Clinical Endocrinology (2009) **70**, 907–913 doi: 10.1111/j.1365-2265.2008.03435.x

ORIGINAL ARTICLE

# Cross-sectional analysis of testosterone therapies in hypopituitary men on stable pituitary hormone replacement

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## Summary

**Objective** The last decade has seen a proliferation in options for testosterone replacement. However, little is known as to the benefits of different treatment modalities. Our objective was to determine the testosterone prescription pattern and to examine the impact on various outcome measures.

**Subjects and methods** A total of 816 adult-onset hypopituitary males on stable pituitary replacement for at least 1 year were identified from the KIMS database. Patients were classified as either eugonadal ($n = 106$), or hypogonadal ($n = 710$) on intramuscular (IM, $n = 558$), oral ($n = 74$), transdermal ($n = 61$), and depot ($n = 17$) testosterone.

**Results** After 1 year of stable pituitary replacement therapy, body composition, cardiovascular parameters, GH replacement and quality of life were not significantly different in androgen-replaced hypogonadal patients compared to eugonadal patients. There were no differences in outcome variables within the hypogonadal group according to the testosterone replacement regimen used and no difference in response to GH therapy.

**Conclusions** The majority of hypopituitary patients in the last decade have received IM testosterone. Body composition, cardiovascular parameters, GH replacement and quality of life were not different between eugonadal and hypogonadal patients and were not differentially affected by the mode of testosterone replacement. These findings are reassuring that there is no major difference in response to different testosterone replacement regimens.

(Received 22 April 2008; returned for revision 18 June 2008; finally revised 6 August 2008; accepted 18 September 2008)

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## Introduction

Benefits of testosterone replacement in overtly hypogonadal men are well-recognized.[1] Apart from maintaining secondary sexual characteristics, libido and erectile function,[2–7] testosterone replacement helps to maintain a favourable body composition by increasing the lean body mass,[2,5–10] muscle mass and strength,[8] bone mineral density[10,11] and by reducing the body fat mass.[2,5,7,9,10] It also creates a favourable cardiovascular risk profile by maintaining a healthy lipid profile,[12,13] glucose homeostasis,[14] blood pressure levels[15] and improves general well-being[6] and quality of life.[16,17]

Testosterone was first chemically synthesized in 1935 and has been used in clinical practice since that time.[18] Due to the first pass elimination of most of the active hormone in the liver when given orally, it was initially compressed into pellets and introduced as subcutaneous implants. Later, alkylated oral preparations and esterified intramuscular preparations were introduced to clinical practice.[18–20] However, the initial oral preparations showed hepatotoxic adverse effects especially when used for longer periods and came out of favour. Due to lack of a better alternative, depot and intramuscular preparations remained the main testosterone preparations used for androgen replacement therapy for decades.[20] However, the last decade has seen a great increase in the options for testosterone therapy in men with hypogonadism with the availability of transdermal, buccal, intramuscular, depot (implants) and safer oral preparations.

The goal of testosterone treatment is to achieve physiological testosterone levels. However, this was not possible with intramuscular, depot and oral testosterone preparations.[21–23] With the newer testosterone preparations, physiological testosterone replacement has been a reality[24–26] and for this reason, the testosterone prescription pattern has changed during the last decade in most parts of the world. However, there is very limited research done comparing different preparations and their effects on response to treatment. In view of the changing market it would be very difficult to establish a large-scale randomised study comparing outcomes for different testosterone regimens. For this reason, we chose to use the surveillance database, KIMS (Pfizer International Metabolic Database), to ask the question whether different testosterone treatment regimens gave a difference in outcome. Our objectives were to investigate the testosterone prescription pattern during the last decade and to study the

replacement efficacies of the different testosterone formulations by comparing clinically relevant measures in hypogonadal men on replacement with those of eugonadal men.

## Subjects and methods

We conducted our study based on data in the KIMS database.

