

Role of FSH in the pathogenesis of osteoporosis

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Osteoporosis, an emerging health and socioeconomic problem, affects millions of women worldwide, with fracture rates that are higher than the combined incidence of breast cancer, stroke, and heart attacks (1). After menopause, resorption significantly exceeds formation resulting in net bone loss. Recent *in vitro* studies suggest that estrogen inhibits osteoclastic bone resorption by decreasing the release of the inflammatory cytokines from osteoblasts and T cells (2). Estrogen also directly inhibits osteoclast differentiation by acting on bone-marrow precursors (3). Therefore, despite the fact that estrogens are used in young peri and postmenopausal women for climacteric complaints and the prevention of osteoporosis, its basic actions at a cellular level are uncertain since estrogen deficiency alone does not completely explain the bone loss associated with hypogonadism.

Importance of intact Hypophysis

Recent experimental data have demonstrated that knockout mice for both estrogen receptors only present slight osteopenia, and those null for either receptor have normal bone mass (4). Furthermore, oophorectomy-induced high turnover in cortical bone is also dependent on pituitary hormones since hypophysectomy prevents bone loss in experimental models (5). This fact points out the need for an intact pituitary function for a maximum decrease in bone mass following bilateral oophorectomy. Moreover, FSH rather than estrogen correlates best with bone turnover markers in menopausal women (6). After HT, decreases in FSH correlate with gains in bone mass (7). Based on these previous data, it may be suggested that hypogonadal bone loss is due to a possible pituitary-determined mechanism.

Role of pituitary hormones beyond target organs

Recent data suggest that the action of pituitary-derived hormones is not only carried out through receptors in target endocrine glands. In previous study we demonstrated that LH suppression by a GnRH analogue results in a decrease in DHEA-sulphate synthesis (7). Other authors have verified that TSH stimulates thyroxine secretion by thyroid and suppressed bone remodelling by acting directly on osteoclasts and osteoblasts (8). In the same way FSH, an essential stimulus for estrogen production, is regulated by estrogenic feedback and recent studies have demonstrated that neither FSH nor FSH receptor null mice have bone loss despite severe hypogonadism (9). Bone mass is increased and osteoclastic resorption is decreased in haploinsufficient FSH+/- mice with normal ovarian function, suggesting that the skeletal action of FSH is estrogen independent. Furthermore, bone loss related to oophorectomy is also dependent on pituitary hormone since hypophysectomy have demonstrated a protective effect in experimental models (5).

Experience in humans

All these experimental data point out the need for an intact pituitary function for a maximum decrease in bone mass following bilateral oophorectomy, and thus, a possible pituitary-determined mechanism may play a role in hypogonadal bone loss. However, it has never been tested directly in humans whether FSH by itself might cause the osteoporosis associated with hypogonadism. Therefore, we decided to evaluate natural experimental models of congenital hyper (Pure gonadal dysgenesis and Turner's Syndrome) and hypogonadotropic (Kallmann's Syndrome) states in order to test whether pituitary function plays a role in the development of human osteoporosis. Our results establish that FSH in the human does not regulate bone loss directly in these congenital conditions. High FSH levels never go together with Turner's and pure gonadal dysgenesis. Risk factors for bone loss around menopause are not well understood. There is increasing evidence to suggest that bone loss is a process that begins prior to the onset of menopause when FSH levels start to increase (10) and FSH rather than estrogen correlates best with bone turnover markers in postmenopausal women (6). This evidence from clinical practice may explain some of the complex mechanisms related to bone loss in peri and postmenopause but they do not completely exclude the major role of hypoestrogenism in osteoporosis development. On the contrary, other recent studies, have suggested that circulating bone markers reflecting bone turnover activity are more related to endogenous estrogen levels (11) or to inhibin (12) than to FSH. It is well known that amenorrheic women with similar estrogen and FSH levels have a lower lumbar spine bone density than eumenorrheic controls (13). Recently it has been suggested that BMD was lower in hypergonadotropic amenorrheic women with high circulating FSH compared with amenorrheic females with normal or low FSH levels reinforcing the hypothesis that the greater bone loss in the hypergonadotropic amenorrheic group could have been caused by a potential direct effect of FSH on bone metabolism (14). However, in this study estradiol levels, although not significantly different, were two-fold higher in hypogonadotropic subjects. Moreover, the criteria for hyper or hypogonadotropic condition was defined considering levels of FSH ≥ 40 IU/L. This implies the potential inclusion of subjects with ovarian failure as normal or hypogonadotropic. Patients with Kallmann's Syndrome, in conjunction with hypoestrogenism, present very low plasma levels of LH, FSH and testosterone (15) and a negative progesterone withdrawal test as well as poor response to Clomiphene

citrate and inadequate gonadotropin response to the LH-RH test (16). This general status of hypogonadism in KS may explain the significantly lower BMD in all evaluated sites compared with TS and GD.

