

Decorin, a growth hormone-regulated protein in humans

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Abstract

Context: Growth hormone (GH) stimulates connective tissue and muscle growth, an effect that is potentiated by testosterone. Decorin, a myokine and a connective tissue protein, stimulates connective tissue accretion and muscle hypertrophy. Whether GH and testosterone regulate decorin in humans is not known.

Objective: To determine whether decorin is stimulated by GH and testosterone.

Design: Randomized, placebo-controlled, double-blind study.

Participants and Intervention: 96 recreationally trained athletes (63 men, 33 women) received 8 weeks of treatment followed by a 6-week washout period. Men received placebo, GH (2 mg/day), testosterone (250 mg/week) or combination. Women received either placebo or GH (2 mg/day).

Main outcome measure: Serum decorin concentration.

Results: GH treatment significantly increased mean serum decorin concentration by $12.7 \pm 4.2\%$; $P < 0.01$. There was a gender difference in the decorin response to GH, with greater increase in men than in women ($\Delta 16.5 \pm 5.3\%$; $P < 0.05$ compared to $\Delta 9.4 \pm 6.5\%$; $P = 0.16$). Testosterone did not significantly change serum decorin. Combined GH and testosterone treatment increased mean decorin concentration by $19.5 \pm 3.7\%$ ($P < 0.05$), a change not significantly different from GH alone.

Conclusion: GH significantly increases circulating decorin, an effect greater in men than in women. Decorin is not affected by testosterone. We conclude that GH positively regulates decorin in humans in a gender-dimorphic manner.

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Introduction

Growth hormone (GH) and testosterone are potent anabolic hormones that interact positively in regulating the muscle structure and function (1, 2, 3, 4). The effects of GH on collagen synthesis, fat mass, lean tissue and physical function are amplified by testosterone. Similarly the effects of testosterone in hypopituitary and normal men are greater when co-administered with GH (4, 5, 6, 7, 8, 9). Both GH and testosterone increase collagen markers, with GH imparting a greater effect, whereas testosterone amplifies the effect of GH on collagen markers, such as PIIINP (4, 5).

Decorin, a small leucine-rich proteoglycan, is a myokine and connective tissue protein (10, 11). Decorin is produced in response to exercise, and it stimulates skeletal muscle differentiation and repair (12, 13, 14, 15, 16). Decorin induces myogenic satellite cell proliferation by inhibiting responsiveness to TGF- β 1 (17). *In vitro* overexpression of decorin enhances the proliferation and differentiation of skeletal muscle cells by repressing the activity of myostatin, an inhibitor of muscle cell growth and differentiation (18). Furthermore, decorin

overexpression in muscle increases the expression of promyogenic genes, while repressing genes involved in muscle atrophy (16). Decorin also stimulates connective tissue collagen synthesis and regulates connective tissue formation in skeletal muscle (19, 20, 21).

No studies to date have assessed the effects of GH or testosterone on decorin production in humans. The aim of the present study is to investigate whether GH and testosterone regulate circulating decorin in healthy men and women.

Subjects and methods

Healthy recreational athletes aged 18–40 years, who had regularly participated in at least twice weekly exercise sessions in the past year were recruited, as previously described (5). Exclusion criteria were participation in sports competitions at the state or national level, self-reported abuse of performance-enhancing drugs, history of diabetes mellitus, cardiovascular, hepatic or renal disease, known cancer or positive urine screen for prohibited anabolic agents. 96 athletes (63 men and 33 women) were included in the study. Participants were instructed not to change their diet or exercise level throughout the study. All study participants provided written informed consent. The study was approved by St. Vincent's Hospital Human Research Ethics Committee, NSW Australia and registered with the Australian New Zealand Clinical Trials Registry ACTRN012605000508673.

