

A Preliminary Phase-2 Study with the Pineal Hormone Melatonin, Centaurea Cyanus, and Magnolia Officinalis in the Treatment of Menopausal Women and on its Effects on Gonadotropin Secretion

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ABSTRACT

The recent advances in the knowledge of the endocrinological changes occurring during the menopause have shown that the reduced production of estrogens is not the only menopause-related deficiency, since at least that in the production of the pineal hormone melatonin (MLT) has to be considered. In fact, preliminary clinical studies have shown that the substitutive therapy with MLT at doses ranging from 3 to 5 mg/day may have some benefits in the treatment of the postmenopausal symptomatology. On these bases, a phase 2 study was planned in 14 menopausal women with MLT at higher doses with respect to those previously reported in the literature, consisting of 10 mg once day during the night, in association with Centaurea Cyanus tincture because of its estrogenic content, and with honokiol (500 mg/day) because of its anti-osteoporotic activity. A progressive resolution of most menopause-related symptoms was achieved in 9/14 (64%) women. FSH serum mean levels significantly decreased under MLT therapy, even though a decline greater than 30% was observed in only 5/14 (36%) women. On the contrary, a decrease in LH concentrations greater than 30% was achieved in 10/14 (71%) women. In conclusion, in agreement with previous clinical investigations, this study confirms the efficacy of MLT therapy in the treatment of most menopausal symptoms, which may be enhanced by the concomitant administration of Centaurea Cyanus and honokiol, by justifying further clinical researches with higher doses of MLT, in particular too achieve a better control of FSH secretion, because of its potential pro-tumoral activity and its involvement in the pathogenesis of ovarian cancer.

Key words: FSH, LH, Melatonin, Menopause, Post-menopausal syndrome.

INTRODUCTION

Menopause is defined as the final menstrual period, resulting from the depletion of ovarian follicular function, with a consequent decline in estradiol levels. Generally, it is common opinion that menopausal symptomatology may substantially depend on the only estradiol deficiency following the exhaustion of ovarian follicles. In addition, hot flashes, which is the expression of a vasomotor condition, could be due to a direct action of the menopause-related abnormally enhanced gonadotropin levels at the hypothalamic temperature center. Because of the

cardiovascular protective activity of estradiol, the decline in its endogenous production would be responsible for the enhanced frequency of systemic pathologies in postmenopausal women, particularly the cardiovascular ones. Estradiol may exert a cardiovascular protective action by stimulating ACE2-Angiotensin (Ang 1-7) axis (1), which plays cardioprotective, anti-thrombotic, and anti-atherosclerotic effects (2). However, most recent clinical investigations have shown that menopause is characterized at least by another endocrine deficiency, consisting of the pineal hormone melatonin (MLT) (3-7), which is mainly released during the night and also plays a cardioprotective activity (9). MLT exerts a fundamental role

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DOI: 10.33309/2638-7697.040202

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in the regulation of the biological rhythms, and their relation with sleep and mood (9). Then, sleep and mood disorders characterizing the menopausal syndrome may depend on at least in part on the progressive MLT deficiency. Moreover, the evident decline in MLT night blood concentrations would represent the main endocrine difference between premenopausal and postmenopausal women in addition to the increase in gonadotropin levels (3-7). All studies on MLT therapy of menopause syndrome have been performed by using low-dose MLT, such as 3 mg/day in the night (3-7), and in any case all authors agree on the capacity of MLT to improve the climacteric syndrome and the quality of life of postmenopausal women, particularly sleep disorders and mood changes (3-6). As far as the gonadotropin menopausal profile, either no correlation (5), or a negative correlation have been observed between FSH and MLT blood concentrations (3,7). The importance of declining FSH blood levels in the postmenopausal women is related to its potential stimulatory action on ovarian epithelium cell proliferation and on tumoral neo-angiogenesis (8), with a following potential increase in ovarian carcinoma risk, whose frequency in effect enhances during the postmenopausal period. Moreover, the expression of FSH receptor by cancer cells has appeared to predict a more aggressive tumor growth in both ovarian cancer and other gynecologic neoplasms, as well as also in non-gynecologic tumors, such as prostate cancer (8). Then, FSH could be considered a non-specific tumor growth factor for several neoplasms, at least in experimental conditions. Therefore, the control of FSH increase occurring during the postmenopausal period could deserve an important role in the prevention in particular of the ovarian cancer (8), and perhaps of other tumor histotypes. On the contrary, the potential pro-tumoral action of LH of ovarian cancer is more controversial (8). MLT has appeared to decline FSH blood levels in a relevant number of postmenopausal women, particularly in those with low levels of MLT itself (3), and this inhibitory action on FSH secretion could be a dose-dependent phenomenon. Osteoporosis is another important symptom of menopause period, and at present there is no standard treatment. Within the phytotherapy approach in the treatment of human diseases, Magnolia plant has been proven to contain molecules, such as honokiol, provided by anti-osteoporotic activity, due to inhibition of osteoclast generation and activation (10). Honokiol has also been important to exert important antidepressant activity (10). A potential anti-osteoporosis activity may be also exerted by MLT itself (4). Finally, natural agents provided by estrogenic activity may be contained within several plants, particularly by the Centaurea Cyanus, which could be employed instead of other most common natural agents. Therefore, according to the previous studies with MLT in postmenopausal women, the present preliminary study was carried out to evaluate the effects of MLT at higher doses with respect to those previously

