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RESEARCH ARTICLE

BIOHORMONAL THERAPYIN EARLY MANAGEMENT OF PREMATURE MENOPAUSE AND ANDROPAUSE

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ABSTRACT

One of the most important chapters of anti-aging and preventive medicine is early recognition and management of premature menopause and andropause. Conventionally these conditions are treated with HRT – hormone replacement therapy. It is proven that HRT carries various risks, such as breast cancer, cardiac hypertrophy, etc. The current article proposes reversal of the hormonal changes occurring in premature menopause and andropause by direct stimulation of the entire chain of endocrine organs' activity with organ specific peptide therapy.
Endocrine stimulation was done via administration of combination of organo-peptides specific to hypothalamus, pituitary gland, adrenals, ovaries or testicles and liver. After 4 months of peptide therapy the promising results were achieved. Biomolecular therapy demonstrated high efficacy and safety, as no side effects or adverse reactions were observed.

INTRODUCTION

Reduction of sexual hormonal expression can be rightfully considered as the main cause for early aging. It affects approximately 1% of the female population and up to 7% of the male population [1, 2].

Premature menopause is defined as decline of ovarian physiologic activity with increased gonadotropin levels and estrogen deficiency occurring before the mean menopausal age of the population [1, 3]. Genetics, life-style, specific infections and previous illnesses, certain medical procedures, and environmental factors are the leading etiologic factors of premature menopause and andropause development.

Premature menopause is clinically manifested with altered menstruation, hot flushes, vaginal dryness, irritable bladder, reduced libido and sexual dysfunction, sleep disorders, psychological and emotional disturbances. Apart from clinical manifestations diagnostic criteria is reduction of serum estradiol level to 30pg/ml and below with simultaneous elevation of Follicle Stimulating Hormone (FSH) above 40mIU/ml. The long term consequences of premature menopause include infertility, osteoporosis, increased risk of cardiovascular and cerebral vascular events, and premature death [1, 3, 4].

Unlike menopause, premature andropause is characterized by insidious onset and slow progression. In men, testosterone level declines with aging at the rate of 1% per year. The rate of decline in testosterone levels is affected by chronic diseases, obesity, emotional and environmental stress, and medical procedures. Premature andropause is often associated with depression, decreased libido, erectile dysfunction, dyslipidemia, diabetes and other endocrine disorders, increase of waist circumference, obesity, osteopenia, and loss of muscle bulk. The diagnostic criteria is presence of at least three clinical symptoms and reduction of total testosterone level (<11nmol/L) and free testosterone level (<220pmol/L) [2, 5, 6].

Analysis of Conventional Approach To Management Of Premature Menopause And Andropause

Conventionally premature menopause and andropause are treated with Hormone Replacement Therapy (HRT). In women usually it includes supplementation or administration of

estradiol, estriol and progesterone. Most of the conducted studies have shown high efficacy of HRT in terms of alleviation of menopausal symptoms, skeletal muscle regeneration, improvements of cognitive function and prevention of osteoporosis [7, 8].

At the same time, HRT has significant risks and adverse effects. Women's Health Initiative trial (Rossouw *et al*, 2002) and the Million Women Study (Beral and Million Women Study Collaborators, 2003) have reported increased risks of breast cancer after HRT. The Breakthrough Generations Study, which recruited 113693 women in United Kingdom during 2003-2015 has shown that the relative risk of breast cancer was 3.5 for 10 years and above of HRT use [9, 10].

A large placebo-controlled HERS study has shown a 50% increased risk of coronary heart disease within a first year. More than 20 other smaller trials have suggested a 1.4-1.8 fold increase risk of coronary heart disease after a short-term estrogen HRT. Another finding of HERS trial was a 3.9 fold increase in venous thromboembolic events in women taking HRT.

Most recently obtained data confirms that standard dose HRT undoubtedly increases risks of stroke and venous thrombo-embolism, and long term risk of breast cancer [11].

A PEPI trial has reported an increased risk of both breast cancer and increased endometrial hyperplasia that also caused precancerous conditions in some women at a rate of 10% per year [9].

Regarding the low testosterone levels, it has been established a while ago that it predicts an increased mortality in a long term. Testosterone replacement therapy is able to reduce mortality to 8.4% compared with the untreated group's 19.2%. It has been suggested also that testosterone may improve survival rates for men with type 2 diabetes. Testosterone HRT is also used to treat men with HIV/AIDS, because those suffering from HIV/AIDS have a tendency towards low testosterone levels. Multiple reports support positive effects of testosterone in management of metabolic syndrome, diabetes type II, and even anemia [12].
Testosterone HRT may be helpful for treatment of anxiety, psychological stress and depression. Studies on HRT with testosterone for hypogonadism have shown significant improvement in sexual function, mental and cardiovascular status in the treated group.

