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BHRT Abstracts & Reviews



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Postgrad Med. 2009 Jan;121(1):73-85.

The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy?

Holtorf K. Holtorf Medical Group, Inc., Torrance, CA 90505.

BACKGROUND: The use of bioidentical hormones, including progesterone, estradiol, and estriol, in hormone replacement therapy (HRT) has sparked intense debate. Of special concern is their relative safety compared with traditional synthetic and animal-derived versions, such as conjugated equine estrogens (CEE), medroxyprogesterone acetate (MPA), and other synthetic progestins. Proponents for bioidentical hormones claim that they are safer than comparable synthetic and nonhuman versions of HRT. Yet according to the US Food and Drug Administration and The Endocrine Society, there is little or no evidence to support claims that bioidentical hormones are safer or more effective. **OBJECTIVE:** This paper aimed to evaluate the evidence comparing bioidentical hormones, including progesterone, estradiol, and estriol, with the commonly used nonbioidentical versions of HRT for clinical efficacy, physiologic actions on breast tissue, and risks for breast cancer and cardiovascular disease. **METHODS:** Published papers were identified from PubMed/MEDLINE, Google Scholar, and Cochrane databases, which included keywords associated with bioidentical hormones, synthetic hormones, and HRT. Papers that compared the effects of bioidentical and synthetic hormones, including clinical outcomes and in vitro results, were selected. **RESULTS:** Patients report greater satisfaction with HRTs that contain progesterone compared with those that contain a synthetic progestin. Bioidentical hormones have some distinctly different, potentially opposite, physiological effects compared with their synthetic counterparts, which have different chemical structures. Both physiological and clinical data have indicated that progesterone is associated with a diminished risk for breast cancer, compared with the increased risk associated with synthetic progestins. Estriol has some unique physiological effects, which differentiate it from estradiol, estrone, and CEE. Estriol would be expected to carry less risk for breast cancer, although no randomized controlled trials have been documented. Synthetic progestins have a variety of negative cardiovascular effects, which may be avoided with progesterone. **CONCLUSION:** Physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal-derived counterparts. Until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT. Further randomized controlled trials are needed to delineate these differences more clearly. PMID: 19179815

Curr Cardiol Rev. 2008 Nov;4(4):309-22.

Experimental benefits of sex hormones on vascular function and the outcome of hormone therapy in cardiovascular disease.

Ross RL, Serock MR, Khalil RA. Division of Vascular Surgery, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts 02115.

Abstract: Cardiovascular disease (CVD) is more common in men and postmenopausal women than premenopausal women, suggesting vascular benefits of female sex hormones. Experimental data have shown beneficial vascular effects of estrogen including stimulation of endothelium-dependent nitric oxide, prostacyclin and hyperpolarizing factor-mediated vascular relaxation. However, the experimental evidence did not translate into vascular benefits of hormone replacement therapy (HRT) in postmenopausal women, and HERS, HERS-II and WHI clinical trials demonstrated adverse cardiovascular events with HRT. The lack of vascular benefits of HRT could be related to the hormone used, the vascular estrogen receptor (ER), and the subject's age and preexisting cardiovascular condition. Natural and phytoestrogens in small doses may be more beneficial than synthetic estrogen. Specific estrogen receptor modulators (SERMs) could maximize the vascular benefits, with little side effects on breast cancer. Transdermal estrogens avoid the first-pass liver metabolism associated with the oral route. Postmenopausal decrease and genetic polymorphism in vascular ER and post-receptor signaling mechanisms could also modify the effects of HRT. Variants of cytosolic/nuclear ER mediate transcriptional genomic effects that stimulate endothelial cell growth, but inhibit vascular smooth muscle (VSM) proliferation. Also, plasma membrane ERs trigger not only non-genomic stimulation of endothelium-dependent vascular relaxation, but also inhibition of $[Ca(2+)]_i$, protein kinase C and Rho kinase-dependent VSM contraction. HRT could also be more effective in the perimenopausal period than in older postmenopausal women, and may prevent the development, while worsening preexisting CVD. Lastly, progesterone may modify the vascular effects of estrogen, and modulators of estrogen/testosterone ratio could provide alternative HRT combinations. Thus, the type, dose, route of administration and the timing/duration of HRT should be customized depending on the subject's age and preexisting cardiovascular condition, and thereby make it possible to translate the beneficial vascular effects of sex hormones to the outcome of HRT in postmenopausal CVD. PMID: 20066139

Maturitas. 2008 May 20;60(1):10-8. Epub 2008 Apr 14.

Metabolic syndrome after menopause and the role of hormones.

Lobo RA. Dept of Obstetrics & Gynecology, Columbia University College of Physicians & Surgeons, New York, NY 10032.

OBJECTIVES: The purpose of this review is to focus on the importance of metabolic syndrome (MBS) and its increased prevalence in postmenopausal (PM) women. Also the role of hormonal therapy in PM women with MBS will be discussed. **METHODS:** Review of the relevant literature and results from recent clinical trials. **RESULTS:** MBS may occur in 40% of PM women and is largely determined by overweight status and obesity. Weight gain, particularly an increase in central fat mass increases in PM women, beginning a few years prior to menopause. Hormonal Therapy (HT) in normal PM women, generally decreases abdominal fat, but the effect of transdermal estrogen is preferable to oral therapy in this regard. In women with MBS, oral therapy was found to increase leptin and the leptin/adiponectin ratio, while transdermal therapy showed no changes. HT has been found to improve insulin resistance in PM women, although the data are mixed. In women with MBS, oral therapy was found to worsen parameters of insulin resistance, while transdermal therapy had minimal effects overall. Women with MBS have elevations in several inflammation and coagulation factors. Both oral and transdermal HT reduce inflammation markers except for levels of CRP and MMP-9, which increase with oral therapy, but are unaffected by the transdermal route. Oral estrogen has a small pro-coagulant effect, not observed with transdermal therapy, in both normal PM women and those with MBS. The beneficial effects of HT on lipids occur in PM women with and without MBS, although the changes in the latter are minimal. Blood pressure was not affected by HT in women with MBS. **CONCLUSIONS:** Weight gain and obesity largely drives the increased prevalence of MBS in PM women. Use of HT is beneficial overall for reducing many of the parameters of MBS. Our own data would suggest that in MBS, transdermal therapy may be preferable to oral therapy, at least in standard doses. PMID: 18407440

Clin Interv Aging. 2008;3(1):51-4.

Transdermal hormone therapy and bone health.

Shulman LP. Division of Reproductive Genetics, Department of Obstetrics and Gynecology, Feinberg School of Medicine of Northwestern University, Chicago, Illinois.

Abstract: The clinical aftermath of the reporting of the initial findings of the Women's Health Initiative (WHI) in 2002 was a profound reduction in the use of hormone therapies by menopausal women. This reduction led to a well documented increase in vasomotor symptoms and vaginal atrophy among those women who discontinued their hormone regimens. However, another adverse impact among these women, as well as many other menopausal women, is the well recognized increased likelihood of osteoporosis resulting from the decline in circulating estradiol levels associated with natural and surgical menopause. Although the use of non-hormonal drugs such as bisphosphonates has been shown to reduce the risk of fracture in women with osteoporosis, bisphosphonates have not been shown to reduce the risk of fracture in non-osteoporotic women. Indeed, only oral estrogen (as demonstrated in the WHI studies) has been shown to reduce the risk of fracture in osteoporotic and non-osteoporotic women. As non-oral hormone therapies have been shown to be as effective in treating vasomotor symptoms and vulvovaginal atrophy and to have a different (and perhaps more beneficial) physiological effect than oral regimens, it behooves us to assess the impact of non-oral hormone regimens on bone mineral density and fracture risk. Although there are no clinical trials that primarily assess the impact of non-oral regimens on fracture risk in menopausal women, numerous studies are consistent in demonstrating the positive impact of non-oral regimens in maintaining and increasing bone mineral density among users, even for those women using estrogen doses that are considered to be "too low" to have a beneficial impact on other menopausal symptoms. PMID: 18488878

Climacteric. 2006 Apr;9(2):108-18.

The long-term impact of 2-3 years of hormone replacement therapy on cardiovascular mortality and atherosclerosis in healthy women.

Alexandersen P, Tankó LB, Bagger YZ, Qin G, Christiansen C. Center for Clinical and Basic Research, Ballerup, Denmark.

OBJECTIVE: The effect of hormone replacement therapy (HRT) on cardiovascular risk is intensely debated. The aim of this study was to investigate the long-term effects of HRT given for a few years on all-cause and cardiovascular mortality and the

severity of atherosclerosis. **METHODS:** This analysis was based on a cohort of 1,458 postmenopausal women (55.8 +/- 6.1 years old) who previously participated in a number of randomized, placebo-controlled, clinical trials assessing the efficacy of 2-3 years of therapy with various estrogen plus progestin combinations for preventing bone loss. Women were followed on average for 9.8 years and came for a follow-up visit. Outcome variables were all-cause and cardiovascular mortality and the severity of atherosclerosis, as estimated by semi-quantitative scoring of vascular calcification in the lumbar aorta on lateral radiographs. **RESULTS:** A total of 174 women died during the observation period. All-cause mortality was decreased by 30% in the HRT+ group compared with the HRT- group (hazard ratio (HR) 0.70; 95% confidence interval (CI) 0.50-0.97) after adjusting for age, body mass index and smoking. Under the same conditions, similar results characterized mortality from cardiovascular disease (n = 61 deaths; 35.1% of all deaths) and coronary heart disease (n = 39 deaths; 22.4% of all deaths), which were decreased by 46% (HR 0.54, 95% CI 0.29-0.98, p = 0.045) and 53% (HR 0.47, 95% CI 0.21-1.03, p = 0.062), respectively. Furthermore, the mean severity score of aortic calcification at follow-up was significantly lower in hormone-treated compared to non-treated women (p < 0.0001). **CONCLUSION:** Women who receive 2-3 years of HRT after menopause do not have increased all-cause mortality, and results of the present study suggest relative cardiovascular benefits compared to those who had not used hormones. PMID: 16698657

Altern Med Rev. 2006 Sep;11(3):208-23.

A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risks.

Moskowitz D. Moskowitz, Deborah. Wellness Designed, LLC.

Abstract: Numerous forms of estrogens and progestins are utilized for the treatment of menopausal complaints and associated conditions that occur temporally. Although known to be different with respect to molecular structure, receptor affinity, metabolism, and other physiological traits, most have been treated as if they were clinically identical. The majority of these hormone preparations, commonly referred to as hormone replacement therapy (HRT), should perhaps be more aptly referred to as hormone substitution therapy, as most of the therapies utilized do not exactly match those produced in the body. Research indicates these synthetic hormones vary clinically in safety and efficacy. As such, women and their physicians have, in increasing numbers, been opting for the use of bioidentical hormones; i.e., those that match the structure and function of hormones produced in the body. With greater utilization and research surrounding bioidentical hormones, the differences can now begin to be fully assessed and appreciated. This article reviews the disparities between synthetic and bioidentical estrogens and progestins/progesterone with respect to safety and efficacy; special attention is devoted to clinical outcomes in the breast, endometrium, bone, cardiovascular system, and brain. The studies reviewed suggest bioidentical progesterone does not have a negative effect on blood lipids or vasculature as do many synthetic progestins, and may carry less risk with respect to breast cancer incidence. Studies of both bioidentical estrogens and progesterone suggest a reduced risk of blood clots compared to non-bioidentical preparations. Bioidentical hormone preparations have demonstrated effectiveness in addressing menopausal symptoms. The author advocates for continued research on bioidentical hormones and concludes there is currently sufficient evidence to support their preferred use over that of their synthetic cousins. PMID: 17217322

Int J Fertil Womens Med. 2004 Nov-Dec;49(6):252-67.

A clinician's review of the WHI-related literature.

Speroff L. Department of Obstetrics and Gynecology, Oregon Health Sciences University Portland, Oregon 97239.

Abstract: When the monitoring board of the Women's Health Initiative (WHI) canceled the estrogen-progestin arm of the study in July 2002, the effect was immediate and dramatic, as several million postmenopausal women with the full agreement of their physicians ceased taking combined hormone therapy. Soon thereafter the manufacturers of conjugated equine estrogens felt compelled to publicize a drastic restriction of the indications for their product. Little notice, except in the medical literature, was given to the continuation of the other treatment arms of the WHI, nor did the rather small (however significant) increases in risk of cardiovascular disease and breast cancer resulting from combined therapy receive widespread serious analysis. In this article, special attention is given to the population sampling involved in setting up the WHI, arm by arm, with full discussion of how these samplings compare with those in other studies--HERS, ERA, WEST, etc. All studies are scrutinized in terms of treatment regimens, follow-up, confounding factors, particularly statins and aspirin, and high drop-out rates in order to discover possible reasons for the results in the WHI for primary and secondary prevention of cardiovascular disease in the combined-therapy arm and slightly disappointing results for breast cancer. Each of the two

main sections of the article, Cardiovascular Disease and Breast Cancer, concludes with a detailed summation of points derived from the often contrasting results of the various studies, which can be used in counseling patients.

PMID: 15751264

Climacteric. 2004 Dec;7(4):347-56.

Transdermal hormone therapy: gels and patches.

Samsioe G. Department of Obstetrics and Gynecology, Lund University Hospital, 221 85 Lund, Sweden.

Abstract: Hormone therapy (HT) in the climacteric has a number of beneficial effects including mitigation of climacteric symptoms and prevention of osteoporosis. Administration of HT via the transdermal route avoids hepatic first-pass metabolism and therefore the high plasma levels of estrogen metabolites that are associated with oral administration. Patch formulations have traditionally been the most common form of transdermal HT. However, as patches may be associated with local skin reactions, gel formulations have been developed in an attempt to improve acceptability and compliance with transdermal HT. Patch and gel formulations are equally as effective in treating climacteric symptoms and improving bone mineral density, and the effects are comparable to those achieved by oral HT.

PMID: 15799606

Clin Pharmacokinet. 2002;41(9):661-80.

Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications.

Zhang H, Zhang J, Streisand JB. Cephalon, Inc., Salt Lake City, Utah 84116, USA. hzhang@anesta.com

Abstract: Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. Several cardiovascular drugs administered transmucosally have been studied extensively. Nitroglycerin is one of the most common drugs delivered through the oral mucosa. Research on other cardiovascular drugs, such as captopril, verapamil and propafenone, has proven promising. Oral transmucosal delivery of analgesics has received considerable attention. Oral transmucosal fentanyl is designed to deliver rapid analgesia for breakthrough pain, providing patients with a noninvasive, easy to use and nonintimidating option. For analgesics that are used to treat mild to moderate pain, rapid onset has relatively little benefit and oral mucosal delivery is a poor option. Oral mucosal delivery of sedatives such as midazolam, triazolam and etomidate has shown favourable results with clinical advantages over other routes of administration. Oral mucosal delivery of the antinausea drugs scopolamine and prochlorperazine has received some attention, as has oral mucosal delivery of drugs for erectile dysfunction. Oral transmucosal formulations of testosterone and estrogen have been developed. In clinical studies, sublingual testosterone has been shown to result in increases in lean muscle mass and muscle strength, improvement in positive mood parameters, and increases in genital responsiveness in women. Short-term administration of estrogen to menopausal women with cardiovascular disease has been shown to produce coronary and peripheral vasodilation, reduction of vascular resistance and improvement in endothelial function. Studies of sublingual administration of estrogen are needed to clarify the most beneficial regimen. Although many drugs have been evaluated for oral transmucosal delivery, few are commercially available. The clinical need for oral transmucosal delivery of a drug must be high enough to offset the high costs associated with developing this type of product. Drugs considered for oral transmucosal delivery are limited to existing products, and until there is a change in the in the selection and development process for new drugs, candidates for oral transmucosal delivery will be limited.

PMID: 12126458

Maturitas. 2001 Dec 14;40(3):195-201.

