CLINICAL STUDY

Growth hormone replacement does not increase serum prostate-specific antigen in hypopituitary men over 50 years

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Abstract

Objective: Epidemiological studies have shown an increased risk for prostate carcinoma in men with serum IGF-I in the upper part of the age-related reference range. Recombinant human GH (rhGH) is widely used in patients with GH deficiency, usually raising the serum IGF-I levels into the normal range; safety surveillance is therefore mandatory, with particular regard to neoplasia. The aim was to examine whether rhGH replacement in hypopituitary adults is associated with changes in serum prostate-specific antigen (PSA) as a surrogate marker of changes in prostatic growth.

Design and methods: A prospective longitudinal study was used with a median follow-up of 22 (range 2.5–32) months, in which 41 men aged over 50 years with adult onset hypopituitarism and GH deficiency during rhGH replacement were examined. Serum PSA and IGF-I were measured at baseline and at latest follow-up.

Results: Mean serum PSA remained unchanged during rhGH replacement, with a median follow-up of 2 years. No correlation was found between the individual changes in serum IGF-I and changes in serum PSA.

Conclusions: These data are reassuring thus far regarding the safety of GH replacement in relation to the prostate in this patient group.

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Introduction

There has been considerable debate surrounding the possible relationship between serum growth hormone (GH), insulin-like growth factor I (IGF-I) and neoplasia (1). Patients with acromegaly are increasingly recognised to have an increased risk of colonic neoplasia and routine screening programmes have been advocated (2). The debate on IGF-I and oncogenesis in the general population has been brought into sharper focus through epidemiological observations showing that normal individuals with a serum IGF-I at the upper end of the age-related reference range are at an increased risk for the subsequent development of prostate carcinoma, while those with higher IGF-binding protein-3 (IGFBP-3) are at lower risk (3). In this study, serum prostate-specific antigen (PSA) was only measured once, on average 7 years prior to the diagnosis of prostate cancer (3). IGF-I promotes prostate epithelial cell proliferation *in vitro* and this could explain the increased risk of carcinoma (4, 5). The ratio of IGF-I/PSA has been suggested as a predictor of prostate carcinoma (6). However, a study of 120 consecutive men undergoing radical prostatectomy for

cancer demonstrated no correlation between immediately preoperative serum IGF-I and the serum PSA or with subsequent progression-free survival (7). A comparison of serum IGF-I levels in these men with those of 20 healthy men and 10 men with untreated metastatic prostate cancer also failed to show any significant difference. Recent work has demonstrated that reducing IGF-I in patients with acromegaly leads to reduction in prostate size (8), a finding consistent with the generalised viseromegaly of acromegaly. It has also recently been shown that chronic GH deficiency (GHD) seems to cause a decrease in prostate size, especially in men younger than 60 years with androgen deficiency (9).

Following the introduction of recombinant human GH (rhGH) there is renewed interest in the effects of GH in the adult population with GHD (10). The recognition of the benefits of rhGH has meant that increasing numbers of GHD adults are being replaced with rhGH (11). A recent consensus statement from the Growth Hormone Research Society has documented currently available safety data for rhGH therapy (12). Clearly long-term safety surveillance is of paramount importance, particularly with respect to any increased risk of neoplasia.

rhGH replacement therapy in hypopituitary adults aims to increase serum IGF-I into the normal range. Our own practice is to target this to between the median and upper end of the age-related reference range, since at least 20% of GHD adults have IGF-I levels already in the normal range, albeit in the lower third (13). If IGF-I is found to be above the age-related reference range the dose of rhGH is decreased to reduce any possible risks associated with raised IGF-I levels. Notably, rhGH therapy raises both IGF-I and IGFBP-3 (13, 14).

The present study was therefore designed to determine whether targeted rhGH replacement in hypopituitary adults could be associated with an increased risk of prostatic hypertrophy or neoplasia, as determined by serum PSA as a surrogate marker.

Patients and methods

Patients

A cohort of 41 men with hypopituitary GHD was studied. Their ages ranged from 50 to 68 years, with a median of 57 years. GHD accompanied or followed treatment of their initial diagnoses of apparently non-secreting pituitary tumours (37%), corticotroph adenomas (20%), lactotroph adenomas (17%), craniopharyngiomas (5%), somatotroph adenomas (2%) and others (17%). None of the patients had received prior rhGH replacement. Other pituitary hormone deficiencies at the time of commencing rhGH included deficiencies in luteinising hormone (LH) or follicle-stimulating hormone (FSH) in 90%, thyroid-stimulating hormone in 75%, adrenocorticotrophin in 85% and antidiuretic hormone in 34%. All patients were on appropriate hormone replacement regimens including testosterone when deficient. However, it is difficult to determine the duration of LH and FSH deficiency prior to commencement of testosterone replacement. Testosterone was replaced as an intramuscular injection of testosterone esters (250–500 mg every 3–4 weeks, depending on pre-dose serum testosterone measurements). Baseline serum IGF-I ranged from 46 to 145 ng/ml with a median of 85 ng/ml (age-related reference range 108–263 ng/ml). Doses of rhGH were titrated to increase the serum IGF-I to between the median and the upper end of the age-related reference range, and patients were followed for a median of 22 (range 2.5–32) months.

