Long-Term Outcomes of Conventional And Novel Steroid Replacement Therapy On Bone Health In Primary Adrenal Insufficiency

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Abstract

Purpose: To compare dual-release hydrocortisone (DR-HC) and conventional glucocorticoids (GCs) on bone metabolism in patients with primary adrenal insufficiency (PAI).

Methods: Thirty-five patients with PAI maintained conventional GCs (group A), while other 35 were switched to DR-HC (group B). At baseline and after 18, 36 and 60 months of conventional GCs and DR-HC treatment, the clinical and bone metabolic parameters were evaluated.

Results: After 60 months of follow-up, patients in group A had a significant increase in Body Mass Index (BMI) (p=0.004) and Waist Circumference (WC) (p=0.026) and a significant decrease in osteocalcin (p=0.002), bone alkaline phosphatase (p=0.029), lumbar spine bone mass density (BMD) T and Z scores (p<0.001 and p=0.001, respectively) than baseline. By contrast, patients in group B had a significant decrease in WC (p=0.047) and increase in bone alkaline phosphatase (p=0.019), lumbar spine BMD T score (p=0.032), femoral neck BMD T and Z scores (p=0.023 and p=0.036, respectively) than baseline.

Conclusions: Long-term conventional steroid replacement therapy is associated with a decrease in BMD, notably at lumbar spine, and an increase in vertebral fractures rate. By contrast, DR-HC treatment is associated with improvement of BMD.

Introduction

Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis and the most common iatrogenic cause of the disease[1]. Patients with adrenal insufficiency (AI) need chronic steroid replacement therapy, exposing them to an increased risk of comorbidities[2]. Conventional glucocorticoid (GC) treatment is associated with bone fragility and vertebral fractures[3]. The negative impact of GCs on bone is well known, being related to a number of factors, such as the dose and type of steroid used, the duration of therapy, and the cumulative dose[4], but also age, white race, female gender, smoking and alcohol can have an impact on bone loss[5]. Generally, GCs can induce bone loss in the short term up to one year of treatment with a loss of bone mass density (BMD) of 6-12% and in the long term with a BMD loss of 3% per year[1]. The risk significantly decreases when the steroid treatment is interrupted[5]. The risk of osteoporosis and fractures is increased for replacement GC doses more than 30 mg/day of hydrocortisone or equivalent[6] or for prednisone treatment, even at low doses[7].

By contrast, novel formulations of hydrocortisone (HC), and specifically dual-release HC (DR-HC), are associated with improvement of BMD[8].

The objective of the current study was to compare the effects of DR-HC and conventional GCs in patients with primary AI (PAI), on bone metabolism, fracture incidence and BMD at lumbar spine and femoral neck during 60 months of follow-up.

Materials And Methods

Study participants

We evaluated data from 70 consecutive patients with PAI on conventional GC treatment. Patients were consecutively referred to the Division of Endocrinology of Palermo University from January 2012 to December 2020. Patients were on conventional GC treatment (cortisone acetate and HC), administered twice or three times a day. Thirty-five patients maintained conventional steroid therapy (17 cortisone acetate and 18 HC) (group A) while the other 35 (16 who were on cortisone acetate and 19 who were on HC) were switched from conventional GC treatment to DR-HC (group B) administered orally in the morning in a fasting state. Patients had a 60-month follow-up. Exclusion criteria were the following: age ≤ 18 years, secondary AI (SAI), treatment with other GCs (prednisone), pregnancy, breastfeeding, premature ovarian failure, hypoparathyroidism, hyperparathyroidism, treatment with estrogens and underweight (BMI <18.5 kg/m^2). The switch to DR-HC was judged to be appropriate on clinical grounds in those patients who complained of fatigue and weakness, presented hyponatraemia (<134 mmol/L) or hypoglycaemia (≤2.78 mmol/L) or showed more than two comorbidities such as diabetes, osteoporosis/osteopenia, arterial hypertension and central obesity. The switch from HC to DR-HC was made with an equivalent dose, while the dose was reduced from cortisone acetate to DR-HC taking into consideration the minor GC activity of cortisone acetate compared to HC and patients' clinical characteristics.

PAI was diagnosed as recommended by international guidelines[9].

