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CAN LONG-TERM MAJOR DEPRESSIVE DISORDER CAUSE OSTEOPOROSIS?

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SUMMARY – A marked clinical, physiologic, and biochemical connection between osteoporosis and major depressive disorder (MDD) is described. There are numerous states and diseases associated with osteoporosis. The aim of the study was to assess the presumed association between hypercortisolism and osteoporosis. Some recent studies provided evidence for association between previous history of MDD and marked osteoporosis. In MDD, there are two well documented biochemical abnormalities, hypercortisolism and its resistance to dexamethasone suppression. The present study included 31 MDD patients (19 male and 12 female), mean age 37±1.3, age range 29-41 years, and 17 healthy male volunteers, mean age 39±1.6, age range 34-45 years. The levels of free cortisol in 24-h urine, serum cortisol at 8 a.m. and 5 p.m., and cortisol in dexamethasone suppression test as well as bone mineral density were measured in all study subjects. The results obtained were analyzed by use of Spearman's nonparametric rank correlation, rho=-0.805, with a statistical significance level of $p<0.01$ (2-tailed). Study results suggested that patients with a long-term history of depression may develop a severe form of osteoporosis. Also, a severe form of osteoporosis has been known to develop in patients with untreated Cushing's syndrome.

Key words: *Osteoporosis, etiology; Depressive disorder, physiopathology; Bone and bone metabolism*

Introduction

Osteoporosis is the most common bone disease frequently leading to bone fracture. In both men and women, the incidence of hip fracture rises exponentially with age, although this increase begins approximately 5 to 10 years later. Approximately one half of these fractures are vertebral fractures, whereas hip fractures and Colles' fractures account for one fourth each. Osteoporosis is the leading cause of morbidity and mortality in elderly people.

The disorders that cause osteoporosis are similar in men and women and include estrogen deficiency, primarily in postmenopausal women, hyperparathyroidism, hyperthyroidism, hypogonadism in men, glucocorticoid therapy, genetic factors, cigarette smoking and alcohol intake, lower calcium intake, decreases in physical activity and muscle strength, gastrointestinal disease, vitamin D deficiency, anticonvulsant therapy, and stress factors with depression. The usual clinical manifestations of osteoporosis are low trauma fractures and radiographic osteopenia detected by chance or during evaluation for musculoskeletal pain, usually back pain.

Measurements of bone mineral density are usually recommended, and if bone mineral density is lower than expected for age and no cause is apparent, further studies are indicated, including measurements of serum testosterone, thyrotropin, calcium, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone, urinary calcium and creatinine, complete blood count, serum and urine protein electrophoresis, and iliac crest bone biopsy.

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If the cause of osteoporosis can be identified, the potential offending agents should be eliminated whenever possible. As a rule, patients should receive adequate calcium (1000 mg/day) and vitamin D (800 IU/day) supplementation. A weight-bearing exercise regimen may also be beneficial, given the association of reduced physical activity.

Major depressive disorder (MDD) is a syndrome of persistingly sad, dysphoric mood accompanied by sleep and appetite disturbances, and inability to experience pleasure. The diagnosis of MDD is made when the patient meets the DSM-IV criteria. At least five of the following symptoms must be present during a 2-week period and show change from the previous condition: depressed mood most of the day, nearly every day; anhedonia and diminished interest in general; significant weight change not related to diet; sleep disturbances; psychomotor agitation or retardation, loss of energy; feeling of worthlessness or inappropriate guilt; concentration disturbances; recurrent thoughts of death; and suicidal ideas or specific plan for committing suicide.

In MDD, there are two well documented biochemical abnormalities: hypercortisolism and its resistance to dexamethasone suppression. Activation of the pituitary-adrenal axis is fairly specific for depression among other conditions of primary affective disorders, and could be observed in as many as 40%-60% of patients in some series. These findings have eventually led to the routine use of dexamethasone suppression test (DST) as a biological tool for both diagnostic and follow-up purposes in such patients. Psychotherapy associated with antidepressants (serotonin reuptake inhibitors, tricyclic antidepressants, anxiolytics, and mood stabilizers) have been found to improve impulsive behavior.

Subjects and Methods

The study included 31 patients with MDD, 19 male and 12 female, mean age 37±1.3, age range 29-41 years, and 17 healthy male volunteers, mean age 39±1.6, age range 34-45 years. In order to determine the hypercortisolic state, it was essential to develop a tool to assess the cortisolic state and to identify, for a given individual, whether it was inappropriately high. An ideal parameter would be the one that shows no overlapping between normal subjects, including the obese, and patients with hypercortisolic state of whatever etiology.

