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SHORT COMMUNICATION

Low serum osteocalcin levels are associated with diabetes mellitus in glucocorticoid treated patients

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Abstract

Summary Bone turnover markers are decreased in GC-treated subjects with DM. Decreased OC levels in GC-treated patients were associated with an increased risk of DM. These results suggest the involvement of OC in glucose homeostasis regulation in DM.

Introduction Osteocalcin (OC) is involved in the regulation of glucose homeostasis. Glucocorticoid (GC) treatment is associated with impaired osteoblast function, decreased OC levels, and the development and/or worsening of pre-existing diabetes mellitus (DM). Whether decreased OC levels in GC-treated subjects contribute to DM is not well known. The aim of this study was to analyse whether OC levels in GC-treated patients are associated with the presence of DM.

Methods One hundred twenty-seven patients (aged 61.5 ± 17.9 years) on GC treatment were included. GC dose, treatment duration, presence of DM and bone formation (OC, bone ALP, PINP) and resorption markers (urinary NTX, serum CTX) were analysed. The cut-offs of each bone turnover marker (BTM) for the presence of DM were evaluated and optimised with the Youden index and included in the logistic regression analysis.

Results Among the patients, 17.3% presented DM. No differences were observed in GC dose or duration or the presence of fractures. Diabetics showed lower levels of OC (7.57 ± 1.01 vs. 11.56 ± 1; $p < 0.001$), PINP (21.48 ± 1.01 vs. 28.39 ± 1; $p = 0.0048$), NTX (24.91 ± 1.01 vs. 31.7 ± 1; $p = 0.036$) and CTX (0.2 ± 1.01 vs. 0.3 ± 1; $p = 0.0016$). The discriminating BTM cut-offs for DM presence were < 9.25 ng/mL for OC, < 24 ng/mL for PINP, < 27.5 nMol/mM for NTX and < 0.25 ng/mL for CTX. In a multivariate logistic regression model adjusted for GC dose, BMI, age and the above four BTMs, only OC remained independently associated with DM presence. Thus, in a model adjusted for GC dose, BMI and age, OC was significantly associated with DM (OR: 6.1; 95%CI 1.87–19.89; $p = 0.001$).

Conclusion Decreased OC levels in GC-treated patients are associated with increased odds of DM, and only OC was independently associated with DM in a model including four BTMs.

Keywords Glucocorticoid-induced diabetes mellitus · Glucocorticoid treatment · Osteocalcin · Type 2 diabetes mellitus

Introduction

Glucocorticoids (GC) constitute one of the principal treatments of chronic inflammatory disorders, including several rheumatic diseases, with nearly 3% of the general adult population receiving GC treatment [1]. Prolonged and/or high-dose GC treatment can be associated with several side effects, including the development of hyperglycaemia, worsening of pre-existing diabetes or new GC-induced diabetes mellitus. In this sense, depending on the patient population and definition criteria, among 1.5 to 47% of subjects treated with GC may develop diabetes mellitus (DM). Factors such as dose, duration of therapy, ethnicity, underlying disease, body mass index

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(BMI) and age have been related to the development of this clinical complication [2].

There is increasing knowledge of the regulators of the glycaemic metabolism. Thus, in recent years, bone-derived factors and hormones have emerged as important regulators of energy metabolism. Osteocalcin (OC), the main non-collagen protein of bone matrix synthesized by osteoblasts, has been linked to the regulation of energy metabolism through effects on beta-pancreatic cells and adipocytes, thereby providing the energy needed for the bone remodelling process [3]. Increasing evidence indicates that OC is involved in the regulation of glucose homeostasis [4, 5]. Nevertheless, recent studies in rodent models generated with a new knockout allele have shown controversial results. Although the authors cannot explain the absence of endocrine effects in this model of OC-deficient mice, possible effects on the transcription of neighbouring genes or differences in genetic background and environment cannot be ruled out, indicating the need for further studies [6, 7].

This protein is present in the systemic circulation in different forms: as totally or partially carboxylated and undercarboxylated. Whereas in animal studies, undercarboxylated OC seems to be the principal form responsible for metabolic actions; in humans, there are controversial results, with several studies showing a similar correlation with both undercarboxylated and total OC serum forms and glucometabolic status [3, 8, 9].

