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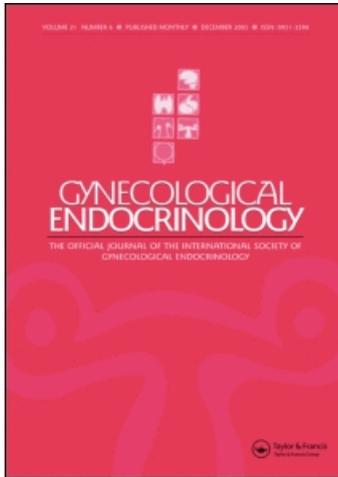
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MENOPAUSE

Cimicifuga racemosa treatment and health related quality of life in post-menopausal Spanish women

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Abstract

Objective. The effect of *Cimicifuga racemosa* (CR) treatment was evaluated in healthy symptomatic post-menopausal women using the Cervantes health-related quality of life (HR-QoL) scale.

Design. A prospective observational study was carried out in 122 healthy symptomatic post-menopausal Spanish women with elevated body weight, aged between 45 and 59 years. Three groups were formed according to age intervals. Each patient completed the Cervantes HR-QoL scale before and after CR treatment (20 mg, twice a day for 3 months). Changes in Cervantes scale global quality of life scores as well as in their domains (menopause and health, psychic, sexuality and couple relationship) were analysed.

Results. The CR treatment ameliorated global quality of life in both the whole group of patients and when women were analysed by age subgroups. There were significant positive changes in Z scores for the Cervantes HR-QoL scale 'menopause and health', and 'psychic' domains in both the entire population and by age groups. The 'sexuality domain' significantly improved when the entire population was assessed, but not when each age-group was separately analysed; while there were no changes in 'couple relationship domain' scores.

Conclusion. CR treatment increased both global quality of life and the four domains of the Cervantes HR-QoL scale, being an effective treatment to reduce symptoms in post-menopausal woman with elevated body weight.

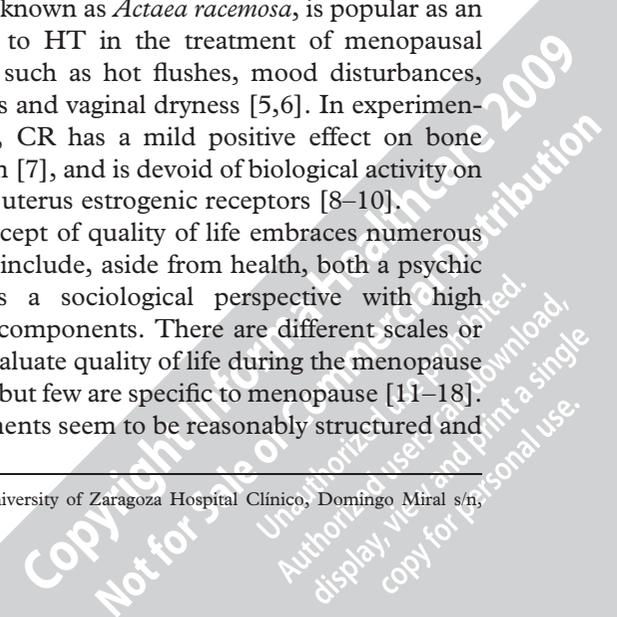
Keywords: *Quality of life, Cervantes Quality of Life Scale, Cimicifuga racemosa, menopause, black cohosh, post-menopausal women, overweight, obesity*

Introduction

The menopause years are associated with symptoms and complaints that interfere with the biopsychosocial woman's life. Hormone therapy (HT), psychotropic drugs and botanical preparations have been proposed to treat menopause-related discomfort. Although the effectiveness of HT in alleviating symptoms is well proven, known side effects include withdrawal bleeds, breast tenderness, fluid retention, weight gain and headaches. Moreover, it may also carry its own increased risks, including breast and genital cancer, cardiovascular disease and thromboembolic disease [1–4]. The optimal treatment of climacteric symptoms would require efficacy and safety. Herbal therapeutics is gaining interest as an alternative to

hormones, since HT is no longer recommended as first-line therapy. The extract of *Cimicifuga racemosa* (CR), also known as *Actaea racemosa*, is popular as an alternative to HT in the treatment of menopausal symptoms such as hot flushes, mood disturbances, palpitations and vaginal dryness [5,6]. In experimental studies, CR has a mild positive effect on bone metabolism [7], and is devoid of biological activity on breast and uterus estrogenic receptors [8–10].