Hormone replacement therapy: the benefits in tailoring the regimen and dose.

Gambacciani M, Genazzani AR. Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynecology Piero Fioretti, University of Pisa, Via Roma 67, 56100 Pisa, Italy.

Abstract: Despite the clear benefits of long-term hormone replacement therapy (HRT), the majority of patients tend to undergo short-term treatment. The cyclical bleedings induced by the sequential progestogen administration are often unacceptable namely in the elderly postmenopausal women. At the standard doses HRT preparations can also induce annoying hormone-related side effects, both in sequential and continuous combined regimens. Lower HRT schedules are reported to be highly effective in the relief of climacteric symptoms, inducing minimal endometrial stimulation with high rates of amenorrhea. Continuous administration of low doses of progestins is safe for endometrium protection and minimizes progestin-related side effects. Indeed, it has been demonstrated that low dose HRT can prevent the increase in bone turnover and the consequent bone loss in postmenopausal women. The choice of lower HRT dosages can also be useful for the number of potential disadvantages of standard HRT doses, mainly for long-term treatments. Low dose regimens should be considered as a starting dose to minimize the occurrence of side effects, improving compliance and, therefore, HRT effects on the prevention of long-term consequences of estrogen deprivation. PMID: 11731180

Maturitas. 2001 Oct 31;40(1):75-83.

Effects of hormonal replacement therapy in postmenopausal hypertensive patients.

Affinito P, Palomba S, Bonifacio M, Fontana D, Izzo R, Trimarco B, Nappi C. Clinical Department of Gynecology, Obstetrics, and Human Reproduction, Facoltà di Medicina e Chirurgia, University of Naples Federico II, Via Pansini 5, 80131 Naples, Italy.

OBJECTIVE: To evaluate the effect of hormonal replacement therapy (HRT) on blood pressure (BP) in postmenopausal hypertensive women. METHODS: Sixty women affected by hypertension were enrolled and randomized in two groups of treatment: transdermal continuous HRT in a sequential regimen (group A) and placebo (group P). At baseline, after 3 and 6 months of treatment, the BP with standard sphygmomanometer and with 24-h ambulatory recording method was evaluated in two periods (from day 10 through day 16 of the cycle and from day 20 through day 27 of the cycle). At the same time, we also evaluated total cholesterol, LDL-c, HDL-c, triglycerides, and fibrinogen levels. RESULTS: After 3 and 6 months of treatment, no significant variations of systolic and diastolic BP measured with standard sphygmomanometer were detected in both groups. On the contrary, in group A in comparison with basal values and group P, and without difference between the two phases of treatment, the 24-h recording showed a significant ($P<0.05$) decrease in BP. No significant variations were detected in group P versus baseline. In particular, we observed in group A at 3 months of treatment a significant ($P<0.05$) decrease only in daytime BP in comparison with basal values and group P, without difference between the two phases of treatment. Indeed, the decrease in daytime BP was significant ($P<0.05$) for both systolic and diastolic BP. At 3 and 6 months a significant ($P<0.05$) decrease in total cholesterol, LDL-c and fibrinogen levels was detected in group A versus baseline and group P. HDL-c and triglyceride concentrations showed no significant variations. CONCLUSIONS: The transdermal HRT induces a significant reduction of BP values and a favorable metabolic action in postmenopausal hypertensive patients. PMID: 11684376

Diabetes Care. 2001 Jul;24(7):1144-50.

Hormone replacement therapy is associated with better glycemic control in women with type 2 diabetes: The Northern California Kaiser Permanente Diabetes Registry.

Ferrara A, Karter AJ, Ackerson LM, Liu JY, Selby JV; Northern California Kaiser Permanente Diabetes Registry. Division of Research, Kaiser Permanente, Oakland, California 94611.

OBJECTIVE: In women with diabetes, the changes that accompany menopause may further diminish glycemic control. Little is known about how hormone replacement therapy (HRT) affects glucose metabolism in diabetes. The aim of this study was to examine whether HbA(1c) levels varied by current HRT among women with type 2 diabetes. RESEARCH DESIGN AND METHODS: In a cohort of 15,435 women with type 2 diabetes who were members of a health maintenance organization, HbA(1c) and HRT were assessed by reviewing records in the health plan's computerized laboratory and pharmacy systems. Sociodemographic and clinical information were collected by survey. RESULTS: The mean age was

64.7 years (SD +/- 8.7). The study cohort comprised 55% non-Hispanic whites, 14% non-Hispanic blacks, 12% Hispanics, 11% Asians, 4% "other" ethnic groups, and 4% with missing ethnicity data. Current HRT was observed in 25% of women. HbA(1c) levels were significantly lower in women currently using HRT than in women not using HRT (age-adjusted mean +/- SE: 7.9 +/- 0.03 vs. 8.5 +/- 0.02, respectively, $P = 0.0001$). No differences in HbA(1c) level were observed between women using unopposed estrogens and women using opposed estrogens. In a Generalized Estimating Equation model, which took into account patient clustering within physician and adjusted for age, ethnicity, education, obesity, hypoglycemic therapy, diabetes duration, self-monitoring of blood glucose, and exercise, HRT remained significantly and independently associated with decreased HbA(1c) levels ($P = 0.0001$). CONCLUSIONS: HRT was independently associated with decreased HbA(1c) level. Clinical trials will be necessary to understand whether HRT may improve glycemic control in women with diabetes. PMID: 11423493

Pellet Implants

Clin Endocrinol (Oxf). 1997 Sep;47(3):311-6.

An analysis of testosterone implants for androgen replacement therapy.

Handelsman DJ, Mackey MA, Howe C, Turner L, Conway AJ. Andrology Unit, Royal Price Alfred Hospital, Sydney NSW, Australia.

OBJECTIVE: To review 13 years of experience using fused crystalline testosterone implants for androgen replacement therapy in order to identify pattern of usage (including continuation rates) and adverse events emerging during therapy and factors associated with adverse events including implant extrusions. DESIGN: Retrospective review of prospectively collected data on characteristics of patients and implant procedures performed as well as adverse events reported during routine follow-up. PATIENTS: Over 13 years 973 implant procedures using fused crystalline testosterone implants were performed in 221 men. MEASUREMENTS: Continuation rates and adverse events such as extrusions, bleeding, infection or others were recorded and analysed in relationship to characteristics of the patient and the implant procedure performed. RESULTS: Overall rate of adverse events (108/973, 11.1%) was significantly related to increased numbers of implants (4.2 +/- 0.1 vs 4.0 +/- 0.03, $P = 0.031$) and higher levels of physical activity at work ($P = 0.030$). The most common adverse effect was extrusion (83/973, 8.5%) which was related to occupational classification ($P = 0.033$) and increasing work activity ($P = 0.044$) and occurred more frequently than by chance in multiple (16 vs 3.3 expected) rather than single (65 vs 76.1 expected) episodes. Bleeding (22/973, 2.3%) was significantly associated with an increased number of implants (4.5 +/- 0.2 vs 4.0 +/- 0.03, $P = 0.020$) but even in the worst cases (3/22) it was of minor clinical importance. Infection was rare (6/973, 0.6%) but occurred more among thinner men. The overall continuation rate was 92.7% increasing from 86% after the first implantation to > 99% after the tenth implant. CONCLUSIONS: This study demonstrates the very satisfactory clinical acceptability of testosterone pellet implants for androgen replacement therapy within a single unit with experienced operators. The only regular adverse effect is extrusion, which may be related to mechanical factors such as habitual work activity but also possibly procedural factors. Other adverse effects such as bleeding, infection and fibrosis were rare. An improved method of implant delivery would enhance this old but durable technology. PMID: 9373452

Maturitas. 1995 Apr;21(3):227-36. Republished: Maturitas. 2008 Sep-Oct;61(1-2):17-26.

Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality.

Davis SR, McCloud P, Strauss BJ, Burger H. Prince Henry's Institute of Medical Research, Clayton, Victoria, Australia.

Abstract: To investigate the role of androgens in increasing bone density and improving low libido in postmenopausal women, we have studied the long-term effects of estradiol and testosterone implants on bone mineral density and sexuality in a prospective, 2 year, single-blind randomised trial. Thirty-four postmenopausal volunteers were randomised to treatment with either estradiol implants 50 mg alone (E) or estradiol 50 mg plus testosterone 50 mg (E&T), administered 3-monthly for 2 years. Cyclical oral progestins were taken by those women with an intact uterus. Thirty-two women completed the study. BMD (DEXA) of total body, lumbar vertebrae (L1-L4) and hip area increased significantly in both treatment groups. BMD increased more rapidly in the testosterone treated group at all sites. A substantially greater increase in BMD occurred in the E&T group for total body ($P < 0.008$), vertebral L1-L4 ($P < 0.001$) and trochanteric ($P < 0.005$) measurements. All sexual parameters (Sabbatsberg sexual self-rating scale) improved significantly in both groups. Addition of testosterone resulted

in a significantly greater improvement compared to E for sexual activity ($P < 0.03$), satisfaction ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$) and relevancy ($P < 0.05$). Total cholesterol and LDL-cholesterol fell in both groups as did total body fat. Total body fat-free mass (DEXA, anthropometry, impedance) increased in the E&T group only. We concluded that in postmenopausal women, treatment with combined estradiol and testosterone implants was more effective in increasing bone mineral density in the hip and lumbar spine than estradiol implants alone. Significantly greater improvement in sexuality was observed with combined therapy, verifying the therapeutic value of testosterone implants for diminished libido in postmenopausal women. The favourable estrogenic effects on lipids were preserved in women treated with T, in association with beneficial changes in body composition. PMID: 7616872

J Clin Endocrinol Metab. 1990 Jul;71(1):216-22.

Pharmacokinetics and pharmacodynamics of testosterone pellets in man.

Handelsman DJ, Conway AJ, Boylan LM. Andrology Unit, Royal Prince Alfred Hospital, Sydney, Australia.

Abstract: We studied the pharmacokinetics and pharmacodynamics of sc implanted pellets of fused crystalline testosterone. Three different regimens (6 x 100 mg, 6 x 200 mg; and 3 x 200 mg) were compared in a prospective, cross-over clinical trial in which androgen deficient men were administered the three-dose combinations in a randomized starting order at intervals of at least 6 months. Plasma free and total testosterone, sex hormone-binding globulin, LH, and FSH were measured before and at monthly intervals for at least 6 months after 111 pellet implantation in 43 men with hypergonadotropic ($n = 22$) or hypogonadotropic ($n = 21$) hypogonadism. Total and free testosterone levels peaked at the first month and were maintained at physiological levels for 4 to 5 (600 mg doses) or 6 (1200 mg dose) months after a single implantation. Absorption of testosterone from 100 mg and 200 mg pellets closely approximated zero-order throughout the effective life of the pellets and exhibited a half-duration of 2.5 months. The estimated rate of release of testosterone was 1.5 (95% confidence limits 1.3-1.6) mg/day. 200 mg pellet as determined from direct measurement of residue in pellets recovered after extrusion and confirmed independently from percent absorbed-time plots. The bioavailability of testosterone was virtually complete and the time course was predictable from the total implant dose and, to a lesser extent, total initial surface areas of pellets. Despite wide fluctuations in testosterone, SHBG levels were not changed during 6 months. In men with hypergonadotropic hypogonadism, both LH and FSH levels were uniformly and markedly suppressed by increased testosterone after pellet implants. LH and FSH were highly correlated with each other ($r = 0.87$) and inversely with total ($r = 0.47$ and 0.45 , respectively) and free ($r = 0.46$ and 0.47) testosterone levels. Nadir LH levels occurred at 1-3 months (600 mg) and 1-4 months (1200 mg) reaching levels comparable with eugonadal controls. In contrast nadir FSH levels occurred at similar times but remained elevated compared with eugonadal controls. We conclude that fused pellets of crystalline testosterone provides very satisfactory depot androgen replacement exhibiting many desirable features for androgen replacement. PMID: 2115044

Lancet. 1987 Feb 7;1(8528):297-9.

Effect of oestrogen and testosterone implants on psychological disorders in the climacteric.

Montgomery JC, Appleby L, Brincat M, Versi E, Tapp A, Fenwick PB, Studd JW.

Abstract: In a double-blind trial oestradiol, oestradiol/testosterone, or placebo implants were assessed for their effects on psychological symptoms in women attending a menopause clinic. After two months, women receiving active treatment scored better than the placebo group on a self-rating scale of distress, on anxiety, and on depression (p less than 0.05). Postmenopausal but not perimenopausal women improved after placebo, and at 4 months the scores in the three groups no longer differed significantly. PMID: 2880114

Lancet. 1984 Jan 7;1(8367):16-8.

Subcutaneous hormone implants for the control of climacteric symptoms. A prospective study.

Brincat M, Magos A, Studd JW, Cardozo LD, O'Dowd T, Wardle PJ, Cooper D.

Abstract: 55 postmenopausal women on established hormone replacement therapy were treated with either oestradiol and testosterone implants or placebo at the time of return of climacteric symptoms. Their response to therapy was assessed prospectively. The statistically highly significant levels of symptom relief that followed an oestradiol and testosterone implant were contrasted sharply with the lack of any significant relief with placebo. Despite the success of oestradiol and testosterone

implants in relieving symptoms of the climacteric, symptoms returned once the treatment was stopped. Evidence is presented that it is the fall in hormone levels rather than the level itself that provokes the return of climacteric symptoms.

PMID: 6140343

Maturitas. 1984 Mar;5(3):177-84.

The effects of subcutaneous hormone implants during climacteric.

Cardozo L, Gibb DM, Tuck SM, Thom MH, Studd JW, Cooper DJ.

Abstract: Climacteric symptoms in 120 women were treated with a total of 469 hormone implants (oestradiol 50 mg and testosterone 100 mg) over a period of four years. All patients with a uterus were given an oral progestogen to prevent endometrial hyperplasia. There was a marked response to treatment, hot flushes being improved in all patients, depression in 99% and loss of libido in 92%. Patient acceptability of this type of treatment was good and there were few side effects or complications. After therapy, the serum oestradiol exceeded the serum oestrone but remained within normal limits. When climacteric symptoms returned and re-implantation occurred the serum levels of oestrone, oestradiol, luteinising hormone (LH), follicle stimulating hormone (FSH) and testosterone were within the normal range for the reproductive age. This indicates that the return of symptoms is due to a change in the hormone levels rather than absolute hypo- oestrogenism.

PMID: 6727691

The Estrogens

Arterioscler Thromb Vasc Biol. 2010 Feb;30(2):340-5. Epub 2009 Oct 15.

Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study.

Canonico M, Fournier A, Carcaillon L, Oli   V, Plu-Bureau G, Oger E, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F, Scarabin PY. Inserm Unit 780, Cardiovascular Epidemiology Section, Cedex, France.

OBJECTIVE: Oral estrogen therapy increases venous thromboembolism risk among postmenopausal women. Although recent data showed transdermal estrogens may be safe with respect to thrombotic risk, the impact of the route of estrogen administration and concomitant progestogens is not fully established. METHODS AND RESULTS: We used data from the E3N French prospective cohort of women born between 1925 and 1950 and biennially followed by questionnaires from 1990. Study population consisted of 80 308 postmenopausal women (average follow-up: 10.1 years) including 549 documented idiopathic first venous thromboembolism. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional models. Compared to never-users, past-users of hormone therapy had no increased thrombotic risk (HR=1.1; 95% CI: 0.8 to 1.5). Oral not transdermal estrogens were associated with increased thrombotic risk (HR=1.7; 95% CI: 1.1 to 2.8 and HR=1.1; 95% CI: 0.8 to 1.8; homogeneity: P=0.01). The thrombotic risk significantly differed by concomitant progestogens type (homogeneity: P<0.01): there was no significant association with progesterone, pregnanes, and nortestosterones (HR=0.9; 95% CI: 0.6 to 1.5, HR=1.3; 95% CI: 0.9 to 2.0 and HR=1.4; 95% CI: 0.7 to 2.4). However, norpregnanes were associated with increased thrombotic risk (HR=1.8; 95% CI: 1.2 to 2.7). CONCLUSIONS: In this large study, we found that route of estrogen administration and concomitant progestogens type are 2 important determinants of thrombotic risk among postmenopausal women using hormone therapy. Transdermal estrogens alone or combined with progesterone might be safe with respect to thrombotic risk.