Taking into account that GC treatment is associated with impaired osteoblast function, decreased OC levels and with the worsening and/or development of DM, it would be of special interest to analyse the role of this bone matrix protein in the glucose homeostasis. It is of note that previous experimental studies in different mice models demonstrated that osteoblast-targeted disruption of GC signalling (due to transgenic overexpression of the GC-inactivating enzyme 11 β-hydroxysteroid dehydrogenase type 2) attenuated the suppression of OC synthesis and prevented the development of insulin resistance, glucose intolerance and abnormal weight gain induced by GC treatment. These results suggest that the effects of exogenous high-dose GC on insulin target tissues may be partly mediated by the skeleton, and particularly by OC [10, 11]. However, in spite of these findings, at present, the contributory role of decreased OC levels in the development and/or worsening of DM in GC-treated subjects has been scarcely analysed. Therefore, the aim of this study was to analyse whether OC levels in GC-treated patients are associated with the presence of DM.

Methods

This was a cross-sectional study initially aimed at analysing the risk factors for osteoporosis and fractures in subjects treated with GC (≥ 5 mg/day of prednisone or equivalent, for > 3 months) for a rheumatological autoimmune disease. The detailed study design and characteristics of the patients have been previously published [12]. Briefly, clinical assessment, biochemical determinations and bone mineral density (BMD) and trabecular bone score (TBS) measurements were performed in all patients. Risk factors for osteoporosis, also including the presence of type 2 DM (having type 1 DM was an exclusion criteria of the study), and GC doses (daily dose, duration and cumulative dose of prednisone or equivalent received) were assessed, in addition to anthropometric data (height, weight, BMI [kg/m^2]) and the presence of fractures. GC-induced DM was defined as new-onset diabetes diagnosed during steroid therapy.

Blood samples were obtained between 8:00 and 10:00 a.m. after overnight fasting, and an automated biochemical profile (including serum calcium, phosphate and complete blood cell count) was performed and measured by standard procedures. The following bone turnover markers were analysed: as markers of bone formation, serum procollagen type I amino-terminal propeptide (PINP), bone alkaline phosphatase (bone ALP) and OC (measured with a Cobas e601 analyser [Roche Diagnostics, Mannheim, Germany], ELISA [Immunodiagnostic Systems, Boldon, UK] and IRMA [Cis Bio, Sorgues, France, which measures the intact and N-terminal OC forms], respectively), and the cross-linked C-terminal and N-terminal telopeptides of type I collagen (serum CTX and urinary NTX), as markers of bone resorption, measured with the Cobas e601 analyser (Roche Diagnostics, Mannheim, Germany) and by ELISA (Osteomark NTx-I, Alere, Sarborough, ME, USA), respectively.

BMD at the lumbar spine and proximal femur was assessed by DXA (Lunar Prodigy, General Electric Medical Systems, WI, USA). Osteoporosis was defined according to the T-score by densitometric criteria [13]. The TBS was calculated using TBS iNsight® software (version 3.0.2.0) (Medimaps group, Geneva, Switzerland) on the DXA lumbar spine images. Standard radiographs of the thoracic and lumbar spine were obtained to evaluate the presence of vertebral fractures (VF).

All patients provided written informed consent to participate, and the study was approved by the Ethics Committee of the hospital (Reg. HCB/2017/0457).

Statistical analysis

Statistical analyses were performed using R v4.0.3 (R Core Team, 2020) [14]. Quantitative variables are described using means and standard deviations or median and quartiles in case of non-normal data with extreme values. Qualitative variables are summarized using counts and percentages. The association with qualitative covariates was assessed using the chi-square test and Fisher's exact test when applicability

conditions were not met. Comparison of means is carried out by applying the *t*- or Mann–Whitney test. To compare the turnover markers means between DM and non-DM groups, the logarithm transformation was applied and a linear regression model was fitted including the age, cumulative GC doses and BMI as covariates. The ANOVA *F* test was used to assess the difference between adjusted means. In case of missing data because values laid below the limit of detection the minimum detectable value was imputed. Optimal cut-off values were estimated by maximising the Youden's index as criteria [15] using the *Threshold ROC* R package [16]. Turnover markers were dichotomized using the optimal cut-offs and included in a logistic regression with GIDM groups as outcome and total cumulative GC, age and BMI as potential confounding covariates. A backward stepwise approach using the likelihood ratio test as criterion was used. Multicollinearity among independent variables was assessed by computing the variance inflation factors. Results were considered as significant if $p < 0.05$ except for the case of multivariate model analysis in which $p < 0.1$ was considered as sufficient to keep the covariates in the model.