In conclusion, the hypothesis that FSH plays a major role in the development of human osteoporosis is not supported in subjects with primary amenorrhea. Thus, we speculate that low steroid levels, more than circulating FSH levels, cause bone loss in congenital hypogonadisms. Thus, at present the real effect of FSH on osteoporosis remains unclear and further studies are warranted to clarify the exact role of FSH on bone metabolism in humans and its clinical implications.

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El Dr. Camil Castelo-Branco es profesor titular de Obstetricia y Ginecología en la Universidad de Barcelona acreditado a cátedra desde 2011. Tras finalizar el periodo de residencia de la especialidad, realizó una estancia de investigación clínica en Menopausia y Endocrinología Ginecológica en el Instituto Clínico de Ginecología, Obstetricia y Neonatología del Hospital Clínic. A lo largo de su carrera, el Dr Castelo-Branco ha desempeñado diferentes puestos docentes incluyendo los de profesor colaborador, asociado y actualmente titular en el departamento de Ginecología y Obstetricia de la Universidad de Barcelona. Actualmente está trabajando en el Hospital Clínic de Barcelona como Consultor Senior (máxima categoría en el sistema de promoción profesional del Hospital Clínic) y Responsable de la Unidad de Endocrinología Ginecológica. El Dr Castelo-Branco también está interesado en la dirección clínica y procesos de gestión de los servicios de salud y hospitales, habiendo obtenido el Máster de Gestión Hospitalaria y Servicios Sanitarios por la Universidad de Barcelona en

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Sociedades: Miembro de la Junta Ejecutiva de la International Menopause Society (IMS). Miembro de la Junta Ejecutiva de la Asociación Española para el Estudio de la Menopausia (AEEM). Miembro del fundador de la AEEM. Presidente y fundador del Grupo del Osteoporosis de la Sociedad Española de Ginecología y Obstetricia. Miembro honorario de varias Sociedades de Ginecología y Obstetricia, de Menopausia y Fertilidad entre las que se incluyen la portuguesa, colombiana, argentina, peruana, gallega ... Miembro de varias sociedades científicas relacionadas con la Menopausia y la Endocrinología Ginecológica entre las que se incluyen la Sociedad Internacional de Menopausia (miembro del executive board), AEEM (miembro de la junta directiva), SEGO, Sociedad Norteamericana de Menopausia.

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Áreas de investigación: Endocrinología Ginecológica y Medicina de la Reproducción en particular las enfermedades metabólicas durante el climaterio y las edades reproductivas. Más de 230 artículos originales y revisiones en revistas nacional e internacionales indexadas (70% en revistas del primer y segundo cuartil, Factor de Impacto >20) y más de 260 conferencias en reuniones científicas nacionales e internacionales. Dr Castelo-Branco es autor de más de 120 libros y/o Capítulos del libro relacionados con la especialidad.

Are hormones the only and best tool to drive women into a healthy *gerontarche*?

by

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The climacteric woman is an aging woman. As such, our most important objective is to prevent biological aging from exceeding her chronological age, thus giving her better quality of life to her coming years and more years to live, free from preventable diseases.

Other than hormonal treatments there are today many proven strategies that e.g. prevent the shortening of the chromosomal telomeres, the markers of biologic aging. Special attention must be paid to a good quality of life, exercise to combat sedentarism, a proper nutrition, tabagism abstention, quality of sleep, relaxation, among many others.

In summary, hormonal treatments should only be prescribed for the relief of disturbing symptoms, if there are no contraindications. When they are used, they carry additional benefits *i.a.* for the prevention of cardiovascular diseases, osteoporosis, CNS diseases, etc.

Otherwise, the proper care of an aging post menopausal woman is based only on the best practice of a **Medicine**. There is no Menopausal Medicine.