reported in the literature (3-6), and in association with Magnolia to counteract the onset of osteoporosis, and Centaurea Cyanus to replace the deficiency of estrogenic molecules occurring with the onset of the menopausal period.

SUBJECTS AND METHODS

The study included 14 consecutive women, who recurred to their Medical Service for important menopause-related symptoms. Eligibility criteria were, as follows: laboratory evidence of abnormally high levels of FSH and LH, and important menopause-related symptoms consisting of the presence of at least one of the following symptoms, hot flashes, sleep disorders, and mood depression, and no other concomitant therapy for the menopausal syndrome. After the approval of the Ethical Committee, the clinical protocol was explained to each woman, and written consent was obtained. The treatment was promptly started at the beginning of symptoms, or in the case of a persistent menopausal symptomatology. Serum levels required to establish the diagnosis of menopause in our laboratory (95% confidence limits) for FSH and LH were respectively above 25 mIU/ml and 16 mIU/ml. The characteristics of women on study and their symptomatology are reported in Table 1. MLT was given at a dose of 10 mg/day in the dark period of the day since recently controversial benefits have been referred with MLT doses lower than 5 mg/day (11). Honokiol was given orally at a dose of 500 mg/day in the morning. Finally, Centaurea Cyanus was administered as a tincture at a dose of 20 drops twice/day (8 AM and 8 PM). FSH and LH were detected before and after two months of treatment. Serum levels of gonadotropins were measured in duplicate by using commercially available kits. Data were reported as mean +/- SE, and statistically analyzed by the chi-square test, the Student's t test, and the analysis of variance, as appropriate.

Table 1. Clinical characteristics of 14 postmenopausal women treated with melatonin, Centaurea Cyanus, and Magnolia

MEDIAN AGE (years)	53 (range 50-59)
FREQUENCY OF MAIN SYMPTOMS	
- Hot flashes	11/14 (79%)
- Sleep disorders	9/14 (64%)
- Anxiety	6/14 (43%)
- Mood depression	4/14 (29%)

RESULTS

A progressive improvement of the symptomatology until the complete resolution of the main menopause-related symptoms

was achieved in 9/14 (64%) women. A decline greater than 30% in FSH levels was observed in only 5/14 (36%) women, while a decline greater than 30% in LH values was achieved in 19/14 (71%) women. The difference was statistically significant ($P < 0.05$). FSH and LH serum mean levels before and after 2 months of treatment are illustrated in Figure 1. As shown, serum mean levels of FSH significantly decreased on therapy ($P < 0.025$), and the decline in LH mean concentrations was more significantly evident ($P < 0.01$). In any case, no significant difference was observed in the clinical efficacy of therapy in terms of resolution of menopausal symptoms between women with an evident decline in FSH levels and those who had no FSH important decrease (3/5 (60%) vs 6/9 (67%)).

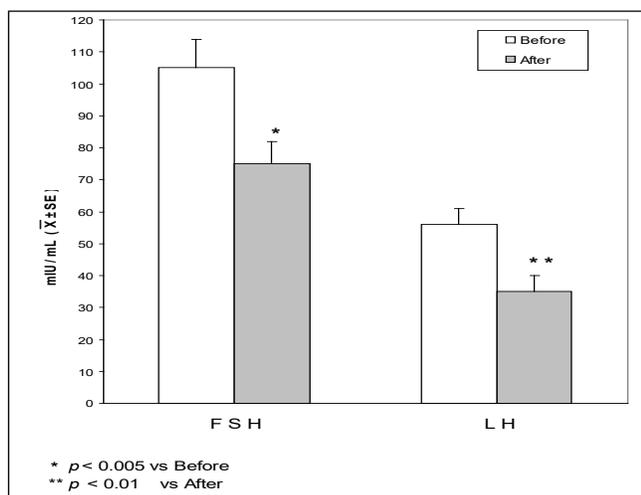


Fig 1. FSH and LH serum levels in menopausal women before and after 2 months of melatonin therapy.