All patients gave written informed consent to the collection of safety surveillance data and its anonymised entry into a multinational surveillance database.

Controls

One hundred healthy men with a median age of 55 (range 50–63) years, undergoing more than one serum PSA measurements for screening purposes,

were used as a control group. The median time-period between measurements was 24 (range 2–33) months.

Methods

Serum PSA was measured by DPC Immulite 2000 (Diagnostic Products Corporation, Llanberis, UK; coefficient of variation (CV) 5.1% at 2.59 g/l, detection limit 0.003 ng/ml). Serum IGF-I was measured by an in-house radioimmunoassay after formic acid acetone extraction with an inter- and intra-assay CV of less than 10% (15).

Statistical analysis

Changes in serum PSA and serum IGF-I before and after rhGH treatment were analysed by Student's paired *t*-test. The Mann–Whitney rank sum test was used to compare the changes in serum PSA between the control group and the 41 patients. Correlation between serum PSA with serum IGF-I or serum testosterone was evaluated by linear regression. The change in serum PSA and the change in serum IGF-I were also compared. The patients were separated into those who showed a decrease and those who showed an increase in serum PSA. The serum IGF-I achieved by each of these groups was compared using the Mann–Whitney U test. The statistical analysis was performed using Sigmastat v. 2.03 (SPSS Science).

Results

During rhGH therapy, serum IGF-I increased significantly from a median of 85 ng/ml (range 46–145 ng/ml) to 191 ng/ml (range 98–364 ng/ml) ($P < 0.001$). In 27%, serum IGF-I was in the upper quartile of the reference range. However, there was no significant change in serum PSA during rhGH treatment, with a median value of 0.77 µg/l at baseline and 0.73 µg/l at latest follow-up ($P = 0.28$).

Figure 1 demonstrates the change in serum PSA in the 41 patients over time. No significant change in the median level of serum PSA was demonstrated, and no patient exceeded a serum PSA of 2.6 µg/l which, for the assay used in this age range, indicates the level at which suspicion is raised regarding prostatic pathology. The changes in serum PSA during follow-up showed no difference between the 100 men in the control group (median change 0.04, range –1.58 to +1.42 µg/l) and the 41 patients ($P = 0.11$). Four patients were treated with rhGH for less than 6 months, but no difference could be shown in changes in serum PSA during follow-up between these patients (median change –0.37, range –1.71 to +0.10 µg/l) and the rest of the group ($P = 0.3$).

In 56% of patients, serum PSA decreased, compared with 44% in whom an increase within the age-related

Figure 1 Longitudinal changes in serum PSA during rhGH replacement therapy.

reference range was noted. There was no correlation between the changes in serum IGF-I and the changes in serum PSA ($R = 0.08$); patients with the highest increment in serum IGF-I demonstrated a similar serum PSA to those with lesser increments in serum IGF-I. Those patients who had a decreased serum PSA did not differ in terms of serum IGF-I compared with those in whom serum PSA increased (Fig. 2). Table 1 demonstrates IGF-I quartiles for the range obtained in this study and, although it differs from the IGF-I quartiles used by Chan *et al.* (3), it does not demonstrate any trend of increasing serum PSA at higher serum IGF-I levels.

In 88% of the patients with decreasing serum PSA over the time studied, the changes were within the CV values of the assay. The remaining five patients (12%) showed a decrease in serum PSA from a median of $2.36 \mu\text{g/l}$ to $0.87 \mu\text{g/l}$. The majority of patients were LH-deficient and needed testosterone replacement ($n = 37$), and on testosterone replacement the median serum testosterone was 10.5 nmol/l (range $2\text{--}23.2 \text{ nmol/l}$). The range reflects the variable periods of time between last testosterone injection and the timing of samples, but no correlation could be demonstrated with serum PSA ($P = 0.64$). The number of patients who did not require testosterone replacement was small ($n = 4$), but the median change in serum PSA between the LH-replete and LH-deficient patients was similar ($-0.024 \mu\text{g/l}$ vs $-0.035 \mu\text{g/l}$). In this

Figure 2 Serum IGF-I on maintenance rhGH replacement in patients with decreased versus increased serum PSA. Boxes indicate the median, 25th and 75th centiles; values outside the 10th and 90th centiles (error bars) are indicated (●).

group of patients no correlation could be demonstrated between serum PSA and testosterone ($P = 0.8$).