Web site: <http://neves-e-castro.pt>

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Perspectives on Hormone Therapy

by
Michelle P Warren

Understanding of the use of hormone therapy has been greatly influenced by the findings of the Women's Health Initiative study published in July 2002. This study was conceived however to examine the effects of hormone therapy on chronic disease in particular heart disease. The findings on this issue are complex and influenced by the fact that most of the women in WHI were not suffering from hot flashes and were on the average older than the symptomatic women who represented the vast majority of the women on menopausal hormone therapy in clinical practice. Recent findings from WHI show striking differences between the effect of estrogen+progestin (E+P) and estrogen alone (E) on cancer and heart disease. Most striking is that E therapy does not appear to increase breast cancer although E+P does have a small effect, particularly after five years. Also, there are definite differences in the age related effects of heart disease with E alone showing a more favorable effect. Since recent studies have shown benefit on symptoms with lower doses a more favorable benefit ratio may be obtained using these doses. Transdermal routes have also been suggested as a possible route to avoid thromboembolic complications although dose equivalent studies have been lacking. New findings on mood changes depression and cognitive functioning and breast cancer have enhanced our understanding of a possible critical window for benefit, and the use of different progestins may also provide benefit. Use of vaginal estrogens has become a important therapeutic tool to treat genitourinary issues. Others have promoted bioidentical or custom compounded hormones without scientific data. For patients unable to take hormones some alternatives are promising. New studies may shed light on these complicated issues.



Dr. Michelle P. Warren earned her medical degree from Cornell University Medical College. She is board-certified in internal medicine and in a subspecialty in endocrinology and has trained in reproductive endocrinology.

Dr Warren is the founder in 1997 and Medical Director of the Center for Menopause, Hormonal Disorders and Women's Health at Columbia University Medical Center. She is professor of obstetrics and gynecology and medicine. A pioneer in the effects of eating disorders and athletics on the menstrual cycle, Dr. Warren was the first to identify skeletal problems, including scoliosis and stress fractures that occur in young women as a result of menstrual irregularities. Over a lifetime of practice focusing on women's health, she has written numerous articles and textbook chapters and lectures and teaches extensively on menopause, oral contraceptives, anorexia nervosa, menstrual irregularities, amenorrhea in athletes, and osteoporosis. She has published a book on sports and hormones. She conducts clinical trials and medical research in the field of eating disorders, hypothalamic amenorrhea, osteoporosis, and menopause and has been awarded multiple grants from the National Institutes of Health. She has published over 200 articles and book chapters in her field. She has been named best doctor by NY Magazine and named best doctor in America since 2004 and holds an endowed professorship in Women's Health at Columbia University Medical Center.

MYTH AND TRUTH ABOUT ANDROGEN SUPPLEMENTATION FOR SEXUAL WELLBEING IN MENOPAUSE WOMEN.

by
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With regard to sexual wellbeing of menopausal women and androgen supplementation, there is the problem to decide what is truth and what is just myth.

Is it just a myth, or is it the truth that...

- androgens are male hormones and irrelevant in women
- androgens have a positive effect in women on bone, muscle, mood, vitality and sexuality
- women find financial security more important than a satisfying sexual relationship
- after menopause, the majority of women lose their desire for sex following a bilateral oophorectomy before menopause this is even worse
- women with a female sexual dysfunction can be identified by measuring their peripheral androgen blood level
- androgen supplementation does not improve sexual wellbeing in women with a female sexual dysfunction
- testosterone should be combined with oestrogens and progestogens to have an increased effect on sexual function
- androgen supplementation has severe side effects such as acne, alopecia, hirsutism, voice deepening and cliteromegalie
- androgens increase breast cancer risk, and therefore are not approved by the FDA
- transdermal androgen supplementation has been proven to be both effective and safe.

Based on the work of the international FSD-education study-group, this presentation will discuss whether or not the statements above are more myth than truth.



Peter Kenemans, MD PhD

Peter Kenemans (1942) is Professor em. of Obstetrics and Gynecology at the VU University Medical Center, Amsterdam, The Netherlands.

Between 1989 and 2003 he was Chairman of this department and head of numerous clinical, training and research programs.

He organized various postgraduate training events (AMS, Davos) and was editor in chief of Maturitas, the European Menopause Journal.

His legacy includes 298 scientific publications in peer-reviewed journals and 30 PhD students, 6 of whom now hold academic chairs themselves.

His present ambition is to apply his vast clinical and research experience and wide range of knowledge to find new, ICT based solutions to improve women's health in sub-Saharan Africa.

ERbeta agonists offering new hope in menopausal women wellbeing

by

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Menopause is a time of turbulent changes in hormones which can be accompanied by unpleasant symptoms such as flushing of the skin, night sweats, insomnia and mood swings.