On the other hand one of the studies has concluded that testosterone HRT may cause a negative effect in terms of worsening of blood pressure readings in men [13]. Although there is no conclusive data supporting that testosterone treatment increases risks of prostate cancer, there is a strong data that testosterone HRT can worsen the existing locally advanced and metastatic prostate cancer.

Other report suggests that therapy with androgens may stimulate development of cardiac hypertrophy and modulate cardiac phenotype [13, 14].

Novice Therapeutical Strategies In Management Of Premature Menopause And Andropause

The scientific progress in biomolecular research in past few decades has opened new prospects for gene and cell therapy applications in various endocrine disorders.

Premature menopause and andropause, when considered from the endocrinology's point of view, is characterized asa subnormal hormone production due to endocrine hypo function. Research advancement in molecular technology has opened the possibility of correcting these defects. Results of decades of scientific exploration and clinical experience exhibit the ability of cellular therapy to exert regulatory and stimulatory effects on the endocrine system [15, 16]. Historically, there are many examples with successful outcomes of cell therapy with anterior lobe of pituitary gland for primary amenorrhea, testicular peptides for male revitalization, ovarian peptides for dysmenorrhea, posterior lobe of pituitary gland for diabetes insipidus, and many more [17].

The initial concept of hypothalamo-hypophyseal relationship and its controlling function over the target endocrine glands, including gonads, has being elaborated by Guillemin and Rosenberg (1955). Since then, the multiple experiments and studies regarding effects of hypothalamus and pituitary gland cellular therapy on the functional activity and maturity of gonads were done.

Based on extensive European experience of cellular therapy application in treatment of endocrine disorders, we have elaborated the idea of prevention and reversal of dishormonal changes occurring in premature menopause and andropause by direct stimulation of gonadal activity and hormone production by organ specific peptide therapy (SBI, MF+).

The **objective** of the study was to assess efficacy of biohormonal therapy using a combination of specific peptides-extracts (Mito Organelles™, MF+, Germany) from hypothalamus, pituitary gland, adrenals, ovaries or testicles and liver in early management of premature menopause and andropause.

MATERIALS AND METHODS

The observed group consisted of 5 men (age 37-49 y.o.; mean age - 43.6 y.o.) and 5 women (age 35-45y.o.; mean age – 39.4 y.o.).

The inclusion criteria in female subgroup were: minimum of three clinical symptoms of premature menopause; reduction of serum estradiol level below 30pg/ml with simultaneous elevation of FSH above 40mIU/ml in at least two biochemical laboratory tests with one month interval. The inclusion criteria for male subgroup were: presence of minimum three symptoms of hypogonadism associated with at least three biochemical laboratory results of total testosterone level less than 11nmol/L and serum free testosterone level below 220pmol/L obtained with one month interval.

The exclusion criteria were: premature menopause or andropause due to chromosomal abnormalities, surgical removal of gonads, pelvic tuberculosis, and history of radiotherapy or drug-induced ovarian or testicular suppression.
Female subgroup received peptide therapy in a form of combination of extracts from Hypothalamus, Pituitary gland, Adrenal cortex, Ovaries and Liver (Mito Organelles™, MF+, Germany).

Male subgroup received peptide therapy in a form of combination of extracts from Hypothalamus, Pituitary gland, Adrenal cortex, Ovaries and Liver (Mito Organelles™, MF+, Germany).

The above mentioned combination of peptides was administered intramuscular (2.5 ml × 5) twice per week with total duration of 4 months.

After the completion of protocol clinical symptoms were reevaluated. Laboratory hormone level investigations were repeated upon completion of the treatment protocol and 3 and 6 months after.

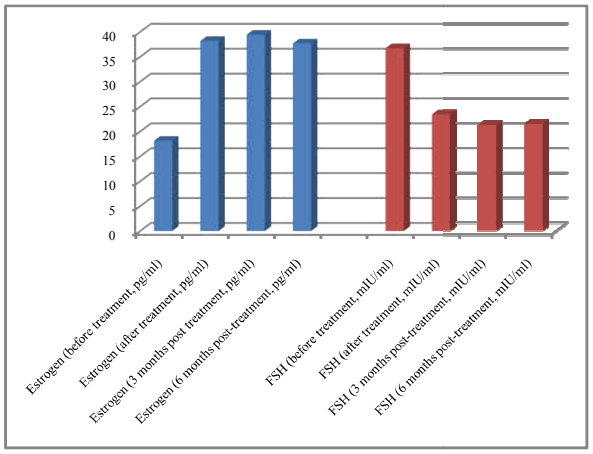
OBTAINED RESULTS OF THE STUDY

Upon initial presentation the basal level of serum estradiol in the female subgroup varied from 15 to 22pg/ml, with the mean level of 18.2±0.2pg/ml. The FSH level varied from 43 to 47mlU/ml, with mean FSH level of 44.8±0.5mlU/ml.