### *Database*

The KIMS database was established in 1994 and has been collecting information about GH replacement therapy in adults. The primary objective was to monitor the safety and outcomes of long-term GH replacement treatment in adult patients with GH deficiency in a conventional clinical setting. It is a condition of entry to KIMS that each centre obtains approval from their local ethics committee and that patients give informed consent. To date, the database contains data of more than 12 000 patients from 31 countries worldwide.[27]

### *Subjects*

GH deficient men above 18 years of age who had been in the KIMS database for a minimum of 2 years follow-up from 1995 to 2005 with at least 1 year of stable pituitary replacement including GH therapy were identified for the study. All patients had severe GH deficiency (GH peak < 3 μg/l after accepted stimulation tests) and were replaced with GH during the study period. Patients with adult-onset pituitary disease with various degrees of pituitary deficiencies were included in the study. Patients with childhood onset disease, craniopharyngiomas, Cushing's syndrome, acromegaly, Prader Willi syndrome and other complex hypothalamic pituitary syndromes, that can severely alter the overall body composition parameters, were excluded as were those who had changed their lipid lowering and/or anti-diabetic medication during that year. Patients from the above cohort who were naïve (never received GH before entry into the KIMS database) and semi-naïve (patients who had received GH treatment in the past but not been on GH therapy for at least 6 months before entry into the KIMS database) were used for analysis. Selected patients were classified as eugonadal ($n = 106$) or hypogonadal ($n = 710$) all of whom were replaced throughout the study evaluation. The androgen-replaced hypogonadal patients were further classified according to the mode of testosterone therapy, intramuscular (excluding 3 monthly testosterone undecanoate injections), oral (oral testosterone undecanoate), transdermal (testosterone patches and testosterone gel) and depot (implants) formulations. No patients were receiving the new three monthly injection, Nebido. We studied the prescription pattern of testosterone during the last 10 years (1995–2005) in different countries. In a cross-sectional analysis, we compared the following parameters between the groups at the end of 1 year of stable pituitary replacement therapy: body composition (height, weight, body mass index, waist circumference, waist/hip ratio, body fat, lean body mass and bone mineral content), cardio-vascular risk parameters (fasting blood glucose, HbA1c, lipid levels and blood pressure), GH-related parameters [GH dose, IGF-1 standard deviation score (SDS)] and quality of life (QoL-AGHDA). To look at the interaction with GH, we compared the change in the same parameters (Delta) between entry to the KIMS database (before GH treatment) with the results at the end of the 1 year of stable pituitary replacement therapy, which included GH replacement for all subjects.

### *Statistical analysis*

Data were analysed using SAS statistical software. Statistical comparisons were done between eugonadal and hypogonadal groups and between eugonadal and different hypogonadal subgroups on different testosterone preparations. Normally distributed parameters were compared using paired *t*-test and non-normally distributed parameters using Wilcoxon rank sum test. Comparisons were done after adjustment for age using multiple linear regression analysis. Multiple linear regression analysis was performed to adjust for other confounders (idiopathic GH deficiency, number of pituitary hormone deficiencies and for the baseline value of each variable) when the parameters were significantly different between groups.

## Results

There were 816 adult male patients in the KIMS database who fulfilled the criteria for the study. The majority, 782 (96%) of these patients were from European countries (Table 1). There were 106 (13%) eugonadal patients and 710 (87%) hypogonadal patients. In the hypogonadal patients, 558 (79%) were on intramuscular testosterone, 74 (10%) were on oral testosterone, 61 (9%) were on transdermal testosterone and 17 (2%) were on depot testosterone. There were variations in the type of testosterone preparations used in different countries. However, intramuscular testosterone was the main route of testosterone replacement in all countries (Table 1).

**Table 1.** Testosterone preparations used in different countries. The percentage of prescriptions for the formulation in a specific country is shown in brackets

| Country | Oral | Transdermal | Intramuscular | Depot |
|---|---|---|---|---|
| Argentina | 0 | 0 | 9 (100%) | 0 |
| Australia | 0 | 0 | 3 (38%) | 5 (62%) |
| Austria | 1 (6%) | 0 | 17 (94%) | 0 |
| Belgium | 9 (14%) | 0 | 54 (86%) | 0 |
| Czech Republic | 16 (80%) | 0 | 4 (20%) | 0 |
| Denmark | 0 | 0 | 18 (100%) | 0 |
| Germany | 7 (5%) | 3 (2%) | 124 (89%) | 5 (4%) |
| Greece | 0 | 0 | 2 (100%) | 0 |
| Hungary | 4 (100%) | 0 | 0 | 0 |
| Ireland | 0 | 0 | 7 (100%) | 0 |
| New Zealand | 0 | 1 (33%) | 2 (67%) | 0 |
| Spain | 0 | 4 (11%) | 32 (89%) | 0 |
| Sweden | 6 (4%) | 33 (17%) | 154 (79%) | 0 |
| Switzerland | 0 | 0 | 5 (100%) | 0 |
| The Netherlands | 18 (24%) | 1 (1%) | 57 (75%) | 0 |
| UK | 13 (12%) | 19 (18%) | 66 (63%) | 7 (7%) |
| USA | 0 | 0 | 4 (100%) | 0 |
| Total | 74 (10%) | 61 (9%) | 558 (79%) | 17 (2%) |