PMID: 19834106

Climacteric. 2009;12 Suppl 1:86-90.

Type and route of estrogen administration.

Stevenson JC. National Heart & Lung Institute, Imperial College London, Royal Brompton Hospital, London, UK.

Abstract: Hormone replacement therapy (HRT) can be administered orally and non-orally. Providing equivalent doses are given, all forms of HRT can equally relieve menopausal symptoms and prevent bone loss and osteoporosis. Different routes of administration will have differing metabolic effects, with oral HRT producing a hepatic first-pass effect not seen with non-oral HRT. The first-pass effect can produce benefits including larger reductions in low density lipoprotein cholesterol, lipoprotein(a) and insulin resistance, and larger increases in high density lipoprotein cholesterol. Unwanted effects are seen in increases in triglycerides and in coagulation activation. Cardiovascular effects of oral and transdermal HRT appear to

be fairly similar, with improvements in vascular endothelial function, angiotensin-converting-enzyme activity, and in most markers of inflammation. There is a paucity of studies on the effects of transdermal HRT on cardiovascular outcomes, but the few data available suggest similar effects to oral HRT, and dose rather than route of administration is probably more important in this respect. Oral HRT may be preferred in women with evidence of insulin resistance, such as in metabolic syndrome or maturity-onset diabetes mellitus. Transdermal HRT may be preferred in women with coagulation disturbances. But, for the majority of women, personal preference should determine their choice of HRT route. PMID: 19811249

Hum Reprod Update. 2007 Mar-Apr;13(2):175-87. Epub 2006 Nov 29.

Estrogen, cognition and female ageing.

Genazzani AR, Pluchino N, Luisi S, Luisi M. Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynecology, University of Pisa, Pisa, Italy.

Abstract: Starting from fetal life, estrogens are crucial in determining central gender dimorphism, and an estrogen-induced synaptic plasticity is well evident during puberty and seasonal changes as well as during the ovarian cycle. Estrogens act on the central nervous system (CNS) both through genomic mechanisms, modulating synthesis, release and metabolism of neurotransmitters, neuropeptides and neurosteroids, and through non-genomic mechanisms, influencing electrical excitability, synaptic function and morphological features. Therefore, estrogen's neuroactive effects are multifaceted and encompass a system that ranges from the chemical to the biochemical to the genomic mechanisms, protecting against a wide range of neurotoxic insults. Clinical evidences show that, during the climacteric period, estrogen withdrawal in the limbic system gives rise to modifications in mood, behaviour and cognition and that estrogen administration is able to improve mood and cognitive efficiency in post-menopause. Many biological mechanisms support the hypothesis that estrogens might protect against Alzheimer's disease (AD) by influencing neurotransmission, increasing cerebral blood flow, modulating growth proteins associated with axonal elongation and blunting the neurotoxic effects of beta-amyloid. On the contrary, clinical studies of estrogen replacement therapy (ERT) and cognitive function have reported controversial results, indicating a lack of efficacy of estrogens on cognition in post-menopausal women aged ≥ 65 years. These findings suggest the presence of a critical period for HRT-related neuroprotection and underlie the potential importance of early initiation of therapy for cognitive benefit. In this review, we shall first describe the multiple effects of steroids in the nervous system, which may be significant in the ageing process. A critical update of HRT use in women and a discussion of possible perspectives for steroid use are subsequently proposed. PMID: 17135285

Psychoneuroendocrinology. 2006 Sep;31(8):965-75. Epub 2006 Jul 10.

A 3-day estrogen treatment improves prefrontal cortex-dependent cognitive function in postmenopausal women.

Krug R, Born J, Rasch B. Department of Neuroendocrinologie, University of Lübeck, Ratzeburger Allee 160, Hs 23a, D-23538 Lübeck, Germany.

Abstract: Estrogen secretion in young women follows a cyclic pattern characterized by a pronounced surge in estrogen around ovulation. The way in which this estrogen peak affects cognitive functioning is unclear. Short-term estrogen treatment for a few days mimicking normal pre-menopausal estrogen dynamics substantially enhanced cognitive functions in ovariectomized animals. Here, we provide evidence that inducing a single estrogen peak in postmenopausal women improves their cognitive abilities. Healthy women (51-64 yrs, $n=14$) received either 100 microg estrogen transdermally for 3 days or placebo in a double-blind within-subject design. The treatment caused a temporary rise in serum estrogen levels roughly comparable to the mid-cyclic changes in estrogen in young women. At the end of the treatment, the women completed two types of tests involving primarily hippocampus-dependent functions of memory retention or prefrontal cortex-dependent functions. Results revealed a clear beneficial effect of estrogen on tasks mainly involving the prefrontal cortex: performance on a digit-ordering task ($p<0.05$) and on a task requiring short-term memory of event sequences in an unfamiliar story ($p<0.01$) were improved, and susceptibility to interference in the Stroop test ($p<0.05$) was diminished after estrogen. On the other hand, estrogen did not affect hippocampus-dependent retention of a story, with delayed recall tested after 30 min or 1 week, although immediate recall was improved by estrogen. We conclude that in postmenopausal women, a transient increase in plasma estrogen concentration acutely improves prefrontal cortex-dependent cognitive functions, whereas hippocampus-dependent memory retention is less affected. Our results encourage future studies to investigate whether repeated induction of short-lasting estrogen peaks could enhance cognitive efficacy of hormonal replacement therapy. PMID: 16831520

Menopause. 2006 May-Jun;13(3):411-22.

Estrogen therapy selectively enhances prefrontal cognitive processes: a randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in perimenopausal and recently postmenopausal women.

Joffe H, Hall JE, Gruber S, Sarmiento IA, Cohen LS, Yurgelun-Todd D, Martin KA. Women's Center for Behavioral Endocrinology, McLean Hospital, Harvard Medical School, Boston, MA.

OBJECTIVE: Estrogen therapy (ET) seems to differentially effect cognitive processes in younger versus older postmenopausal women, suggesting a window of opportunity when ET is most beneficial. Cognitive improvement in younger postmenopausal women has been attributed to ET's influence on hot flashes and sleep, but empiric examination of the mediating role of menopause symptoms versus direct effects of ET on the brain is limited. DESIGN: In a double-blind trial, 52 women were randomly assigned to estradiol 0.05 mg/day (n = 26) or placebo transdermal patches (n = 26) for 12 weeks. Women completed tests of memory, learning, and executive functioning, and hot flush and sleep assessments at baseline and study end. A subset of women (five ET treated, six placebo treated) also underwent blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) studies. RESULTS: Nondepressed perimenopausal and postmenopausal women were studied. The majority had hot flashes and sleep impairment. Compared with placebo, ET selectively reduced errors of perseveration during verbal recall (P = 0.03), a frontal system-mediated function, but did not influence other cognitive processes. Women with baseline hot flashes had greater cognitive benefit with ET (P < 0.05). Cognitive benefit was not associated with sleep problems or its improvement. Measures of fMRI BOLD activation during tests of verbal and spatial working memory showed significant increases in frontal system activity with ET (P < 0.001). CONCLUSIONS: Estrogen therapy selectively improves executive functioning as demonstrated by reduced perseverative errors and prefrontal cortex activation during verbal recall tasks. Cognitive improvement with ET is associated with hot flashes, but not with sleep, suggesting that ET has a direct central nervous system effect, rather than an indirect effect mediated through improvement of sleep. PMID: 16735938

Ann Intern Med. 2003 Jan 7;138(1):1-9.

Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial.

Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, Cauley JA, Barrett-Connor E; Heart and Estrogen/progestin Replacement Study. Division of General Internal Medicine, University of California, San Francisco, 1701 Divisadero Street, Suite 536, San Francisco, CA 94143-1732.

BACKGROUND: Randomized trials of postmenopausal hormone therapy have found differing effects on fasting glucose levels. No trial has evaluated the effect of hormone therapy on diabetes incidence. OBJECTIVE: To evaluate the effect of hormone therapy on fasting glucose level and incident diabetes. DESIGN: Randomized, double-blind, placebo-controlled trial. SETTING: 20 U.S. clinical centers. PARTICIPANTS: 2763 postmenopausal women with coronary heart disease who were followed for 4.1 years. At baseline, 734 women had diabetes, 218 women had impaired fasting glucose, and 1811 women were normoglycemic; the 2029 women without diabetes were followed for incident diabetes. INTERVENTION: 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate daily, or placebo. MEASUREMENTS: Fasting glucose level was measured at baseline, at year 1, and at the end of the trial. Incident diabetes was defined by self-report of diabetes or disease complication, fasting glucose level of 6.9 mmol/L or greater (> or =126 mg/dL), or initiation of therapy with diabetes medication. RESULTS: Fasting glucose levels increased significantly among women assigned to placebo but did not change among women receiving hormone therapy. The incidence of diabetes was 6.2% in the hormone therapy group and 9.5% in the placebo group (relative hazard, 0.65 [95% CI, 0.48 to 0.89]; P = 0.006). The number needed to treat for benefit to prevent one case of diabetes was 30 (CI, 18 to 103). Changes in weight and waist circumference did not mediate this effect. CONCLUSIONS: In women with coronary disease, hormone therapy reduced the incidence of diabetes by 35%. This observation provides important insights into the metabolic effects of postmenopausal hormones but is insufficient to recommend the use of hormones for secondary prevention of heart disease. PMID: 12513038

J Clin Endocrinol Metab. 2002 Mar;87(3):1062-7.

Estrogen status correlates with the calcium content of coronary atherosclerotic plaques in women.

Christian RC, Harrington S, Edwards WD, Oberg AL, Fitzpatrick LA. Division of Endocrinology, Metabolism, and Nutrition, Department of Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905.

BACKGROUND: Coronary artery calcium, a radiographic marker for atherosclerosis and a predictor of coronary heart disease (CHD), is less extensive in women than in men of the same age. The role of estrogen in the pathogenesis of coronary artery calcification is unknown. We examined the association of estrogen status with extent of calcification and atherosclerotic plaque in coronary arteries of deceased women. **METHODS:** Coronary arteries were obtained at autopsy from 56 white women age 18–98 yr, 46 postmenopausal and 10 premenopausal. Exclusion criteria included patients with coronary stents, coronary artery bypass surgery, and medical-legal cases. Medical records were reviewed for demographics, CHD risk factors, menstrual status, and use of estrogen replacement therapy. Contact microradiography of coronary arteries assessed true calcium content and atherosclerotic plaque area was analyzed histologically. **RESULTS:** The coronary arteries from estrogen-treated postmenopausal women had lower mean coronary calcium content ($P = 0.002$), mean plaque area ($P < 0.0001$), and calcium-to-plaque area ratio ($P = 0.004$) than those from untreated menopausal women. Estrogen status, age, diabetes, and hypertension predicted calcium and plaque area by univariate analysis. After controlling for these CHD risk factors, estrogen status remained an independent predictor of both calcium ($P = 0.014$) and plaque area ($P = 0.001$) in all women. Mean calcium area ($P < 0.05$) but not plaque area ($P = 0.44$) was significantly greater in women treated with estrogen replacement therapy than in premenopausal women. Coronary calcium ($P < 0.007$) and plaque area ($P < 0.03$) varied significantly with age in untreated postmenopausal women, but not in the estrogen-treated or premenopausal women ($P = 0.33$). **CONCLUSIONS:** Estrogen status is associated with coronary calcium and plaque area independent of age and CHD risk factors. Estrogen may modulate the calcium content of atherosclerotic plaques, as well as plaque area and may slow the progression of atherosclerosis in women. PMID: 11889163

Menopause. 2001 Sep-Oct;8(5):347-52.

Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on cardiovascular risk factors.

Chen FP, Lee N, Soong YK, Huang KE. Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan, Republic of China.

OBJECTIVE: To determine the effects of oral and transdermal hormone replacement therapy on lipid profile and hemostatic factors in postmenopausal women. **DESIGN:** Twenty subjects were treated with oral E2 valerate (2 mg) combined with cyproterone acetate (1 mg) (group I) and 21 with transdermal E2 (1.5 mg) plus oral medroxyprogesterone acetate (5 mg) (group II). The effects on lipid profile and hemostatic parameters were evaluated at baseline and after 3, 6, and 12 months of treatment. **RESULTS:** Group I showed a stronger increase of high-density lipoprotein (HDL) cholesterol levels (2-8%) and stronger reduction of atherogenic indices (total cholesterol/HDL cholesterol and low-density lipoprotein/HDL cholesterol) than group II. Group II showed a more pronounced reduction of triglyceride (21-31%) and factor VII (6-10%) levels than group I. Both groups showed reduced concentrations of total cholesterol, low-density lipoprotein cholesterol, tissue plasminogen activator, plasminogen activator inhibitor-1, antithrombin III, and protein S, whereas protein C was increased after 12 months of treatment. **CONCLUSIONS:** The cardioprotective effects of hormone replacement therapy are demonstrated by favorable effects on lipid profile and fibrinolytic activity. Oral hormone replacement therapy showed a more prominent effect on lipoprotein metabolism than did transdermal administration, but transdermal medication had a stronger effect on triglyceride and coagulation factors. However, it needs to be considered that there is an increased risk of venous thrombotic events in the first year of treatment. PMID: 11528361

Lancet. 1996 Aug 17;348(9025):429-32.

Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease.

Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H, Mayeux R. Gertrude H Serglevsky Center, Columbia University, New York, NY 10032.

BACKGROUND: Oestrogen use by postmenopausal women has many health benefits, but findings on the effect of oestrogen in Alzheimer's disease are conflicting. Oestrogen promotes the growth and survival of cholinergic neurons

and could decrease cerebral amyloid deposition, both of which may delay the onset or prevent Alzheimer's disease. To investigate whether use of oestrogen during the postmenopausal period affects the risk of Alzheimer's disease, we studied 1124 elderly women who were initially free of Alzheimer's disease, Parkinson's disease, and stroke, and who were taking part in a longitudinal study of ageing and health in a New York City community. **METHODS:** Relative risks and age-at-onset distributions were calculated from simple and adjusted Cox proportional hazards models. Standard annual clinical assessments and criterion-based diagnoses were used in follow-up (range 1-5 years). **FINDINGS:** Overall, 156 (12.5%) women reported taking oestrogen after onset of menopause. The age at onset of Alzheimer's disease was significantly later in women who had taken oestrogen than in those who did not and the relative risk of the disease was significantly reduced (9/156 [5.8%] oestrogen users vs 158/968 [16.3%] nonusers; 0.40 [95% CI 0.22-0.85], $p < 0.01$), even after adjustment for differences in education, ethnic origin, and apolipoprotein-E genotype. Women who had used oestrogen for longer than 1 year had a greater reduction in risk; none of 23 women who were taking oestrogen at study enrolment has developed Alzheimer's disease. **INTERPRETATION:** Oestrogen use in postmenopausal women may delay the onset and decrease the risk of Alzheimer's disease. Prospective studies are needed to establish the dose and duration of oestrogen required to provide this benefit and to assess its safety in elderly postmenopausal women. PMID: 8709781

Drugs. 1990 Feb;39(2):203-17.

Estrogen therapy during menopause. Practical treatment recommendations.

Sitruk-Ware R. Medical Department, Ciba-Geigy Ltd, Basle, Switzerland.

