

Effect of Korean Red Ginseng on Psychological Functions in Patients with Severe Climacteric Syndromes: A Comprehensive Study from the Viewpoint of Traditional KAMPO-medicine and Western Medicine

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Abstract

Objective; Antistress effect of Korean red ginseng (RG) on postmenopausal women with severe climacteric syndrome (CS) were evaluated from the viewpoint of traditional KAMPO-medicine and Western medicine. Methods; All patients with CS were treated with daily oral administration of 6g RG for 30 days. Nine patients with CS were evaluated with the use of diagnostic scores for KI-deficiency (deficiency of vital energy) and OKETSU (blood stagnation) syndrome from the viewpoint of KAMPO-medicine. In the same patients with CS, peripheral blood levels of β -endorphin and total plasminogen activator inhibitor-1 (t-PAI-1) were measured before and after treatment with RG. In another group, 12 patients with CS, psychological test using CMI, STAI and SDS were performed from the viewpoint of Western medicine. Stress related hormones, such as ACTH, cortisol and DHEA-S in those 12 patients with CS were also measured before and after treatment with RG. Results; KI-deficiency score and OKETSU score in patients with CS were significantly ($p < 0.001$) higher than those in patients without CS. After treatment with RG, both scores were markedly ($p < 0.001$) decreased compared to before treatment with RG. β -endorphin levels in patients with CS were significantly ($p < 0.05$) higher than those in patients without CS. Total PAI-1 levels in patients with CS were increased before treatment with RG. No significant difference, however, were observed between patients with and without CS. After treatment with RG, both levels of β -endorphin and total PAI-1 in patients with CS were significantly ($p < 0.01$ and $p < 0.05$, respectively) decreased compared to before treatment with RG. CMI and STAI scores in patients with CS were significantly ($p < 0.05$) higher than those in patients without CS. SDS scores in patients with CS were also markedly ($p < 0.001$)

higher than in those without CS. After treatment with RG, all scores decreased within normal range. DHEA-S levels in patients with CS were about a half of those without CS. Consequently, cortisol/DHEA-S (C/D) ratio was significantly ($p < 0.001$) higher in patients with CS than in those without CS. Although the decreased DHEA-S levels were not restored to the levels in patients without CS, the C/D ratio decreased significantly ($p < 0.05$) after treatment with RG. Conclusion; Reinforcement of vital energy and improvement of stagnant blood circulations by oral administration of RG were elucidated from the viewpoint of traditional KAMPO-medicine. From the viewpoint of Western medicine, effect of RG on postmenopausal women with CS seemed to be brought about in part by not only an improvement of psychoneuroendocrine dysfunctions but also an amelioration of blood coagulation systems.

Introduction

Various psychosomatic symptoms in climacteric syndrome have been considered to result in estrogen deficiency. Subsequently, estrogen replacement therapy (HRT) has been prescribed as treatment of climacteric syndrome. In the women's aging process, rapid hormonal changes that occur during climacteric are associated with vasomotor episode referred to as hot flush. For some women hot flushes induced by estrogen deficiency may be so frequent and severe as to interfere with sleep, secondarily leading to psychological symptoms. The loss of fertility and menstrual function may have a negative impact on women's sense of well being. Many problems that occur in middle aged women, especially in postmenopausal women, health-related problems, psychological problems such as poor marital relations, or stressful life events are considered to cause psychological distress. Consequently, distinctive psychosomatic symptoms, depression, fatigue, insomnia, hot flush, or undefined complaints, so called climacteric syndrome, appear more or less in postmenopausal women. Therefore, such treatment as to alleviate psychological stresses seems to be an attractive therapy of postmenopausal women with severe climacteric syndromes (CS). In traditional Oriental medicine (KAMPO-medicine; traditional medicine in Japan based on ancient Chinese medicine), many practitioners attribute symptoms such as fatigue, depression, insomnia, hot flush and mysterious psychosomatic symptoms in postmenopausal women with CS to decreased elemental energy levels (KI-deficiency in KAMPO-medicine) and stagnant peripheral blood circulation (OKETSU in KAMPO-medicine), and subsequently prescribe

various herbal medicines to reinforce the vital energy and to overcome the blood stagnation. Korean red ginseng (RG) is a traditional medicine in Korea China and Japan, and it has become popular in Western countries. RG has been used as a tonic medicine, improving the state of KI-deficiency and OKETSU syndrome. Furthermore, it has been reported from the viewpoint of Western medicine to have multi-potential activity, including estrogenic activity (1), antistress activity (2), and immunostimulative activity (3). Thus, we evaluated the effect of RG on psychological stresses in postmenopausal women with CS from the viewpoint of KAMPO-medicine and Western medicine.