In the end of the 4th month of therapy with organ-specific peptides Mito Organelles™ (MF+, Germany) 4 out of 5 women had nearly complete disappearance of clinical signs of menopause that they had during initial presentation. Such improvements corresponded to changes in serum hormone's levels. The serum estradiol level in 4 women with good clinical response upon completion of the protocol was in the range 35-41pg/ml (mean serum estradiol level 38.25±0.5pg/ml; $p<0.05$) and serum FSH level 21-26mlU/ml (mean serum FSH 23.5±0.25mlU/ml; $p<0.05$) (graph 1).

One female participant had no clinical improvements and changes in serum estradiol and FSH levels before and after the treatment protocol had no significant difference.

The repeated examinations 3 and 6 months after the end of the treatment protocol has shown a stable effect in those 4 female volunteers who had good clinical response, however still neither clinical, no biochemical response noted in the fifth volunteer.

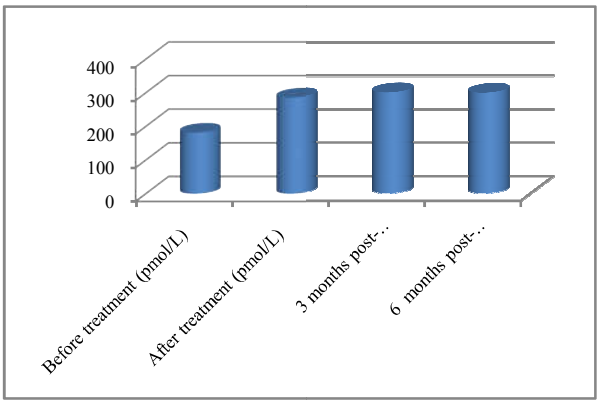


Graph 1 Changes in serum estradiol and FSH levels in the 4 out of 5 female volunteers who responded to treatment

Initial levels of total testosterone in the male subgroup varied in the range between 7 to 10nmol/L (mean level 9±0.5nmol/L), free testosterone – between 172 to 195pmol/L (mean level 182±1.2nmol/L).

Dramatic clinical improvements after the proposed treatment protocol were noted in all 5 male volunteers. All observed men noted significant increase of libido, improvement of sexual function, increase of energy level and better physical performance. Mean total testosterone level increased to 18.6±0.2nmol/L ($p<0.05$) and mean free testosterone level increased to 286.2±2.5pmol/L ($p<0.05$).

During the follow-up 5 out of 5 male participants had demonstrated a stable clinical and biochemical effect from the proposed treatment protocol with Mito Organelles™ peptides. Serum testosterone levels were maintained within the normal range half year after the completion of the treatment (graph 2).



Graph 2 Changes in the serum free testosterone levels in the observed men (n=5).

DISCUSSION

Indeed, premature menopause and andropause present a particular challenge for medical practitioner. HRT possesses substantial risks that gradually increase with the duration of therapy. The main concern of medical researchers is to reduce those risks. Biohormonal therapy with organ-specific peptides is based on modulation of endocrine function and past experience of such therapies has proven its potential.

The proposed protocol includes combination of extracts from hypothalamus, pituitary gland, adrenal cortex, gonads and liver (Mito Organelles™, MF+, Germany) and is addressing to all levels of sexual hormones synthesis by modulating the function of the targeted organs. The current observational pilot study has shown that four months of peptide therapy targeting endocrine function in individuals with premature menopause and andropause have brought dramatic improvement of symptoms and normalization of hormonal profile in 80% of women and 100% men. The reason behind one female patient not responding to the provided therapy requires further investigation and profound analysis.

No side effects or adverse reactions were observed and none of the participants had need for further use of HRT.

CONCLUSION

Although the obtained preliminary results are promising, such therapeutic approach needs further studies and analysis involving larger cohorts as well as further evaluation of late results and outcomes. However, undoubtedly the main benefit of the proposed therapy compared to conventional HRT is its safety and absence of negative risks.

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