Abstract: The potential benefits of estrogen replacement therapy (ERT) for postmenopausal women are now generally recognised, and no scientist involved in this field of research will deny the gratifying results of hormone therapy. However, in the risk-benefit equation the adverse effects of ERT must be carefully considered. Most of the harmful adverse effects of ERT have been related firstly to the absence of progestational balance, and secondly to the fact that most of the estrogens previously available for clinical use were artificial and administered orally, resulting in intensive hepatic metabolism, leading to metabolic disturbances. The need for the addition of progestogen leads also to consideration of the adverse effects of these substances. During the past decade therapeutic improvements have been achieved. Knowledge about the different types of steroids now available, the right choice of dosage and duration of therapy according to the needs of the patient, and the new alternative delivery systems improves day by day. Various steroids are now available for clinical use. Among the estrogens, orally administered drugs, natural derivatives of estradiol, and nonoral drugs delivered by injection, implant, vaginal ring or cream, ointment or transdermal system are at the prescriber's disposal. Among the progestogens available to the prescriber and recommended to be added to ERT, the molecules derived from testosterone [norethisterone (norethindrone), norgestrel] are less prescribed than the molecules derived from progesterone (didrogesterone) or from 17-hydroxyprogesterone (medroxyprogesterone acetate). In menopausal therapy the latter derivatives from progesterone or 17-hydroxyprogesterone are preferable, but low doses of any type of progestogen could be both protective of the target organs and devoid of harmful effects. Careful consideration of contraindications of treatment and regular follow-up are prerequisites for safe therapy. Recent epidemiological data now demonstrate clearly that the use of ERT under these conditions affords protection against osteoporosis and cardiovascular disease. Clear benefits to women's health may therefore be obtained from the adequate choice and surveillance of therapy. PMID: 2183999

Praxis (Bern 1994). 1997 Aug 13;86(33):1245-8.

Topical hormonal treatment and urogenital atrophy.

Sitruk-Ware R, Thomas JL. Service d'Endocrinologie, Hôpital Saint Antoine, Paris.

Abstract: Hypoestrogenemia-derived urogenital symptoms after menopause manifest after some years of hormonal deficit and appear commonly in elderly, untreated women. In the urogenital tract low postmenopausal estrogen levels lead to vaginal irritation and dryness and to dyspareunia, often accompanied by other symptoms like uriesthesis, incontinence or recurrent infections. Every systemic estrogen treatment is accepted as efficient for the correction of urogenital symptoms, often even at doses lower than those necessary for the correction of vasomotor symptoms. Diverse local treatments have been proposed: estriol, promestriene and low-dose estrone or estradiol. Promestriene applied locally stimulates differentiation and maturation of vaginal mucosa and compensates local hypoestrogenic effects without marked hormonal effects outside the vagina. Vaginal application of estrone, on the other hand, has rather been proposed for systemic hormone substitution and elevated levels of estrone and estradiol observed in the plasma render this method in-appropriate in cases where

strictly local effects are desired. Recently, very low doses of estradiol in a range of 7.5 micrograms/day have been proposed for the treatment of urogenital atrophy by means of a prolonged release regimen. Among the described preparations, those with strictly local (devoid of systemic) effects should be restricted to patients with contraindications for systemic substitution therapy. Local estrogen therapies are recommended for the treatment of complaints due to vulvar and vaginal atrophy. They have also been proposed by certain authors for the acceleration of the cervico-vaginal and vulvar cicatrisation after surgical interventions or postpartum. The presence of miction disorders in elderly postmenopausal women is also a point in favour of local treatment. PMID: 9381009

Estriol

Menopause. 2009 Sep-Oct;16(5):978-83.

Efficacy and safety of vaginal estriol and progesterone in postmenopausal women with atrophic vaginitis.

Chollet JA, Carter G, Meyn LA, Mermelstein F, Balk JL. Beth Israel Deaconess Medical Center, Boston, MA, USA.

OBJECTIVE: The aim of this study was to assess the efficacy and safety of intravaginal estriol and progesterone on atrophic vaginitis in postmenopausal women. **METHODS:** Under a physician-sponsored Investigational New Drug application, 19 healthy postmenopausal women with atrophic vaginitis received vaginal suppositories containing estriol (1 mg) and progesterone (30 mg). The participants were instructed to insert one suppository intravaginally once daily for 2 weeks and thrice weekly for a total of 6 months. Vaginal pH, Vaginal Maturation Index, urinalysis, self-reported vaginal dryness, menopausal quality of life, and serum estriol and progesterone levels were measured at enrollment and after 3 and 6 months of suppository use. Endometrial biopsies were obtained at enrollment and at 6 months. After 2 weeks of therapy, six participants had serum estriol and progesterone measured. **RESULTS:** The Vaginal Maturation Index, vaginal pH, and vaginal dryness rating improved significantly at 3 and 6 months compared with baseline. Menopausal quality of life scores improved significantly in all domains, with the sexual subscale showing the most improvement. There were no cases of endometrial hyperplasia after 6 months of suppository use. Serum preinsertion estriol at week 2 and months 3 and 6 were similar to baseline levels. Serum preinsertion progesterone increased but returned to baseline preinsertion levels at month 6, and preinsertion levels were significantly less at month 6 compared with month 3. **CONCLUSIONS:** Intravaginal administration of a combination estriol and progesterone agent to women with atrophic vaginitis may represent a safe and effective alternative to systemic hormone replacement, although this study was not adequate to provide proof of efficacy given that it was uncontrolled. PMID: 19390463

Menopause. 2004 Jan-Feb;11(1):49-56.

Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women.

Dessole S, Rubattu G, Ambrosini G, Gallo O, Capobianco G, Cherchi PL, Marci R, Cosmi E. Department of Pharmacology, Gynecology and Obstetrics, University of Sassari, Sassari, Italy.

OBJECTIVE: To assess the efficacy and safety of intravaginal estriol administration on urinary incontinence, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women. **DESIGN:** Eighty-eight postmenopausal women with urogenital aging symptoms were enrolled in this prospective, randomized, placebo-controlled study. Participants were randomly divided into two groups, with each group consisting of 44 women. Women in the treatment group received intravaginal estriol ovules: 1 ovule (1 mg) once daily for 2 weeks and then 2 ovules once weekly for a total of 6 months as maintenance therapy. Women in the control group received inert placebo vaginal suppositories in a similar regimen. We evaluated urogenital symptomatology, urine cultures, colposcopic findings, urethral cytologic findings, urethral pressure profiles, and urethrocystometry before as well as after 6 months of treatment. **RESULTS:** After therapy, the symptoms and signs of urogenital atrophy significantly improved in the treatment group in comparison with the control group. Thirty (68%) of the treated participants, and only seven (16%) of the control participants registered a subjective improvement of their incontinence. In the treated participants, we observed significant improvements of colposcopic findings, and there were statistically significant increases in mean maximum urethral pressure, in mean urethral closure pressure as well as in the abdominal pressure transmission ratio to the proximal urethra. Urethrocystometry showed positive but not statistically significant modifications. **CONCLUSIONS:** Our results show that intravaginal administration of estriol may represent a satisfactory therapeutic choice for those postmenopausal women with urogenital tract disturbances who have contraindications or refuse to undergo standard hormone therapy. PMID: 14716182

Maturitas. 2001 Sep 28;39(3):253-7.

Short term oral estriol treatment restores normal premenopausal vaginal flora to elderly women.

Yoshimura T, Okamura H. Department of Obstetrics and Gynecology, Kumamoto University School of Medicine, Honjo 1-1-1, 860-8556, Kumamoto, Japan.

OBJECTIVE: Estriol is an estrogen with considerably weaker stimulatory effects on endometrial proliferation than estradiol. A study was conducted to determine the effects of oral estriol on vaginal flora and endometrial thickness. **METHODS:** Fifty-nine postmenopausal women (50-75 years of age), complaining of pruritus or vaginal discharge, participated in the study. Vaginal flora and endometrial thickness were evaluated before treatment and after receiving oral estriol (2 mg/day) for 14 days. **RESULTS:** Prior to treatment, lactobacilli were found in vaginal cultures from only six of the 59 study participants, whereas after treatment, the vaginal flora of 27 women showed a presence of lactobacilli ($P < 0.0001$). Endometrial thickness exceeded 5 mm in only five cases. No side effects were reported. **CONCLUSION:** Estriol, which has little effect on the endometrium, has the potential to be highly useful for the treatment of atrophic vaginitis. PMID: 11574185

Maturitas. 2000 Feb 15;34(2):169-77.

Efficacy and safety of oral estriol for managing postmenopausal symptoms.

Takahashi K, Manabe A, Okada M, Kurioka H, Kanasaki H, Miyazaki K. Department of Obstetrics and Gynecology, Shimane Medical University, Izumo, Japan.

OBJECTIVE: to assess the therapeutic efficacy and safety of oral estriol for the treatment of climacteric symptoms in postmenopausal women. **METHODS:** 68 postmenopausal women with climacteric symptoms received oral estriol, 2 mg/day, daily for 12 months. We evaluated the degree of climacteric complaints with estriol therapy; serum levels of gonadotropins, estradiol (E2) and lipids; biochemical markers of bone metabolism; blood pressure; and side effects both at baseline and during treatment. Climacteric symptoms were assessed according to the menopausal index (MI), a version of the Kupperman index that had been modified for Japanese women. **RESULTS:** oral estriol therapy significantly reduced total MI scores. The greatest relief was noted for hot flushes, night sweats, and insomnia. Estriol treatment significantly lowered serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) concentrations but did not affect any of the other parameters (lipids, bone, liver and blood pressure) during the study period. Slightly vaginal bleeding occurred in 14.3% of those who underwent natural menopausal women. Histologic evaluation of the endometrium and ultrasound assessment of the breasts following 12 months of estriol treatment found normal results in all women. **CONCLUSION:** Estriol is a safe and effective alternative for relieving climacteric symptoms in postmenopausal Japanese women. PMID: 10714912

Altern Med Rev. 1998 Apr;3(2):101-13.

Estriol: safety and efficacy.

Head KA. Thorne Research, Inc., Dover, ID 83825, USA.

Abstract: While conventional hormone replacement therapy provides certain benefits, it is not without significant risks. Estriol has been found to provide some of the protection without the risks associated with stronger estrogens. Depending upon the situation, estriol may exert either agonistic or antagonistic effects on estrogen. Estriol appears to be effective at controlling symptoms of menopause, including hot flashes, insomnia, vaginal dryness, and frequent urinary tract infections. Results of research on its bone-density-maintaining effects have been contradictory, with the most promising results coming from Japanese studies. Estriol's effect on cardiac risk factors has also been somewhat equivocal; however, unlike conventional estrogen prescriptions, it does not seem to contribute to hypertension. Although estriol appears to be much safer than estrone or estradiol, its continuous use in high doses may have a stimulatory effect on both breast and endometrial tissue. PMID: 9577246

Estradiol

Maturitas. 2008 Jul-Aug;60(3-4):185-201. Epub 2008 Sep 5.

Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review.

L'hermite M, Simoncini T, Fuller S, Genazzani AR. Department of Gynecology and Obstetrics, Université Libre de Bruxelles, Bruxelles, Belgium.

Abstract: Hormone replacement therapy (HRT) in young postmenopausal women is a safe and effective tool to counteract climacteric symptoms and to prevent long-term degenerative diseases, such as osteoporotic fractures, cardiovascular disease, diabetes mellitus and possibly cognitive impairment. The different types of HRT offer to many extent comparable efficacies on symptoms control; however, the expert selection of specific compounds, doses or routes of administration can provide significant clinical advantages. This paper reviews the role of the non-oral route of administration of sex steroids in the clinical management of postmenopausal women. Non-orally administered estrogens, minimizing the hepatic induction of clotting factors and others proteins associated with the first-pass effect, are associated with potential advantages on the cardiovascular system. In particular, the risk of developing deep vein thrombosis or pulmonary thromboembolism is negligible in comparison to that associated with oral estrogens. In addition, recent indications suggest potential advantages for blood pressure control with non-oral estrogens. To the same extent, a growing literature suggests that the progestins used in association with estrogens may not be equivalent. Recent evidence indeed shows that natural progesterone displays a favorable action on the vessels and on the brain, while this might not be true for some synthetic progestins. Compelling indications also exist that differences might also be present for the risk of developing breast cancer, with recent trials indicating that the association of natural progesterone with estrogens confers less or even no risk of breast cancer as opposed to the use of other synthetic progestins. In conclusion, while all types of hormone replacement therapies are safe and effective and confer significant benefits in the long-term when initiated in young postmenopausal women, in specific clinical settings the choice of the transdermal route of administration of estrogens and the use of natural progesterone might offer significant benefits and added safety.

PMID: 18775609

Endocrinology. 2001 Mar;142(3):969-73.

Minireview: neuroprotective effects of estrogen-new insights into mechanisms of action.

Wise PM, Dubal DB, Wilson ME, Rau SW, Böttner M. Department of Physiology, College of Medicine, University of Kentucky, Lexington, Kentucky 40536, USA.

Abstract: An accumulating body of evidence clearly establishes that estradiol is a potent neuroprotective and neurotrophic factor in the adult: it influences memory and cognition, decreases the risk and delays the onset of neurological diseases such as Alzheimer's disease, and attenuates the extent of cell death that results from brain injuries such as cerebrovascular stroke and neurotrauma. Thus, estradiol appears to act at two levels: 1) it decreases the risk of disease or injury; and/or 2) it decreases the extent of injury incurred by suppressing the neurotoxic stimulus itself or increasing the resilience of the brain to a given injury. During the past century, the average life span of women has increased dramatically, whereas the time of the menopause has remained essentially constant. Thus, more women will live a larger fraction of their lives in a postmenopausal, hypoestrogenic state than ever before. Clearly, it is critical for us understand the circumstances under which estradiol exerts protective actions and the cellular and molecular mechanisms that underlie these novel, nonreproductive actions.

PMID: 11181507

Obstet Gynecol. 2001 Sep;98(3):391-7.

Sleep quality, estradiol levels, and behavioral factors in late reproductive age women.

Hollander LE, Freeman EW, Sammel MD, Berlin JA, Grisso JA, Battistini M. Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104-4283.

OBJECTIVE: To estimate the prevalence of perceived poor sleep in women aged 35-49 years and to correlate sleep quality with levels of gonadal steroids and predictors of poor sleep. **METHODS:** A cohort of 218 black and 218 white women aged 35-47 years at enrollment (aged 37-49 at final follow-up) with regular menstrual cycles was identified through random digit dialing for a longitudinal study of ovarian aging correlates. Data obtained at four assessment periods, including enrollment, over a 2-year interval were collected between days 1 and 6 (mean = 3.9) of the menstrual cycle. The primary outcome

measure was subjects' rating of sleep quality at each assessment period. Associations of sleep quality with hormone levels (estradiol, follicle-stimulating hormone, luteinizing hormone, testosterone, and dehydroepiandrosterone sulfate) and other clinical, behavioral, and demographic variables were examined in bivariable and multivariable analyses. RESULTS: Approximately 17% of subjects reported poor sleep at each assessment period. Significant independent associations with poor sleep included greater incidence of hot flashes (odds ratio [OR] 1.52; 95% confidence interval [CI] 1.08, 2.12, $P = .02$), higher anxiety levels (OR 1.03; 95% CI 1.00, 1.06, $P = .04$), higher depression levels (OR 1.05; 95% CI 1.02, 1.07, $P < .001$), greater caffeine consumption (OR 1.25; 95% CI 1.04, 1.49, $P = .02$), and lower estradiol levels in women aged 45-49 (OR 0.53; 95% CI 0.34, 0.84, $P = .006$), after adjustment for current use of sleep medications. CONCLUSION: Both hormonal and behavioral factors were associated with sleep quality. Estradiol levels are an important factor in poor sleep reported by women in the 45-49 age group. Further evaluation of estrogen treatment for poor sleep of women 45 years and older is warranted. PMID: 11530118

Menopause. 2000 Sep-Oct;7(5):318-26.

Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density.

Miller BE, De Souza MJ, Slade K, Luciano AA. Center for Fertility and Reproductive Endocrinology, New Britain General Hospital, Connecticut 06050.