This was a double-blind placebo-controlled randomized study, as previously described (5). Briefly, women were assigned to receive either 2 mg/day GH ($n=17$) or placebo ($n=16$). Men were assigned to receive 2 mg/day GH ($n=15$), 250 mg/week testosterone ($n=16$), GH plus testosterone ($n=16$), or double placebo ($n=16$). Participants self-administered GH (Somatropin, 1 mg/mL;

Novo Nordisk) or matched placebo subcutaneously each evening at dosages of 1.0 mg/day in the first week, 1.5 mg/day in the second week and 2.0 mg/day for the remaining 6 weeks. Testosterone (Sustanon, Organon, Oss, the Netherlands; 250 mg/week) or placebo was administered from the end of the third week as weekly intramuscular injections (5). The effects of the interventions on IGF-I, collagen peptides, body composition and physical function have been published (4, 5).

We examined whether serum decorin concentrations were affected by supplementation with GH in men and women, and testosterone in men. We also investigated whether co-administration with testosterone enhanced the effects of GH alone. We compared changes in decorin to GH-regulated proteins, IGF-I and collagen peptides and changes in body composition. Body composition was measured by dual-energy x-ray absorptiometry and included lean body mass (LBM) assessment and a functional measure of muscle mass – body cell mass (derived by subtracting extracellular water from the LBM), as previously described (4).

Assays

Serum samples were collected at baseline (week 0), during treatment (week 4), end of treatment (week 8) and after a 6-week washout period (week 14) and stored at -80°C for analysis. Decorin levels were measured using the Decorin Human ELISA kit (Abcam) according to manufacturer instructions. Serum samples were diluted 100-fold and all samples for each subject were measured in duplicates in the same assay run. The sensitivity of the assay is $<1.5\text{ pg/mL}$ with $>93\%$ recovery rate. The intra-assay and inter-assay coefficients of variation (CVs) were $<2\%$ and $<12\%$, respectively. IGF-1, testosterone, PINP, PIIINP and ICTP were assayed as previously described (5).

Table 1 Baseline characteristics of the study subjects. The table shows the age, body mass index (BMI), and serum levels of IGF-1, testosterone, PIIINP and decorin of the subjects in various treatment groups. Data are shown as mean \pm S.E.M.

Treatment	Age (year)	BMI (kg/m^2)	IGF-1 ($\mu\text{g/L}$)	T (nmol/L)	PIIINP ($\mu\text{g/L}$)	Decorin (pg/mL)
Women						
Placebo	27.8 ± 1.3	22.8 ± 0.8	137 ± 10.0	1.4 ± 0.2	4.5 ± 0.3	6481 ± 203
GH	29.7 ± 1.6	22.9 ± 0.7	124 ± 7.9	1.2 ± 0.2	3.7 ± 0.2	6127 ± 349
Men						
Placebo	28.9 ± 1.3	26.1 ± 0.8	110 ± 9.6	21.9 ± 1.9	3.4 ± 0.2	5748 ± 275
GH	25.2 ± 1.4	23.8 ± 0.7	128 ± 9.7	25.3 ± 2.1	4.2 ± 0.4	5748 ± 269
T	29.0 ± 1.5	25.4 ± 1.0	128 ± 9.5	23.5 ± 2.0	4.1 ± 0.3	6304 ± 448
GH + T	26.8 ± 1.3	24.4 ± 0.7	113 ± 10.3	23.1 ± 1.3	4.0 ± 0.2	5953 ± 312

GH, growth hormone; T, testosterone.

Statistical analysis

Treatment effects on decorin levels were evaluated by one-way ANOVA for repeated measures, followed by Dunnett's *post hoc* multiple comparison test to evaluate treatment effects at individual time points. Data are expressed as mean \pm S.E.M. Multiplicity adjusted *P* values are reported, and differences relative to the placebo group considered significant at $P < 0.05$. Spearman's rank correlation was used for the analysis of correlation between the serum decorin concentration and the IGF axis, collagen markers and body composition. Unadjusted *P* values are reported, and correlations were considered significant at $P < 0.05$. Statistical analyses were performed using RStudio (Boston, MA, USA) (22).

Results

Table 1 shows the baseline characteristics of the 96 subjects, serum concentration of decorin, and previously reported measures of body mass index (BMI), IGF-1 and PIIINP (5). There were no significant differences in the baseline decorin levels between the treatment groups. At baseline, there was a positive and significant correlation between serum levels of decorin and the collagen marker, PIIINP ($R = 0.34$, $P < 0.01$). There were no significant associations between baseline serum decorin concentrations and any other endpoint measures.

