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Article

Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes

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Abstract

Objective: To evaluate the degree of psychological dysfunction and levels of stress hormones in postmenopausal women with climacteric syndromes and effect of Korean red ginseng (RG) on them. *Methods:* ACTH, cortisol and DHEA-S in peripheral blood from 12 postmenopausal women with climacteric syndromes or 8 postmenopausal women without any climacteric syndrome were measured before and 30 days after treatment with daily oral administration of 6 g RG. Blood samples were collected in the early morning on the bed-rest. In postmenopausal women with climacteric syndromes such as fatigue, insomnia and depression, psychological tests using the Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI) were performed before and 30 days after treatment with RG. *Results*: CMI score as well as anxiety (A)-state in STAI score in postmenopausal women with climacteric syndromes was significantly higher than that without climacteric syndrome, while DHEA-S levels in postmenopausal women with climacteric syndromes were about a half of those without climacteric syndrome. Consequently, cortisol/DHEA-S (C/D) ratio was significantly higher in postmenopausal women with climacteric syndromes than in those without climacteric syndrome. When postmenopausal women with climacteric syndromes were treated with daily oral administration of 6 g RG for 30 days, CMI and STAI A-state scores decreased within normal range. Although the decreased DHEA-S levels were not restored to the levels in postmenopausal women without climacteric syndrome, the C/D ratio decreased significantly after treatment with RG. *Conclusions:* Improvement of CMI and STAI scores in postmenopausal women suffering climacteric syndromes, particularly fatigue, insomnia and depression, by RG seemed to be brought about in part by effects of RG on stress-related hormones as shown by a decrease in C/D ratio. © 1999 International Federation of Gynecology and Obstetrics.

Keywords: Climacteric syndromes; Korean red ginseng; Stress hormones; Psychological dysfunctions

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1. Introduction

Although many symptoms and signs of various mood disturbances have been considered to result in estrogen deficiency during the climacteric, there seem to be no psychological symptoms specific to the menopause [1]. The literature concerning psychological symptoms accompanying menopause is confusing. A number of investigators have attempted to link menopause with various psychological diseases, particularly depression. Many have been unsuccessful. However, more recent data have suggested a link between menopause and changes in mood and psychological functions [2].

It has been assumed that estrogen replacement therapy improves psychological function, specifically depression and memory dysfunction, in postmenopausal women [3,4]. Dehydroepiandrosterone (DHEA) is the androgen produced by the adrenal in largest quantity. The psychological roles of DHEA and of its sulfate (DHEA-S), which is thought to be produced exclusively by the adrenal cortex, are unknown. They are considered to have weak androgens, but also appear to have estrogenic properties [5]. Blood levels of DHEA(S) are low in the first year of life, increasing quite rapidly from approximately 8 years (adrenarche) through puberty to reach their highest levels during early adult life, declining thereafter to values in old age that are only a quarter or a third of those at the maxima [6]. Although the full significance of the decline in DHEA(S) with age are not understood, recent findings suggest that it may be associated with the increasing incidence of some age-related processes and diseases. There are indications that age-related decreases in DHEA(S) may show marked individual differences and be under partial hereditary control, which has led some investigators to suggest that DHEA(S) may be a measurable component of individual differences in the aging process itself [7]. A variety of circumstances or stresses seem to be able to lower DHEA(S) [8,9].

DHEA(S) behaves in a manner opposite to that of cortisol, which tends to increase under stressful conditions. Because most DHEA(S) comes from the adrenal [10], it is clear that cortisol and DHEA(S) can be regulated independently both during the aging process and within more-restricted time spans, as during episodes of stress or illness.

Korean red ginseng (RG) used in this study have been reported to have multi-potential activity, including estrogenic action [11], anti-stress action [12,13], and immuno-stimulative action [14]. Thus, we attempted to further elucidate the effects of RG on stress-related hormones and psychological functions in postmenopausal women.

2. Methods

Patients' characteristics enrolled in the present study are summarized in Table 1. Age of patients without climacteric syndromes (CS) and with CS was 52.0 ± 3.4 (mean $\pm$ S.D.) and 52.1 ± 4.1, respectively. Years after menopause they were 2.1 ± 1.5 and 2.5 ± 1.8 in patients without CS and with CS, respectively. These values did not show

Table 1
Patients' characteristics[a]

	No. of cases	Age	Body weight (kg)	BMI	Years after menopause
Postmenopausal women without CS	8	52.0 ± 3.4[b]	50.3 ± 2.6	21.5 ± 1.0	2.1 ± 1.5
Postmenopausal women with CS	12	52.1 ± 4.1	49.0 ± 3.8	20.4 ± 1.2	2.5 ± 1.8

[a] Estrogen levels of postmenopausal women without or with CS were less than 10 pg/ml. BMI, body mass index = body weight (kg)/[height (m)]^2. CS, climacteric syndromes.
[b] Mean $\pm$ S.D.

statistically significant difference. Patients with CS were treated with daily oral administration of 6 g Korean red ginseng (RG) for 30 days, while patients without CS were not treated.