Patients and Methods

Total 37 patients without or with CS were enrolled in this study. All patients with CS were treated with daily oral administration of 6 g RG for 30 days. Nine patients with CS were evaluated from the viewpoints of KAMPO-medicine with the use of diagnostic scores for KI-deficiency and OKETSU syndrome (4). Patients' characteristics were shown in Table 1. Total counts of more than 30 points indicate KI-deficiency. A total score more than 20 points indicates a condition of OKETSU and more than 40 points indicate severe OKETSU state. In the same patients with CS peripheral blood levels of β -endorphin and a fibrinolytic factor, total plasminogen activator inhibitor-1 (t-PAI-1) were measured before and after treatment with RG. To evaluate the effect of RG on psychoneuroendocrine functions, 12 patients with CS were evaluated from the viewpoint of Western medicine. Patients' characteristics were summarized in

Table 1. Patients' characteristics

	No. of cases	Age	Bodyweight (kg)	BMI	Years after menopause
Postmenopausal women without CS	8	51.6 \pm 1.5 ^a	50.4 \pm 2.8	21.0 \pm 0.8	2.2 \pm 1.0
Postmenopausal women with CS	9	51.2 \pm 1.7	50.3 \pm 1.8	20.6 \pm 0.9	2.3 \pm 1.1

Estrogen levels of postmenopausal women with or without CS were less than 10 pg/ml

BMI : Body mass index = body weight (kg)/ [height (m)]², CS : severe climacteric syndrome

a: Mean \pm SD

Table 2. Patients' characteristics

	No. of cases	Age	Bodyweight (kg)	BMI	Years after menopause
Postmenopausal women without CS	8	52.0 ± 3.4 ^a	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: Mean ± SD

Table 2. Psychological functions of patients with CS were assessed with the use of Cornell Medical Index (CMI), State-Trait Anxiety Inventory (STAI) and Self-rating Depression Scale (SDS). Stress related hormones, ACTH, cortisol and Dehydroepiandrosterone-sulfate(DHEA-S) in patients with CS were also measured before and after treatment with RG. All blood samples were collected in early morning on the fasting state.

Results

When postmenopausal women were evaluated from the viewpoint of KAMPO-medicine using diagnostic scores for KI-deficiency and OKETSU syndrome, both diagnostic scores in postmenopausal women with CS were markedly ($p < 0.001$) higher than those in postmenopausal women without

Table 3. KI-deficiency score, OKETSU score, and plasma levels of β -endorphin and t-PAI-1 in postmenopausal women with or without severe climacteric syndrome (CS)

	Postmenopausal women without CS	Postmenopausal women with CS	
		Before treatment with RG	After treatment with RG
KI-deficiency score	22.3 ± 3.9 ^a	60.9 ± 7.0 ^b	29.0 ± 6.2 ^c
OKETSU score	42.0 ± 4.1	58.3 ± 7.3 ^b	41.2 ± 4.2 ^c
β -endorphin (pg/ml)	7.2 ± 0.9	9.9 ± 2.3 ^d	8.3 ± 2.4 ^e
t-PAI-1 (ng/ml)	13.4 ± 3.3	29.6 ± 13.2	22.6 ± 6.7 ^f

KI: Elemental energy or vital energy circulating in the human body. More than 30 points indicate KI-deficiency
 OKETSU: State of insufficient peripheral blood circulation and blood stasis. More than 40 points indicate severe OKETSU syndrome.

a: Mean ±SD, b: $p < 0.001$ & d: $p < 0.05$ ((Student's t-test), compared to postmenopausal women without CS), c: $p < 0.001$, e: $p < 0.01$ & f: $p < 0.05$ ((Paired t-test), compared to before treatment with RG)