In detail, among the total of 70 patients, 42 had autoimmune polyglandular syndrome (APS), while 28 had isolated autoimmune AI. Among patients with APS, 26 had combined Addison's disease and autoimmune thyroid disease, 6 had combined Addison's disease, type 1 diabetes mellitus and autoimmune hypothyroidism and 10 had combined Addison's disease, autoimmune hypothyroidism and celiac disease. Patients with celiac disease were on a stable gluten-free diet. All patients with PAI were also on stable treatment with fludrocortisone (0.05-0.1 mg/day, once). Patients with hypothyroidism were treated with levo-thyroxine at the average dose of 1.2-1.5 mcg/kg. Patients with type 1 diabetes were on basal-bolus treatment on flash blood glucose monitoring. Five postmenopausal women were on DHEA treatment.

During the 60-month treatment period, the conventional GC and the DR-HC doses were changed based on the physician's judgement of a patient's need in both groups of patients (Table 1). Each patient received instructions for treatment in special or emergency situations. Patients treated with DR-HC were instructed to add a rescue dose of HC during an intercurrent illness or stress (5 or 10 mg according to severity of stress and symptoms). Overall, 8 patients had to take a rescue dose of HC, 5 of them less than 10 times and 3 of them from 20 to 30 times during the 60-month period.

Table 1
Dose adjustments according to the physician's judgement during the 60 months of conventional glucocorticoid and dual-release hydrocortisone treatments

	Dose at 60 months of DR-HC				
Baseline dose (N°=35)	**20 mg/day**	**25 mg/day**	**30 mg/day**	**35 mg/day**	**40 mg/day**
20 mg/day (no.= 15)	13	1	0	0	1
25 mg/day (no.=12)	0	10	1	1	0
30 mg/day (no.=3)	0	0	3	0	0
40 mg/day (no.=5)	0	0	2	0	3
	Dose at 60 months of cortisone acetate				
Baseline dose (N=17)	**25 mg/day**	**37,5 mg/day**	**47,75 mg/day**	**50 mg/day**	**62,5 mg/day**
25 mg/day (no.= 1)	1	0	0	0	0
37,5 mg/day (no.= 2)	0	2	0	0	0
47,75 mg/day (no.=1)	0	0	1	0	0
50 mg/day (no.= 8)	0	1	0	7	0
62,5 mg/day (no.= 5)	0	0	0	1	4
	Dose at 60 months of hydrocortisone				
Baseline dose (N°=18)	**15 mg/day**	**20 mg/day**	**25 mg/day**	**30 mg/day**	**35 mg/day**
15 mg/day (no.= 6)	6	0	0	0	0
20 mg/day (no.= 7)	0	6	1	0	0
25 mg/day (no.= 3)	0	0	3	0	0
30 mg/day (no.= 1)	0	0	0	1	0
35 mg/day (no= 1)	0	0	0	0	1

The current study was carried out in accordance with the recommendations of the Paolo Giaccone Policlinico ethics committee, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Paolo Giaccone Policlinico ethics committee.

Study Design

At baseline and after 18, 36 and 60 months of conventional GC and DR-HC treatment, clinical and bone metabolic parameters were evaluated.

Anthropometric parameters such as BMI and waist circumference (WC), measured at the midpoint between the lower rib and the iliac crest, were evaluated. In addition, sodium, potassium, serum 25hydroxyvitamin-D (vitaminD), parathyroid hormone, calcium, phosphorus, creatinine, osteocalcin and bone alkaline phosphatase were assayed.

The blood sample was taken about 2 hours after GC administration (patients took the dose in the morning on waking) to avoid patients experiencing fatigue or other symptoms due to delayed intake of the drug.

In both groups, hypovitaminosis D was observed at baseline and a pharmacological supplementation was started in 26 patients of group A and 25 of group B, at the mean dose of 800 UI/day and maintained during the follow-up. Hypovitaminosis D was defined as a serum 25-hydroxy vitamin D level below the normal range (<30 ng/ml). All patients supplemented with vitamin D reached the threshold of 30 ng/ml.

BMD was measured by DXA at lumbar spine and femoral neck (Hologic Horizon Inc., QDR-4500W Waltham, MA) at baseline and after 18, 36 and 60 months of follow-up.

