Is the DHEAS/cortisol ratio a potential filter for non-operable constipated cases?

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Abstract

Constipation is a significant manifestation of a number of psychological disorders. Published papers recommend using self-assessment questionnaires for discriminating psychological from non-psychological constipated patients before operating on them but reports from major surveys revealed that general practitioners failed to diagnose 70% of depressed patients using self-assessment questionnaires. Lower circulating concentrations of progesterone, 17-hydroxyprogesterone, cortisol, testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) during the follicular phase in constipated young women compared with respective controls were found during the follicular phase of the menstrual cycles. During the luteal phase of the cycle, reductions were identified in estriol, cortisol and testosterone in the constipated group. Likewise, circulating concentrations of DHEAS were found to be lower in depressed patients than comparable healthy controls. DHEAS/cortisol ratios in morning serum and salivary samples were lower than those retrieved during other times of the day in depressed patients. The idea of recognizing major depression in constipated patients by measuring DHEAS/cortisol ratios in saliva and serum may be plausible but this possibility needs to be confirmed in well-designed studies.

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INTRODUCTION

Constipation is a prominent feature amongst patients with depression[1-8], anorexia nervosa, weight loss, sleep disorders[9,10], fatigue, and decreased sexual interest, particularly with menarche or after a stressful emotional experience[9,10], or surgical operation[9,10]. The outcome of treatment in patients with chronic constipation is unpredictable. This may be a consequence of the lack of effectiveness of such treatment or may reflect heterogeneity within patient subgroups.

IDIOPATHIC CHRONIC CONSTIPATION AND PSYCHOLOGICAL VARIABLES

A positive link was identified by Martelli et al[11] between various psychiatric variables and both outlet obstruction and colonic inertia. These results were further confirmed
Reports revealed that general practitioners could not diagnose endocrine glands, transported through the bloodstream, and exerting actions on the brain. Ever since the biosynthesis of steroid hormones in the brain and their rapid non-genomic actions were first reported, specific targets for so-called “neurosteroids” in plasma membranes have been postulated.

DHEA and its metabolites, DHEAS and androsterone, have been identified recently as having neurosteroid activity.

DHEAS modulates the actions of the gamma-aminobutyric acid type A (GABA) receptor, the N-methyl-D-aspartate receptor, and the sigma subtype 1 (σ1) receptor among others. DHEA and DHEAS generally act as noncompetitive antagonists of the GABA receptor. GABA receptor-mediated regulation of 5-hydroxytryptamine (5-HT) neuronal firing was found to be sensitive to negative modulation by DHEA and DHEAS, and to positive modulation by androsterone. GABAA receptor-mediated regulation of 5-HT firing may be responsible for some of the reported behavioral and psychological effects of endogenous and exogenous DHEA. An assessment of depression ratings in relation to plasma concentrations of several steroid hormones (estradiol, testosterone, estrone, androstenedione, cortisol, DHEA) and DHEAS in 699 postmenopausal women (aged 50-90 years) who were not taking the contraceptive pill found that only DHEAS concentrations were negatively correlated with ratings of depressed mood. Explicitly, higher DHEAS concentrations were associated with less depression, and this association was independent of age, physical activity and weight change. Furthermore, women with categorical diagnoses of depression had significantly lower plasma DHEAS concentrations compared to age-matched non-depressed women. Similarly, in a large-scale study of 2855 well-functioning elderly men and women, serum DHEAS concentrations were inversely correlated with depressive symptoms. Women whose first onset of major or minor depression occurred during the peri-menopause showed low morning plasma DHEA and DHEAS concentrations. Lower plasma DHEA concentrations during pregnancy and during the postpartum period were associated with higher postpartum ratings of depression.

Physiology of Steroids Hormones and Menstrual Cycle

Adrenal androgens represent an important component (> 50%) of the circulating androgens in menstruating females. In males, the adrenal contribution is much less because of the testicular production of androgens. Adrenal secretion of androgens in men is about the same as in women during the follicular phase. The adult adrenal gland secretes dehydroepiandrosterone (DHEA) at approximately 4 mg/d, DHEA sulfate (DHEAS) at 7-15 mg/d, and androstenedione at 1.5 mg/d.