The concept of quality of life embraces numerous facets that include, aside from health, both a psychic as well as a sociological perspective with high subjective components. There are different scales or index to evaluate quality of life during the menopause transition, but few are specific to menopause [11–18]. All instruments seem to be reasonably structured and



have their place in applied research, although they are not available in different languages. Any evaluation should contemplate different aspects, including the physical, social and emotional domains, thereby allowing the evaluation of possible benefits or risks from different recommendations and therapies. Some quality of life scales only assess the climacteric aspects while the subjective and cultural components are not included, thus being of limited value. The Cervantes health-related quality of life (HR-QoL) scale is a simple, easy to apply, specific instrument for measuring quality of life during the menopause years, endorsed by the Spanish Menopause Society. It consists of 31 items that evaluate the quality of life in relation to health, symptoms of menopause and other aspects such as emotions, couple relationships and sexuality [13,18]. Menopausal status and body weight excess had a significant effect on women's quality of life, since post-menopausal women with elevated body mass index (BMI) have more limitations in social activity and less vitality than lean women [19,20]. Overweight and obese post-menopausal women have increased risk of heart disease, hypertension, diabetes, cancer, osteoarthritis and mental health problems. In addition, women with high BMI have an increased risk for moderate to severe hot flushes compared to women with low BMI [15,21]. Since the scarce information concerning the CR effects on quality of life in women with elevated BMI, this study assessed the effect produced by CR in symptomatic post-menopausal women as evaluated by the Cervantes HR-QoL scale.

Materials and methods

Healthy symptomatic Spanish post-menopausal women, aged between 45 and 59 years, with at least 12 months of amenorrhea and with mild to severe hot flushes were prospectively studied. The study was approved by the Institutional Board Review of the 'Hospital La Fe' in Valencia as an observational study of 150 patients, and women signed an informed consent form as a necessary requisite for their enrolment in the study. Patients were recruited from gynaecologic consultations if they have climacteric symptoms, would benefit from the use of CR treatment, and expressed their desire to take part in

the study. Patients were excluded if they had gynaecological surgery in the last 6 weeks, a history of hypersensitivity to CR, cardiac, renal or liver pathology, or any other serious illness. Women were not selected by any other criteria, and were representative of the general Spanish population, including their BMI values. General clinical characteristics are given in Table I. The final analysis included 122 patients who gave their informed consent, and completed the Cervantes HR-QoL scale, both before and after CR treatment. This scale is a 31-item, self-reporting questionnaire, including four categories or domains: 'Menopause and Health' with 15 items including vasomotor symptoms, health and ageing; 'Psychical Domain' with 9 items; 'Sexuality' with 4 items and 'Couple Relationship' with 3 items. Patients should rate each item between 0 and 5 using a Likert scale, and item responses are summed to create a global score and four different domain scores. Global and domain higher scores denote worse quality of life than lower values, and reduction of score values after an intervention indicates amelioration of the global or a domain quality of life. The Cervantes HR-QoL scale score can range from 0 to 155 points (from better to worse quality of life), and the scores can be compared with reference values in younger women and women of the same age (*Z* score). On the process of validation of the Cervantes scale, mean value for global score was 50.73 (SD 23.89), for menopause and health was 25.1 (SD 12.83), for menopause and psychical domain was 10.81 (SD 8.30), for sexuality was 10.54 (SD 5.00) and for couple relationship was 3.91 (SD 4.17) [13,18]. Values above +2 SD over the reference score in women of the same age and educational level were considered as 'severe symptoms', between +2 SD and +1 SD were considered as 'high-problem level', between +1 SD and -1 SD were considered as 'low-medium level' of HR-QoL and values below -1 SD were considered 'good level' of HR-QoL [13].