Plasma cortisol is measured by the competitive protein binding assay, or recently by more specific immunoassays. Plasma free cortisol is the best indicator of the cortisolic state. It is a biologically relevant and highly sensitive parameter.

Serum cortisol level was determined by standard radioimmunoassay (RIA) using 125 J labeled hormone, since it binds non-labeled serum cortisol to specific antibodies according to their concentration in the radioactive mixture. Venous blood samples of 5 ml were obtained in the morning (8 a.m.) and in the afternoon (5 p.m.) after 30-min bed rest. According to cyclic hypothalamic secretion of CRF, the rate of cortisol secretion in a healthy person is higher in the early morning and lower in the early evening. Falsely elevated values can be found in pregnancy and in women taking oral contraceptives, whereas no normal diurnal variations are found in stress patients. At our laboratory, normal values are 138-800 nmol/L at 8 a.m., and 50%–70% of the morning values at 5 p.m.

Free 24-hour urinary cortisol excretion is an almost ideal marker of the cortisolic state. Urinary cortisol is measured by the competitive protein binding assay after extraction, or by immunoassay. Study subjects were instructed to collect urine samples after first morning void until the next morning, including first void on the next day. Normal values are 150-750 mmol/24 h. Since it correlates with the levels of plasma free cortisol, urinary cortisol excretion has several invaluable properties: it is biologically relevant, being a reflection of how much biologically active, free cortisol has been circulating over the last 24-h period; it is a highly sensitive marker. It is not altered in obese subjects, estrogen-treated females, or by drugs or conditions that modify the metabolism of cortisol.

DST included oral administration of two 0.5-mg dexamethasone tablets at 11 p.m., followed by venous blood sampling at 8 a.m. and 5 p.m. on the next day. In DST, synthetic steroid analogs have been chosen for their high glucocorticoid potency; they would suppress the adrenocorticotropic hormone (ACTH) given in minute amounts as compared with the daily amount or normally secreted cortisol. It has been established that 0.5 mg of dexamethasone given every 6 hours in eight doses (2 mg/day) induce almost complete suppression. In the present study, serum cortisol level, 24-h urinary free cortisol and DST were determined in both patients and control subjects.

Results

Results of the study showed the mean basal 24-h urinary cortisol in MDD patients to be 1067±61.8 nmol/l.

Serum cortisol at 8 a.m. and 5 p.m. was 618±43.2 and 347±34.2 nmol/l, respectively. Cortisol in DST was 165±36.8 nmol/l. Plasma levels of cortisol in MDD patients were just above the normal range. MDD patients also showed deficient cortisol suppression in DST. These results indicated that, although showing an increase in the urinary level of cortisol, MDD patients had some circadian rhythm of cortisol preserved (Figs. 1 and 2).

The study revealed a significant correlation between years of therapy and grade of osteoporosis in MDD patients (Fig. 4). So, a patient treated with antidepressant therapy for a longer period of time was more likely to develop osteoporosis. MDD patients had statistically significantly higher levels of cortisol in 24-h urine.

Statistical analysis was performed by use of nonparametric rank correlation, where Spearman's rho was -0.805, with correlation significance at a level of $p<0.01$ (Tables 1 and 2).

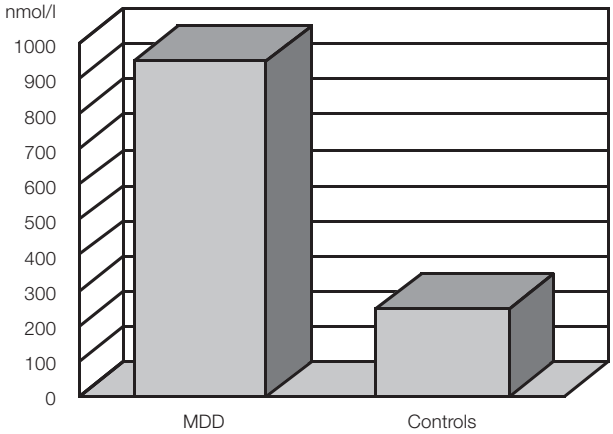

Fig. 1. Urinary free cortisol in MDD patients and healthy controls.

