Hormonal replacement therapy in the prevention and treatment of glucocorticoid-induced osteoporosis

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Clin Exp Rheumatol 2000; 18 (Suppl. 21): S57-S59.

Key words: Hypogonadism, hormonal replacement therapy, bisphosphonates, glucocorticoids, osteoporosis.

ABSTRACT

Hypogonadism is a complication of glucocorticoid therapy. Postmenopausal women on glucocorticoids suffer more fractures than premenopausal women on glucocorticoids. The use of oral contraceptives has been recommended in hypo- and amenorrhoeic premenopausal women receiving high doses of corticosteroids, as long as its use is compatible with other medical conditions of the patient. In postmenopausal women, the effect of hormonal replacement therapy in glucocorticoid-induced osteoporosis has only been studied in small prospective trials. These studies show an increase in bone density in the spine. The effect on hip bone density was not consistent. No data are available on the effect of hormonal replacement therapy on fracture incidence in glucocorticoid-induced osteoporosis. Bisphosphonates are an alternative for hormonal replacement therapy in women and men that do not tolerate hormonal replacement therapy or when contraindications for hormonal replacement therapy are present. Further prospective studies will be necessary before hormonal replacement therapy can be recommended in the prevention of glucocorticoid-induced osteoporosis in men and women.

Introduction

One of the mechanisms by which glucocorticoid (GC) therapy influences bone metabolism is by its influence on gonadal function, both in men (1) and in women (2). Hypogonadism is indeed a complication of glucocorticoid therapy. The mechanisms involved include inhibition of pituitary gonadotrophin secretion (2) and a direct effect on the ovary and testes (1). This may result in increased bone turnover and bone loss.

Bone loss according to gonadal status in glucocorticoid-induced osteoporosis (GIOP)

In women with RA treated with GC, the role of menopause is controversial. Some authors found bone loss in premenopausal women (3), while others demonstrated accentuated bone loss before (4) or after menopause (5). The finding that GC could decrease bone loss in RA by suppressing disease activity further complicates the role of GIOP in RA (6).

In premenopausal women, GC can induce hypo- and amenorrhoea, especially when other immunosuppressive drugs are added. This has been shown in systemic lupus erythematosus, where 10% of premenopausal women had amenorrhoea (7).

Postmenopausal women suffer more fractures than premenopausal women with RA on GC (3). The effect of hypogonadism on bone loss and fracture incidence can furthermore be deduced from the data on control patients reported in recent double-blind placebo controlled studies focusing on bisphosphonate treatment in patients with GIOP (8-10) (Table I). No differences in bone loss were found between pre- and postmenopausal women. However, vertebral fractures were only seen in postmenopausal women (Table II).

Hormonal replacement therapy in women

The mechanisms of action by which HRT acts in GIOP could be different from that in women without GC. Apart from inhibiting bone resorption, HRT stimulate calcitonin secretion (11) and progesterone could be a more important component in HRT in the treatment of GIOP (12).

In premenopausal regularly menstruating women, it is believed that there is no place for HRT (13, 14). No data are available on the effect of HRT in hypogonadal premenopausal women. However, the use of oral contraceptives has been recommended in hypo- and amenorrhoeic premenopausal women receiving high doses of corticosteroids, as long as its use is compatible with the other medical conditions of the patient (13, 14).

Table I. Bone loss in pre- and postmenopausal women, and in control patients followed during randomised, double-blind controlled studies on GIOP.

Author Year/ref.	Duration of study (months)	CS therapy duration (months)	Dose (mg/d)	Additional therapy Calcium (mg/day)	Additional therapy Vitamin D (IU/day)	Change in BMD (%) Spine Pre-	Spine Post-	Fem. neck Pre-	Fem. neck Post-
Adachi 1997 (9)	12	< 3	23	500	no	-4.6*	-3.3*	-3.0*	-0.9
Saag 1998 (8)	12	< 4 to > 12	11	800-1000	250-500	-0.3	-0.6 -0.1#	ND	ND
Cohen 1999 (10)	12	< 3	22	500	if low $25(OH)D_3$ at baseline	-1.6*	-2.9*	-3.3	-2.8*

* $p < 0.05$ versus baseline; # postmenopausal women on HRT; ND: not done.

Table II. Fracture incidence in pre- and postmenopausal women and in control patients as reported in randomised, double-blind controlled studies on GIOP.