 

**Table 2.** Patient characteristics

| | Eugonadal group | Hypogonadal group | Significance level (*P* value) |
|---|---|---|---|
| Median age (years) | 48·8 ($n = 106$) | 52·6 ($n = 694$) | < 0·01 |
| Median age at pituitary disease onset (years) | 43·5 ($n = 105$) | 44·1 ($n = 709$) | NS |
| Idiopathic GH deficiency | 19% ($n = 106$) | 5% ($n = 710$) | < 0·001 |
| Number of pituitary hormone deficiencies* | 0·59 ($n = 106$) | 2·8 ($n = 709$) | < 0·001 |
| ACTH deficiency (%) | 28% ($n = 106$) | 80% ($n = 707$) | < 0·001 |
| TSH deficiency (%) | 25% ($n = 106$) | 82% ($n = 708$) | < 0·001 |

N, number of patients; *Additional to GH; NS, not significant.

The hypogonadal group was older when compared to eugonadal group ($P < 0·01$). There was a significantly higher proportion of idiopathic GH deficiency (19% *vs.* 5%) in the eugonadal group *vs.* hypogonadal group. In addition to GH deficiency, the hypogonadal group had a higher number of pituitary deficiencies when compared to patients in the eugonadal group (0·59 *vs.* 2·8, $P < 0·001$). However, the age of pituitary disease onset was similar in both eugonadal and hypogonadal groups (Table 2).

### *Body composition*

Height, weight, BMI, waist circumference and waist/hip ratio were not significantly different in hypogonadal ($n = 710$) and eugonadal ($n = 106$) patients. When analysed according to the type of testosterone treatment, no significant differences were observed between eugonadal and hypogonadal patients on different testosterone formulations (Table 3). There were no differences in body composition within the hypogonadal group, between the different testosterone groups, with respect to the response to GH therapy (Table 4).

### *Body fat*

Total body fat content (BIA) was not significantly different in the hypogonadal group ($n = 266$, 37%; oral = 15, transdermal = 31, IM = 213, depot = 7) when compared to the eugonadal group ($n = 101$, 55%) and there was no difference between the different modes of testosterone treatment (Table 3). The percentage of body fat was not different in eugonadal and hypogonadal patients. The changes in total body fat content with GH therapy were not different between eugonadal and hypogonadal patients (Table 4).

### *Lean body mass*

Hypogonadal patients had a significantly higher lean body mass ($P < 0·001$) compared to eugonadal patients. In hypogonadal subgroups, oral ($n = 15$), transdermal ($n = 31$) and IM ($n = 212$) groups had significantly higher lean body mass ($P < 0·01$, 0·01 and 0·001) compared to eugonadal group (Table 3). The change in lean body mass was not significantly different between eugonadal and hypogonadal patients with GH therapy (Table 4). However, when adjustments were made for idiopathic GH deficiency, the number of pituitary hormone deficiencies and for the baseline value of the individual variable, these differences became non-significant.

### *Bone mineral content*

There was no significant difference in the bone mineral content in the hypogonadal group when compared to eugonadal group. However, in the hypogonadal subgroups, the IM ($n = 55$) group had a higher BMC ($P < 0·01$) when compared to eugonadal group ($n = 7$) (Table 3). There was no difference in bone mineral content in response to GH treatment.