CS (Table 3), indicating postmenopausal women with CS to be under the condition of KI-deficiency and OKETSU. After treatment with RG, subjective symptoms in postmenopausal women with CS were obviously improved. In addition, both diagnostic scores for KI-deficiency and OKETSU syndrome were significantly ($p < 0.001$) decreased, compared to before treatment with RG (Table 3). Before treatment with RG, β -endorphin levels in postmenopausal women with CS were significantly ($p < 0.05$) higher than those in postmenopausal women without CS (Table 3). After treatment with RG, those levels markedly ($p < 0.01$) decreased compared to before treatment with RG (Table 3). t-PAI-1 levels in postmenopausal women with RG were increased before treatment with RG, but no significant difference was observed between postmenopausal women with CS and without CS. After treatment with RG, t-PAI-1 levels in postmenopausal women with CS, however, significantly ($p < 0.05$) decreased, compared to before treatment with RG (Table 3) To evaluate the psychological dysfunctions in postmenopausal women with CS psychological tests using CMI, STAI and SDS were performed from the viewpoint of Western medicine. CMI and STAI scores in postmenopausal women with CS were significantly ($p < 0.05$) higher than those without CS. SDS score was also markedly ($p < 0.001$) higher than those of postmenopausal women without CS (Table 4). After treatment with RG, CMI, STAI and SDS scores returned to the levels in postmenopausal women without CS (Table 4). DHEA-S levels in postmenopausal women with CS were decreased to less than a half of those

Table 4. CMI score, STAI score and SDS score in postmenopausal women with or without severe climacteric syndrome (CS)

	Postmenopausal women without CS (n=8)	Postmenopausal women with CS (n=12)	
		Before treatment with RG	After treatment with RG
CMI score			
M-R	9.0 ± 1.3 ^a	11.8 ± 1.7 ^b	8.7 ± 2.1 ^d
I	1.7 ± 0.6	3.1 ± 0.5 ^b	1.3 ± 0.5 ^d
STAI score			
A-State	40.0 ± 2.7	45.5 ± 4.2 ^b	37.0 ± 1.5 ^d
A-Trait	55.3 ± 4.3	55.9 ± 5.0	55.4 ± 3.8
SDS score	35.1 ± 5.1	48.4 ± 4.4 ^c	41.3 ± 3.3 ^d

M-R: psychosomatic state, I: fatigability, A-state: Anxiety State, A-Trait: Anxiety Trait

a: Mean ± SD, b: $p < 0.05$ & c: $p < 0.001$ ((Student's t-test), compared to postmenopausal women without CS), d: $p < 0.001$ (paired t-test), compared to before treatment with RG)

Table 5. Plasma levels of stress related hormones (ACTH, cortisol, DHEA-S), in postmenopausal women with or without climacteric syndrome (CS)

	Postmenopausal women without CS (n=8)	Postmenopausal women with CS (n=12)	
		Before treatment with RG	After treatment with RG
ACTH (pg/ml)	31.3 ± 18.6 ^a	30.3 ± 8.5	27.8 ± 4.6
cortisol (µg/ml)	11.0 ± 3.4	13.6 ± 3.8	12.3 ± 3.6 ^d
DHEA-S (µg/ml)	149.0 ± 53.9	70.1 ± 26.1 ^b	79.1 ± 33.0
C/D ratio	0.08 ± 0.02	0.21 ± 0.08 ^c	0.17 ± 0.06 ^d

C/D : cortisol/DHEA-S, a: Mean ± SD, b: p<0.01 & c: p<0.001 ((Student's t-test), compared to postmenopausal women without CS), d: p<0.05 ((Paired t-test), compared to before treatment with RG)

in postmenopausal women without CS, subsequently resulting in more than twofold increase of C/D ratio (Table 5). When postmenopausal women with CS were treated with RG, cortisol levels and C/D ratio were significantly (p<0.05) decreased, compared to before treatment with RG (Table 5).