In patients aged 50 or more, BMD was expressed as the T-score, comparing the results with those obtained in a sex-matched Caucasian population at the peak of bone mass. A T-score less than or equal to -2.5 SD at the neck or spine was defined as osteoporosis, whereas osteopenia was defined as a T-score between -1 and -2.5 SD. In patients younger than 50 years, the results were expressed as a/the Z-score, comparing the results with those obtained in an age and sex-matched Caucasian population. A Z-score of -2.0 SD or lower was used to define a BMD "below the expected range for age"[10]. The coefficients of variation in the DXA measurements for BMD, bone mineral content (BMC) and area were 0.61%, 2.98% and 2.89%, respectively.

Assays

Sodium, potassium, serum 25hydroxyvitamin-D (vitamin-D), parathyroid hormone, calcium, phosphorus, creatinine, osteocalcin and bone alkaline phosphatase were measured with standard methods (Modular P800, Roche, Milan).

Statistical analysis

The Statistical Packages for Social Science SPSS version 19 (SPSS, Inc., IBM, New York, USA) were used for data analysis. The normality of quantitative variables was tested with the Shapiro-Wilk test. The baseline characteristics of the groups were presented as mean ± SD for continuous variables, while the rates and proportions were calculated for categorical data. The differences between groups were performed using ANOVA for quantitative variables and the χ^2-test for categorical variables. A comparison between numerical variables at baseline, 18-, 36- and 60-month follow-up was performed with the Friedman analysis. In addition, Spearman's correlation was used to assess the association between BMD and daily hydrocortisone equivalent dose, daily GC dose per body surface and duration of disease and between fractures and daily GC dose per body surface. A p value <0.05 was considered statistically significant.

Results

The baseline characteristics of all patients with PAI and subgroups (A and B) are shown in Table 3. During the 60-month period of observation, 4 out of 35 patients had an adrenal crisis in group A and none in the group B.

At baseline, patients in group B had a higher frequency of osteoporosis/osteopenia (p=0.001) and visceral obesity (p=0.020), higher WC values (p=0.048) and lower osteocalcin levels (p=0.004) than group A (Table 2).

Table 2
General characteristics of all patients and subgroups A and B at baseline

	All Baseline (No.=70)	**Group A Baseline (No.= 35)**	**Group B Baseline (No.= 35)**	***p****
	Subjects (%)	Subjects (%)	Subjects (%)	
Gender	26 (37.1%)	15 (42.8%)	11 (31.4%)	0.462
Male	44 (62.8%)	20 (57.1%)	24 (68.5%)	
Female				
Arterial hypertension	12 (17.1%)	5 (21.3%)	7 (20%)	0.488
Osteoporosis/osteopenia	20 (28.5%)	3 (8.5%)	17 (48.5%)	0.001
Rib fractures	2 (2.8%)	0	2 (5.7%)	0.403
Femoral neck fractures	1 (1.4%)	0	1 (2.8%)	0.556
Hypovitaminosis D	51 (71.4%)	26 (74.2%)	25 (71.4%)	0.924
Bone resorption inhibitors	17 (24.2%)	5 (14.3%)	11 (31.4%)	0.297
Visceral obesity	37 (52.8%)	12 (34.3%)	25 (71.4%)	0.020
Hypercholesterolemia	11 (15.7%)	2 (5.7%)	9 (25.7%)	0.220
Diabetes mellitus	14 (20%)	4 (11.4%)	10 (28.5%)	0.425
Replacement therapy	35 (50%)	17 (48.5%)	18 (51.5%)	0.479
• Cortisone acetate	35 (50%)	18 (51.5%)	17 (48.5%)	
• Hydrocortisone				
	Mean ± SD	Mean ± SD	Mean ± SD	
Duration of disease (yrs)	14.7 ± 11.6	14.7 ± 12.2	14.9 ± 10.8	0.942
Age (yrs)	49.7 ± 22.1	50.9 ± 17.4	49.5 ± 13.4	0.754
Anthropometric parameters				
BMI (Kg/m^2)	26.4 ± 5.31	26.2 ± 5.94	27.3 ± 5.71	0.679
Waist circumference (cm)	96.2 ± 13.2	94.2 ± 12.3	98.7 ± 13.8	0.048
Electrolytes				
Na (mmol/L)	136.3 ± 3.71	137.7 ± 0.97	136.1 ± 3.21	0.326