Indicative of the effect of intervention, in women GH administration increased IGF-1 by $86 \pm 12\%$ ($P < 0.0001$). In men, IGF-1 significantly ($P < 0.0001$) increased by $144 \pm 23\%$ and $160 \pm 24\%$ when treated with GH alone or when combined with testosterone, respectively. Serum testosterone increased significantly ($P < 0.01$)

in men treated with testosterone alone (23.5 ± 2.0 vs 32.2 ± 2.5 nmol/L) or when combined with GH (23.1 ± 1.3 vs 31.2 ± 1.7 nmol/L).

Table 2 shows serum decorin levels during the hormone treatments and withdrawal. The mean decorin concentration increased significantly ($P < 0.01$) during eight weeks of GH treatment, returning to baseline after withdrawal (Fig. 1A). The increase in decorin concentration was greater in men ($16.5 \pm 5.3\%$; $P < 0.05$, Fig. 1C) than in women ($9.4 \pm 6.5\%$; $P = 0.16$; Fig. 1B). Decorin levels did not change during placebo treatment. Testosterone treatment did not significantly affect circulating decorin levels ($\Delta 4.2 \pm 3.6\%$; $P = 0.30$; Fig. 2). Co-administration of testosterone with GH significantly increased decorin levels ($\Delta 19.5 \pm 3.7\%$ $P < 0.01$; Fig. 2). However, no additive effect of the co-treatment was observed compared to GH alone.

Changes in serum decorin correlated significantly ($P < 0.001$) with changes in IGF-1, PINP, ICTP and PIIINP (Fig. 3). Changes in serum decorin showed significant positive correlation with changes in LBM ($R = 0.50$; $P < 0.001$) and body cell mass ($R = 0.31$; $P < 0.05$).

Discussion

This study investigated whether decorin is regulated by GH or testosterone in humans. Our data demonstrate that GH significantly increases serum decorin concentration with the effect greater in men than in women. Testosterone did not affect decorin and co-treatment did not have additional effect to that of GH alone. The changes in decorin induced by GH correlated with those of other GH-responsive proteins in blood.

Table 2 Mean serum decorin concentrations before treatment (week 0), during treatment (week 4), end of treatment (week 8) and after a 6-week washout period (week 14). Men received either placebo, GH (2 mg/day), testosterone (250 mg/week), or combined treatments. Women received either placebo or GH (2 mg/day). Data are shown as mean \pm S.E.M.

	<i>n</i>	Treatment	Serum decorin (pg/mL)			
			Week 0	Week 4	Week 8	Week 14
Women and men	32	Placebo	6114 \pm 181	6075 \pm 216	6017 \pm 185	5838 \pm 225
	32	GH	5950 \pm 223	6452 \pm 269 ^a	6652 \pm 312 ^a	5931 \pm 252 ^b
Women	16	Placebo	6481 \pm 203	6220 \pm 329	6218 \pm 220	6189 \pm 300
	17	GH	6127 \pm 349	6491 \pm 364	6591 \pm 434	5902 \pm 352 ^b
Men	16	Placebo	5748 \pm 275	5930 \pm 285	5816 \pm 297	5487 \pm 320
	15	GH	5748 \pm 269	6408 \pm 413	6721 \pm 465 ^a	5965 \pm 373 ^b
	16	T	6304 \pm 448	6664 \pm 505	6547 \pm 492	5937 \pm 426 ^b
	16	GH+T	5953 \pm 312	6600 \pm 355 ^a	7061 \pm 368 ^a	5438 \pm 250 ^b

^aDecorin significantly different from week 0 within group ($P < 0.05$); ^bDecorin at week 14 significantly different from week 8 within group ($P < 0.05$). GH, growth hormone; T, testosterone.

