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Depressive Disorder as Possible Risk Factor of Osteoporosis

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A B S T R A C T

Hipothalamo-pituitary-adrenal (HPA) axis is a very complicated control system playing an important role in stress reaction, where glucocorticoids suppress the autonomic (vegetative), endocrine, immunologic and psychic responses to stressful stimuli. We described the marked clinical, physiological, and biochemical connection between osteoporosis and major depressive disorder (MDD). Both conditions are associated with a hyperactive HPA axis and LC/NE system, and hence with increased CRH, cortisol, and catecholamine secretion. There are numerous states or diseases associated with osteoporosis and we were looking for a hypercorticism value as a one of these. Some recent studies demonstrated that earlier history of MDD was associated with 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 males and 12 females, 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 each of our patients 24-hour urinary free cortisol, serum cortisol level at 8 a.m. and 5 p.m., cortisol in dexamethasone suppression test and bone mineral density were measured. We have, therefore, analyzed a group of young men and women with normal menstrual cycles, who were without signs of osteoporosis in the beginning, and who received anti-depressive therapy for many years. Analysis showed that increased levels of cortisol and the occurrence of osteoporosis, that developed as the result of elevated cortisol level. For our workshop we used nonparametric rang-correlation with Spearman's ro = –0.805, with statistic significant at the 0.01 level (2-tailed). Patients under long-term history of depression could develop a very stronger type of osteoporosis i.e. it is before known that the patients with untreated Cushing syndrome developed hard osteoporosis.

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Introduction

Osteoporosis is a skeletal disorder characterized by two elements that distinguish it from other causes of osteopenia such as hyperparathyroidism and osteomalacia[1]; low bone mass and microarchitectural disruption[2]. Osteoporosis is the most common bone disease and its leading to fracture is a common problem[3,4]. In men, as in women, the incidence of hip fractures increases exponentially with aging although the increase begins approximately 5 to 10 years later[5,6]. Approximately one-half of these fractures are vertebral fractures, one-quarter are hip fractures, and one-quarter are Colles' fractures[7,8]. Osteoporosis is a leading cause of morbidity and mortality in elderly people.

The disorders that cause osteoporosis are similar in men and women[9–11]: estrogen deficiency – primarily in postmenopausal women[12,13], hyperparathyroidism, hyperthyroidism, hypogonadism in men[14], glucocorticoid therapy[15], genetic factors[16,17], cigarette smoking and alcohol intake, lower calcium intake, decreases in physical activity and muscle strenght[18], gastrointestinal disease[8], vitamin D deficiency, anti-convulsant therapy and stress factors with depression[19–22].

The usual clinical manifestations of osteoporosis are low-trauma fractures and radiographic osteopenia detected by chance or during evaluation for musculosceletal pain, usually back pain[9].

Measurements of bone mineral density are usually recommended, and if bone mineral density is lower than experienced for age and no cause is apparent, further studies are indicated; measurements of serum testosterone, thyrotropin, calcium, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone, urinary calcium and creatinine, a complete blood count, serum and urine protein electrophoresis, iliac crest bone biopsy[10–12].

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

Mayor depressive disorder (MDD) is a syndrome of persistently sad, dysphoric mood accompanied by sleep and appetite disturbances, and inability to experience pleasure[18]. 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; 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 of depression among other conditions of primary affective disorders and may be observed in as many 40–60% of patients in some series[18,19].

These findings have eventually led to the routine use of dexamethasone suppression test (DST) as a biologic tool for both the diagnosis and follow-up of such patients.

Psychotherapy, associated with antidepressants(serotonin re-uptake 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 males and 12 females, 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 two 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 125J 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 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. According to 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-h 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. Patients 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/24h. Since it correlates with the levels of plasma free cortisol, urinary cortisol excretion has several invaluable qualities: 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 highly sensitive marker. It is not altered in obese patients in estrogen-treated females or by drugs or conditions that modify cortisol metabolism.

Dexamethasone suppression test 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 ACTH when given in minute amounts as compared to 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 each of our patients, serum cortisol level, 24h urinary free cortisol and DST were determined.

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 p.m. was 618 43.2 nmol/l, and at 5 p.m. 347 34.2 nmol/l. Cortisol in DST was 165 36.8 nmol/l.

Plasma cortisol levels in MDD patients were just above the normal range. Also, in patient with MDD we found deficient cortisol suppression in DST test.