Abstract: OBJECTIVES: The purpose of this investigation was to evaluate the relative efficacy of the sublingual administration of micronized estradiol (E2), progesterone (P4), and testosterone (T) on bone mineral density and biochemical markers of bone metabolism. DESIGN: In this double-blind, prospective study, postmenopausal women were randomly assigned to one of four treatment groups: hysterectomized women were assigned to either 1) micronized E2 (0.5 mg) or 2) micronized E2 (0.5 mg) + micronized T (1.25 mg). Women with intact uteri were assigned to either 3) micronized E2 (0.5 mg) + micronized P4 (100 mg) or 4) micronized E2 (0.5 mg) + micronized P4 (100 mg) + micronized T (1.25 mg). For the purpose of this study, the four treatment groups were combined into two groups for all comparisons. The E2 and E2+P4 groups were combined into the HRT alone group ($n=30$), and the E2+T and E2+P4+T groups were combined into the HRT + T group ($n=27$). Hormones were administered sublingually as a single tablet twice a day for 12 months. Bone mineral density was measured in the anterior-posterior lumbar spine and total left hip via dual energy x-ray absorptiometry. Bone metabolism was assessed via serum bone-specific alkaline phosphatase and urinary deoxypyridinoline and cross-linked N-telopeptide of type I collagen, both normalized to creatinine. Data were analyzed via a repeated measures analysis of variance and a Student's t test ($\alpha=0.05$). RESULTS: The subjects were of similar age (54.0 ± 0.8 years), height (64.0 ± 0.3 in), weight (157.6 ± 4.2 lb), and had similar baseline follicle-stimulating hormone (66.4 ± 3.2 mIU/L), E2 (26.4 ± 1.5 pg/ml), P4 (0.3 ± 0.1 ng/ml), total T (19.0 ± 1.5 ng/dL), and bioavailable T (3.7 ± 0.3 ng/dL) levels. During therapy, serum levels increased ($p < 0.05$) for each hormone. Bone mineral density and bone markers at baseline were similar for each treatment group. Bone-specific alkaline phosphatase decreased ($p < 0.05$) by $-14.3 \pm 4.1\%$ in the HRT alone group and by $-8.2 \pm 4.6\%$ in the HRT + T group. Deoxypyridinoline levels decreased significantly in the HRT alone and HRT + T groups, $-14.4 \pm 6.8\%$ and $-26.9 \pm 7.6\%$, respectively. Significant reductions ($p < 0.05$) in cross-linked N-telopeptide of type I collagen were also observed in both groups, $-24.4 \pm 6.5\%$ and $-39.5 \pm 8.6\%$, respectively. Bone mineral density in the lumbar spine increased ($p < 0.05$) by $+2.2 \pm 0.5\%$ in the HRT alone group and by $+1.8 \pm 0.6\%$ in the HRT + T group. Total hip bone mineral density was maintained in the HRT alone group ($+0.4 \pm 0.4\%$) and increased ($p < 0.05$) in the HRT + T group ($+1.8 \pm 0.5\%$). CONCLUSIONS: Sublingual micronized HRT favorably decreases serum and urine markers of bone metabolism, prevents bone loss, and results in a slight increase in spine and hip bone mineral density. Although the addition of testosterone to HRT for 1 year did not result in added benefit to the spine bone mineral density, it did result in a significant increase in hip bone mineral density. Longer duration of therapy may have further improved these outcomes.

PMID: 10993031

Am J Hypertens. 1999 Oct;12(10 Pt 1):1000-8.

Double-blind randomized placebo-controlled study of transdermal estrogen replacement therapy on hypertensive postmenopausal women.

Modena MG, Molinari R, Muia N Jr, Castelli A, Pala F, Rossi R. Institute of Cardiology II, Department of Internal Medicine, Policlinico Hospital, University of Modena, Italy.

Abstract: We investigated the effects of transdermal 17beta-estradiol, combined with standard antihypertensive therapy, on the modification of the cardiovascular risk profile in hypertensive postmenopausal women. In a randomized, double-blind, placebo-controlled study, we enrolled 200 postmenopausal women with mild to moderate hypertension. Patients received 17beta-estradiol (50 microg/day, transdermal) and norethisterone acetate (2.5 mg/ day, orally) or placebo. At baseline serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, and fibrinogen plasma levels were measured and all subjects underwent complete M-mode and 2-D echocardiograms, which were repeated after 6, 12, and 18 months of hormonal replacement therapy. Compared with placebo, all values decreased significantly except for HDL cholesterol. In both groups, no modifications were observed in echocardiographic parameters, except for left ventricular mean diastolic and systolic wall thickness and left ventricular mass index, which showed a significant decrease in both groups. The reduction was greater in the treated group; the percentage of patients with left ventricular hypertrophy was 46% before randomization and 17.2% after 18 months of treatment ($P < .0001$), whereas in group II the percentage was 48% at baseline and 31.5% after 18 months ($P < .05$). In conclusion, transdermal 17beta-estradiol, associated with antihypertensive therapy, may contribute to the reduction of cardiovascular risk profile in hypertensive postmenopausal women.

PMID: 10560786

Hypertension. 1999 May;33(5):1190-4.

Estradiol with or without progesterone and ambulatory blood pressure in postmenopausal women.

Seely EW, Walsh BW, Gerhard MD, Williams GH. Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts.

Abstract: The purpose of this study was to determine whether transdermal estradiol and intravaginal progesterone given in doses to mimic the premenopausal state would lower blood pressure (BP) in postmenopausal women. Fifteen healthy postmenopausal women were studied in each of 3 conditions: on placebo, after 8 weeks of transdermal estradiol 0.2 mg twice per week, and again 2 weeks after addition of intravaginal progesterone 300 mg/d. Women were studied at each point after 2 days of 100 mmol/d sodium intake. Twenty-four-hour ambulatory BP monitoring was performed, and blood was assayed for estradiol, progesterone, and hormones of the renin-angiotensin-aldosterone system (RAAS). ANOVA with pairwise comparisons was used for analysis. Urinary sodium excretion was similar at each time point. Levels of estrogen and progesterone similar to those in premenopausal women were achieved. On estradiol, nocturnal systolic BP (110 ± 3 mm Hg), diastolic BP (63 ± 2 mm Hg), and mean BP (77 ± 2 mm Hg) fell significantly ($P < 0.02$) compared with placebo systolic BP (116 ± 2 mm Hg), diastolic BP (68 ± 2 mm Hg), and mean BP (82 ± 2 mm Hg). Daytime BP followed the same trend but was significantly lower only for mean BP. There was no activation of the RAAS. The addition of progesterone resulted in no further fall in BP but a significant activation of the RAAS. Thus, contrary to what is often assumed, administration of estradiol with or without progesterone not only did not raise BP but rather substantially lowered BP. This BP-lowering effect may be responsible for the lower incidence of hypertension in premenopausal than in postmenopausal women.

PMID: 10334810

Atherosclerosis. 1998 Jun;138(2):255-62.

Antioxidant protection of LDL by physiologic concentrations of estrogens is specific for 17-beta-estradiol.

Shwaery GT, Vita JA, Keaney JF Jr. Evans Memorial Department of Medicine, and Whitaker Cardiovascular Institute, Boston University Medical Center, MA 02118.

Abstract: Risk for coronary artery disease is reduced by exposure to estrogens, although the mechanisms of protection are not fully defined. Recent observations have shown that physiologic concentrations of 17-beta-estradiol (E2) exhibit antioxidant activity in vitro, slowing the formation of atherogenic, oxidized low-density lipoprotein (LDL). Using concentrations physiologically relevant for premenopausal women, we compared the antioxidant potency of estrone (E1), E2, and estril (E3) as measured by their ability to inhibit LDL oxidation. Plasma was incubated with 10 nmol/l estrogens for 4 h at 37 degrees

C, followed by LDL isolation and Cu²⁺-mediated oxidation in conjugated diene assays. Only E2 demonstrated antioxidant activity at these physiologic concentrations. Resistance to oxidation was not associated with sparing of endogenous alpha-tocopherol during plasma incubations. Incubation of plasma with radiolabeled estrogens yielded similar association of E1 and E2 with LDL which was 5-8-fold greater than the association of E3. Chromatographic analysis revealed the association of authentic E1 with LDL, while plasma-derived E2 esters were the major form of E2 associated with LDL which was resistant to oxidation. Thus, conjugation in plasma and association of E2 esters with LDL appear to be specific for E2 among these estrogens and render this LDL resistant to oxidation by Cu²⁺. This antioxidant activity may be another means whereby E2 protects against coronary artery disease in women. PMID: 9690908

Maturitas. 1997 Apr;26(3):211-7.

Percutaneous estradiol gel with an intrauterine levonorgestrel releasing device or natural progesterone in hormone replacement therapy.

Suvanto-Luukkonen E, Sundström H, Penttinen J, Läärä E, Pramila S, Kauppila A. Kainuu Central Hospital, Department of Obstetrics and Gynecology, Oulu, Finland.

OBJECTIVE: To evaluate the bleeding patterns and clinical compliance associated with postmenopausal amenorrhea-inducing forms of hormone replacement therapy using either percutaneous estradiol-gel and a levonorgestrel-releasing intrauterine device or an oral/vaginal natural progesterone. **METHODS:** Sixty postmenopausal women with an intact uterus were followed over 12 months in this open, non-randomised, parallel group study. All patients continuously received a gel containing 1.5 mg of estradiol daily. The women were divided into three groups on the basis of progestin administration. Twenty women (group I) had a levonorgestrel-releasing device (LNG-IUD) inserted at the beginning of the study. Twenty-one women (group II) received oral natural micronised progesterone (oral P) 100 mg daily during 25 calendar days each month, and 19 women (group III) used vaginal natural micronised progesterone (vaginal P) 100-200 mg daily during 25 calendar days each month (higher dose if spotting occurred). Clinic visits were at 0, 3, 6 and 12 months. Bleeding patterns were recorded by the patient in a diary and clinical compliance was evaluated at control visits during the treatment. Symptoms were recorded using a modified Kuppermann index. The serum estradiol concentration was determined at the 0, 6 and 12 month control visits. **RESULTS:** 80% (n = 16) of the patients in the LNG-IUD group, 67% (n = 14) in the oral P group II and 53% (n = 10) in the vaginal P group were without bleeding at 12 months. Spotting was common during the first 3 months. Symptom relief was good in each group. The LNG-IUD did not cause any serious side-effects. Compliance was good for LNG-IUD and oral progesterone but not for vaginal progesterone. **CONCLUSIONS:** Percutaneous estradiol-gel associated with LNG-IUD is an appropriate method of hormone replacement therapy. The combination of oral natural progesterone with estradiol-gel is also useful, although bleeding episodes complicated the treatment in one third of the patients. The vaginal administration of natural progesterone was impractical due to bleeding disorders. PMID: 9147353

Am J Med. 1997 Sep 22;103(3A):19S-25S.

Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer's disease.

Simpkins JW, Green PS, Gridley KE, Singh M, de Fiebre NC, Rajakumar G. Department of Pharmacodynamics and Center for the Neurobiology of Aging, University of Florida, Gainesville 32610.

Abstract: Recent evidence supports a role for estrogens in both normal neural development and neuronal maintenance throughout life. Women spend 25-33% of their life in an estrogen-deprived state and retrospective studies have shown an inverse correlation between dose and duration of estrogen replacement therapy (ERT) and incidence of Alzheimer's disease (AD), suggesting a role for estrogen in the prevention and/or treatment of neurodegenerative diseases. To explore these observations further, an animal model was developed using ovariectomy (OVX) and ovariectomy with estradiol replacement (E2) in female Sprague-Dawley rats to mimic postmenopausal changes. Using an active-avoidance paradigm and a spatial memory task, the effects of estrogen deprivation were tested on memory-related behaviors. OVX caused a decline in avoidance behavior, and estrogen replacement normalized the response. In the Morris water task of spatial memory, OVX animals showed normal spatial learning but were deficient in spatial memory, an effect that was prevented by estrogen treatment. Together these data indicate that OVX in rats results in an estrogen-reversible impairment of learning/memory behavior. Because a plethora of information has been generated that links decline in memory-related behavior to dysfunction of cholinergic neurons, the effects of estrogens on cholinergic neurons were tested. We demonstrated that OVX causes a decrease in high affinity choline uptake and choline acetyltransferase activity in the hippocampus and

frontal cortex; ERT reverses this effect. Further, we showed that estrogens promote the expression of mRNA for brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), 2 neurotrophic substances that have been shown to ameliorate the effects of age and injury on cholinergic neurons. Tissue culture models were used to evaluate whether estrogen treatment increases the survival of neurons when exposed to a variety of insults. 17-beta-Estradiol (beta-E2) protects cells from the neurotoxic effects of serum deprivation and hypoglycemia in human neuroblastoma cell lines. We have also observed that 17-alpha-estradiol (alpha-E2), a weak estrogen, shows neuroprotective efficacy in the SK-N-SH cell line at concentrations equivalent to beta-E2. Finally, we have observed that tamoxifen, a classic estrogen antagonist, blocks only one-third of the neuroprotective effects of either alpha-E2 or beta-E2. Collectively, these results indicate that estrogen is behaviorally active in tests of learning/ memory; activates basal forebrain cholinergic neurons and neurotrophin expression; and is neuroprotective for human neuronal cultures. We conclude that estrogen may be a useful therapy for AD and other neurodegenerative diseases. PMID: 9344403

Maturitas. 1996 May;24(1-2):43-50.

Transdermal estrogen replacement therapy: beneficial effects on hemostatic risk factors for cardiovascular disease.

Lindoff C, Peterson F, Lecander I, Martinsson G, Astedt B. Department of Obstetrics and Gynecology, University Hospital, Lund, Sweden.

OBJECTIVES: To assess the effect of estrogen replacement therapy on hemostatic risk factors for cardiovascular disease (CVD) in postmenopausal women during 2 years of treatment. **METHODS:** In an open prospective study, patients (n = 42) were investigated before and during 2 years of treatment, and compared to an untreated postmenopausal control group (n = 18) followed during the same period, healthy premenopausal women (n = 20) being included as a reference group for premenopausal values. The patients underwent treatment with transdermal 17 beta-estradiol (E2) (50 micrograms/24 h), oral medroxyprogesterone acetate (5 mg/day) being added for 12 days every second month. **RESULTS:** After 2 years of treatment there was a significant increase in t-PA antigen (P = 0.01) and a significant decrease in F VII antigen (P = 0.01). PAI-1 antigen concentrations decreased slightly. Fibrinogen concentrations were already significantly decreased at 3-month follow-up (P = 0.01), and were still low after 2 years. By contrast, at 2-year follow-up the postmenopausal control group manifested significant increases in F VII and PAI-1 antigen and slight increases in fibrinogen, which resulted in significant differences between patients and controls. Regression analysis showed the increase in the serum estradiol concentrations to be inversely correlated to the decreases in the plasma concentrations of F VII antigen (r = -0.34, P = 0.001) and fibrinogen (r = -0.35, P = 0.001). There were no changes in AT III or protein C in any group. **CONCLUSIONS:** The increase in serum estradiol concentrations due to replacement therapy did not adversely affect the studied components of the fibrinolytic and protein C defense system against thrombosis, and resulted in beneficial decreases in F VII antigen and fibrinogen. These findings may help to explain the beneficial effects of estrogen replacement therapy in terms of protection from cardiovascular disease. PMID: 8794433

N Engl J Med. 1986 Jun 19;314(25):1615-20.

Biologic effects of transdermal estradiol.

Chetkowski RJ, Meldrum DR, Steingold KA, Randle D, Lu JK, Eggens P, Hershman JM, Alkjaersig NK, Fletcher AP, Judd HL.