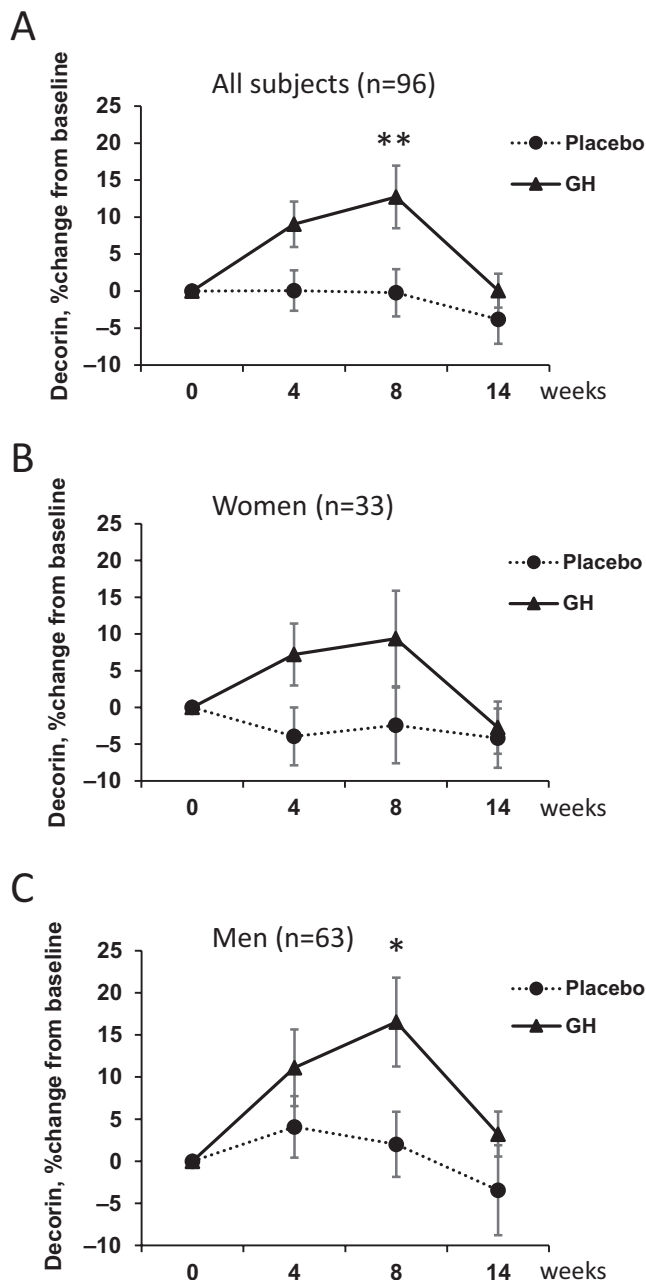


Figure 1
Change in serum decorin concentration in men and women in response to hormone treatment. Data are presented as mean percentage changes in serum decorin at week 4 (during treatment), week 8 (end of treatment) and week 14 (after a 6-week washout period) from baseline (week 0) for: (A) GH treatment group (men and women combined), (B) women and (C) men. Data are mean \pm S.E.M. * $P < 0.05$, ** $P < 0.01$.

Very little is known about decorin regulation by GH or testosterone. To our knowledge, only one previous study undertaken in rodents observed an increase in decorin

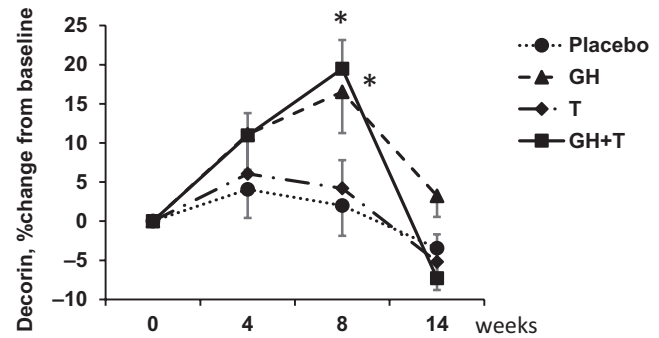


Figure 2
Change in serum decorin concentration in men in response to hormone treatment. Mean percentage changes in serum decorin at week 4 (during treatment), week 8 (end of treatment) and week 14 (after a 6-week washout period) from baseline (week 0). Data are shown as mean \pm S.E.M. * $P < 0.05$.

production in the extracellular matrix of developing incisors in response to GH (23). In young males, GH administration for 2 weeks did not affect decorin mRNA expression in tendon during immobilization; however, circulating decorin was not measured (24). Thus, our study is the first to report that GH stimulates decorin production in humans.