*p value between patients in group A and B at baseline

	All Baseline (No.=70)	Group A Baseline (No.= 35)	Group B Baseline (No.= 35)	*p**
K (mmol/L)	4.63 ± 0.51	4.31 ± 0.75	4.56 ± 0.47	0.399
Bone metabolic parameters				
Calcium (mg/dL)	9.61 ± 0.58	10.1 ± 0.65	9.51 ± 0.51	0.073
Phosphorus (mg/dL)	3.86 ± 0.68	4.06 ± 0.37	3.72 ± 0.71	0.420
Parathyroid hormone (pg/mL)	48.3 ± 33.1	54.4 ±20.7	75.3 ± 15.8	0.788
VitaminD (ng/ml)	17.3 ± 3.61	18.1 ± 8.58	16.4 ± 5.51	0.600
Creatinine (mg/dL)	0.91 ± 0.43	1.04 ± 0.82	0.85 ± 0.19	0.239
Osteocalcin (ng/mL)	34.6 ± 12.8	32.4 ± 9.87	23.7 ± 14.7	0.004
Bone alkaline phosphatase (U/L)	74.4 ± 32.7	62.7 ± 20.2	58.4 ± 32.7	0.296
Lumbar spine (L1-L4) BMD T score	-1.29 ± 1.23	-0.96 ± 0.84	-2.14± 1.46	0.028
Lumbar spine (L1-L4) BMD Z score	-0.48 ± 0.85	-0.16 ±0.58	-0.94 ± 0.92	0.025
Femoral neck BMD T score	-1.71 ± 1.44	-1.2 ± 0.76	-1.59 ± 1.74	0.093
Femoral neck BMD Z score	-0.67 ± 1.03	-0.61 ± 0.59	-0.76 ± 0.51	0.740
**p* value between patients in group A and B at baseline				

After 60 months of follow-up, patients in group A had a significant increase in BMI (p=0.004), WC (p=0.026), vitamin D (p=0.005), and a significant decrease in osteocalcin (p=0.002), bone alkaline phosphatase (p=0.024), lumbar spine BMD T and Z scores (p<0.001 and p=0.001, respectively) compared to baseline (Table 3). By contrast, patients in group B had a significant decrease in WC (p=0.047) and increase in vitamin D (p<0.001), bone alkaline phosphatase (p=0.019) lumbar spine BMD T score (p=0.032), femoral neck BMD T and Z scores (p=0.023 and p=0.036, respectively) compared to baseline (Table 3). In addition, at 60 months of follow-up we observed significantly higher values of WC (p= 0.045) and bone alkaline phosphatase (p<0.001) and significantly lower values of osteocalcin (p=0.001), lumbar spine and femoral neck Z scores (p=0.045 and p= 0.047, respectively) in group A compared to group B (Table 3).

Table 3
Anthropometric and metabolic parameters in patients of groups A and B with primary adrenal insufficiency (PAI) at baseline and after 60 months of treatment.