Abstract: We conducted a dose-response study in 23 postmenopausal women to compare the physiologic effects of transdermal estradiol and oral conjugated equine estrogens. The doses studied were 25, 50, 100, and 200 micrograms of transdermal estradiol per 24 hours, and 0.625 and 1.25 mg of oral conjugated estrogens. Transdermal estradiol increased circulating concentrations of estradiol and estrone. Oral conjugated estrogens also raised the levels of estrogen, particularly estrone. Both preparations lowered gonadotropin levels, decreased the percentages of vaginal parabasal cells, increased the percentage of superficial cells, and lowered urinary calcium excretion. The effects of 0.625 and 1.25 mg of oral estrogens were similar to those of 50 and 100 micrograms of transdermal estradiol per 24 hours, respectively. Oral estrogens significantly increased circulating levels of renin substrate, sex-hormone-binding globulin, thyroxine-binding globulin, and cortisol-binding globulin; transdermal estradiol had no effect. The higher dose of oral estrogens had favorable effects on concentrations of low-density and high-density lipoproteins, but transdermal estradiol did not. Neither preparation affected any of the four clotting factors studied. These data indicate that transdermal estradiol can elicit many of the desirable actions of estrogen while avoiding the pharmacologic effects of oral estrogens on hepatic proteins. PMID: 3012339

Obstet Gynecol. 1991 May;77(5):758-64.

Pharmacokinetics of percutaneous estradiol: a crossover study using a gel and a transdermal system in comparison with oral micronized estradiol.

Scott RT Jr, Ross B, Anderson C, Archer DF. Department of Obstetrics and Gynecology, Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk.

Abstract: The pharmacokinetics of three transdermal estradiol (E2) replacement regimens were studied following establishment of steady-state dynamics. Oestrogel 3.0 mg, Oestrogel 1.5 mg, and Estraderm transdermal delivery system 4 mg (0.05 mg/day) were administered for 14 days each to 15 postmenopausal volunteers, with a 14-day washout period between each regimen. The percutaneous E2 pharmacokinetics were compared with an oral micronized E2 preparation. Venous samples were obtained at 0, 1, 2, 4, 8, 12, and 24 hours on 3 sequential days 11 days after initial application of the Oestrogel and the transdermal delivery system, and at the same times after oral E2 ingestion. All three percutaneous regimens provided nearly constant serum E2 and estrone (E1) levels throughout their use. The mean serum E2 levels were 102.9 +/- 39.9, 68.1 +/- 27.4, and 41.1 +/- 13.5 pg/mL for Oestrogel 3.0 mg, Oestrogel 1.5 mg, and Estraderm, respectively. Oral E2 resulted in a mean serum E2 level of 114.0 +/- 65.2 pg/mL with marked peak and nadir values. The E1/E2 ratio was comparable with all three percutaneous regimens (1.08-1.33) and was significantly lower than that found with oral Estrace (5.05).
PMID: 2014092

Progesterone

Exp Clin Psychopharmacol. 2007 Oct;15(5):427-44.

Progesterone: review of safety for clinical studies.

Goletiani NV, Keith DR, Gorsky SJ. Alcohol and Drug Abuse Research Center, Harvard Medical School, McLean Hospital, Massachusetts.

Abstract: Progesterone is a steroid hormone that is important for reproductive function. Progesterone is used in a number of clinical applications and has been investigated as a possible novel approach for treatment of stimulant drug abuse. Extensive clinical studies have been conducted to examine the subjective and physiological effects of exogenous progesterone administration and to evaluate its side effects. This review summarizes the safety and side effects of acute and chronic administration of 3 progesterone formulations (synthetic, natural, and micronized natural), several routes of administration (oral, intramuscular, intravenous, intravaginal, intranasal, transdermal, and rectal), and dosing regimens. Synthetic progestins marketed as Provera, PremPro, and Cycrin are widely used but may produce a number of significant side effects, such as fatigue, fluid retention, lipid level alterations, dysphoria, hypercoagulant states, and increased androgenicity. Natural progesterones are reported to have milder adverse effects, depending on the route of administration. Micronized natural progesterone is available for oral administration, has better bioavailability and fewer side effects than natural progesterone, and is convenient to administer. Therefore, micronized natural progesterone appears to be a safe and effective alternative to synthetic and natural progesterone formulations for variety of clinical and research applications.
PMID: 17924777

Menopause. 2005 Mar;12(2):232-7.

Percutaneous administration of progesterone: blood levels and endometrial protection.

Stanczyk FZ, Paulson RJ, Roy S. Department of Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles, CA.

Abstract: There is controversy about the beneficial effects of topical progesterone creams used by postmenopausal women. A major concern is that serum progesterone levels achieved with progesterone creams are too low to have a secretory effect on the endometrium. However, antiproliferative effects on the endometrium have been demonstrated with progesterone creams when circulating levels of progesterone are low. Thus, effects of topical progesterone creams on the endometrium should not be based on serum progesterone levels, but on histologic examination of the endometrium. Despite the low serum progesterone levels achieved with the creams, salivary progesterone levels are very high, indicating that progesterone levels in serum do not necessarily reflect those in tissues. The mechanism by which the serum progesterone levels remain low is not known. However, one explanation is that after absorption through the skin, the lipophilic ingredients of creams, including progesterone, may have a preference for saturating the fatty layer below the dermis. Because there appears to be

rapid uptake and release of steroids by red blood cells passing through capillaries, these cells may play an important role in transporting progesterone to salivary glands and other tissues. In contrast to progesterone creams, progesterone gels are water-soluble and appear to enter the microcirculation rapidly, thus giving rise to elevated serum progesterone levels with progesterone doses comparable to those used in creams. PMID: 15772572

Gynecol Obstet Invest. 2002;53(1):32-7.

The clinical usefulness of salivary progesterone measurement for the evaluation of the corpus luteum function.

Ishikawa M, Sengoku K, Tamate K, Takaoka Y, Kane M, Fottrell PF. Department of Obstetrics and Gynecology, Asahikawa Medical College, Asahikawa, Japan.

Abstract: The present study was designed to construct reliable daily salivary progesterone profiles throughout the luteal phase to accurately evaluate the corpus luteum function. Furthermore, we investigated the clinical relevance of a simple midluteal salivary progesterone estimation for the diagnosis of luteal phase insufficiency by determining the diagnostic efficiency and cutoff values. A total of 121 women were divided into 3 groups; normal luteal function, luteal phase insufficiency and unclassified group, based on basal body temperature recordings and serum progesterone levels at 3 sampling points during the midluteal phase. Salivary progesterone values across the luteal phase of the normal luteal function group were significantly increased from day 1 to day 4, remained constant from day 5 to day 9 (mean \pm SD, 318 \pm 170 pmol/l on day 5, 287 \pm 169 pmol/l on day 9; urinary LH surge = day 0) and decreased thereafter. Salivary progesterone concentrations in the luteal phase insufficiency group showed significantly lower values compared with those in the normal group between days 3 and 10. The cutoff values of 189 pmol/l in the midluteal phase yielded a sensitivity of 78.0% and a specificity of 76.5%. Our results suggest that daily salivary progesterone profiles during the luteal phase and a simple estimation of midluteal salivary progesterone appeared to be useful for the diagnosis of luteal phase defects. PMID: 11803226

J Vasc Surg. 2002 Oct;36(4):833-8.

Progesterone inhibits human infragenicular arterial smooth muscle cell proliferation induced by high glucose and insulin concentrations.

Carmody BJ, Arora S, Wakefield MC, Weber M, Fox CJ, Sidawy AN. Department of Surgery, Veterans Affairs Medical Center, Walter Reed Army Medical Center, USA.

INTRODUCTION: Diabetes mellitus is a significant risk factor for atherosclerotic peripheral vascular disease. Hyperglycemia and hyperinsulinemia, as encountered in patients with type II diabetes, have been shown to stimulate vascular smooth muscle cell (VSMC) proliferation, a paramount feature in atherosclerosis. Female sex hormones, such as estrogen, have been suggested to inhibit VSMC proliferation. However, the role of progesterone, particularly in patients with diabetes mellitus, has not been examined. Therefore, we studied the effect of progesterone on VSMCs exposed to various concentrations of glucose and insulin. **METHODS:** Human infragenicular VSMCs isolated from the tibial arteries of five male patients with diabetes undergoing lower extremity amputation were used. Immunocytochemical studies with confocal microscopy were performed for progesterone receptor identification in these VSMCs. Cells were grown to subconfluence, followed by exposure to deprived media with various glucose (100 and 200 mg/dL) and insulin (no insulin and 100 ng/mL) concentrations. Cells were then additionally exposed to physiologic progesterone (10 ng/mL, progesterone group) and compared with a no-progesterone group. Cell count and methyl-(3)H-thymidine incorporation were used to determine cellular proliferation. Cell count with hemocytometry was performed on day 6. DNA synthesis as reflected through methyl-(3)H-thymidine incorporation was measured at 24 hours. **RESULTS:** Immunocytochemical studies with confocal microscopy showed cytosolic progesterone receptors. The no-progesterone group showed a significant rise in cell count ($P < .05$) at all concentrations of glucose or insulin compared with the control group containing 100 mg/dL glucose concentration. The no-progesterone group also showed a significant rise in thymidine incorporation ($P < .05$) in the 100 mg/dL glucose-100 ng/mL insulin group and the 200 mg/dL glucose-100 ng/mL insulin group compared with the 100 mg/dL glucose group. In the cell count studies, progesterone significantly inhibited cellular proliferation in several settings. All cell groups cultured with insulin or an elevated glucose concentration showed a significant ($P < .05$) antiproliferative effect when exposed to progesterone. With thymidine incorporation, progesterone showed a similar antiproliferative effect in cells stimulated with glucose or insulin. **CONCLUSION:** Significant reductions in cell proliferation as determined with both cell count and thymidine incorporation suggest that progesterone is an inhibitor of VSMC proliferation induced by our in vitro models of hyperglycemia and hyperinsulinemia. Therefore, progesterone may have a protective role against the atherosclerotic changes associated with type II diabetes. PMID: 12368746

J Am Coll Cardiol. 2000 Dec;36(7):2154-9.

Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women.

Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P. Department of Cardiology, Ospedale San Raffaele, Rome, Italy.

OBJECTIVES: We sought to compare the effects of estrogen/transvaginal progesterone gel with estrogen/medroxyprogesterone acetate (MPA) on exercise-induced myocardial ischemia in postmenopausal women with coronary artery disease or previous myocardial infarction, or both. **BACKGROUND:** Estrogen therapy beneficially affects exercise-induced myocardial ischemia in postmenopausal women; however, women with an intact uterus also take progestin to protect against uterine malignancies. The effects of combination estrogen/progestin therapy on myocardial ischemia are unknown. **METHODS:** Eighteen postmenopausal women (mean \pm SD age 59 \pm 7 years) were given 17-beta-estradiol in single-blinded manner for four weeks (1 mg/day for three weeks then 2 mg/day for one week). Estradiol (2 mg/day) was then continued, and the patients were randomized (double-blind) for 12 days to either transvaginal progesterone gel (90 mg on alternate days) and oral MPA placebo (10 mg/day), or vice versa. After another two weeks on estradiol alone, the patients crossed over to progestin treatment and repeated the protocol on the opposite treatment. Patients underwent treadmill exercise testing after each estradiol phase and at day 10 of each progestin phase. **RESULTS:** Exercise time to myocardial ischemia increased after the first estrogen phase as compared with baseline (mean difference with 95% confidence interval [CI]: 72 s [34 to 110], $p = 0.001$), and was increased by combination estradiol/progesterone therapy as compared with estradiol/MPA therapy (92 s [35 to 149], $p = 0.001$). Two patients (11%) were withdrawn while taking estradiol/MPA owing to unstable angina. **CONCLUSIONS:** Combination estrogen/transvaginal progesterone gel increases exercise time to myocardial ischemia, as compared with estrogen/MPA. These results imply that the choice of progestin in women at higher cardiovascular risk requires careful consideration. PMID: 11127455

J Womens Health Gend Based Med. 2000 May;9(4):381-7.

Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey.

Fitzpatrick LA, Pace C, Wiita B. Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905.

Abstract: A cross-sectional survey was conducted to examine quality of life (QOL) related to physiological, somatic, and vasomotor effects of changing progestogen treatment from medroxyprogesterone acetate (MPA) to micronized progesterone in postmenopausal women. Eligible women ($n = 176$) were currently using hormone replacement therapy (HRT) containing micronized progesterone for 1-6 months and had previously received HRT containing MPA. QOL was assessed via telephone interview using the Greene Climacteric Scale and the Women's Health Questionnaire. When compared with the MPA-containing regimen, women using micronized progesterone-containing HRT experienced significant improvement in vasomotor symptoms, somatic complaints, and anxiety and depressive symptoms. Women reported improved perceptions of their patterns of vaginal bleeding and control of menopausal symptoms while on the micronized progesterone-containing regimen. Approximately 80% of women reported overall satisfaction with the micronized progesterone-containing regimen. A micronized progesterone-containing HRT regimen offers the potential for improved QOL as measured by improvement of menopause-associated symptoms. PMID: 10868610

Clin Ther. 1999 Jan;21(1):41-60; discussion 1-2.

Oral micronized progesterone.

de Lignières B. Department of Endocrinology and Reproductive Medicine, Hôpital Necker, Paris, France.

Abstract: This review sought to examine the rationale for selecting an oral micronized progesterone formulation rather than a synthetic progestin for some of the main indications for progestogens. Unopposed estrogen use is associated with a high risk (relative risk, 2.1 to 5.7) of endometrial hyperplasia and adenocarcinoma, and it has been understood for some time that a progestogen must be added for at least 10 to 14 days per month to prevent these effects. However, the most commonly used synthetic progestins, norethisterone and medroxyprogesterone acetate, have been associated with metabolic and vascular side effects (eg, suppression of the vasodilating effect of estrogens) in both experimental and human controlled studies. All comparative studies to date conclude that the side effects of synthetic progestins can be minimized or eliminated

through the use of natural progesterone, which is identical to the steroid produced by the corpus luteum. The inconvenience associated with the use of injectable, rectal, or vaginal formulations of natural progesterone can be circumvented by using orally administered micronized progesterone. The bioavailability of micronized progesterone is similar to that of other natural steroids, and interindividual and intraindividual variability of area under the curve is similar to that seen with synthetic progestins. A clear dose-ranging effect has been demonstrated, and long-term protection of the endometrium has been established. Micronized progesterone has been used widely in Europe since 1980 at dosages ranging from 300 mg/d (taken at bedtime) 10 days a month for women wishing regular monthly bleeding to 200 mg 14 days a month or 100 mg 25 days a month for women willing to remain amenorrheic. This therapy is well tolerated, with the only specific side effect being mild and transient drowsiness, an effect minimized by taking the drug at bedtime. The prospective, comparative Postmenopausal Estrogens/Progestin Intervention trial has recommended oral micronized progesterone as the first choice for opposing estrogen therapy in nonhysterectomized postmenopausal women. PMID: 10090424

Am J Obstet Gynecol. 1999 Jun;180(6 Pt 1):1504-11.

Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen.

Burry KA, Patton PE, Hermsmeyer K. Department of Obstetrics, Oregon Health Sciences University, Portland.

OBJECTIVE: The objective of this study was to evaluate the serum levels of progesterone resulting from the application of a progesterone cream to the skin. STUDY DESIGN: Six postmenopausal women were evaluated at a university clinic over a 4-week period. RESULTS: Transdermal estradiol 0.05 mg was applied 2 days before the first application of progesterone (30 mg/d) and was continued throughout the study. Patches were changed twice a week. Progesterone cream was applied once a day for 2 weeks. On day 15 and for the next 2 weeks, the progesterone cream was applied twice daily (60 mg/d). Serum 17beta-estradiol and progesterone were measured at 9 different times over a 24-hour period on day 1 and at weekly intervals for the 4-week duration of the study. Serum 17beta-estradiol concentrations varied among women, with mean concentrations of 40 to 64 pg/mL observed. Consistency in 17beta-estradiol concentrations was found within individual persons throughout the study. Serum progesterone concentrations also varied among women, with mean concentrations ranging from 1.6 to 3.3 ng/mL. After 2 weeks of percutaneous dosing, progesterone concentrations were sustained for at least 8 hours and were consistent within a given person. An appropriate increase in progesterone concentration occurred after 4 weeks compared with 2 weeks of application. Individually, a 0.53 correlation, significant at $P < .0001$, was seen between the absorption of 17beta-estradiol and progesterone. CONCLUSION: Significant increases in serum concentrations of progesterone were observed in all of the women studied. The percutaneous absorption of progesterone correlates strongly with the absorption of transdermal 17beta-estradiol. There is variance in absorption of progesterone just as with 17beta-estradiol, and the 2 measures are closely correlated. The percutaneous application of progesterone cream appears to be a safe and effective route of administration. PMID: 10368498

Fertil Steril. 1999 Sep;72(3):389-97.