Results

We included 127 patients (aged 61.5 ± 17.9 years, 63% women) on GC treatment for autoimmune diseases (≥ 5 mg/day, > 3 months), 22 of whom (17.3%) presented DM (7/22 had GC-induced DM and the remaining 15 had type 2 DM, all of whom worsened after GC treatment). Table 1 shows and compares the clinical characteristics of the patients (with and without DM). When comparing patients with and without DM, those with DM were older (70.5 ± 12.2 vs. 59.6 ± 18.4, $p = 0.001$), had a higher BMI (30 ± 5.2 vs. 26 ± 4.2, $p = 0.002$) and presented lower TBS values (1.114 ± 0.136 vs. 1.238 ± 0.175, $p = 0.001$). Nonetheless, these subjects presented higher T-score values in lumbar spine and a lower prevalence of densitometric osteoporosis compared to non-diabetic patients. No differences were observed in daily and/or cumulative GC doses. The presence of vertebral fractures or any type of fracture (vertebral and non-vertebral fractures) was similar in both groups of patients. Diabetics showed lower values

Table 1 Baseline characteristics of glucocorticoid-treated patients according to the presence of diabetes mellitus

	All *N* = 127	With DM *N* = 22	Without DM *N* = 105	*P**
Age (years)	61.5 ± 18	70.5 ± 12.2	59.6 ± 18.4	0.001
BMI (Kg/m^2)	26.7 ± 4.6	30.0 ± 5.15	26.0 ± 4.24	0.002
Disease duration (months)	17.0 [5.75;75.5]	21.5 [13.8;77.4]	16.0 [5.00;75.5]	0.377
Current GC dose (mg/day)	8.8 [5.0;15.0]	6.9 [5.0;11.9]	10.0 [5.0;17.5]	0.211
Cumulative GC dose (mg)	6980 [2916;16492]	7454 [4336;14173]	6858 [2793;18180]	0.566
Lumbar spine T-score	− 0.84 ± 1.73	0.00 ± 1.50	− 1.02 ± 1.73	0.008
Femoral neck T-score	− 1.38 ± 0.99	− 1.36 ± 0.85	− 1.39 ± 1.02	0.911
Total hip T-score	− 1.10 ± 1.05	− 0.93 ± .08	− 1.14 ± 1.05)	0.418
Densitometric osteoporosis	37 (29.1%)	2 (9.1%)	35 (33.3%)	0.044
TBS	1.217 ± 0.175	1.114 ± 0.136	1.238 ± 0.175	0.001
Patients with vertebral fractures	21 (16.7%)	4 (19.0%)	17 (16.2%)	0.752
Patients with fragility fractures (VF + non-VF)	36 (28.3%)	7 (31.8%)	29 (27.6%)	0.891
OC (ng/mL)	10.7 [6.40;16.7]	7.30 [5.00;9.82]	12.2 [7.12;17.4]	0.001
Bone ALP (ng/mL)	10.2 [8.2;12.7]	10.3 [8.1;11.9]	10.1 [8.20;13.4]	0.837
PINP (ng/mL)	25.8 [16.8;42.8]	18.6 [14.2;24.0]	28.2 [19.6;46.3]	0.006
NTX (nMol/mM)	35.0 [19.5;49.0]	23.5 [13.5;37.8]	35.0 [20.0;52.0]	0.041
CTX (ng/mL)	0.31 [0.17;0.48]	0.18 [0.12;0.31]	0.33 [0.18;0.49]	0.003
OC (n* above/below 9.25)	74 (54.68%) / 50 (40.32%)	6 (27.27%) / 16 (72.73%)	68 (66.67%) / 34 (33.33%)	–
PINP (n* above/below 24)	69 (54.33%) / 58 (45.67%)	6 (27.27%) / 16 (72.73%)	63 (60.00%) / 42 (40.00%)	–
NTX (n* above/below 27.5)	70 (59.91%) / 53 (43.09%)	8 (36.36%) / 14 (63.64%)	62 (61.39%) / 39 (38.61%)	–
CTX (n* above/below 0.25)	78 (61.42%) / 49 (38.59%)	9 (40.90%) / 13 (59.09%)	69 (65.71%) / 36 (34.29%)	–