Discussion

Recent epidemiological evidence, suggesting that IGF-I might be a major determinant of several carcinomas including prostate, has raised legitimate concerns regarding the safety of rhGH replacement therapy. The present study therefore examined the possibility that serum PSA might systematically increase with rhGH therapy over time, and thus possibly indicate an increased risk for prostatic carcinoma. No evidence for this was found, in that serum PSA did not rise significantly during rhGH treatment, nor did it rise to a clinically relevant level in any patient. However, a possible factor confounding interpretation of the changes in serum PSA could be decreased testosterone levels. Although all patients were made testosterone-replete when required, it remains difficult to establish the duration of time between onset of testosterone deficiency and initiation of replacement.

Prostate carcinoma is the second most common malignancy in men, with a peak incidence after the

Table 1 Serum PSA according to quartiles of serum IGF-I.

	IGF-I quartiles			
	66–153 ng/ml ($n = 10$)	154–193 ng/ml ($n = 10$)	194–216 ng/ml ($n = 10$)	217–364 ng/ml ($n = 11$)
Median PSA ($\mu\text{g/l}$)	0.74	1.21	0.55	0.56
S.E.M.	0.14	0.44	0.16	0.28
Minimum PSA ($\mu\text{g/l}$)	0.14	0.09	0.08	0.06
Maximum PSA ($\mu\text{g/l}$)	1.51	3.69	1.64	2.53

sixth decade of life (16). Benign prostatic hypertrophy (BPH) is under the influence of dihydrotestosterone (17), and may act as a premalignant step in the development of prostate cancer. BPH is strongly associated with testosterone and it is well recognised that hypogonadal men do not suffer from prostatism due to BPH (16). What has been difficult to determine is the significance of microscopic foci of carcinoma incidentally found at autopsy. Men aged 50–60 years have an incidence of 50%, while 100% of men over 75 years have microscopic foci of mitotic cells in their prostates (16). Prostate carcinoma is a hormone-dependent tumour in that testosterone and dihydrotestosterone have clearly been shown to promote prostate cell growth, and treatment of the malignancy relies on their reduction through surgery, radiotherapy or endocrine therapies (18).

Serum PSA is specifically produced by prostate acinar cells and ductal epithelium and is proportional to the volume of the prostate (19). An increased serum PSA provides a surrogate marker of increased risk for prostate cancer (20); the prediction of malignancy within 4 years with a single elevated serum PSA has a specificity of 91% but a sensitivity of just 46% (20). However, a rising serum PSA is found to precede other indicators of prostate carcinoma progression, and regular serial measurements have therefore been suggested (21). Screening with a single serum PSA measurement in asymptomatic men is not recommended, but serial serum PSA measurement is being advocated as a screening tool by the American Urological Society and new trials are planned to establish the benefit of serial serum PSA in the general population.

A possible explanation for the lack of observational evidence on increased prevalence of prostate carcinoma in patients with long-term elevation of IGF-I in acromegaly might be the increased premature mortality in these patients. Long-term studies are required to exclude increased risk now that patients are surviving longer. Surveillance databases of rhGH replacement in hypopituitary adults have accumulated several thousand patient years of observation and have thus far not shown any increased incidence of malignancy (22).

The risk of developing prostate cancer seems to be a function of a patient's genetic risk, environment, serum testosterone and serum IGF-I exposure, linked possibly with low serum IGFBP-3. We have no reason to believe that the patients with GHD had a different genetic risk or environmental exposure as compared with the general population, although the majority did receive testosterone replacement and had IGF-I levels in the upper part of the reference range during rhGH therapy. Nonetheless, an additional effect of rhGH replacement is to increase serum IGFBP-3 level and this is likely to confer some protection. This study demonstrated that there is no change in serum PSA in a group of 41 men given rhGH for treatment of GHD and this is

evidence against pathological prostatic growth. However, it does not exclude other reasons for increased risk. No conclusions can be drawn regarding the risk of patients with elevated serum PSA prior to rhGH treatment. Our observations are encouraging, but continuing surveillance is required and long-term studies are needed to compare the incidence of prostate cancer in rhGH-treated patients with that of the background population.

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