Author Year (ref.)	Prevalent vertebral fractures	Incident vertebral fractures Pre-	Incident vertebral fractures Post-
Adachi 1997 (8)	49%	0/8	7/32 (22%)[a]
Saag 1998 (9)	17%	0 0	4/53 (8%)[b] 7/54 (13%)[c]
Cohen 1999 (10)	29%	0/11	5/24 (21%)[b]

[a] Change in > 1 grade (grade 0 = normal, grade 1 = 20-25% reduction, grade 2 = 26-40% reduction, grade 3 = > 40% reduction);
[b] Quantitative morphometry (> 20% and > 4 mm decrease);
[c] Binary semiquantitative assessment (change in > 1 grade)

Table III. Studies on hormone replacement therapy in female and male patients with glucocorticoid-induced osteoporosis.

Author/ Year (ref.)	Type of study	Patients' characteristics	No.	Follow-up (months)	Study medication	Method of measurement	Effect on BMD
Women							
HRT							
Studd 1989 (15)	Prospective?	Asthma	4	12	Oestradiol 75 mg + testosterone 100 mg	DPA	Spine: +13.4% Hip: +6.3%
Lukert 1992 (16)	Retrospective	Asthma	15	12	Estrogen 0.625 mg + medroxyprogesterone 5 mg	DXA DPA	Spine: +4.1%
Sambrook 1992 (17)	Subanalysis	RA	5/38	48	Different oestrogen regimens	DPA	Spine: +0.7% Hip: NS
Hall 1994 (18)	Subanalysis	RA	21	24	Estradiol 50µg + norethisterone 1 mg or estraderm 50	DXA	Spine: +3.5% Hip: +1.6%
Anabolic steroids							
Adami 1991 (20)	Prospective randomised	Rheumatic diseases	35	18	Nandrolone + calcium + vitamin D	DPA	Distal Forearm: +5.1%
Men							
Grecu 1990 (12)	Prospective Randomised	Asthma	23	12	Medroxyprogesterone 200 mg+ Calcium	qCT	Spine: +17%
Reid 1996 (21)	Prospective randomised	Asthma	15	2 x 12	30 mg Testosterone propr, 60 mg Phenylpropr, 60 mg Isocaproate 100 mg Nandrolone 250 mg/month IM depot	DXA	Spine: +5.0%

RA = rheumatoid arthritis, DPA = dual photon absorptiometry, BMD = bone mineral density, qCT = quantitative computer tomography, DXA = dual X-ray absorptiometry.

In postmenopausal women, the effect of HRT in GIOP has only been studied in small prospective trials (15-19) (Table III). These studies show an increase in BMD in the spine. The effect on hip BMD was not consistent.

Anabolic steroids with calcium and vitamin D supplements resulted in an increase in BMD in the forearm of 5.1% (20).

No data are available on the effect of HRT on the fracture incidence in GIOP.

Hormonal replacement therapy in men

In men, the effect of HRT has been reported in 2 prospective randomised trials (12, 21) (Table III). An increase in BMD has been shown in both studies, but no data on the effect in the hip or on the fracture incidence are available.

Non-hormonal treatments of GIOP with hypogonadism

Several studies using non-hormonal drugs have included patients on GC with hypoganodism. These include the bisphosphonates alendronate (8), etidronate (9) and risedronate (10). In all of these studies, prevention of bone loss by bisphosphonates has been shown to be consistent in pre- and postmenopausal women and in men with hypogonadism (22). Therefore, bisphosphonates are an alternative to HRT for the prevention of hypogonadism-associated bone loss in GIOP in women and men who do not tolerate HRT or when contraindications for HRT are present.

Conclusions

We currently lack clear evidence for a beneficial effect of HRT in women in the treatment of GIOP. The use of HRT in women with GIOP should therefore be limited to hypogonadism in premenopausal women, and can be considered after the menopause for the prevention of postmenopausal bone loss. In men with GIOP hypogonadism is frequent and, although evidence is scarce, HRT should be considered. However, the long-term effect and safety of HRT in men is not known. Bisphosphonates represent an alternative to HRT in the prevention of hypogonadism-associated bone loss in GIOP in women and men who do not tolerate HRT or when contraindications for HRT are present. Further prospective studies are necessary before HRT can be recommended for the prevention of GIOP in men and women.

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