### *Cardiovascular risk parameters: Blood pressure, fasting blood sugar, HbA1c, lipids*

There were no significant differences in blood pressure, fasting blood sugar, HbA1c and lipid levels between eugonadal and hypogonadal group. However, significantly higher HDL cholesterol levels were seen in hypogonadal patients on oral testosterone ($P < 0·01$) and a lower HbA1c level on IM testosterone ($P < 0·01$), when compared to eugonadal patients (Table 3). There was no difference in these parameters in response to GH treatment between the groups (Table 4).

### *GH related parameters: GH dose and IGF-1 SDS*

There were no significant differences in the GH dose or IGF-1 SDS between the eugonadal and hypogonadal group. However, the oral group received a slightly lower GH dose ($P < 0·05$) and the depot group had a slightly higher IGF-1 SDS ($P < 0·05$) when compared to eugonadal group (Table 3).

### *Quality of life*

Quality of life score (QoL-AGHDA score) was not different between the eugonadal and the hypogonadal patients who were on different testosterone preparations and there was no difference in change during GH therapy (Tables 3 and 4).

## Discussion

We have analysed the testosterone prescription in a large cohort of hypopituitary patients.

Intramuscular testosterone remained the most common form of testosterone substitution in the last decade representing 75% of prescriptions. We found no significant difference in body composition,

**Table 3.** Patient characteristics: median (10th, 90th centiles)

| | Eugonadal (a) ($n = 106$) | Oral/Buccal (b) ($n = 75$) | Transdermal (c) ($n = 60$) | Intramuscular (d) ($n = 558$) | Depot (e) ($n = 17$) | $P$ value |
|---|---|---|---|---|---|---|
| Age (years) | 48·8 (31·2, 68·6) | 53·5 (39·2, 67·2) | 53·6 (34·4, 65·0) | 52·4 (36·0, 66·8) | 46·5 (33·9, 62·9) | $P < 0{\cdot}01$* |
| Age of pituitary disease onset (years) | 43·5 (23·4, 60·6) | 45·6 (30·8, 60·2) | 44·0 (24·9, 59·5) | 44·0 (24·9, 59·5) | 42·6 (25·5, 56·4) | NS |
| Height (cm) | 176·0 (166, 187·6) | 175·9 (170, 186) | 178 (171, 187) | 177·0 (166·4, 186) | 177·0 (169, 187) | NS |
| Weight (kg) | 84·2 (67·4, 110·2) | 90·7 (75, 111·4) | 89·7 (73·4, 108·6) | 88·5 (71·3, 109·3) | 91·0 (79·2, 109·7) | NS |
| BMI (kg/m$^2$) | 27·7 (23·1, 35·2) | 29·1 (23·5, 36·7) | 28·6 (23·5, 33·4) | 28·2 (23·4, 34·3) | 28·7 (26·7, 33·2) | NS |
| Waist (cm) | 97·5 (83, 115) | 100 (91, 115) | 98·0 (84·5, 110·5) | 99·0 (86, 114) | 96·5 (86·5, 106·0) | NS |
| Hip (cm) | 104·0 (94, 115) | 104·0 (98, 115) | 103·5 (94·5, 111) | 103·0 (94, 116) | 105·0 (98, 111) | NS |
| Waist : Hip ratio | 0·9 (0·9, 1·0) | 1·0 (0·9, 1·0) | 0·9 (0·9, 1·0) | 1·0 (0·9, 1·0) | 0·9 (0·8, 1·0) | NS |
| Systolic BP (mmHg ) | 125 (110, 150) | 130 (115, 150) | 130 (110, 150) | 130 (110, 160) | 130 (114,140) | NS |
| Diastolic BP (mmHg) | 80 (66·5, 90) | 80 (70, 90) | 80 (69, 91) | 99 (86, 114) | 81·5 (70, 90) | NS |
| BIA body fat (kg) | 19·9 (10·4, 34·6) | 19·4 (9·4, 32·7) | 21·5 (13·4, 36·0) | 19·5 (11·1, 32·5) | 23·8 (15·6, 29·8) | NS |
| BIA lean body mass (kg) | 62·4 (52·3, 77·1) | 70·8 (53·9, 85·1) | 68·6 (59·1, 84·9) | 68·2 (54·7, 80·9) | 63·2 (55·4, 75·6) | $P < 0{\cdot}05$* |
| DEXA bone mineral content (kg) | 2·4 (1·8, 3·5) | 2.5 (2·1, 3·6) | 3·3 (2·5, 4·1) | 3·2 (2·7, 3·8) | 2·6 (2·2, 2,9) | $P < 0{\cdot}01$† |
| Total cholesterol (mmol/l) | 5·4 (4·1, 6·7) | 5·4 (4·1, 7·2) | 5·5 (4·2, 6·9) | 5·3 (4·2, 6·7) | 5·5 (3·7, 6·8) | NS |
| LDL-cholesterol (mmol/l) | 3·1 (2·2, 4·4) | 3·5 (1·9, 4·8) | 3·3 (2·5, 4·1) | 3·3 (2·2, 4·6) | 3·2 (1·9, 4·6) | NS |
| HDL-cholesterol (mmol/l) | 1·2 (0·8, 1·8) | 1·0 (0·8, 1·6) | 1·2 (0·9, 1·7) | 1·1 (0·8, 1·6) | 1·3 (0·9, 1·5) | $P < 0{\cdot}01$‡ |
| Triglycerides (mmol/l) | 1·4 (0·8, 2·7) | 1·6 (0·8, 3·4) | 1·7 (0·7, 3·4) | 1·8 (0·9, 3·4) | 1·3 (0·6, 2·8) | NS |
| Fasting glucose (mmol/l) | 5·0 (4·2, 6·6) | 4·9 (4·3, 6·1) | 4·7 (3·8, 6·7) | 4·8 (4·0, 5·8) | 4·9 (4·4, 5·9) | NS |
| HbA1c (%) | 5·5 (4·36, 6·7) | 5·5 (4·6, 6·4) | 4·8 (3·9, 6·7) | 5·1 (4·3, 6·1) | 5·6 (3·9, 6·4) | $P < 0{\cdot}01$§ |
| GH dose (mg/day) | 0·3 (0·2, 0·8) | 0·27 (0·1, 0·5) | 0·3 (0·2, 0·5) | 0·3 (0·2, 0·7) | 0·4 (0·2, 1·2) | $P < 0{\cdot}05$‡ |
| IGF-1 SDS | 1·0 (–0·4, 2·3) | 1·0 (–0·8, 2·2) | 1·0 (–0·4, 2·9) | 0·9 (–0·8, 2·3) | 2·6 (–1·2, 4·8) | $P < 0{\cdot}05$** |
| QoL-AGDHA score | 3 (0, 14) | 6 (0, 15) | 3 (0, 13) | 2 (0, 13) | 3 (0, 18) | NS |