After treatment with 20 mg of CR (Remifemin[®], Schaper & Brümmer GMBH & Co. KG- Salzgitter Germany) twice a day orally for 3 months, subjects repeated the Cervantes scale questionnaire. Changes in the overall quality of life score and in the four domains of the questionnaire were analysed. The

Table I. Patient characteristics: mean \pm SD age, weight, height, body mass index, systolic and diastolic blood pressure.

	Age (M \pm SD)	Weight (M \pm SD)	Height (M \pm SD)	BMI (M \pm SD)	SBP (M \pm SD)	DBP (M \pm SD)
Total	52.3 \pm 4.5	69.9 \pm 11.6	1.6 \pm 0.6	28.2 \pm 4.7	127.2 \pm 19.1	78.0 \pm 11.2
45-49 years (<i>n</i> = 35)	48.3 \pm 1.6	68.1 \pm 12.6	1.6 \pm 0.1	26.9 \pm 4.4	121.0 \pm 16.4	76.2 \pm 11.4
50-54 years (<i>n</i> = 54)	51.5 \pm 1.4	68.7 \pm 12.1	1.6 \pm 0.5	27.5 \pm 4.8	123.8 \pm 18.2	78.4 \pm 11.3
55-59 years (<i>n</i> = 33)	56.6 \pm 1.5	69.2 \pm 10.7	1.6 \pm 0.6	28.3 \pm 4.3	128.3 \pm 20.2	78.6 \pm 11.1

There were no significant differences among age groups.

M, mean; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

analysis was carried out using the statistical program SPSS 11.0. The *t*-Student test was used for comparison of the quantitative variables, and the Chi-square test for qualitative variables. Statistical significance was considered for a $p < 0.05$.

Results

Patient demographic characteristics and relevant medical data are shown in Table I. They were representative of the general population, and as a group had an elevated mean BMI. The majority of patients belonged to the age group of 50–54 years. There were no significant differences among the variables when women were classified in three age groups, and CR treatment did not induce any significant change as compared with baseline values.

The mean scores (initial and after CR treatment) of the answers to the items of the Cervantes scale are shown in Table II. Overall quality of life scores significantly improved in women of all ages during CR treatment. There were significant positive changes in *Z* scores for the Cervantes HR-QoL scale ‘menopause and health’, and ‘psychic’ domains in both the entire population and in age groups. The ‘sexuality domain’ significantly improved when the entire population was assessed, but not when classified in three age

groups; while there were no changes in ‘couple relationship domain’ scores after CR treatment.

Discussion

Menopause is influenced by sociodemographic, psychosocial, culture and lifestyle factors [11–19]. Different studies have demonstrated that menopause supposes a deterioration in the quality of life [13,14,22]. Over the last years, it has become more frequent that studies incorporate this information as an instrument to assess the action of pharmacological, lifestyle or other interventions [23]. The assessment of menopause requires a variety of validated instruments to capture its influence in different populations, under different conditions and for a variety of outcomes. The Cervantes quality of life scale score creates a patient profile that can be used for clinical evaluation as well as when taking decisions. The instrument has been used in relation with the general population, for comparative purposes in obese and non-obese menopausal women, to study the metabolic syndrome, and to determine women’s perception of soy extract effects on climacteric-related symptoms [13,18,26,27]. In the present study, we used the Cervantes scale to evaluate healthy post-menopausal women with elevated body weight who complained to have hot flushes and received CR treatment.