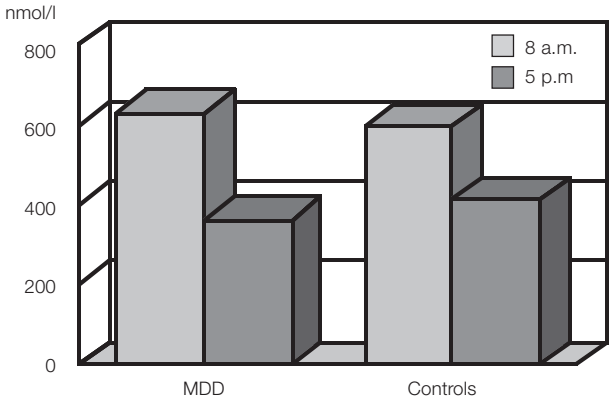

Fig. 2. Plasma cortisol in MDD patients and healthy volunteers at 8 a.m. and 5 p.m.

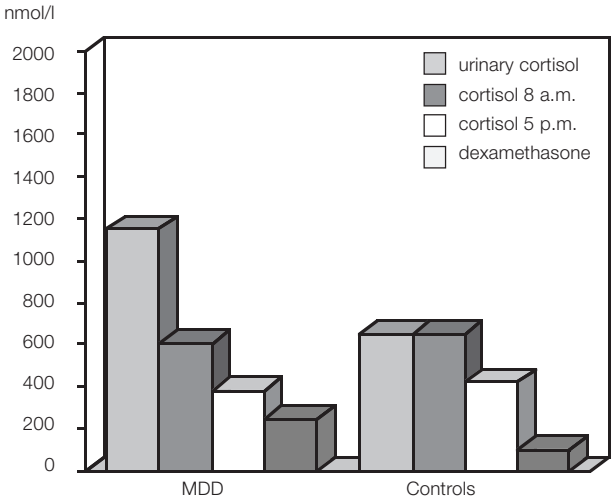

Fig. 3. Urinary free cortisol, plasma cortisol at 8 a.m. and 5 p.m., and cortisol in dexamethasone suppression test in MDD patients and healthy controls.

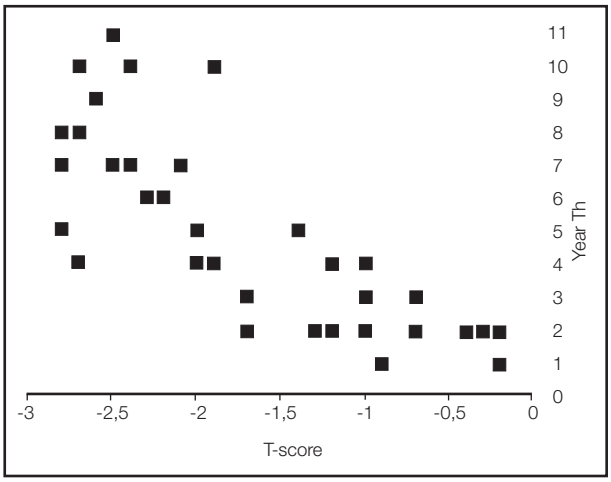

Fig. 4. Correlation between years of therapy and T score in patients with MDD and osteoporosis.

Discussion

The hypothalamo – pituitary – adrenal (HPA) axis is a very complex control system playing an important role primarily in stress reaction. Glucocorticoids are secreted in response to stressful conditions, and have an important task to block the function of stress mediators that have previously been brought to liberation. In other words, glucocorticoids suppress the autonomic (vegetative), behavioral, endocrine, and immune responses to stressful stimuli in a time-dependent way.

Table 1. Correlation between years of therapy and T score in MDD patients

Correlation		Year of therapy	T score
Year of therapy	Pearson's correlation	1,000	-,787*
	Sig. (2-tailed)	,	,000
	n	37	37
T score	Pearson's correlation	-,787*	1,000
	Sig. (2-tailed)	,000	,
	n	37	37

*correlation significant at a level of 0.01 (2-tailed)

Table 2. Correlation between years of therapy and T score in MDD patients

Non-parametric correlation		Years of therapy	T score
Spearman			
Years of therapy			
	Correlation coefficient	1,000	-,805
	Sig. (2-tailed)	,	,000
	n	37	37
T score			
	Correlation coefficient	-,805*	1,000
	Sig. (2-tailed)	,000	,
	n	37	37

*correlation significant at a level of 0.01 (2-tailed)

HPA axis is under control of various neurotransmitter systems. Some authors consider that serotonin, acetylcholine and histamine show stimulatory, and noradrenaline and GABA inhibitory effects. During stress, HPA axis acts differently according to the actual task, i.e. 'to fight or to flight'. Immobilization reflex (withdrawal reaction from fight) with motility inhibition and conservation of energy is under control of hippocampus and adrenal cortex activation by ACTH and corticosterone increase.