NS, not significant; AGDHA, adult growth hormone deficiency health assessment.
*a *vs.* b, c and d; †a *vs.* d; ‡a *vs.* b; §a *vs.* c and d; **a *vs.* e.

**Table 4.** Changes of individual parameters in eugonadal and hypogonadal patients from KIMS entry to 1 year of stable pituitary treatment

| | Eugonadal | Hypogonadal | *P* value |
|---|---|---|---|
| Height (cm) | 0·00 | 0·00 | 0·2613 |
| Weight (kg) | 0·95 | 0·90 | 0·7525 |
| BMI (kg/m$^2$) | 0·32 | 0·29 | 0·9318 |
| Waist (cm) | 0·00 | –1·00 | 0·0609 |
| Hip (cm) | 0·50 | 0·00 | 0·1005 |
| Waist : Hip ratio | 0·00 | –0·01 | 0·8423 |
| Systolic BP (mmHg) | 0·00 | 0·00 | 0·9538 |
| Diastolic BP (mmHg) | 0·00 | 0·00 | 0·6315 |
| BIA body fat (kg) | –0·81 | –0·24 | 0·4713 |
| BIA lean body mass (kg) | 1·70 | 1·20 | 0·9684 |
| Total cholesterol (mmol/l) | –0·60 | –0·50 | 0·6839 |
| LDL cholesterol (mmol/l) | –0·53 | –0·45 | 0·8358 |
| HDL cholesterol 9mmol/l) | 0·00 | 0·00 | 0·8189 |
| Triglycerides (mmol/l) | –0·10 | 0·00 | 0·1057 |
| Fasting glucose (mmol/l) | 0·10 | 0·33 | 0·3510 |
| HbA1c (%) | 0·10 | 0·10 | 0·6469 |
| GH dose (mg/day) | 0·30 | 0·30 | 0·4018 |
| IGF-1 SDS | 1·84 | 2·15 | 0·3823 |
| QoL-AGHDA score | –4·5 | –3 | 0·3891 |

AGDHA, adult growth hormone deficiency health assessment.

cardiovascular risk parameters, GH replacement and quality of life between hypogonadal patients on different forms of testosterone preparations. There was no difference in response to GH treatment between hypogonadal and eugonadal patients.