DISCUSSION

According to the results of previous clinical studies (3-7), which have been recently confirmed by a systematic review and meta-analysis of the medial literature (12), the present study confirms that the pineal hormone MLT at relatively low pharmacological doses may be effective in the treatment of most menopause-related symptoms in a considerable number of women. MLT-induced improvement of mood could be also amplified by the concomitant administration of Magnolia, because of its antidepressant and anti-stress properties (9). The importance of MLT replacement therapy in postmenopausal women is also justified by the evidence that the common hormonal substitutive therapy may further delayed the nocturnal increase in MLT levels (13). Same considerations may be proposed for the premenopausal phase, since the postmenopausal period would be simply characterized by a further decline in MLT levels with respect to that already occurred with the onset of the premenopausal symptoms,

including anxiety, sleep and mood disturbances (14). As far as the influence of treatment on gonadotropin secretions, few months are sufficient to obtain endocrine effects. In more detail, MLT administrations tends to exert an inhibitory action on gonadotropin secretion in menopausal women, but this inhibitory action is more evident for LH than for FSH, whose decline was observed in only less than half women. Then, the inhibitory action of MLT on FSH secretion could be a dose-dependent phenomenon, and it would increase with increasing MLT doses. In any case, further clinical studies would have to include the determination of anti-mullerian hormone (AMH), which represents the best predictor of time of menopause (15). In addition, because of the inhibitory action of PRL on gonadotropin secretion and the influence of MLT on PRL secretion itself (9), further studies will have to include also PRL detection to exclude that MLT effects of gonadotropin production may be mediated by PRL. Centaurea cyanus tincture was particularly appreciated by women, probably for its mystic symbolic significance by consisting of the flower that in the popular imagination represents the symbol of God's Mother, with a following unconscious stimulation of positive psychic reactions. Finally, the influence of Magnolia on menopause-related osteoporosis needs to be established by longitudinal studies and by monitoring the bone mineral density. Moreover, more recent studies have shown that in addition to the two main menopause-related endocrine deficiencies, consisting of estradiol and MLT diminished secretion (3-7), the postmenopausal period is also characterized by a progressive decline in the neuro-hypophyseal secretion of oxytocin (16), which could deserve important therapeutic implications in the treatment of both cardiovascular and menopause disorders, because of its cardioprotective activity, and its fundamental role in the regulation of the affective and sexual life (17). Therefore, further studies will be required to establish whether the concomitant administration of oxytocin in addition to MLT and estrogenic molecules, could further improve the clinical benefits of therapy on the quality of life of women. Moreover, further clinical studies will be needed to establish whether the same regimen of therapy may be also effective in the treatment of the postmenopausal syndrome, whose complexity could be superior to that of menopause itself. Finally, because of the stimulatory action of estradiol on brain cannabinoid system (18), which plays a fundamental role in the perception of pleasure and in the amplification of consciousness status (19), menopause could be also characterized by an endocannabinoid deficiency, which could justify the use of anti-anxiety cannabinoid agents, such as cannabidiol (CBD) or cannabigerol (CBG) (19,20), in the treatment of menopause disturbances. Then, it will be also necessary to establish which cannabinoid agent may play more benefits in the therapy of both pre- and postmenopausal symptoms, by investigating the endocrine and neuropsychological effects, and particularly by comparing the

action of CBD with respect to CBG.

CONCLUSION

In conclusion, this study confirms that the postmenopausal period is not an irreversible condition, since it may be improved by correcting the main menopause-related endocrine deficiencies, which cannot be limited to the only estrogens, but they must include at least still now the pineal hormone MLT, and perhaps in the future oxytocin and cannabinoids themselves.

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How to cite this article: Lissoni P, Zecchinato F, A Preliminary Phase-2 Study with the Pineal Hormone Melatonin, Centaurea Cyanus, and Magnolia Officinalis in the Treatment of Menopausal Women and on its Effects on Gonadotropin Secretion. *Clin Res Obstet Gynecol* 2022;4(2):06-09.
DOI: 10.33309/2638-7697.040202