Micronized progesterone: clinical indications and comparison with current treatments.

Fitzpatrick LA, Good A. Dept Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905.

OBJECTIVE: To integrate and evaluate the pharmacokinetic, endocrine, and clinical effects of micronized progesterone formulations. DESIGN: Published articles concerning the pharmacokinetics of orally administered progesterone and the potential clinical uses of oral micronized progesterone were reviewed. Results concerning their use for secondary amenorrhea, premenopausal bleeding disorders, luteal phase dysfunction, termination of premature labor, hormone replacement therapy, and premenopausal syndrome are summarized. Critical issues to be resolved through ongoing preclinical and clinical research are highlighted. RESULT(S): Because of the enhanced bioavailability of oral micronized progesterone, the compound may be useful for a variety of therapeutic indications. Oral micronized progesterone is available in France, and a formulation recently has been approved in the United States for the treatment of secondary amenorrhea and postmenopausal hormone replacement therapy. A large body of evidence, including the Postmenopausal Estrogen/Progestin Interventions study, suggests that the use of a combination of estrogen and oral micronized progesterone is optimal for long-term hormone replacement therapy. There also are data indicating that oral micronized progesterone could be of potential use for the treatment of premenopausal bleeding disorders, luteal phase disorders, and premature labor. CONCLUSION(S): Oral micronized progesterone has widespread clinical potential, particularly for the treatment of secondary amenorrhea and dysfunctional premenopausal bleeding, and as a component of postmenopausal hormone replacement therapy.

PMID: 10519605

Obstet Gynecol. 1999 Aug;94(2):225-8.

Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss.

Leonetti HB, Longo S, Anasti JN. Department of Obstetric and Gynecology, St. Luke's Hospital, Bethlehem, Pennsylvania 18015.

OBJECTIVE: To determine effectiveness of transdermal progesterone cream for controlling vasomotor symptoms and preventing postmenopausal bone loss. **METHODS:** We randomly assigned 102 healthy women within 5 years of menopause to transdermal progesterone cream or placebo. Study subjects and investigators were masked until data analysis was completed. An initial evaluation included complete history, physical examination, bone mineral density determination, and serum studies (TSH, FSH, lipid profile, and chemistry profile). Subjects were instructed to apply a quarter teaspoon of cream (containing 20 mg progesterone or placebo) to the skin daily. Each woman received daily multivitamins and 1200 mg of calcium and were seen every 4 months for review of symptoms. Bone scans and serum chemistries were repeated after 1 year. **RESULTS:** Thirty of the 43 (69%) in the treatment group and 26 of the 47 (55%) in the placebo group complained initially of vasomotor symptoms. Improvement or resolution of vasomotor symptoms, as determined by review of weekly symptom diaries, was noted in 25 of 30 (83%) treatment subjects and five of 26 (19%) placebo subjects ($P < .001$). However, the number of women who showed gain in bone mineral density exceeding 1.2% did not differ ($\alpha = .05$, power of 80%). **CONCLUSION:** Although we found no protective effect on bone density after 1 year, we did see a significant improvement in vasomotor symptoms in the treated group. PMID: 10432132

Compr Ther. 1998 Jun-Jul;24(6-7):336-9.

Differentiating between natural progesterone and synthetic progestins: clinical implications for premenstrual syndrome and perimenopause management.

Martorano JT, Ahlgrim M, Colbert T. PMS Medical Center, New York, NY 10022, USA.

Abstract: Critical differences between natural progesterone and synthetic progestins are often misunderstood. Synthetic progestins should not be used interchangeably with natural progesterone. This article describes their differences and the clinical implications for their use in managing premenstrual syndrome and perimenopause. PMID: 9669099

Nat Med. 1997 Mar;3(3):324-7.

Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm.

Miyagawa K, Rösch J, Stanczyk F, Hermsmeyer K. Oregon Regional Primate Research Center, Oregon 97006.

Abstract: Cardiovascular disease, the major cause of death in post-menopausal women, can be reduced by replacement of ovarian steroid hormones. To compare medroxyprogesterone with progesterone as the progestin in hormone replacement therapy from the standpoint of coronary artery vasospasm, we treated ovariectomized rhesus monkeys with physiological levels of estradiol-17 beta in combination with medroxyprogesterone or progesterone for four weeks. Coronary vasospasm in response to pathophysiological stimulation without injury showed that progesterone plus estradiol protected but medroxyprogesterone plus estradiol failed to protect, allowing vasospasm. We conclude that medroxyprogesterone in contrast to progesterone increases the risk of coronary vasospasm. PMID: 9055861

Obstet Gynecol. 1997 Sep;90(3):396-401.

Transvaginal administration of progesterone.

Fanchin R, De Ziegler D, Bergeron C, Righini C, Torrisi C, Frydman R. Department of Obstetrics and Gynecology and Reproductive Endocrinology, Hôpital Antoine Bécélère, Clamart, France.

OBJECTIVE: To examine the endometrial effects of three different doses of progesterone administered vaginally. **METHODS:** Forty women 25-41 years old deprived of ovarian function received estradiol (E2) for 28 days. From days 15 to 27, a new mucus-like vaginal gel of progesterone was administered every other day, randomly, dosed at 45 mg (group A, $n = 14$), 90 mg (group B, $n = 13$), or 180 mg (group C, $n = 13$). Plasma gonadotropins, estrone, E2, and progesterone were measured. An endometrial biopsy was performed on day 20 ($n = 20$) or 24 ($n = 20$) for endometrial dating and for estrogen and progesterone receptor determinations. **RESULTS:** Plasma estrogen levels were in the menstrual cycle range. Mean

progesterone levels were lower in group A (2.4 +/- 0.2 ng/mL) than in group B (3.6 +/- 0.2 ng/mL) or C (3.4 +/- 0.4 ng/mL) ($P < .005$). Plasma FSH and LH decreased significantly during progesterone treatment. In all groups, we observed secretory transformation in the glands (day 20) and stroma (day 24) and the distribution of estrogen and progesterone receptors seen in normal menstrual cycles. **CONCLUSION:** Transvaginal administration of progesterone induced normal secretory transformation of the endometrium despite low plasma levels, suggesting a direct transit into the uterus or "first uterine pass effect." PMID: 9277651

J Steroid Biochem Mol Biol. 1996 Jan;56(1-6 Spec No):209-19.

Diverse modes of action of progesterone and its metabolites.

Mahesh VB, Brann DW, Hendry LB. Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, 30912-3000.

Abstract: Progesterone and its metabolites have a variety of diverse effects in the brain, uterus, smooth muscle, sperm and the oocyte. The effects include changes in electrophysiological excitability, induction of anesthesia, regulation of gonadotropin secretion, regulation of estrogen receptors, modulation of uterine contractility and induction of acrosome reaction and oocyte maturation. The latency of the effects vary from several seconds to several hours. Thus, it is not surprising that multiple mechanisms of action are involved. The classical mechanism of steroid hormone action of intracellular receptor binding has been supplemented by the possibility of the steroid acting as a transcription factor after the binding of the receptor protein to DNA. Other mechanisms include influence of the steroids on membrane fluidity and acting through other cell signalling systems, membrane receptors and GABA(A) receptors. Of particular interest are multiple mechanisms for the same types of action. For example the effect of progesterone on gonadotropin release is largely exerted via the classical intracellular receptor as well as membrane receptors, whereas 3(alpha),5(alpha)-tetrahydroprogesterone-induced LH release occurs via the GABA(A) receptor system. The inhibition of uterine contractility by progesterone is regulated by progesterone receptors while the action of 3(alpha),5(alpha)-tetrahydroprogesterone on uterine contractility is regulated by GABA(A) receptors. The regulation of the differences in the pattern of progesterone effects on estrogen receptor dynamics in the anterior pituitary and the uterus in the same animal are also of considerable interest. PMID: 8603042

Med Hypotheses. 1991 Aug;35(4):316-8.

Is natural progesterone the missing link in osteoporosis prevention and treatment?

Lee JR. Erratum in: Med Hypotheses 1991 Oct;36(2):178.

Abstract: Conventional treatment with vitamin D, calcium, and estrogen will delay but not reverse osteoporosis. The addition of fluoride may increase bone mass but fails to increase bone strength; fracture incidence is actually increased in non-vertebral bone by fluoride. Clearly, successful treatment of osteoporosis remains an unsolved problem. In women, osteoporosis coincides with menopause. The hypothesis that progesterone and not estrogen is the missing factor was tested in a clinical setting and was found to be extraordinarily effective in reversing osteoporosis. PMID: 1943883

Endocr Rev. 1990 May;11(2):386-98.

Progesterone as a bone-trophic hormone.

Prior JC. Division of Endocrinology and Metabolism, University of British Columbia, Vancouver, Canada.

Abstract: Experimental, epidemiological, and clinical data indicate that progesterone is active in bone metabolism. Progesterone appears to act directly on bone by engaging an osteoblast receptor or indirectly through competition for a glucocorticoid osteoblast receptor. Progesterone seems to promote bone formation and/or increase bone turnover. It is possible, through estrogen-stimulated increased progesterone binding to the osteoblast receptor, that progesterone plays a role in the coupling of bone resorption with bone formation. A model of the interdependent actions of progesterone and estrogen on appropriately-"ready" cells in each bone multicellular unit can be tied into the integrated secretions of these hormones within the ovulatory cycle. Figure 5 is an illustration of this concept. It shows the phases of the bone remodeling cycle in parallel with temporal changes in gonadal steroids across a stylized ovulatory cycle. Increasing estrogen production before ovulation may reverse the resorption occurring in a "sensitive" bone multicellular unit while gonadal steroid levels are low at the time of menstrual flow. The bone remodeling unit would then be ready to begin a phase of formation as

progesterone levels peaked in the midluteal phase. From this perspective, the normal ovulatory cycle looks like a natural bone-activating, coherence cycle. Critical analysis of the reviewed data indicate that progesterone meets the necessary criteria to play a causal role in mineral metabolism. This review provides the preliminary basis for further molecular, genetic, experimental, and clinical investigation of the role(s) of progesterone in bone remodeling. Much further data are needed about the interrelationships between gonadal steroids and the "life cycle" of bone. Feldman et al., however, may have been prophetic when he commented; "If this anti-glucocorticoid effect of progesterone also holds true in bone, then postmenopausal osteoporosis may be, in part, a progesterone deficiency disease." PMID: 2194787

Hum Reprod. 1990 Jul;5(5):537-43.

Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure.

Bourgain C, Devroey P, Van Waesberghe L, Smits J, Van Steirteghem AC. Department of Pathology, Akademisch Ziekenhuis, Vrije Universiteit Brussel, Belgium.

Abstract: In 43 patients without ovaries, endometrial biopsies at day 21 of 75 substituted cycles were studied by light and electron microscopy. The morphology of the endometrium was compared after oral, vaginal or intramuscular administration of progesterone, and correlated with the serum levels of 17-beta oestradiol and progesterone and the pregnancies obtained after oocyte donation. After vaginal application of micronized progesterone, endometrial morphology closely matched that of a natural cycle. This therapy was able to support two ongoing pregnancies. No adequate endometrial response was noted after oral ingestion of progesterone. The maturation of the endometrium after intramuscular injections of progesterone in oil was heterogeneous. It was concluded that the vaginal route for administering micronized progesterone can be advised as the treatment of choice in patients without ovarian function. PMID: 2394784

Br Med J (Clin Res Ed). 1985 Jun 1;290(6482):1617-21.

Progesterone and the premenstrual syndrome: a double blind crossover trial.

Dennerstein L, Spencer-Gardner C, Gotts G, Brown JB, Smith MA, Burrows GD.

Abstract: A double blind, randomised, crossover trial of oral micronised progesterone (two months) and placebo (two months) was conducted to determine whether progesterone alleviated premenstrual complaints. Twenty three women were interviewed premenstrually before treatment and in each month of treatment. They completed Moos's menstrual distress questionnaire, Beck et al's depression inventory, Spielberger et al's state anxiety inventory, the mood adjective checklist, and a daily symptom record. Analyses of data found an overall beneficial effect of being treated for all variables except restlessness, positive moods, and interest in sex. Maximum improvement occurred in the first month of treatment with progesterone. Nevertheless, an appreciably beneficial effect of progesterone over placebo for mood and some physical symptoms was identifiable after both one and two months of treatment. Further studies are needed to determine the optimum duration of treatment. PMID: 3924191

Fertil Steril. 1985 Nov;44(5):622-6.

Bioavailability of oral micronized progesterone.

Maxson WS, Hargrove JT.

Abstract: Progesterone (P) has not been administered orally because of reportedly poor bioavailability and a rapid clearance rate. Unfortunately, the synthetic derivatives, although orally active, have a number of disadvantages and fail to mimic natural P completely. To investigate the bioavailability and short-term toxicity of oral micronized P, a standardized dose of 200 mg of micronized P was administered to nine healthy postmenopausal women and one male subject. Serial determinations of serum P concentrations demonstrated rapid absorption of P. Peak concentrations of P rose from a negligible baseline level to 17.0 +/- 4.9 ng/ml at an average of 2.8 +/- 0.35 hours after administration. The peak concentrations of P were equivalent to those observed in the midluteal phase in normal control cycles (14.1 +/- 2.7 ng/ml). All subjects exhibited significant elevation of P over baseline levels that persisted for at least 6 hours after the single oral dose and returned to initial levels by 24 hours. There was no significant change in estradiol, follicle-stimulating hormone, luteinizing hormone, cortisol, aldosterone, lipids, or hepatic enzymes during the 24-hour study interval. PMID: 4054341

Testosterone & Androgens: For Women

Gynecol Endocrinol. 2009 Jan;25(1):12-20.

Testosterone replacement therapy in the climacteric: benefits beyond sexuality.

Maia H Jr, Casoy J, Valente J. CEPARH, Rua Caetano Moura 35, Salvador, Brazil.

Abstract: Testosterone therapy during menopause has a wide range of benefits that reach beyond the realm of human sexuality. This is a consequence not only of the widespread distribution of androgen receptors in various extragonadal tissues but also of the conversion of androgens to estrogens in the tissues in which aromatase expression is present. For this reason, testosterone therapy during the climacteric years will not only supply androgens but will also stimulate estrogen production in tissues that express aromatase. Furthermore, the bioavailability of androgens to the tissues depends not only on the rate of their production by the postmenopausal ovaries and adrenals but also on the circulating levels of sex hormone-binding globulin (SHBG). Tibolone inhibits SHBG production in the liver, thus increasing free testosterone levels. The association of tibolone with testosterone as a form of androgen replacement therapy during the climacteric is discussed, as is the use of low-dose testosterone, tibolone or the association of both in perimenopausal patients with signs of androgen deficiency. Testosterone treatment has a boosting effect not only on human sexuality but also on the sensation of well-being, a stimulatory effect conferred by the increase in beta-endorphins. PMID: 19165658

J Sex Med. 2009 Jan;6(1):8-18; quiz 19-20.

Testosterone replacement therapy in naturally and surgically menopausal women.

Panzer C, Guay A. Rose Medical Center-Department of Endocrinology, Denver, Colorado.

