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Outcome of glucose homeostasis in patients with glucocorticoid-induced osteoporosis undergoing treatment with bone active-drugs ☆

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ABSTRACT

Over the last few years, there has been experimental evidence for the existence of cross-talking between bone remodeling and glucose metabolism. Whether this experimental model can be translated to humans is still debated, and it is also unclear whether the modulation of bone turnover by anti-osteoporotic drugs may lead to changes in glucose metabolism. The aim of this 12-month prospective study was to investigate whether treatment of glucocorticoid-induced osteoporosis (GIO) with bipshosphonates or teriparatide may influence serum glycated hemoglobin (HbA1c) and fasting plasma glucose. One-hundred-eleven patients (70 F, 41 M, median age 70, range: 55–89) chronically treated with glucocorticoids were evaluated for changes in serum HbA1c and fasting plasma glucose during treatment with bisphosphonates (45 cases) or teriparatide (33 cases) as compared to those occurring during treatment with calcium and vitamin D alone (33 cases).
In patients treated with teriparatide, but not in those treated with bisphosphonates or calcium and vitamin D alone, a statistically significant (p =0.01) decrease in serum HbA1c was observed during the follow-up, the change being greater (p = 0.01) in patients with diabetes as compared to those without diabetes. In most cases, the decrease of serum HbA1c was relatively limited and in some patients the improvement of glucose homeostasis was concomitant with implementation of anti-diabetic treatments. Fasting plasma glucose did not change significantly during either bisphosphonates or teriparatide treatments.
In conclusion, currently used bone active drugs may produce limited effects on glucose metabolism in patients with GIO. Interestingly, the bone anabolic drug teriparatide was shown to be associated with some improvement in serum HbA1c in this clinical context.

Introduction

Glucocorticoids are widely used in the treatment of autoimmune, pulmonary and gastrointestinal disorders, as well as in patients after organ transplantation and with neoplastic diseases [1,2]. In these clinical contexts, exposure to glucocorticoid excess may lead to the appearance of symptoms and signs of Cushing's syndrome with development of chronic and potentially debilitating complications, such as diabetes mellitus, hypertension, coronary artery disease, congestive heart failure and osteoporosis.

Glucocorticoids inhibit a number of steps in the insulin signaling network in the liver, muscle and adipose tissue leading to the development of insulin resistance [3]. Glucocorticoids were also shown to cause beta-cell dysfunction resulting in a blunted compensatory increase of insulin secretion in response to the glucocorticoid-induced insulin-resistance [4]. As a matter of fact, diabetes mellitus occurs frequently in patients exposed to chronic glucocorticoid excess, and it may play an important role in determining cardiovascular morbidity and mortality of patients with Cushing syndrome [5].

Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis, and impairment of bone formation is the central pathophysiological mechanism of bone loss induced by glucocorticoids [6]. Serum levels of osteocalcin, a marker of osteoblast activity, are invariably reduced in patients receiving glucocorticoids even when given at lower doses [7,8].

Over the last few years, there has been experimental evidence for the existence of cross-talking between bone remodeling and glucose metabolism with uncarboxylated osteocalcin postulated to play a central role in the control of fuel metabolism via improvement of insulin secretion and sensitivity [9–14]. Specifically, glucocorticoid-induced suppression of osteoblast function led to the occurrence of diabetes mellitus in mice exposed to glucocorticoid excess [13,14]. Whether this experimental model can be translated to humans is still debated, and it is also unclear whether modulation of bone turnover by anti-

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osteoporotic drugs (i.e. anti-resorptive and anabolic drugs) can lead to changes in glucose metabolism [15–20].

In this prospective observational study, we investigated the effects of treatment with bipshosphonates or teriparatide on serum glycated hemoglobin (HbA1c) and fasting plasma glucose in patients exposed to systemic glucocorticoids.

Materials and methods

Subjects

In the period between December 2009 and October 2012, 142 patients taking oral glucocorticoids and attending bone clinics were consecutively screened for this study. The inclusion criteria were: 1) age >50 years; 2) duration of glucocorticoid treatment >6 months; and 3) mean glucocorticoid dose ≥5 mg per day of prednisone or equivalent. Exclusion criteria were: 1) treatment with bone-active drugs prior the study; 2) treatment with drugs known to affect bone turnover except for glucocorticoids [2]; and 3) treatment with drugs known to affect glucose homeostasis, except for glucocorticoids and anti-diabetic drugs.

According to the inclusion and exclusion criteria, 111 out of 142 patients (70 F, 41 M, median age 70, range: 55–89) were enrolled in the study.

The patients gave informed consent to the study that was approved by the local ethical committee.

Protocol

The primary end-point of the study was the change of HbA1c after 12 months of treatment with bisphosphonates or teriparatide, whereas the change in fasting plasma glucose was a secondary end-point of the study.