Continued loss of estrogen during menopause is associated with more serious sequelae such as breast cancer, cardiovascular disease and cognitive decline. We are interested in studying the effects of loss of estrogen on the health of the brain and breast. We use ovariectomized mice as our estrogen deprivation model to study the consequences of long-term removal of estrogen on serotonergic neurons. In the second model we use biopsies from normal postmenopausal women to study changes in the breast after menopause.

We conclude that estrogen is essential for survival of neurons in the Dorsal Raphe. The tryptophan hydroxylase may be recovered by estradiol or by ERβ agonists within 5 weeks of ovariectomy but after longer periods of estrogen depletion; some neurons are permanently lost and are not recovered upon treatment.

In post menopausal women, breast biopsies permitted us to examine which histological changes can account for dense breasts and allowed us to study the effects of replacement with estrogen or with estrogen plus progesterone. The results will be presented and discussed.



Jan-Åke Gustafsson, M.D., Ph.D.

Ph.D., Dept of Chemistry, Karolinska Institutet, 1968, M.D., Karolinska Institutet, 1971

Career/Academic Appointments:

1976 Professor of Chemistry, Karolinska Institutet

1979 Professor of Medical Nutrition and Chairman of the Dept of Medical Nutrition, Huddinge University Hospital, Karolinska Institutet

2006-2008 Professor of Medical Nutrition and Chairman of the Dept of Biosciences and Nutrition, Karolinska Institutet

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Administrative Positions:

1985 Director of the Center for Biotechnology, Huddinge University Hospital, Karolinska Institutet

1987 Founder of KaroBio AB (a campus-situated biotechnology company sponsored by pension and governmental funds with about 80 employees).

2004-2009 Coordinator for the EU funded CASCADE Network of Excellence

Professional Honors & Recognition

A) International/National/Regional

2009 The Grand Nordic Fernström Prize of the University of Lund

2009 Award of Merit, Princess Takamatsu Cancer Research Fund

2009 Geoffrey Harris Prize

2008 International Member American Philosophical Society

2004 Bristol-Meyers Squibb/Mead Johnson Award for Nutrition Research

2002 Foreign Honorary Member of the US National Academy of Sciences

2002 Chairman of the Nobel Assembly of the Karolinska Institutet

2002 Fred Conrad Koch Award (Endocrine Society USA)

2000 Foreign Honorary Member of the American Academy of Arts and Sciences

1999 Fogarty Scholar NIH

1998 Adjunct Member of the Nobel Committee of the Karolinska Institutet

1998 The Söderberg Prize in Medicine

1998 Member of the Swedish Academy of Engineering Sciences

1997 Member of the Swedish Academy of Sciences

1994 Gregory Pincus Medal and Award, Worcester Foundation

1992 The Anders Jahre Prize, Oslo

1992 Medal from Collège de France, Paris

1990 Honorary Member of the American Society for Biochemistry and Molecular Biology

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1983 The Fernström Prize of the Karolinska Institutet

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2011 Honorary Doctor in Medicine, University of Turku, Turku, Finland

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**MYTH and TRUTH :
IF EVERY WOMAN IS DIFFERENT, MUST HER TREATMENT BE DIFFERENT TOO ?**

by
DRAŽEN POSTRUŽNIK

There has been million words written and said in discussions about hormonal menopausal therapy, especially after the (misinterpreted!) results of WHI study back in 2011.

Ten years after – today – we are witnessing a return to reasonable. Main points in discussing and choosing an adequate hormonal menopausal therapy are in fact a few; they could be summarized in three chapters: the first one is the fact that estrogens *per se* are “good guys” and their use should offer to the patient clear benefits in osteoporosis prevention and cardiovascular protection; the second one is the story about inevitable progestins and how important is to choose the most metabolic friendly one; the third is the almighty word “individualisation”.

Indeed, it is of utmost importance to personalize hormonal replacement and adapt it to every single woman – similar to the routine procedure when administrating insuline to various diabetic patients.

How different women really are?

Do they really metabolize sexual steroids in a different way, specific fashion?

A straight affirmative answer to this question would be pretentious indeed, but it is clear that differences exist, that they are less qualitative, more quantitative, but surely have to be taken into account when deciding about the hormonal therapy in perimenopausal and postmenopausal women. After all, this is supposed to be a long lasting, long-term administration, and the importance of the right choice is great.

Details of the above will be presented and discussed, based upon existing clinical and laboratory experience.



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DEPRESSION AND HRT

By
Adriana Vilariño

According to World Health Organization depression is the number one ranked disease World Wide in women.

It is estimated that as many as 33 % of women suffer a major depressive episode in their lifetime.