	PAI Group A (No.= 35)			**PAI Group B (No.= 35)**			
	Baseline Mean ± SD	60 months Mean ± SD	*p**	Baseline Mean ± SD	60 months Mean ± SD	*p***	*p****
Anthropometric parameters							
BMI (Kg/m^2)	26.2 ± 5.94	28.5 ± 5.81	0.004	27.3 ± 5.71	26.3 ± 4.09	0.098	0.083
WC (cm)	94.2 ± 12.3	101.2 ± 13.8	0.026	98.7 ± 13.8	96.1 ± 13.4	0.047	0.045
Bone metabolic parameters							
Calcium (mg/dL)	9.91 ± 0.53	9.28 ± 0.56	0.056	9.65 ± 0.68	9.51 ± 0.51	0.410	0.403
Phosphorus (mg/dL)	3.93 ± 0.51	3.89 ± 0.69	0.244	4.05 ± 0.72	3.69 ± 0.68	0.180	0.240
Parathyroid hormone (pg/mL)	48.7 ± 24.1	46.7 ± 23.5	0.828	50.5 ± 43.5	47.2 ± 13.2	0.762	0.470
Vitamin D (ng/mL)	18.3 ± 9.55	37.4 ± 8.19	0.005	16.4 ± 5.51	37.8 ± 5.41	<0.001	0.505
Creatinine (mg/dL)	0.76 ± 0.11	0.75 ± 0.16	0.689	0.83 ± 1.38	0.76 ± 0.06	0.510	0.183
Osteocalcin (ng/mL)	32.4 ± 9.87	18.6 ± 11.5	0.002	23.7 ± 14.7	34.7 ± 7.86	0.139	0.001
Bone alkaline phosphatase (U/L)	62.7 ± 20.2	53 ± 13.8	0.024	58.4 ± 32.7	72.5 ± 26.8	0.019	<0.001
Lumbar spine (L1-L4) BMD T score	-0.96 ± 0.84	-2.08 ± 0.93	<0.001	-2.14 ± 1.46	-1.48 ± 1.65	0.032	0.085

*p: comparison between baseline and 60 months of treatment in group A

**p: comparison between baseline and 60 months of treatment in group B

***p: comparison between groups A and B at 60 months of treatment

	PAI Group A (No.= 35)			PAI Group B (No.= 35)			
Lumbar spine (L1-L4) BMD Z score	-0.16 ± 0.58	-1.31 ± 0.83	0.001	-0.94 ± 0.92	-0.44 ± 0.54	0.067	0.045
Femoral neck BMD T score	-1.21 ± 0.76	-1.71 ± 1.16	0.050	-1.59 ± 1.74	-0.87 ± 1.74	0.023	0.487
Femoral neck BMD Z score	-0.61 ± 0.59	-0.96 ± 0.79	0.689	-0.76 ± 0.51	-0.27 ± 1.21	0.036	0.047
	Subjects (%)	Subjects (%)		Subjects (%)	Subjects (%)		
Osteoporosis/Osteopenia	3 (14.3%)	11 (31.4%)	0.091	15 (42.8%)	15 (42.8%)	1	0.327
Rib fractures	0	5 (14.2%)	0.183	2 (5.7%)	2 (5.7%)	1	0.550
Neck fractures	0	1 (2.8%)	0.556	1 (2.8%)	1 (2.8%)	1	1
Hip fractures	0	2 (5.7%)	0.403	0	0	1	0.403
*p: comparison between baseline and 60 months of treatment in group A							
**p: comparison between baseline and 60 months of treatment in group B							
***p: comparison between groups A and B at 60 months of treatment							

A significant trend of decrease in BMD lumbar spine T and Z scores was observed in group A, while in group B we observed a significant trend of increase during the follow-up (figure 1A and B). In addition, a significant trend of increase was also observed in the BMD femoral neck T and Z scores of group B during the follow-up, while no differences were observed in group A (figure 1C and D).

The duration of disease negatively correlated with T scores of femoral neck (R= -0.542, p=0.017) and lumbar spine (R= -0.423; p=0.043) at 60 months. The daily GC dose per body surface negatively correlated with Z scores of femoral neck (R=-0.997; p=0.048) and lumbar spine (R=-0.768; p=0.045) at 60 months (figure 2). The rate of vertebral fractures in group A was also positively correlated with daily GC dose per body surface (R=0.875; p=0.048).

Discussion

In the current study, we demonstrated that patients on conventional steroid treatment had a significant decrease in lumbar spine BMD T and Z scores, with increased risk of fractures in the 5-year period of observation. This resulted in a significant correlation between GC dose, duration of disease and BMD.

Fracture incidence was correlated with GC dose per body surface. By contrast, DR-HC was associated with improvement in BMD and no new cases of fractures.

GCs induce osteoporosis by several mechanisms such as inhibition of osteoblast activity, stimulation of osteoclast activity and inhibition of calcium absorption, stimulating renal excretion[11]. GCs act not only by decreasing BMD, but also by altering the structure of the bone, favouring the risk of fracture[12]. Generally, there is a rapid fall in BMD due to bone resorption, followed by a slow decline due to altered bone formation[5].