These results indicated that, although MDD patients showed an increased the urine cortisol level. They had some circa-

TABLE 1
PATIENT WITH MDD AND HEALTHY VOLUNTEERS

	N	Males	Females	Age (years)		A	B	C	Cort/24	Cort /dex
MDD	31	19	12	37	1.3	12	6	31	1067 + 61	165 + 36
Controls	17	17	0	39	1.6	0	0	0	590 + 87	86 + 37

A = regular cycles; B = impotency; C = psych. therapy; Cort/24 = cortisole in 24 hour urine

dian rhythm of cortisol preserved (Figures 1 and 2).

In our examination, we found significant correlation between years of therapy and degree of osteoporosis in patient with MDD. (Figure 4) As we see, the patient who was longer time on antidepressant therapy, had more chance to develop osteoporosis. As we could see, the patient with MDD had statistical significant higher levels of cortisol in 24-h urine.

In our workshop we used (was recommended) the nonparametric rang-correlation, in which the Spearman's ro = –0.805, and correlation is significant at the 0.01 level ($p < 0.01$) (Tables 2 and 3).

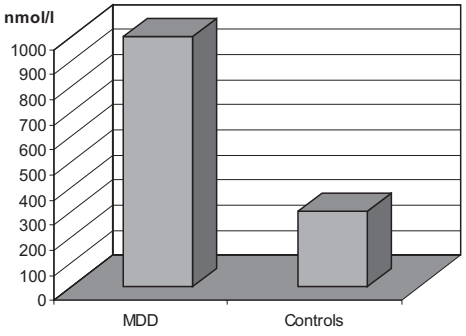

Fig. 1. Urinary free cortisol in patients with mayor depressive disorder (MDD) and in healthy volunteers.

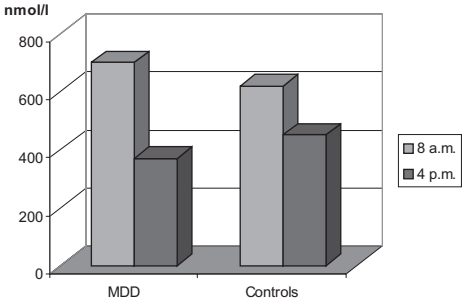

Fig. 2. Plasma cortisol in patients with mayor depressive disorder (MDD) and healthy volunteers at 8 a.m. and 4 p.m.

Discussion

The hypothalamo-pituitary-adrenal (HPA) axis is a very complex control system playing an important role primarily

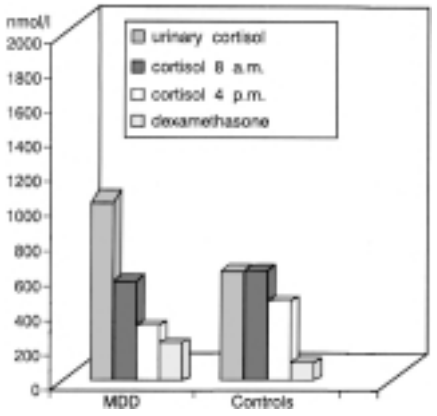

Fig. 3. Urinary free cortisol, plasma cortisol at 8 a.m. and 5 p.m., and cortisol in dexamethasone suppression test in patients with major depressive disorder (MDD) and in healthy control volunteers.

TABLE 2
CORRELATION BETWEEN YEARS OF THERAPY AND T SCORE IN PATIENT WITH MDD

	Pearson correlations	Years of therapy	T score
Years of therapy	Correlation	1.000	–0.787 (*)
	Sig. (2-tailed)	0.000	0.000
	N	37	37
T score	Correlation	–0.787 (**)	1.000
	Sig. (2-tailed)	0.000	0.000
	N	37	37

* Correlation is significant at the 0.01 level (2-tailed)

TABLE 3
NONPARAMETRIC CORRELATION BETWEEN YEARS OF THERAPY AND T SCORE IN PATIENT WITH MDD

	Spearman's correlation	Years of therapy	T score
Years of therapy	Correlation	1.000	–0.805
	Sig. (2-tailed)	0.000	0.000
	N	37	37
T score	Correlation	–0.805 (*)	1.000
	Sig. (2-tailed)	0.000	0.000
	N	37	37

* Correlation is significant at the.01 level (2-tailed)

in stress reaction[23]. Glucocorticoids are secreted in response to stressful conditions, and have an important task to block the functions of stress mediators that have previously been brought to liberation. In other words, glucocorticoids suppress the autonomic (vegetative), behavioral, endocrine and immunologic responses to stressful stimuli in a time-dependent way.

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 hyppocampus and adrenal cortex activation by ACTH and corticosterone increase[24–26].