Biological abnormality is frequently observed in patients with MDD, presumably secondary to ACTH hypersecretion. The ability of the glucocorticoid negative feedback system to limit the production of cortisol during stress can be impaired by chronic emotional or physical stress, and by old age. Glucocorticoid-induced hippocampal neuron damage and deficient transmission of suprahypothalamic negative feedback have been proposed as a major mechanism mediating this phenomenon. Indeed, in patients with depression, the 24-h urinary free cortisol excretion increases with age, while studies of HPA axis in aging population that included persons with chronic emotional or physical diseases have shown progressive elevations of evening plasma cortisol concentrations with age.

In MDD, hypercortisolism does not give rise to the usual physical stigmata of hypercortisolic state (moon face, buffalo hump, hypertension, easy bruising, purple striae) and reverts to normal when the depression remits, either spontaneously or due to antidepressants or other therapy. Some studies have shown that urinary cortisol excretion in depression never exceeds 3-fold upper limit of the normal. The circadian pattern of plasma cortisol is less disrupted.

Activation of pituitary – adrenal axis is fairly specific for depression among other conditions of primary affective disorders. So, these findings have eventually led to the routine use of DST as a biological tool for both the diagnosis and follow-up of these patients. Studies focused on the pathophysiology of the HPA axis dysfunction in MDD patients have been reported. Four hypotheses have been proposed to explain why nonsuppression occurs. These include: 1) increased metabolism of dexamethasone in patients with MDD, which results in less dexamethasone available to suppress the production of ACTH in the pituitary gland; 2) decreased sensitivity of the pituitary glucocorticoid receptors to dexamethasone, resulting in less ACTH suppression and cortisol elevation; 3) hyperresponsitivity of the adrenal gland to ACTH stimulation, resulting in continued cortisol secretion despite moderate to significant ACTH suppression with dexamethasone; and 4) increased central drive of the pituitary from the hypothalamic-limbic structures, which overrides the action of dexamethasone. The more so, a combination of the hypotheses should by no means be neglected.

The use of anticortisol drugs has already been demonstrated to be beneficial in depression. There must have been misinterpretation of cortisol results. If serum cortisol levels were normal at 8 a.m. and 5 p.m., they used to be considered normal, without realizing that changes, sometimes at the immunosuppressive level, might occur during the 24-h circadian rhythm.

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Sažetak

MOŽE LI DUGOTRAJNA VELIKA DEPRESIJA IZAZVATI OSTEOPOROZU?

M. Vrkljan, B. Vizner, M. Bekić, V. Thaller i Z. Sonicki

Opisana je klinička, fiziološka i biokemijska povezanost osteoporoze i velike depresije. U oba stanja dolazi do hiperaktivnosti osi HPA, sustava LC/NE, te povišenog lučenja CRH, kortizola i katekolamina. Mnoga stanja i bolesti povezane su s osteoporozom, uključujući hiperkorticizam. Novija istraživanja povezuju raniju povijest velike depresije s osteoporozom. U velikoj depresiji zabilježene su dvije biokemijske abnormalnosti: hiperkorticizam i rezistencija na supresiju deksametazonom. U naše je istraživanje bio uključen 31 bolesnik s velikom depresijom (19 muškaraca i 12 žena) prosječne dobi od 37±1,3 godine, te 17 muških dobrovoljaca u dobi od 34 do 45 godina, prosječne dobi od 39±1,6 godina. U svih je bolesnika određivana razina kortizola u 24-satnoj mokraći, serumski kortizol, kortizol u testu supresije deksametazonom, a gustoća kostiju je određivana denzitometrijski. Bila je to skupina mlađih muškaraca i žena s održanim menstruacijskim ciklusom, u početku bez osteoporoze, ali godinama pod antidepresivnom terapijom. Analiza rezultata pokazala je povišene vrijednosti kortizola, te pojavu osteoporoze razvoj koje je bio posljedica povišene razine kortizola. U analizi rezultata primijenjena je neparametrijska korelacija rangova, pričem je Spearmanov rho bio -0,805 uz statističku značajnost od $p<0,01$. Na temelju rezultata ispitivanja zaključeno je da bolesnici liječeni zbog depresije imaju povišenu razinu kortizola u 24-satnoj mokraći. Bolesnici koji su duže bolovali od depresije imali su jače izraženu osteoporozu. Kortizol vjerojatno ima značajnu ulogu u nastanku osteoporoze u bolesnika s depresijom, a poznato je da se u bolesnika s neliječenim Cushingovim sindromom također razvija jak oblik osteoporoze.

Ključne riječi: *Osteoporoza, etiologija; Depresija, fiziopatologija; Kost i koštani metabolizam*