The GC effects on BMD and fractures in patients with AI have been investigated, providing conflicting results. The first studies conducted on patients with AI did not report changes in BMD in patients on long-duration treatment with steroids[13,14]. Other studies suggested a gender difference in BMD values, unfortunately providing conflicting results[15–17]. Braatvetdt et al. did not report differences between patients with AI and healthy controls, even though they showed a negative correlation among BMD, GC dose and duration of disease[18].

Several recent studies have investigated the relationship between conventional GC dose and BMD. Koetz et al. did not show changes in BMD in patients treated with low doses of GCs[19]. Lovas et al. reported a decrease in BMD in patients with PAI treated with HC at a dose of 30 mg/day or more compared to healthy controls[20]. Schulz et al. observed improved BMD in patients on low doses of HC, while high doses were associated with decreased BMD[21]. Similarly, Danilowicz et al. and Chikada et al. reported no changes in BMD with low HC doses of 10-15 mg in patients with SAI[22,23]. Overall, patients treated with prednisolone showed lower BMD values compared to the other conventional steroid therapies[24].

With regard to the correlation between fractures and GCs, a large study on 3129 patients with PAI conducted from 1964 to 2006 reported 221 hip fractures, notably in the first year of observation[25]. Camozzi et al. showed a 3-4 fold risk increase of vertebral fractures compared to healthy controls[26], but they did not report any correlation with BMD. Recently, a metanalysis on 7 studies and a systematic review on 17 studies on fracture rate in patients with CAH, SAI and PAI showed an increased overall risk of fractures compared to healthy controls with a slight and not significant correlation between GC equivalent dose and osteoporotic fracture rate[27]. However, this metanalysis had several limitations due to the heterogeneity of the studies included.

DR-HC has been shown to ensure a more physiological release of HC due to its pharmacokinetics, with favourable effects on glucose metabolism, body weight, low-grade inflammation and immune response, and reducing the adverse metabolic effects and the related mortality risk frequently observed in patients chronically treated with conventional steroids[28–32]. The switch from conventional steroids to DR-HC is associated with resynchronization of clock genes and restoration of expression of many genes involved in inflammation, immune response, adipogenesis, and oxidative stress[33,34]. Only one study investigated the effects of DR-HC on BMD, showing a significant improvement in BMD values at lumbar spine and femoral

neck after 24 months of treatment. However, this study had a retrospective design and was conducted in a small sample of patients with SAI[8].

The limitations of the current study are the following: first, the lack of randomization in assignment of patients to group A or group B; second, the small sample of patients enrolled due to the rarity of the disease; third, the uncontrolled selection of patients who were shifted to DR-HC; forth, most of the patients enrolled in the study had combined autoimmune deficiencies which could play an adjunctive negative role on bone health; fifth, higher frequency of osteoporosis in patients of group B than group A could be a bias of the study. However, we excluded patients with premature ovarian failure to avoid any interference from gonadal hormones on bone. Lastly, we did not evaluate genetic polymorphisms in P-glycoproteins, 11-B-hydroxylase and GC receptors, which could have an influence on BMD. The strength of the study was the comparison of the effects of two different schemes of steroid replacement treatment for PAI on bone health and metabolism, the conventional one subdivided into two or three daily doses, and the novel one administered once daily. To our knowledge, this has never been done before.

In conclusion, our study shows that long-term conventional steroid replacement therapy is associated with a decrease in BMD T score and Z score, notably at lumbar spine, and an increase in vertebral fractures, after 60 months of follow-up. The decrease in BMD is correlated with duration of disease and daily GC dose per body surface, while the increased rate of vertebral fractures is correlated with the daily GC dose per body surface. By contrast, long-term DR-HC treatment is associated with an improvement of BMD T and Z scores and is not related to new fractures.

However, further larger randomized studies are required to confirm our data.

Declarations

Author Contributions: VG, CD and CG had full control of study design, data analysis and interpretation, and preparation of the article. All authors were involved in planning the analysis and drafting the article. The final draft article was approved by all the authors.