Despite the availability of newer physiological testosterone replacement options at the time of this study, the majority of clinicians were still using intramuscular testosterone as the main form of testosterone substitution. The newer testosterone formulations such as transdermal testosterone were predominantly being used in countries such as UK and Sweden. It is likely that the prescription pattern is driven by many factors including cost, reimbursement and availability.

There is very limited research done comparing the biological actions of different testosterone preparations. The few studies reported suggest that the newer testosterone preparations such as transdermal and buccal testosterone are more physiological according to pharmacokinetic profile,[23,24,28] efficacious[29] and have a better safety profile[23] compared to older preparations. However, the advantages of physiological testosterone replacement are yet to be substantiated with long-term randomized clinical trials. In contrast, some studies suggest that there is no real advantage of using the more expensive newer preparations over the conventional intramuscular and depot preparations.[30,31] In our study, we did not see any difference in effects on body composition, cardiovascular parameters, GH response and quality of life with different testosterone preparations. These findings are reassuring that there is no major difference in response to different replacement regimens of testosterone. However, long-term randomized control trials will be required to determine the benefits of physiological replacement regimens.

The co-administration of testosterone and GH has been shown to have synergistic effects on energy metabolism and body composition in men.[32–37] There is a greater increase in energy expenditure, fat oxidation, protein metabolism and in the lean body mass including the extra-cellular fluid volume with the combination treatment than with testosterone alone.[33–35] There is also a greater reduction in body fat mass (both subcutaneous and visceral) with the combination therapy than that achieved with testosterone alone.[32–35] We did not see a significant change in lean body mass in response to GH therapy in our hypogonadal patients.

A limitation of the present study is the selective nature of the study population, which reduces external validity, and prescription bias that may be dictated by local factors. However, there is very limited research done comparing the biological actions of different testosterone preparations because of the difficulty of obtaining funding and permission to use preparations of testosterone from different companies and also using treatment regimens that have generally been superseded without direct comparison. We acknowledge that a control group of normal age-matched men and a control group of hypogonadal men not on treatment is required for an optimal study but it would be extremely difficult to generate such a large data set and ethically problematic not to treat hypogonadal patients. Taking these provisos into account, the most striking feature in our study was the lack of a significant difference in the studied parameters between eugonadal and hypogonadal patients. The higher lean body mass that we observed in hypogonadal patients also became non-significant when adjustments were made for idiopathic GH deficiency, number of pituitary hormone deficiencies and for the baseline value of these variables. This suggests that the difference in the lean body mass was likely to be related to the aetiology of hypopituitarism rather than gonadal status or testosterone replacement.

There were certain other limitations related to our study. First of all, the KIMS database collects information on adult hypopituitary patients with GH deficiency and thus by definition, patients with other diseases, who require testosterone treatment, were not included in this study. Another difficulty that we encountered was caused by differences between the hypogonadal and eugonadal groups with regard to primary aetiology and extent of hypopituitarism. To adjust for such potential confounders, we used multiple regression analysis – a statistical method, which compares the studied parameters regardless of the underlying differences between the groups. In this way, we believe, it was possible to eliminate impact of other factors. Finally, KIMS is an observational study, therefore its role is mainly to suggest or indicate the directions to aid further research. By its nature, it is complementary to randomized clinical trials but cannot replace them.

Our data indicate that the majority the hypogonadal patients used intramuscular testosterone as replacement during the last decade. All the testosterone preparations had similar effects on body composition, cardiovascular risk parameters, GH treatment and quality of life indistinguishable from eugonadal men. This surveillance study shows that current androgen replacement regimens employed in clinical practice are efficacious in hypopituitary men regardless of the mode of administration.

## Acknowledgement

Authors express their thanks to the KIMS investigators all over the world who provided the data on their patients. KIMS is supported by Pfizer.

 

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