Discussion

We found a remarkable effect of RG on psychological dysfunctions in postmenopausal women with CS, suggesting a link between climacteric syndrome and psychological stresses. Women's reproductive lives are marked by distinct milestones such as menarche, first intercourse, conception, first and subsequent delivery and menopause. Many of those milestones are considered to be closely related with psychosocial problems, socioeconomic problems or cultural problems. Therefore, negative feelings evoked by those events in women's reproductive lives seem to act as psychological distress. When personality characteristics of postmenopausal women with CS are evaluated using CMI and Egogram Check List (ECL), which is analysis of a person's functional egostate, characteristic patterns can be observed. Psychosomatic state scores in CMI are significantly higher than those in postmenopausal women without CS (Table 4). In addition, adapted child (AC) scores of ECL in postmenopausal women with CS are also prominently high, compared to those in postmenopausal women without CS (data not shown). Such postmenopausal women with CS may be easily moved to stressful events and accumulate negative feelings continuously in their minds, compared to postmenopausal women without CS.

Therefore, it is most likely that a main causal factor of climacteric syndromes may be psychological stresses. Subsequently, antistress therapy is considered to be a useful treatment of postmenopausal women with CS. RG used in this study has been reported to have multi-potential activity such as estrogenic activity or antistress activity. Furthermore, influence on blood coagulation systems has been also reported (5). According to the KAMPO-medical theory, declining psychic power, physical weakness, fatigue, declining nerve activity and insufficient blood circulation are some kind of symptoms of KI-deficiency. On the other hand, OKETSU is a state of insufficient blood circulation and blood stasis causing lesions of endothelial cells and hemorrhagic diathesis. Furthermore, psychological stress is an initiating factor of OKETSU state. Symptoms such as hot flush, insomnia or nervousness, which are representative symptoms of climacteric syndrome, are accompanying OKETSU state from the viewpoint of traditional KAMPO-medicine. RG has been considered to improve KI-deficiency as well as OKETSU state, and stress burden patients such as postmenopausal women with CS are diagnosed to be under condition of KI-deficiency and/or OKETSU state. Therefore, RG may be a suitable agent for treatment of postmenopausal women with CS from the viewpoint of KAMPO-medicine. When postmenopausal women with CS were treated with RG, subjective symptoms were obviously improved. In addition, both diagnostic scores for KI-deficiency and OKETSU syndrome were significantly improved. Although modern medicine has not yet made clear scientifically the cause of KI-deficiency and OKETSU state, genesis of these conditions may be related to the function of central nervous systems or blood coagulation systems. Thus, we preliminary investigated the plasma levels of β -endorphin and t-PAI-1 in postmenopausal women with CS. Beta-endorphin is an opioid neuropeptide induced by emotional changes. On the other hand, t-PAI-1 is one of the fibrinolytic factors and an important index for predicting hypercoagulability in peripheral blood. Moreover, chronic stresses such as fatigue, lack of energy have been suggested to correlate with increased t-PAI-1 levels in peripheral blood (6). After treatment with RG, significant decrease of plasma levels of β -endorphin and t-PAI-1 were observed in postmenopausal women with CS. From the viewpoint of Western medicine, many symptoms and signs of various mood disturbances in postmenopausal women have been considered to result in estrogen deficiency during climacteric. Although many studies have addressed the beneficial effects of estrogen on psychological functions, unfortunately few have been well controlled. Psychological stresses as well as estrogen deficiency may impair brain functions, especially

psychoneuroendocrine functions. Through the treatment of postmenopausal women with CS using oral administration of RG, specific effect of RG on psychoneuroendocrine functions were suggested. Thus, the effect of RG on psychological functions and levels of stress related hormones in postmenopausal women with CS were evaluated. Treatment with RG resulted in improvement of psychosomatic functions in postmenopausal women with CS as measured by CMI, STAI and SDS. Furthermore, RG caused a decrease of cortisol and increase of DHEA-S, subsequently showing a significant decrease of C/D ratio. In postmenopausal women with CS, estrogen does not appear to have a beneficial effect on psychiatric symptoms (7). Moreover, estrogen has been reported to lower serum androgen and DHEA-S levels (8). 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 dysfunctions in postmenopausal women with CS without declining serum DHEA-S levels, unlike estrogen. RG has been used as an elixir of life for more than 2000 years in Asian countries. No adverse effects have been reported about the long-term administration of RG. The dose of RG used in the present study did not result any adverse side effects. RG may be a beneficial agent for the treatment of stress burden patients such as postmenopausal women with CS.

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