Competing interests: The authors Valentina Guarnotta, Claudia Di Stefano and Carla Giordano declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported

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Figures

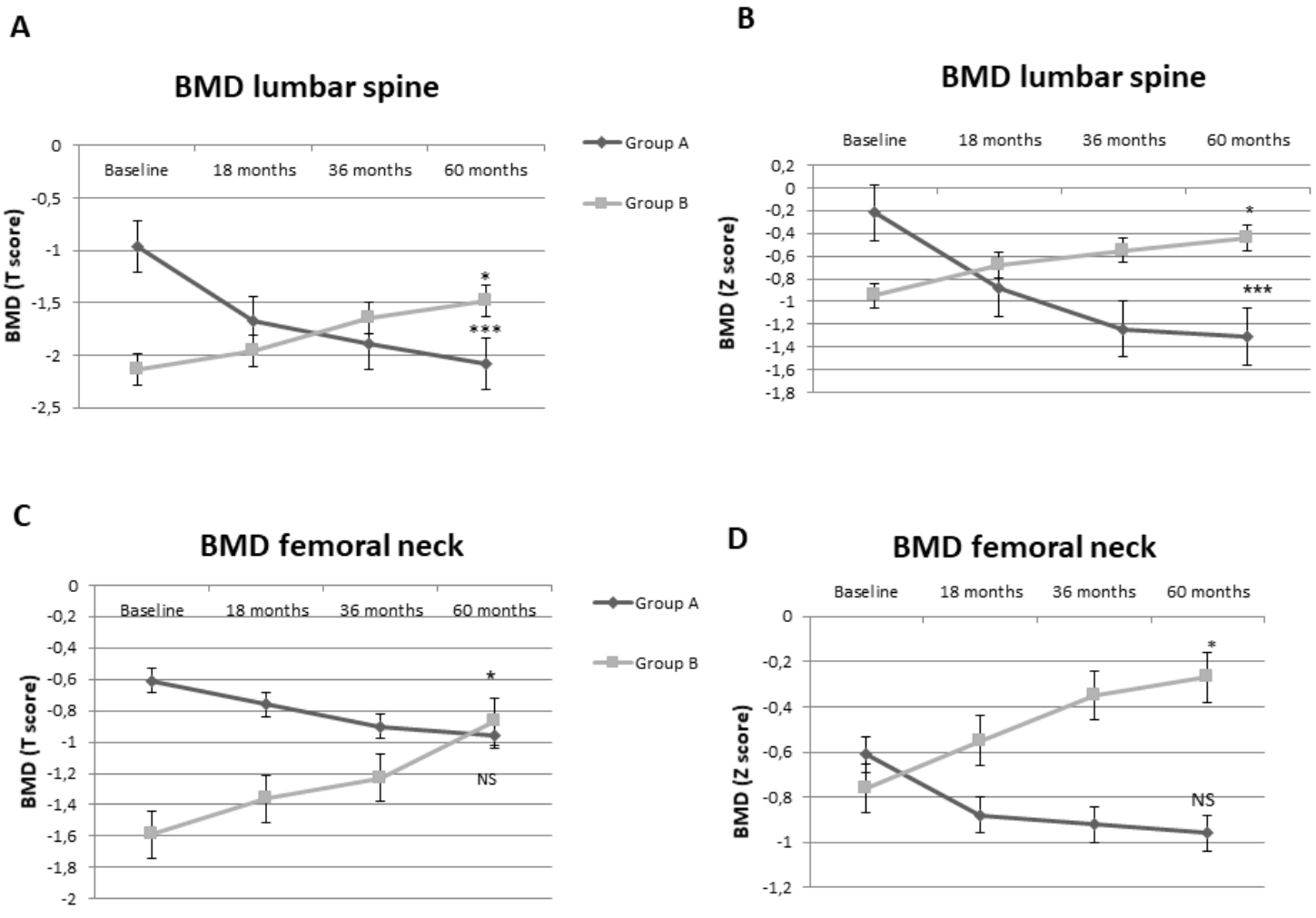

Figure 1

A. Changes in BMD lumbar spine T score from baseline to 60 months for patients of groups A and B. **p*<0.05, ***p* <0.01; ****p* <0.001 vs. baseline using the Friedman analysis. Data are means (S.D.).