Blood samples were drawn in the early morning on the bed-rest and fasting state. Serum was separated immediately and frozen at −80°C for future analysis. Stress-related hormones measured were ACTH, cortisol and dehydroepiandrosterone-sulfate (DHEA-S). The radioimmunoassays used were as follows: ACTH (aregro ACTH kit; Japan Mediphysics), cortisol (γ-coat cortisol kit; Dadebaehring, Germany) and DHEA-S (DPC DHEAS kit; Japan DPC).

Patients without or with SC were assessed with the use of the Cornell Medical Index (CMI)-Health Questionnaire [15] which is a self-administered instrument that collects a large body of significant medical and psychiatric data without the physician's participation, so that the physician may have available, even before he interviews the FM patient, information on which to base tentative diagnostic appraisals of the patients total medical problem, and the State-Trait Anxiety Inventory (STAI) [16] which is best-known as a self-rating anxiety scale and consists of two sections: 20 items that assess the patients anxiety at the time of evaluation (state) and 20 items that evaluate the patients long-standing, characteristic level of anxiety (trait).

In order to determine the effect of RG in patients with CS, the CMI and STAI scores and the stress-related hormone levels after treatment with RG were compared to those before treatment.

3. Results

Although there was no significant difference in age, body weight, body mass index (BMI) and years after menopause between postmenopausal women without CS and with CS examined, and estrogen levels of these patients were less than 10 pg/ml (Table 1), CMI score and anxiety (A)-state in STAI score in postmenopausal women with CS was significantly ($P < 0.05$) higher than those without CS (Table 2), suggesting psychological problems in postmenopausal women with CS. In addition, DHEA-S levels in postmenopausal women with CS were decreased to less than a half of those in postmenopausal women without CS, subsequently resulting in more than twofold increase of C/D ratio (Table 3). When postmenopausal women with CS were treated with 6 g RG for 30 days, CMI score and A-state in STAI score returned to the levels in postmenopausal women without CS (Table 4). Furthermore, cortisol and C/D ratio were significantly ($P < 0.05$) decreased

Table 2
Comparison of CMI and STAI scores in postmenopausal women without or with climacteric syndrome (CS)

	Postmenopausal women ($n = 8$) without CS	Postmenopausal women ($n = 12$) with CS
CMI		
M-R	9.0 ± 1.3[a]	11.8 ± 1.7[b]
I	1.7 ± 0.6	3.1 ± 0.5[b]
STAI		
A-State	40.0 ± 2.7	45.5 ± 4.2[b]
A-Trait	55.3 ± 4.3	55.9 ± 5.0

Abbreviations: M-R, psychosomatic state; I, fatigability; A-State, anxiety state; A-Trait, anxiety trait.

[a] Mean ± SD.

[b] $P < 0.05$ (Student's *t*-test), compared to postmenopausal women without CS.

Table 3
Comparison of plasma ACTH, cortisol and DHEA-S in postmenopausal women without or with climacteric syndrome (CS)

	Postmenopausal women ($n = 8$) without CS	Postmenopausal women ($n = 12$) with CS
ACTH (pg/ml)	31.3 ± 18.6[a]	30.3 ± 8.5
Cortisol (μg/ml)	11.0 ± 3.4	13.6 ± 3.8
DHEA-S (μg/ml)	149.0 ± 53.9	70.1 ± 26.1[b]
C/D ratio	0.08 ± 0.02	0.21 ± 0.08[c]

[a] Mean ± S.D.

[b] $P < 0.01$ (Student's *t*-test), compared to postmenopausal women without CS.

[c] $P < 0.001$ (Student's *t*-test), compared to postmenopausal women without CS.

Table 4
Effect of RG on CMI and STAI scores of 12 postmenopausal women with climacteric syndromes

	Before treatment with RG	After treatment with RG[a]
CMI score		
M-R	11.8 ± 1.7[b]	8.7 ± 2.1[c]
I	3.1 ± 0.5	1.3 ± 0.5[c]
STAI score		
A-State	45.5 ± 4.2	37.0 ± 1.5[c]
A-Trait	55.9 ± 5.0	55.4 ± 3.8

[a] Thirty days after daily oral treatment with RG (6 g/day).
[b] Mean ± S.D.
[c] $P < 0.001$ (paired t-test), compared to before treatment with RG.

after treatment with RG, compared to before treatment with RG (Table 5). The dose of RG used in the present study did not result in any adverse side effects.