After the enrolment, 45 patients started bisphosphonates (alendronate 70 mg per week in 25 patients, risedronate 35 mg per week in 15 patients, zoledronic acid 5 mg intravenously per year in 5 patients) and 33 patients started teriparatide (20 μg sc daily), all taking also calcium and vitamin D3 at recommended doses [21]. Thirty-three patients were treated with calcium and vitamin D alone (Table 1). According to the current guidelines at the time of study design [21], bisphosphonates were prescribed to patients with one or more of the following clinical features: 1) BMD T-score <— 1.0 either at lumbar spine or femoral neck or total hip; 2) history of hip fracture; and 3) prevalent/incident vertebral fractures, demonstrated by a radiological and morphometric approach [22]. According to the current Italian regulations, teriparatide was used in place of bisphosphonates when at least one severe (>40%) or two moderate (25–40%) vertebral fractures, as assessed by a morphometric analysis [22], were demonstrated in patients who were on oral glucocorticoids for more than one year. Patients without the aforementioned clinical criteria were given only calcium and vitamin D at the recommended doses [21].

At study entry, all patients were evaluated for fasting plasma glucose, HbA1c, osteocalcin and C-telopeptide of type-1 collagen (ß-CTX), bone mineral density (BMD) and vertebral fractures. All patients were also evaluated for their body weight and body mass index (BMI), calculated by weight (in kilograms) over the height squared (in meter). All patients were also evaluated by a questionnaire investigating whether they had been exposed to antidiabetic treatments in the year before the enrollment (type and dose of drugs, duration of treatment). Diabetes was diagnosed in patients with fasting plasma glucose higher than 125 mg/dl (in at least two measurements), and/or random plasma glucose ≥200 mg/dl and/or HbA1c >6.5% and/or undergoing active anti-diabetic treatments [23].

Parameters of glucose homeostasis and bone turnover were evaluated longitudinally after 6 ± 1 and 12 ± 1 months of follow-up in all patients taking bisphosphonates (45 cases) or teriparatide (33 cases). All patients taking calcium and vitamin D alone were evaluated longitudinally (after 6 ± 1 and 12 ± 1 months of follow-up) for glucose homeostasis and 14 of them were also evaluated for bone turnover. In patients with diabetes,

Table 1
Baseline clinical and demographical data of 111 patients exposed to chronic glucocorticoid therapy candidate to start three different bone-active treatments. Data are presented as median (and ranges) ,unless otherwise stated, and comparisons were performed by non-parametric tests.

	111 enrolled patients		
	BPs plus calcium and vitamin D3	1-34PTH plus calcium and vitamin D3	Calcium and vitamin D3 alone
Patients (*n*)	45	33	33
Age (yrs)	67 (55-88)	73 (59–86)	70 (65–89)
Sex (F/M)	30/15	21/12	19/14
BMI (kg/m^2)	27 (23–38)	26 (18–38)[b]	29 (21–34)
Duration of GC therapy (yrs)	4.0 (1.0–13.0)	5.0 (1.0–9.0)	4.5 (1.5–15.0)
Daily dose of GC (mg of prednisone)	15.5 (5.0–75.0)	12.5 (5.0–75.0)	18.0 (5.0–75.0)
Daily dose of vitamin D3 (IU)	1200 (800–2400)	1000 (800–1200)[b]	1200 (800–2000)
Median daily dose of calcium (mg)	1000 (600–2000)	800 (600–1200)[b]	1200 (600–1800)
Underlying diseases (*n*)			
RA	30	20	22
PM	7	5	7
COPD	3	2	1
Others	5	6	3
Fasting plasma glucose (mg/dl)	95 (87–167)	96 (85–170)	100 (67–174)
HbA1c (%)	5.0 (4.2–8.3)	5.2 (4.0–8.5)	5.6 (4.1–8.2)
Diabetes mellitus (%)	37.8%	30.3%	45.5%
Duration of diabetes mellitus (yrs)	9.5 (2.0–15.0)	10.0 (1.0–20.0)	7.5 (3.0–25.0)
Serum ß-CTX (μg/l)	0.2 (0.05–0.30)	0.10 (0.06–0.20)	0.10 (0.05–0.22)
Serum osteocalcin (μg/l)	13 (4–32)	15 (3–40)	17 (2–35)
Normal BMD (*n*)*	14[a]	13[a]	33
Osteopenia (*n*)**	22[a]	15[a]	0
Osteoporosis (*n*)**	9[a]	5[a]	0
Vertebral fractures (*n*)	35/[a]	33/[b]	0/

yrs: years; F: females; M: males; BMI: body mass index; GC: glucocorticoid; RA: rheumatoid arthritis; PM: polymialgia; COPD: chronic obstructive pneumonia disease; ß-CTX: C-telopeptide of type-1 collagen; BMD: bone mineral density; BPs: bisphosphonates;1-34 PTH: teriparatide.

* at all sites.

** at any site.

[a] $p < 0.01$ vs. patients treated with calcium and vitamin D alone.

[b] $p < 0.01$ vs. patients treated with calcium and vitamin D alone and those treated with BPs plus calcium and vitamin D.