B. Changes in BMD lumbar spine Z score from baseline to 60 months for patients of groups A and B. **p*<0.05, ***p* <0.01; ****p* <0.001 vs. baseline using the Friedman analysis. Data are means (S.D.).

C. Changes in BMD femoral neck T score from baseline to 60 months for patients of groups A and B. **p*<0.05, ***p* <0.01; ****p* <0.001 vs. baseline using the Friedman analysis. Data are means (S.D.).

D. Changes in BMD femoral neck Z score from baseline to 60 months for patients of groups A and B. **p*<0.05, ***p* <0.01; ****p* <0.001 vs. baseline using the Friedman analysis. Data are means (S.D.).

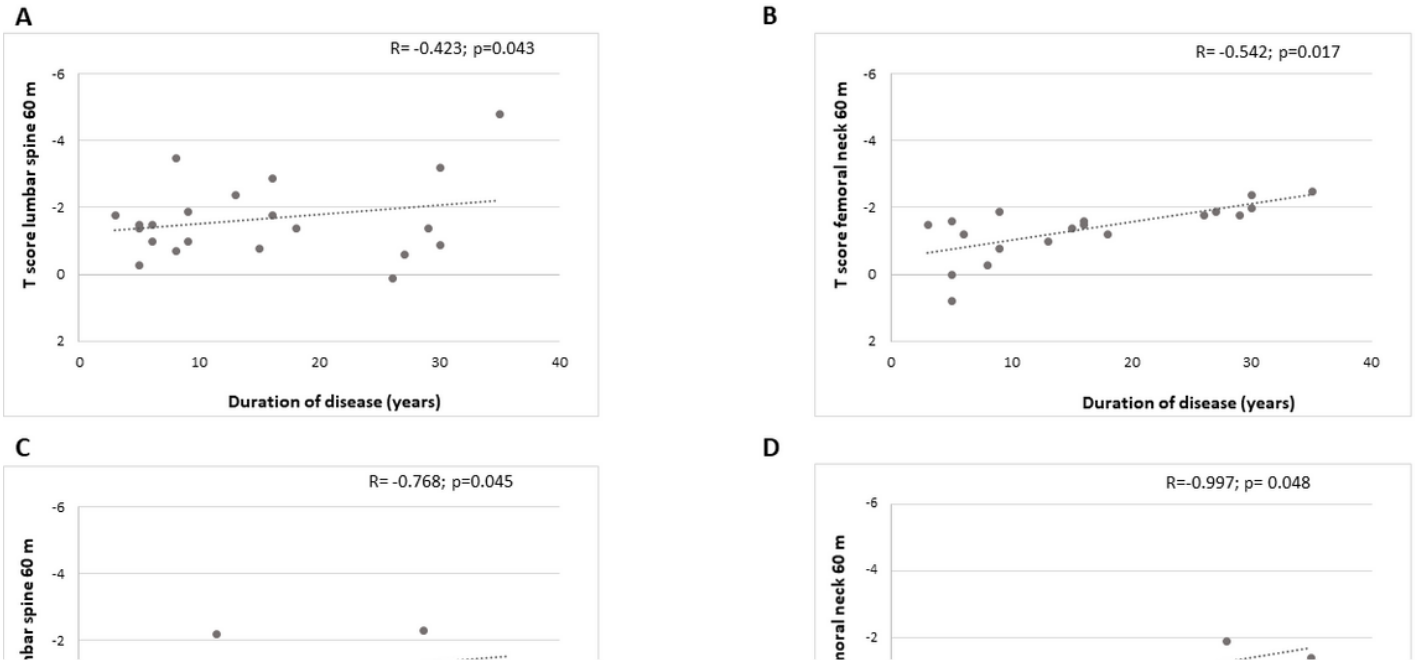

Figure 2

A. Correlation between T score at lumbar spine and duration of disease at 60 months of follow-up.

B. Correlation between T score at femoral neck and duration of disease at 60 months of follow-up.

C. Correlation between Z score at lumbar spine and daily GC dose per body surface at 60 months of follow-up. GC= glucocorticoid.

D. Correlation between Z score at femoral neck and daily GC dose per body surface at 60 months of follow-up. GC= glucocorticoid.