Biological abnormality is frequently observed in patients with major depression, 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[27,28]. Glucocorticoid-induced hippocampal neuron damage and deficient transmission of suprahypothalamic negative feedback has been proposed as a major mechanism mediating this phenomenon. Indeed, in patients with depression, the 24-h urinary free cortisol excretion increases with age,

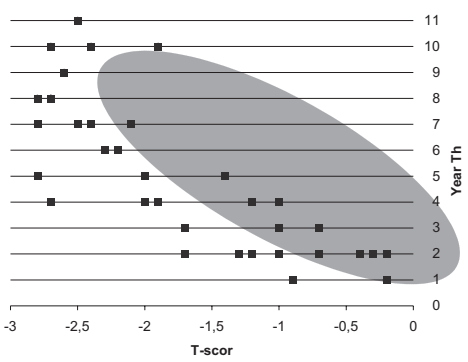

Fig. 4. Corelation between years of therapy and T score in patient with MDD and osteoporosis.

while studies of the HPA axis in aging population that include persons with chronic emotional or physical diseases have shown progressive elevations of evening plasma cortisol concentrations with age[29].

In MDD hypercortisolism does not give rise to the usual physical stigmata of hipercortisolic 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[30,31].

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 the pituitary-adrenal axis is fairly specific of depression among other conditions of primary affective disorders. So, these findings have eventually led to the routine use of dexamethasone suppression test (DST) as a biologic tool for both the diagnosis and follow-up of such patients. The research to answer questions concerning the pathophysiology of the hypothalamo-pituitary-adrenal (HPA) axis dysfunction in patients with MDD has been focused on MDD. Four hypotheses have been proposed to explain why non-suppression occurs[32–34].

These include: 1) increased metabolism of dexamethasone in patients with MDD[35 36], which results in less dexamethasone available to suppress the production of adrenocorticotropic hormone (ACTH) in the pituitary; 2) decreased sensitivity of pituitary glucocorticoid receptors to dexamethasone, resulting in less ACTH suppression and cortisol elevation; 3) hyperresponsivity 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 hypothalamic/limbic structures, which overrides the action of dexamethasone. The more so, a combination of the hypotheses should by no means be neglected[37,38].

The use of anticortisol drugs has already produced beneficial conditions in depression. The mayor role played with cortisol must have been defective interpretation of cortisol results. If serum cortisol levels are normal at 8 a.m. and 4 p.m., it has always been considered normal, without realizing that changes, sometimes at the immunosuppressive level, might occur during 24-h circadian rhythm[39,40].

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DEPRESIVNI POREMEĆAJ KAO MOGUĆI ČIMBENIK RIZIKA ZA RAZVOJ OSTEOPOROZE?

S A Ž E T A K

Hipotalamo-hipofizno-adrenalna os složeni je kontrolni sustav koji igra značajnu ulogu prvenstveno u reakciji na stres, pri čemu glukokortikoidi potiskuju autonomne (vegetativne), endokrine, imunološke i psihičke odgovore na stresni stimulus. Opisali smo kliničku, fiziološku i biokemijsku povezanost između osteoporoze i velike depresije. U oba stanja dolazi do hiperaktivnosti HPA osi, LC/NE sustava te povišenog lučenja CRH, kortizola i katekolamina. Mnoga stanja i bolesti su povezana uz osteoporozu,

pa i hiperkorticizam gledamo kao jedno od takvih. Neka novija istraživanja povezuju raniju povijest MDD sa osteoporozom. U velikoj depresiji (engl. Major Depressive Disorder, MDD) su zabilježene dvije biokemijske abnormalnosti: hiperkorticizam i rezistencija na supresiju deksametazonom. Naše je istraživanje uključivalo 31 bolesnika s MDD (19 muškaraca i 12 žena prosječne dobi 37 1,3 godine i raspona od 29–41 godinu) i 17 muških dobrovoljaca (prosječne dobi 39 1,6 godina, raspona 34–45 godina). Svim bolesnicima je određivana razina kortizola u 24-satnom urinu, serumski kortizol u 8h i 17h, kortizol u testu supresije deksametazonom te denzitometrijski određivana gustoća kosti. Radilo se, dakle, o skupini mlađih muškaraca i žena s održanim menstruacijskim ciklusom, u početku bez osteoporoze, ali godinama pod antidepresivnom terapijom. Analizirajući ih, našli smo povišene vrijednosti kortizola te pojavu osteoporoze, čiji je razvoj bio posljedica povišene razine kortizola. U radu je korištena neparametrijska rang-korelacija, kod koje je Spearmanov ro = –0.805, imao statističku značajnost $p < 0.01$. Iz svega navedenog se nameće zaključak, da što se bolesnici dulje liječe od depresije razviti će jači oblik hiperkorticizma, što bi moglo biti uzrokom osteoporoze jer je već poznato da bolesnici sa neliječenim Cushingom razvijaju jaki oblik osteoporoze.