Hot flushes often begin before menopause, tend to peak within 2–3 years after menopause, and lessen thereafter. But the range of patterns among menopausal women is quite diverse [28,29]. Previous results indicated that a higher percentage of body fat was associated with increased odds of reporting vasomotor symptoms in age- and site-adjusted models [15,21,29]. Recent studies suggest that hot flushes are triggered by small increases in the core body temperature, and that excess fat makes it more difficult for the body to dissipate heat.

In addition, obesity may be associated with hot flushes through mechanisms involving multiple hormones and sex hormone binding globulin [21]. Severe hot flushes are associated with chronic insomnia, increased blood pressure, mood disorders and decreased cognitive function that reduces quality of life [28–31]. In our present study, the whole population as well as age subgroups had elevated mean body weight values, and were representative of the Spanish general population [18,32]. Although Llana et al. [18] reported similar quality of life in post-menopausal women with elevated body weight, overweight and no-obese, other studies showed the opposite and firm conclusions are not possible since the lack of linear relationship between BMI and quality of life [15,19,33].

CR is indicated to treat menopause vasomotor and psychic symptoms due to its effects on the central

Table II. Mean scores (initial and after CR treatment) of the global and four domains of the Cervantes scale.

	Initial score (Mean ± SEM)	Final score (Mean ± SEM)
Cervantes scale global score		
Total ($n = 122$)	1.39 ± 0.08	0.64 ± 0.07*
45–49 years ($n = 35$)	1.46 ± 0.15	0.56 ± 0.15*
50–54 years ($n = 54$)	1.47 ± 0.11	0.75 ± 0.11*
55–59 years ($n = 33$)	1.25 ± 0.17	0.56 ± 0.13*
Menopause and health domain		
Total ($n = 122$)	1.58 ± 0.07	0.59 ± 0.07*
45–49 years ($n = 35$)	1.62 ± 0.13	0.53 ± 0.14*
50–54 years ($n = 54$)	1.57 ± 0.10	0.59 ± 0.11*
55–59 years ($n = 33$)	1.61 ± 0.15	0.63 ± 0.14*
Psychic domain		
Total ($n = 122$)	0.83 ± 0.08	0.37 ± 0.07*
45–49 years ($n = 35$)	0.97 ± 0.17	0.39 ± 0.16*
50–54 years ($n = 54$)	0.84 ± 0.11	0.40 ± 0.11*
55–59 years ($n = 33$)	0.79 ± 0.18	0.33 ± 0.16*
Sexuality domain		
Total ($n = 122$)	0.62 ± 0.08	0.49 ± 0.07**
45–49 years ($n = 35$)	0.59 ± 0.20	0.32 ± 0.16
50–54 years ($n = 54$)	0.81 ± 0.11	0.71 ± 0.11
55–59 years ($n = 33$)	0.38 ± 0.16	0.30 ± 0.13
Couple relationship domain		
Total ($n = 122$)	0.66 ± 0.08	0.60 ± 0.08
45–49 years ($n = 35$)	0.58 ± 0.17	0.42 ± 0.16
50–54 years ($n = 54$)	0.84 ± 0.14	0.84 ± 0.13
55–59 years ($n = 33$)	0.46 ± 0.15	0.36 ± 0.15

SEM, Standard error of the mean.

* $p < 0.001$ as compared to initial score.