Some but not all studies reflect an association between menopausal transition and significant vulnerability to depressive symptoms, recently results documented some events related to menopausal transition that could play a role in the onset of depression 1) investigations demonstrating the widespread neuroregulatory effects of ovarian steroids. 2) fluctuating estrogens , sustained estrogens deficit .and sudden estrogen withdrawal correlating with significant mood disturbance.

Perimenopause represent a period of higher vulnerability for depression.

Estrogen therapy in the perimenopausal period can decrease depression .

There are several mechanism of action of ovarian hormones that could explain their effect on mood in women, estrogens increases serotonergic system, increasing serotonergic receptors and neurotransmitter , alteration of dopaminergic ,cholinergic, GABAergic, and serotonergic neurotransmission through estrogen has been consistently established.

Estrogen replacement therapy may be appropriate for improving the menopausal symptoms in some perimenopausal women with depression.

Several meta analisis were conducted. the more restricted analisis provided information on the effectiveness of hormone treatments on depressed mood ,used alone and in combination with other hormones .

Studies which compared estrogen treatment with estrogen plus progesterone indicated that the addition of progesterone reduced the effect of hormone replacement therapy on depressed mood.

At the present time there is insufficient evidence to recommend estrogen as a first time treatment in affective disorders.

Our future efforts should be directed to identify populations responsive to antidepressant, to estrogen or the combinations of both based in genetic markers.



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Myth and truth: HRT effects on coronary heart disease

by

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Beneficial effects of oestrogen on metabolic risk factors for coronary heart disease (CHD), as well as on arterial function and on surrogate clinical markers of CHD, have been widely demonstrated. Thus hormone replacement therapy (HRT) should benefit CHD in postmenopausal women. Observational studies have consistently shown a benefit of HRT on CHD prevention, although it has been noted that the biggest beneficial impact has been seen in those women who initiated HRT close to the menopause. However, randomised clinical trials of HRT have not shown any significant benefit on CHD, and there has even been a report of harm from the initial publication of the Women's Health Initiative (WHI). This has led to the abandonment of HRT for prevention of CHD by cardiologists and other physicians, but they have failed to realise the shortcomings in the interpretation of the data. Firstly, the WHI finding of a significant increase in CHD events was published in the preliminary analysis of their data. Subsequent publications of the complete data showed that there was no significant increase in CHD events. Secondly, most randomised trials using defined clinical events as outcomes have studied just one dose of one HRT regimen, a dose inappropriately high with the average starting age of the participants being in their mid-sixties. In contrast, the observational population studies that do show benefit largely comprise women starting on HRT around the age of menopause, i.e. early fifties. In fact, it is the older women in the randomised trials that failed to show benefit, whereas there was evidence of benefit in the younger ones. Thus, the age at initiation of HRT seems to be important for cardiovascular benefit and risk, with the biggest benefit being seen in women starting treatment below 60 years of age and within 10 years of onset of menopause. This gives rise to the concept of a "window of opportunity" for HRT to help prevent CHD around the menopause, and in the UK this is the usual time of initiation of HRT. Does this mean that older women cannot benefit? The optimal dose of oestrogen at initiation may be very dependent on the age of the individual. Older women need less oestrogen than younger ones for almost any of its effects. Inappropriately high doses of oestrogen could cause cardiovascular harm due to transient disturbances in thrombogenesis and vascular remodelling. Indeed, a pilot study of lower dose HRT in older women did not show any cardiovascular harm. Whilst the greatest CHD benefit may be seen by starting HRT in the early postmenopause, this does not exclude benefit in older women providing they are given appropriate low dose therapy. HRT may therefore prove useful for the primary prevention of CHD in women. This could be an important option, as agents that are effective for the primary prevention of CHD in men do not appear as effective in women. The myth is that HRT is harmful to the cardiovascular system; the truth is that HRT is probably the best effective treatment for CHD prevention in postmenopausal women.

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Dr Stevenson is currently Chairman of the charity Women's Health Concern, Executive Committee Member of the British Menopause Society, Fellow of the European Society of Cardiology, Foundation Member of the Faculty of Sports and Exercise Medicine (UK), and Editor of *Maturitas*. He is a past Chairman of the British Menopause Society, past Treasurer of the UK Bone and Tooth Society, past Non-US Section Head, Cardiovascular diseases in women (reproductive & post-reproductive age), Women's Health Faculty, Faculty of 1000 Medicine, and past Executive Committee Member of the International and European Menopause Societies.