Data expressed as mean ± standard deviation, median [first and third quartile] and as percentage

* *P* value refers to the comparison between patients with and without DM

SD standard deviation, *DM* diabetes mellitus, *BMI* body mass index, *GC* glucocorticoids, *BMD* bone mineral density, *TBS* trabecular bone score, *OC* osteocalcin, *Bone ALP* bone alkaline phosphatase, *PINP* procollagen type I N-propeptide, *NTX* cross-linked N-terminal telopeptide of type I collagen, *CTX* cross-linked C-terminal telopeptide of type I collagen, *n** number of patients above/ and below the discriminating cut-off values

(adjusted for cumulative GC doses, age and BMI) of OC (log-scale; 7.57 ± 1.01 vs. 11.56 ± 1; $p < 0.001$), PINP (log-scale; 21.48 ± 1.01 vs. 28.39 ± 1; $p = 0.0048$), NTX (log-scale; 24.91 ± 1.01 vs. 31.7 ± 1; $p = 0.036$) and CTX (log-scale; 0.2 ± 1.01 vs. 0.3 ± 1; $p = 0.0016$) with similar BAP values. In addition, the presence of undetectable OC values (< 4.6 ng/mL) was more commonly observed among diabetic subjects. Thus, 41% of diabetics presented undetectable values, a finding that was observed in only 9% of non-diabetics ($p = 0.0006$).

The best discriminating cut-off values for each bone turnover marker for the presence of DM were < 9.25 ng/mL (95%CI: 8.11–10.52) for OC, < 24 ng/mL (95%CI: 20.7–27.5) for PINP, < 27.5 nMol/mM (95%CI: 23.8–31.8) for NTX and < 0.25 ng/mL (95%CI: 0.21–0.28) for CTX. In the multivariate analysis that included all the cut-off values of the bone markers (adjusted for cumulative GC doses, BMI and age), having OC values < 9.25 ng/mL was the only risk factor related to the presence of DM (OR 6.1; 95%CI 1.87–19.89; $p = 0.001$) (Table 2).

Table 2 Multivariate analysis including the bone turnover markers dichotomized by cut-off values for the presence of diabetes mellitus

Model 1: Model with four BTMs		
	OR (95% CI)	*p*
OC (ng/mL) *	5.26 (1.02–27.09)	0.037
PINP (ng/mL) *	1.05 (0.20–5.47)	0.958
NTX (nMol/mM)*	0.99 (0.19–5.06)	0.890
CTX (ng/mL) *	1.24 (0.23–6.75)	0.803
Model 2: PINP left out		
OC (ng/mL) *	5.40 (1.45–20.07)	0.008
NTX (nMol/mM)*	0.98 (0.19–4.98)	0.985
CTX (ng/mL) *	1.26 (0.25–6.32)	0.803
Model 3: PINP + NTX left out		
OC (ng/mL) *	5.58 (1.52–20.48)	0.007
CTX (ng/mL) *	1.22 (0.37–4.04)	0.750
Model 4: PINP + NTX + CTX left out. Only OC in the model		
	OR (95% CI)	*p*
OC (ng/mL) *	6.10 (1.87–19.89)	0.001

* Analysis adjusted for cumulative GC dose, BMI and age

OC osteocalcin, *PINP* procollagen type I N-propeptide, *NTX* cross-linked N-terminal telopeptide of type I collagen, *CTX* cross-linked C-terminal telopeptide of type I collagen

A backward stepwise approach was applied for variable selection. The bone turnover markers were consecutively left out depending on their *p* value (*p*)

Discussion

This study shows that having low OC levels during GC treatment constitutes a risk factor for presenting DM. Thus, subjects treated with GC with serum OC levels < 9.25 ng/mL presented a sixfold higher risk for DM. Diabetic patients were older and had a higher BMI, both of which are well known factors related to the development of DM, not only in the general population but also in subjects treated with GC [2, 17]. Although there were no significant diferences, diabetic subjects showed a trend to having higher cumulative doses of GC and longer disease duration.