** $p < 0.05$ as compared to initial score.

nervous system [5,6,33]. In the present study, CR treatment was associated with a significant improvement in global Cervantes HR-QoL score in post-menopausal women with elevated BMI. This intervention was not associated with changes in body weight. Quality of life improvements were quantified by global *Z* score reductions. We also found significant improvements in both the menopause and health domain and the psychic domain in both the whole studied population and in the three age groups. These results are concordant with those from Nappi et al. [34]. However, Osmer et al. [6] found a psychic improvement only in those patients with less than 3 years since the beginning of the symptoms, and the effectiveness of CR diminishes with years of menopause. A significant improvement in sexuality domain was associated to CR treatment in the entire population, but not in age groups probably due to the small number of cases; while there were no changes in the couple relationship domain scores. Since CR had no effects on vaginal epithelium, endometrium or reproductive hormones [35], our finding may be mainly related to a general neuronal effect of CR as a partial serotonin agonist at the receptor level [36], and to a dopaminergic action [6]. These mechanisms may explain the detected amelioration in both neurovegetative symptoms – such as flushes or sweats – and psychological symptoms – such as nervousness, irritability and sleep disorders – which affect the quality of life in post-menopausal women. Physical changes in quality of life as measured by the menopause and health domain, and on psycho-sexual aspects as measured by the psychic and sexuality domains, were improved in all age subgroups.

We are conscious of the limitations of a HR-QoL study and the difficulties involved in the interpretation of our data due to the problems associated with conducting and reporting subgroup analyses which can lead to overstated and misleading results. Other possible implications for data evaluation are the fact that samples were taken from gynaecological consultations and that women are a sample of urban, healthy, post-menopausal women. Considering these limitations, our data suggest that CR seems to be an acceptable option for the treatment of climacteric complaints which may deteriorate quality of life in post-menopausal women with elevated body weight. Although there are some controversial results, CR decreases climacteric complaints, has some antiproliferative effects, and is safe [6,7,9,34,35,37]. Its effectiveness has been evaluated in controlled as well as in uncontrolled trials. In a randomised, double blind study, the CR extract was as effective as equine conjugated estrogens in reducing menopausal symptoms, and also produces a reduction in anxiety and depression as determined with the Menopause Rating Scale [38]. In a prospective randomised study carried out in symptomatic menopausal women,

Nappi et al. [34] demonstrated that CR reduces the number of flushes and vasomotor symptoms at a similar level to that obtained with 25 µg/day of transdermal estradiol plus 10 mg/day of dihydrogesterone, as evaluated with the Greene scale. In symptomatic menopausal women, Osmer et al. [6] demonstrated that the effectiveness of a 12-weeks CR treatment was greater as compared with placebo. The authors also evaluated four subscores (flushes, psyche, soma and atrophy), being the treatment most useful for flushes. In post-menopausal women treated with either fluoxetine or CR, the Kupperman Index decreased significantly under CR treatment as compared with the fluoxetine group by the end of the third month, whereas scores for hot flushes and night sweats significantly decreased in both groups [39]. However, CR reduced hot flushes and night sweats scores to a greater extent than did fluoxetine. The present study demonstrated that CR produced measurable benefits in climacteric complaints and quality of life in post-menopausal women with elevated body weight, which are considered as a high risk population to suffer hot flushes. The changes can be detected with the Cervantes HR-QoL scale. However, placebo effect cannot be ruled out by this treatment, moreover if observational design has been used.

Phytotherapy has been questioned due to a possible placebo effect [40]. The impact of placebo effect may be included in the assessment of symptoms and functional impairments or improvements where subjectivity, expectancy and motivation may significantly impact outcome evaluation. This phenomenon is also present in the conventional pharmacological interventions [41,42]. Nevertheless, it has been said that to induce a placebo effect to reduce discomfort associated to hot flushes might be helpful [43]. Thus, in some way the placebo effect is a part of the therapeutic effect. It is plausible that the strong affective component in high selected and motivated population, like in the present study, may have some bias. Further studies are needed to confirm the present results, and the effects of CR in longer duration treatment in post-menopausal women with the same cultural background. Prevention and early treatment of overweight and obesity are crucial to ensure health to post-menopausal women.

It can be concluded that the Cervantes scale allows the detection of changes in HR-QoL in post-menopausal women under CR treatment, and open a new avenue to use this instrument in other clinical interventions. Furthermore, quality of life was significantly improved by CR therapy system in post-menopausal women with elevated body weight. In all cases women's perception about their climacteric symptoms showed a significant improvement with CR treatment.

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