Decorin is a structural protein in the skeletal muscle extracellular matrix and regulates genes for muscle growth and repair (16, 18), suggesting a role in the regulation of muscle structure and function. There is strong evidence that exercise positively regulates decorin gene expression and protein production in muscle, contributing to a rise in blood decorin during exercise (15, 16). Because exercise also stimulates the release of GH (25, 26), our findings provide evidence that the stimulation of decorin production may in part be GH mediated.

As decorin stimulates collagen fibrillogenesis (11), we postulate that the upregulation of decorin by GH may play a role in collagen tissue anabolism. GH stimulates muscle and tendon collagen synthesis (24, 27), and we have previously reported that GH significantly increases the markers PINP and PIIINP, indicative of collagen synthesis (5). Thus, GH exerts a significant positive effect on collagen tissue formation. Decorin is known to play a role in collagen formation and has been shown to bind to collagen types I and III (28, 29). In our study, decorin levels correlated with those of PIIINP, which has particular importance in bone and tendon tissue repair (30). Furthermore, decorin modulates bone collagen matrix assembly and mineralization (31). Thus, decorin plays a role in the structural properties of muscle and bone by

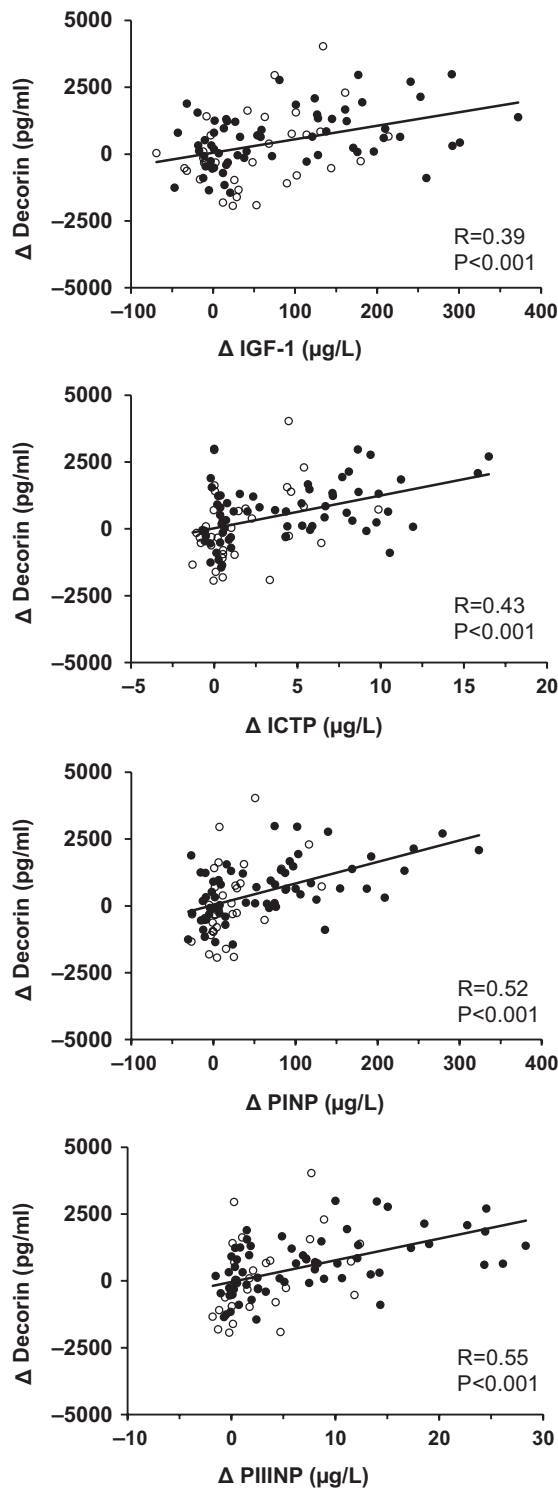


Figure 3
Relation between changes in serum decorin concentrations at week 8 from baseline, vs the changes in IGF-1, PINP, ICTP, and PIIINP in men (solid circles) and women (clear circles). The Spearman correlation coefficients and *P* values are indicated for each correlation.

positively regulating collagen synthesis, an effect which is co-regulated by GH.

