects occurring sometimes, ×: no side effects

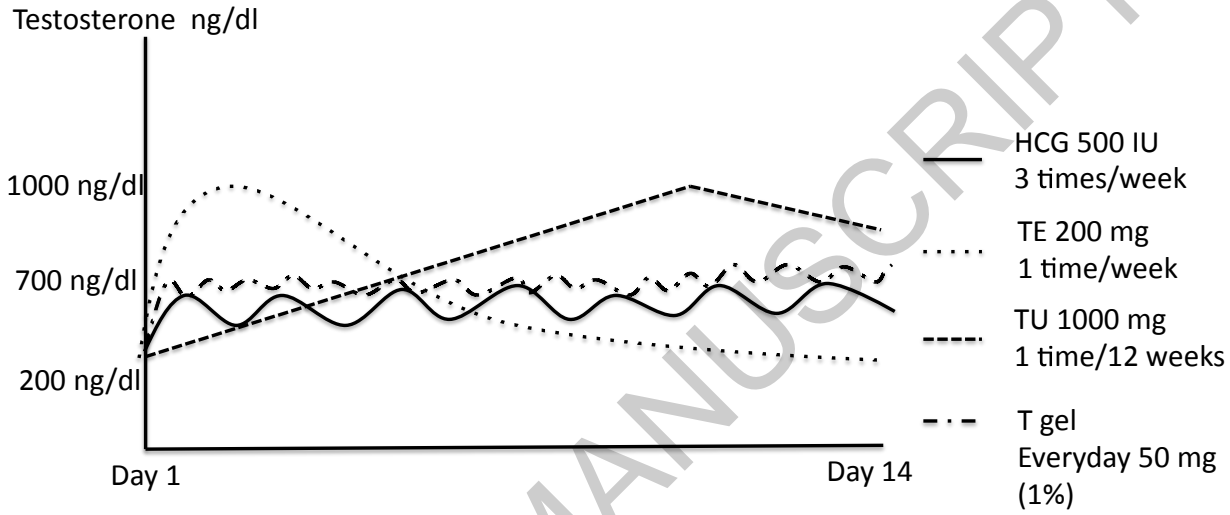

Figure 1. Representation of serum testosterone fluctuations after several different administration methods. TE: Testosterone Enanthate, TU: Testosterone Undecanoate, T gel: Testosterone gel.

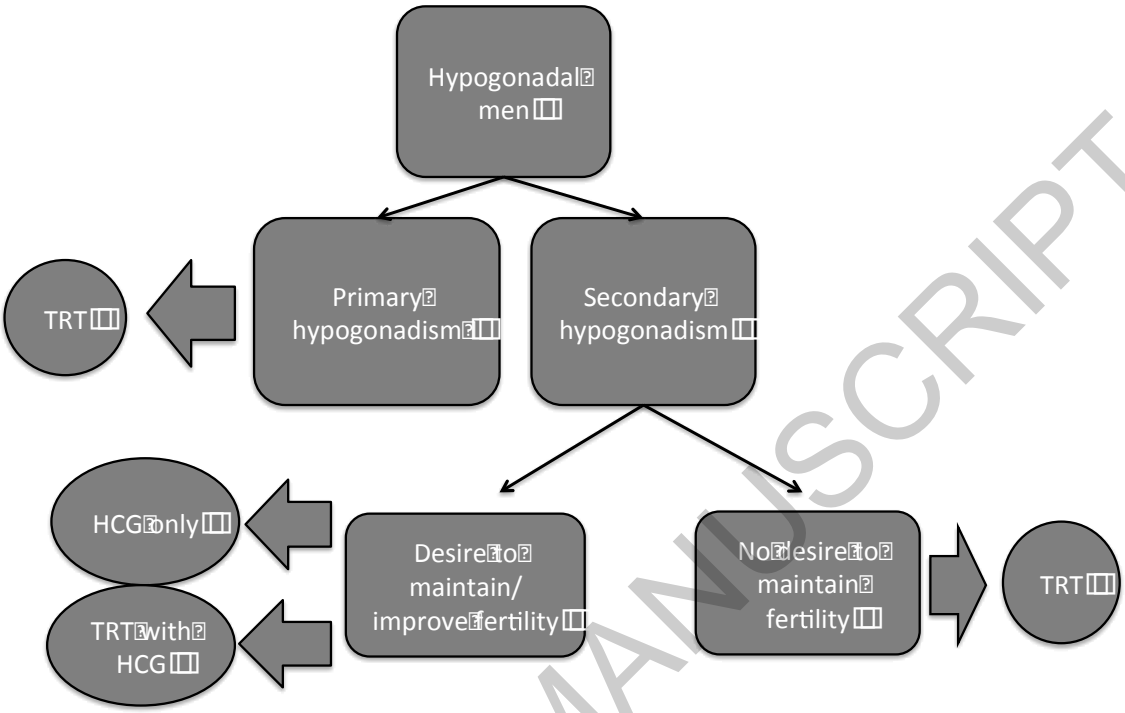

Figure 2. Several methods of restoring testosterone levels for different kinds of hypogonadal conditions.