Relationships between Steroid Hormones and Brain Functions

The relationships between steroid hormones and brain functions have mostly been considered within the framework of endocrine mechanisms as genomic responses, elicited by secretory products from steroidogenic endocrine glands, transported through the bloodstream, and exerting actions on the brain. Ever since the biosynthesis of steroid hormones in the brain and their rapid non-genomic actions were first reported, specific targets for so-called “neurosteroids” in plasma membranes have been postulated.

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Pathophysicsiology of Steroid Hormones in Severely Constipated Patients

Levels of progesterone, 17-hydroxyprogesterone, cortisol, testosterone, androstenedione, and DHEAS were found to be lower during the follicular phase of the menstrual cycle in patients diagnosed with idiopathic chronic constipation compared with respective healthy controls. A lack of estriol, cortisol and testosterone was identified during the luteal phase of the cycle in the constipated group. The high prevalence of idiopathic constipation in pre-menopausal women is likely a result of the high affinity of progesterone for progesterone receptors together with the non-specific affinity for adrenal androgen receptors, and the lack of a stimulatory effect of estrogen on the wall of the bowel.
MEASUREMENT OF DHEAS/CORTISOL RATIO AND PSYCHOLOGICAL VARIABLES

A deficiency of DHEAS is thus identified in depression and constipation and it would be impossible to rely on it for distinguishing depressed, severely constipated patients. However, estimates of DHEA-to-cortisol ratios in serum and saliva, are likely to be more reliable than concentrations of either hormone alone, with lower morning ratios seen in depression\(^\text{46-48}\). The molar DHEAS/cortisol ratio was significantly lower in non-medicated depressed patients than in controls, and the evening salivary DHEA/cortisol ratio was inversely correlated with the length of the current depressive episode\(^\text{49}\). Morning salivary DHEA hyposecretion as well as evening cortisol hypersecretion were significantly and independently associated with major depression in young patients\(^\text{49}\).

IMPLICATIONS IN RESEARCH AND IN CLINICAL PRACTICE

This review hypothesizes that measurement of the DHEAS/cortisol ratio in constipated patients could filter out those patients with a psychological disorder and improve the outcome after surgery.

For assessing the credibility of this measurement, a well-designed study needs to be conducted. The recruited constipated patients should have no personal or family background of a major psychological disorder. Participants should be asked to complete a stool diary. In this diary, they would be asked to report on the frequency, shape, consistency of stool, and whether they strained at defecation or not. The starting day would be their first menstruating day of the nearest menstruation cycle and the end would be the commencement of the next one. They would comment on the day and timing of defecation, stool consistency, stool form and the presence or absence of straining at stool.

They would also be asked to give 3 blood samples and 3 samples of saliva in any day during the mid-follicular period (days 7-10). The first samples would be collected early in the morning, the second on the afternoon and the third would be collected early in the evening.

Similarly, the same process would be repeated in any day during the mid-luteal period (days 18-20) to measure the DHEAS/cortisol ratio in serum and in saliva. The whole process would be repeated over the second consecutive menstrual cycle to obtain an average of each measurement. On these 2 d, participants would also be asked to fill in the Hospital Anxiety & Depression Scale questionnaire and General Health Questionnaire.

During the mid luteal period, the value of the DHEAS/cortisol ratio is supposed to be higher than that during the mid-follicular period in purely constipated patients. Because of ovarian secretions during the luteal phase, the concentration of DHEAS would be nearly normal but that of cortisol would still be low. However, in mixed cases, the ratio would be low, and in particular in the early morning samples.

CONCLUSION

The use of self-assessment questionnaires for excluding a psychological disorder in severely constipated patients seems insufficient, but the idea of measuring serum and salivary DHEAS/cortisol ratios before embarking upon invasive treatments appears to be more specific. This conclusion warrants confirmation in well-designed studies.

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