4. Discussion

We found high CMI scores and high A-state scores in STAI in postmenopausal women with CS, suggesting a link between menopause and psychosomatic functions (Table 2). Women's reproductive lines are marked by distinct milestones: menarche, first intercourse, conception, first and subsequent deliveries, and menopause. The cessation of monthly bleeding signifies entry of a woman into an 'older' category. Menopause has been considered to frequently precipitate a developmental crisis or psychiatric illness, although other studies indicate that there is no association between clinical depression and menopause as a physiological event [1,17]. The hormonal changes that occur during the climacteric are associated with vasomotor episodes commonly referred to as 'hot flashes' and with changes in vaginal lubrication and other functions. For some women, hot flashes may be so frequent and severe as to interfere with sleep, secondarily leading to psychological symptoms.

Table 5
Effect of RG on plasma ACTH, cortisol and DHEA-S levels in 12 postmenopausal women with climacteric syndromes

	Before treatment with RG	After treatment with RG[a]
ACTH (pg/ml)	30.3 ± 8.5[b]	27.8 ± 4.6
Cortisol (μg/dl)	13.6 ± 3.8	12.3 ± 3.6[c]
DHEA-S (mg/dl)	70.1 ± 26.1	79.1 ± 33.0
C/D ratio	0.21 ± 0.08	0.17 ± 0.06[c]

[a] Thirty days after daily oral treatment with RG [6 g/day].
[b] Mean ± S.D.
[c] $P < 0.05$ (paired t-test), compared to before treatment with RG.

In addition, postmenopausal women with CS showed lower DHEA-S levels and higher C/D ratio than those without CS, while difference in ACTH levels was not observed (Table 3). The decline of estrogen in postmenopausal women is well known. During the climacteric, the levels of androgens, particularly those associated with ovarian secretion, also decline, but the decline is probably less than that of the estrogens [18]. Although the adrenals secrete only small amounts of estrogens, they secrete substantial amounts of estrogen precursors, such as the androgen dehydroepiandrosterone and its sulfate [18]. These levels decrease at menopause as ovarian secretion declines [19]. In the present study, we have demonstrated that serum DHEA-S levels in postmenopausal women with CS were less than a half of those in postmenopausal women without CS. Similarly decreased DHEA or DHEA-S levels in postmenopausal women with ovarian cancer [20] or men with chronic severe stress [21] have been reported, although the cause of this change is unknown. Although DHEA is a major secretory product of the adrenal cortex, it is unclear what mechanism controls the secretion of this steroid sulfate. In postmenopausal women with CS there seemed to be a shift in pregnenolone metabolism away from both the mineralcorticoid and adrenal androgen pathways toward the glucocorticoid pathway. It is possible that stress-induced prolonged ACTH secretion may be associated with decreased mineralcorticoid and adrenal androgen stimulation.

Korean red ginseng (RG), the root of *Panax ginseng C.A, Meyer* is a traditional medicine in Korea, China, and Japan, and it has become popular in Western countries. The major active ingredients of ginseng have been demonstrated to be a group of ginsenosides isolated and purified from ginseng saponin fraction (ginseng total saponin) and whose chemical structures have been established [22]. Thus, we examined the effects of RG on psychosomatic functions and stress-related hormones of postmenopausal women with CS. Treatment with RG resulted in improvement of psychosomatic functions in postmenopausal women with CS as measured by CMI and A-state in STAI (Table 4). In addition, RG caused a decrease of cortisol and an increase of DHEA-S, subsequently showing a significant decline of C/D ratio (Table 5). Many symptoms and signs of various mood disturbances have been shown to be attributed to estrogen deficiency during the climacteric. Therefore, estrogen treatment of postmenopausal women has been suggested to improve mood and psychlogical function [2,3]. In women, 0.625 or 1.25 mg conjugated equine estrogen alleviates dysphoric symptoms [3], but has no effect on a true clinical depression [23], which may be alleviated by very large pharmacologic doses of estrogen [24]. Since administration of estrogen to postmenopausal women with a true clinical depression would be ineffective, alternative medicine such as Korean red ginseng (RG) should be addressed. Moreover, estrogen has been reported to lower serum androgen and DHEA-S levels [25]. We have demonstrated that serum DHEA-S levels of postmenopausal women with CS were significantly lower than those without CS. Therefore, estrogen will further exacerbate the endogenous adrenal and ovarian androgen deficiency state seen in postmenopausal women with CS.

It is noteworthy that RG improves psychosomatic dysfunction of postmenopausal women with CS without declining serum DHEA-S levels, unlike estrogen. Further studies are ongoing to confirm these preliminary results in a randomized prospective double-blinded cross-over.

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