We observed a greater increase in decorin levels in men than in women, in the face of a lower body weight-adjusted dose of GH in men than in women. The actions of GH on a range of biological effects are sexually dimorphic (32, 33, 34, 35). In GH-deficient adults, men are more sensitive to GH replacement therapy than women and exhibit significantly greater responses to GH with regard to IGF-1, body composition and bone metabolism markers (36, 37, 38, 39). This clinically significant gender difference may be attributed to the inhibitory effects of estrogens on the GH receptor signaling in women (40). In this study, GH therapy increased collagen markers (PINP, ICTP, PIIINP) to a much greater extent in men than in women (5). As decorin also is a connective tissue protein, the greater increase in decorin in men could relate to the well-known gender difference in the response to GH.

The gender difference in decorin cannot be explained by testosterone because we did not observe an effect of testosterone either alone or co-administered with GH. Testosterone is a potent stimulator of skeletal muscle anabolism, dose dependently increasing muscle mass (1, 2, 3). Although testosterone substantially amplifies the GH effect on collagen marker PIIINP (5), we observed no significant effect on decorin by the co-administration of these hormones. This implies minimal physiological effect of testosterone on circulating decorin in men.

GH may exert its anabolic effects directly through its receptor or indirectly via actions mediated by IGF-1. Besides increasing the levels of circulating IGF-1, GH stimulates the local production of IGF-1 in tissues such as muscle, tendon and cartilage (41, 42). Our study design does not allow to differentiate GH and IGF-1 effect on decorin. *In vitro* reports suggest that IGF-1 stimulates decorin production in a dose-dependent manner (43, 44, 45). Furthermore, connective tissue growth factor (CTGF) is an inducer of decorin synthesis (46) and has been shown to bind to IGF-1 to enhance its effects on collagen (47). In Laron syndrome of GH insensitivity, IGF-1 administration increases circulating collagen markers, providing evidence that IGF-1 plays an important role in connective tissue metabolism (48). As decorin levels change in parallel to other connective tissue markers, it is plausible that IGF-1 directly stimulates decorin production. Thus, GH through IGF-1 may regulate circulating decorin.

IGF-1 and PIIINP are endorsed biomarkers for GH doping. In our study, the peak response to GH administration in men was around 140% and 250% increase for IGF-1 and PIIINP, respectively (5). Decorin

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levels increased by 16.5% during GH administration at supraphysiological doses. After 6 weeks of withdrawal from GH, collagen markers (PINP, ICTP and PIIINP) were significantly higher in the GH group compared to placebo (5), whereas decorin returned to baseline upon GH withdrawal. Furthermore, the rather small increase and large variation in decorin during GH administration in women also indicates that decorin may not have a potential to be used as a marker for GH doping in sport.

There are some limitations to our study. Serum levels of decorin may not reflect tissue concentration of decorin. Furthermore, the effect of testosterone may be apparent if different doses or duration of testosterone administration had been used or patients with hypogonadism are studied instead of healthy adults. Nevertheless, we observed no significant effect on circulating decorin using supraphysiological doses of intramuscular testosterone administration 3–4 times that of normal production rate, indicating that in healthy adults testosterone supplementation does not increase circulating decorin.

In summary, we show that administration of GH in healthy adults increases circulating decorin, with the effect greater in men than in women. Testosterone has no significant effect on decorin concentration. We conclude that GH increases serum decorin levels in a gender-dependent manner. We postulate that the upregulation of decorin by GH may play a role in collagen tissue anabolism, enhancing the structural properties of muscle, tendon and bone.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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