It was of note that the low bone remodelling state in DM patients treated with GC was significantly lower than that observed in the non-diabetic subjects. This finding has been previously reported in patients with DM [18], and it has been suggested that a low bone remodelling state could lead to an increase in bone fragilty in these subjects. Indeed, type 2 DM has been associated with an increase in fracture risk, that is commontly not reflected by the bone mass measurement [18]. Krakauker et al. attributed the higher-than-expected BMD in type 2 DM to a low bone turnover state. After a dynamic bone histomorphometric analysis performed in a small group of diabetic patients, the authors indicated that the preserved BMD in type 2 diabetic subjects was likely caused by a decrease in age-related bone loss [19]. Although DM patients in our study showed a lower presence of osteoporosis and higher T-score values at the lumbar spine, the prevalence of fractures was similar to that of the non-diabetic patients. Conversely, DM subjects presented lower TBS values, suggesting that TBS may be of potential value for evaluating additional aspects of bone quality in diabetic subjects [20].

Although all bone turnover markers, with the exception of BAP, were significantly decreased in patients with DM, in the multivariate analysis OC was the only bone marker significantly related to the presence of diabetes in GC-treated subjects. Thus, having low values of this marker (< 9.25 ng/mL) increased the odds of presenting DM by more than sixfold (OR 6.1; 95%CI 1.87–19.89; $p = 0.001$). Although these results do not imply a causal role of OC compared with the other BTMs (being also possible a lower variability and collinearity when compared with the other BTMs analysed in this study), they show that low OC values constituted a good predictor for the presence of type 2 DM. In addition, 41% of diabetic patients presented undetectable serum OC levels, a finding that was observed in only 9% of non-diabetics, further supporting the role of OC in the pathogenesis of DM. Nevertheless, whereas previous studies in humans have linked serum levels of OC with glucose metabolism and type 2 DM development [8, 9, 21], there are limited clinical data on the relation of this bone protein and GC-induced DM development. A recent study showed that GC decreased total OC and PINP in a dose-dependent manner and that these changes were related to the GC-induced adverse effects on glucose and lipid metabolism [22]. In addition, a previous

prospective clinical study examined the effect of teriparatide and bisphosphonates on serum glycated haemoglobin (HbA1c) and fasting plasma glucose. In that study, treatment with bisphosphonates did not influence changes on glucose metabolism. Nevertheless, treatment with teriparatide, a therapy that is associated with an increase of bone formation, and therefore, OC values, was associated with a significant decrease in serum HbA1c in diabetic patients, indicating that an anabolic drug could produce some improvement in glucose homeostasis in this clinical context [4, 23]. Indeed, recent evidence support the notion that OC could have an important role in DM treatment [5].

Our study has some limitations, such as those related to the characteristics of the study—namely a cross-sectional study and the absence of a control group. Thus, the cross-sectional design does not allow identification of a causal effect. Therefore, it is not possible to know whether lower OC levels led to diabetes or diabetes led to lower OC in these patients. Nevertheless, it should be noted that although most of the BTM were decreased in the DM patients treated with GC, OC was the only BTM associated with the presence of DM in these subjects. In addition, we did not analyse the undercaboxylated OC fraction, which has shown to be the biologically active form in animal models. However, taking into account that several studies did not show significant differences between the different OC fractions, together with the current limitations in the measurement of underdercarboxylated OC levels, the assay used in our study is justified [3, 8, 9].

In conclusion, decreased OC levels in GC-treated patients are associated with increased odds of DM, and only OC was independently associated with DM in a model including four BTMs. Further studies are needed to confirm these results and to determine the causal effect of OC.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Conflicts of interest None.

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