INTRODUCTION: Testosterone replacement therapy in naturally and surgically menopausal women is a complex and currently highly debated topic. Opposing guidelines for the use of testosterone exist, which create a therapeutic dilemma for clinicians confronted by severely distressed women who experience a decrease in sexual desire after surgical or natural menopause. **AIM:** In this review, we will address the current knowledge on androgen physiology, conditions associated with a low androgen state, and risks and benefits of androgen therapy. **METHODS:** An English-language Medline review was performed. **MAIN OUTCOME MEASURE:** Review of available literature. **RESULTS:** A review of normal androgen physiology in women is summarized and a brief review of prior use of androgens over the last six decades is included. The data on the use of androgen replacement in pre- and postmenopausal women is evaluated, especially its relationship to sexual functioning. Special concerns about the effect of androgens on cardiovascular disease, breast, and endometrial tissue are discussed. The balance of evidence seems to show that androgens have more of a positive effect than a negative effect in women if used properly. **CONCLUSIONS:** Testosterone replacement therapy for surgically and naturally menopausal women with low sexual desire can be accomplished physiologically and effectively after ruling out other medical conditions leading to low sexual desire and after proper information of the patient that testosterone therapy is not an FDA-approved medication in the United States. The majority of available data suggests that testosterone replacement in women can be used safely without increased risk of endometrial or breast cancer. PMID: 19170830

J Sex Med. 2009 Jul;6(7):1850-6. Epub 2009 Apr 24.

The incidence of invasive breast cancer among women prescribed testosterone for low libido.

Davis SR, Wolfe R, Farrugia H, Ferdinand A, Bell RJ. Women's Health Program, Department of Medicine, Central & Eastern Clinical School, Monash University, Alfred Hospital, Prahran, Victoria 3181, Australia.

INTRODUCTION: Although the efficacy of testosterone for the treatment of hypoactive sexual desire disorder is well established, the effect of testosterone therapy on breast cancer risk remains uncertain. **AIM:** The incidence of invasive breast cancer among past and current testosterone users. **METHODS:** Retrospective cohort study of 631 women ever treated with testosterone between January 1989 and December 2007 in a clinical endocrinology practice. **MAIN OUTCOME MEASURE:** The incidence of invasive breast cancer since first exposure, and the standardized incidence rate ratio (IRR) calculated using Australian age-specific incidence rates for 2005. **RESULTS:** The mean age of the women at first exposure to testosterone therapy was 49.1 +/- 8.2 years, median treatment duration, 1.3 years, and mean follow-up of 6.7 +/- 4.6 years, providing 4,015 woman-years of follow-up. Twelve cases of invasive breast cancer occurred among 599 women

breast cancer-free before treatment, giving an age adjusted IRR of 1.35 (95% confidence interval 0.76-2.38). There was no evidence of an independent effect of duration of exposure on breast cancer risk. CONCLUSION: In this study, testosterone use was not associated with a significant increase in breast cancer risk. PMID: 19453875

Menopause Int. 2008 Sep;14(3):117-22.

Testosterone and the breast.

Shufelt CL, Braunstein GD. Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048.

Abstract: Although women have been treated with testosterone (T) for female sexual dysfunction since the 1950s, the role of T in normal female physiology is not yet fully defined. One of the major safety concerns of androgen therapy is whether androgens have a stimulatory effect on the breast that could lead to breast carcinomas. The proposed mechanisms for such stimulation include local estrogen production from the aromatase enzyme complex present in the breast tissue or by the direct stimulation of the androgen receptor. Predominant data from in vitro studies have shown that androgens actually have apoptotic and antiproliferative effects and not stimulatory effects. Animal models have shown similar results to in vitro studies, finding that androgens inhibit breast cancer growth. Prospective and retrospective epidemiological analyses have shown mixed outcomes, with no clear consensus regarding androgen use and breast cancer risk. Hyperandrogenism in patients with polycystic ovarian syndrome with elevated levels of endogenous T is not associated with an increased risk of breast cancer and may, in fact, be protective. Another human model with excess of T is female-to-male transgenderism, in which genotypic women are treated with large doses of exogenous T with no increased risk. High-dose androgen therapy also has been effective in treating patients with advanced breast cancer. Thus, the preponderance of data suggests that T use in females is not associated with an increased risk of breast carcinoma. PMID: 18714077

Maturitas. 2008 Sep-Oct;61(1-2):17-26.

Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality.

Davis SR, McCloud P, Strauss BJ, Burger H. Prince Henry's Institute of Medical Research, 246 Clayton Road, Clayton, Victoria 3168, Australia.

Abstract: To investigate the role of androgens in increasing bone density and improving low libido in postmenopausal women, we have studied the long-term effects of estradiol and testosterone implants on bone mineral density and sexuality in a prospective, 2 year, single-blind randomised trial. Thirty-four postmenopausal volunteers were randomised to treatment with either estradiol implants 50 mg alone (E) or estradiol 50 mg plus testosterone 50 mg (E&T), administered 3-monthly for 2 years. Cyclical oral progestins were taken by those women with an intact uterus. Thirty-two women completed the study. BMD (DEXA) of total body, lumbar vertebrae (L1-L4) and hip area increased significantly in both treatment groups. BMD increased more rapidly in the testosterone treated group at all sites. A substantially greater increase in BMD occurred in the E&T group for total body ($P < 0.008$), vertebral L1-L4 ($P < 0.001$) and trochanteric ($P < 0.005$) measurements. All sexual parameters (Sabbatsberg sexual self-rating scale) improved significantly in both groups. Addition of testosterone resulted in a significantly greater improvement compared to E for sexual activity ($P < 0.03$), satisfaction ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$) and relevancy ($P < 0.05$). Total cholesterol and LDL-cholesterol fell in both groups as did total body fat. Total body fat-free mass (DEXA, anthropometry, impedance) increased in the E&T group only. We concluded that in postmenopausal women, treatment with combined estradiol and testosterone implants was more effective in increasing bone mineral density in the hip and lumbar spine than estradiol implants alone. Significantly greater improvement in sexuality was observed with combined therapy, verifying the therapeutic value of testosterone implants for diminished libido in postmenopausal women. The favourable estrogenic effects on lipids were preserved in women treated with T, in association with beneficial changes in body composition. PMID: 19434876

Mayo Clin Proc. 2004 Apr;79(4 Suppl):S8-13.

Hot flashes and androgens: a biological rationale for clinical practice.

Notelovitz M. Adult Women's Health & Medicine, Boca Raton, FL.

Abstract: Hot flashes are the most prevalent symptom of menopause. Although the etiology of hot flashes has yet to be determined, it is increasingly apparent that the physiology of the underlying vasomotor instability is multifactorial. Estrogen

and androgen receptors are present in the areas of the central nervous system relevant to hot flashes. Androgens are central to the synthesis of estrogen and to the bioavailability of free estrogen in peripheral tissues. In addition, androgens have direct central nervous system effects that modulate other endocrine factors associated with hot flashes. The pharmacodynamic differences of testosterone and methyltestosterone are briefly reviewed in the context of choice for individualized clinical use. PMID: 15065632

Mayo Clin Proc. 2004 Apr;79(4 Suppl):S19-24.

The role of androgens in female sexual dysfunction.

Shifren JL. Menopause Program, Vincent Memorial Obstetrics and Gynecology Service, Massachusetts General Hospital and Harvard Medical School, Boston, Mass 02114, USA.

Abstract: There are many treatment options for female sexual dysfunction (FSD), with the optimal therapy depending on the etiology of the problem. The cause of sexual dysfunction is multifactorial and may include psychological problems such as depression or anxiety disorders, conflict within the relationship, partner performance and technique, issues relating to prior abuse, medical illness, medications, fatigue, stress, or gynecological problems that make sexual activity uncomfortable. The role of low androgen concentrations in FSD is gaining increasing attention. Available therapeutic options include adjusting medications, counseling, treating depression or anxiety, reducing stress and fatigue, sex therapy, devices, estrogen therapy for genitourinary atrophy, and possibly vasoactive substances. Although no androgen therapies are currently approved by the Food and Drug Administration for FSD, they are being used in clinical practice, and early clinical trial results suggest that they may be both effective and safe in the treatment of FSD, specifically low libido. Androgen therapy should be considered primarily in women who have a physiological reason for reduced androgen concentrations, including aging, hypopituitarism, oophorectomy, or adrenal insufficiency. Products in use include oral methyltestosterone and dehydroepiandrosterone, topical testosterone ointment, and testosterone implants and injections. Products available for men, including skin patches and gels, are currently being studied at doses appropriate for women. Possible risks include hirsutism, acne, liver dysfunction, lowering of the voice, adverse lipid changes, virilization of a female fetus, and, as androgens are aromatized to estrogens, potentially the risks of estrogen therapy. PMID: 15065634

Mayo Clin Proc. 2004 Apr;79(4 Suppl):S3-7.

Formulations and use of androgens in women.

Chu MC, Lobo RA. Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, 622 W 168th St, PH 16-77, New York, NY 10032.

Abstract: The physiology of normal androgen production in women has been poorly understood. Defining an androgen insufficiency state in women, in the absence of adrenal suppression and/or bilateral oophorectomy, has been difficult. Nevertheless, beneficial effects of androgen on many organ systems, including bone and the brain, are well documented. This review discusses the definition of androgen insufficiency, anticipated effects of androgen treatment on several factors of health, and treatment options for women with androgen insufficiency. PMID: 15065631

Menopause. 2003 Sep-Oct;10(5):390-8.

Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women.

Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Jean Hailes Foundation Research Unit, Clayton, Victoria, Australia.

OBJECTIVE: Circulating testosterone in women declines during the late reproductive years such that otherwise healthy women in their 40s have approximately half the testosterone level as women in their 20s. Despite this, research showing the benefits of androgen replacement has been limited to the postmenopausal years. In view of the known premenopausal physiological decline in testosterone, we have evaluated the efficacy of transdermal testosterone therapy on mood, well-being, and sexual function in eugonadal, premenopausal women presenting with low libido. DESIGN: Premenopausal women with low libido participated in a randomized, placebo-controlled, crossover, efficacy study of testosterone cream (10 mg/day) with two double-blind, 12-week, treatment periods separated by a single-blind, 4-week, washout period. RESULTS: Thirty-four women completed the study per protocol, with 31 women (mean age 39.7 +/- 4.2 years; serum testosterone 1.07 + 0.50

nmol/L) providing complete data. Testosterone therapy resulted in statistically significant improvements in the composite scores of the Psychological General Well-Being Index [+12.9 (95% CI, +4.6 to +21.2), $P = 0.003$] and the Sabbatsberg Sexual Self-Rating Scale [+15.7 (95% CI, +6.5 to +25.0), $P = 0.001$] compared with placebo. A mean decrease in the Beck Depression Inventory score approached significance [-2.8 (95% CI, -5.7 to +0.1), $P = 0.06$]. Mean total testosterone levels during treatment were at the high end of the normal range, and estradiol was unchanged. No adverse effects were reported. **CONCLUSIONS:** Testosterone therapy improves well-being, mood, and sexual function in premenopausal women with low libido and low testosterone. As a substantial number of women experience diminished sexual interest and well-being during their late reproductive years, further research is warranted to evaluate the benefits and safety of longer-term intervention.

PMID: 14501599

N Engl J Med. 2000 Sep 7;343(10):682-8.

Transdermal testosterone treatment in women with impaired sexual function after oophorectomy.

Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA. Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston 02114.

BACKGROUND: The ovaries provide approximately half the circulating testosterone in premenopausal women. After bilateral oophorectomy, many women report impaired sexual functioning despite estrogen replacement. We evaluated the effects of transdermal testosterone in women who had impaired sexual function after surgically induced menopause. **METHODS:** Seventy-five women, 31 to 56 years old, who had undergone oophorectomy and hysterectomy received conjugated equine estrogens (at least 0.625 mg per day orally) and, in random order, placebo, 150 microg of testosterone, and 300 microg of testosterone per day transdermally for 12 weeks each. Outcome measures included scores on the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index, and a sexual-function diary completed over the telephone. **RESULTS:** The mean (\pm SD) serum free testosterone concentration increased from 1.2 ± 0.8 pg per milliliter (4.2 ± 2.8 pmol per liter) during placebo treatment to 3.9 ± 2.4 pg per milliliter (13.5 ± 8.3 pmol per liter) and 5.9 ± 4.8 pg per milliliter (20.5 ± 16.6 pmol per liter) during treatment with 150 and 300 microg of testosterone per day, respectively (normal range, 1.3 to 6.8 pg per milliliter [4.5 to 23.6 pmol per liter]). Despite an appreciable placebo response, the higher testosterone dose resulted in further increases in scores for frequency of sexual activity and pleasure-orgasm in the Brief index of Sexual Functioning for Women ($P=0.03$ for both comparisons with placebo). At the higher dose the percentages of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased two to three times from base line. The positive-well-being, depressed-mood, and composite scores of the Psychological General Well-Being Index also improved at the higher dose ($P=0.04$, $P=0.03$, and $P=0.04$, respectively, for the comparison with placebo), but the scores on the telephone-based diary did not increase significantly. **CONCLUSIONS:** In women who have undergone oophorectomy and hysterectomy, transdermal testosterone improves sexual function and psychological well-being.

PMID: 10974131

Menopause. 2000 Nov-Dec;7(6):395-401.

Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women.

Davis SR, Walker KZ, Strauss BJ. Dept of Epidemiology and Preventive Medicine, Monash University, Australia.

OBJECTIVE: The cardioprotective effects of postmenopausal estrogen replacement therapy are mediated by several mechanisms, including favorable effects on lipids and lipoproteins. The extent to which the latter reflects modification of body fat distribution by sex steroids is not known. Hence, we investigated the relationships between changes in lipids and measures of body composition in postmenopausal women who were administered estrogen therapy with and without testosterone. **DESIGN:** We randomized 33 postmenopausal women to treatment with either estradiol 50 mg (E) alone or estradiol 50 mg plus testosterone 50 mg implants (E&T) administered every 3 months for 2 years in conjunction with cyclic oral progestins for women with an intact uterus. **RESULTS:** Both therapies were associated with sustained reductions in total cholesterol and low-density lipoprotein (LDL) cholesterol. In women who received E but not E&T, hip ($p < 0.001$) and abdominal circumferences ($p < 0.05$) and fat mass:fat-free mass (FM:FFM) ratio over the abdomen ($p < 0.05$) declined. E&T but not E resulted in increased FFM ($p < 0.001$) and a reduced FM:FFM ratio ($p < 0.05$). For E but not E&T, the decrease in LDL cholesterol was significantly related to changes in total and compartmental body fat and to change in the FM:FFM

ratio ($p < 0.05$). **CONCLUSION:** Estrogen replacement has effects on body fat distribution in postmenopausal women that are associated with improved lipid parameters. Addition of parenteral testosterone does not negate the favorable effects of estrogen on LDL cholesterol levels but may attenuate the reduction in centralized body fat achieved with E implants.

PMID: 11127762

Endocr Res. 2000 Nov;26(4):505-11.

DHEA replacement in women with adrenal insufficiency--pharmacokinetics, bioconversion and clinical effects on well-being, sexuality and cognition.

Arlt W, Callies F, Allolio B. Department of Internal Medicine, University of Würzburg, Germany.

Abstract: Standard replacement for adrenal insufficiency (AI) consists of glucocorticoids and mineralocorticoids while DHEA deficiency is routinely ignored. Thus, AI represents the ideal pathophysiological model of isolated DHEA deficiency. We investigated the effects of DHEA replacement in 24 women with primary and secondary AI employing a double blind, placebo-controlled, randomized crossover design. A DHEA dose of 50 mg/d was chosen based on preceding single-dose pharmacokinetics and bioconversion studies. Each patient received four months of treatment with DHEA and four months placebo, with a one-month washout period. Measurements included serum steroid hormones, somatotrophic parameters and psychometric assessment of well-being, mood, cognition and sexuality. Treatment with DHEA raised the initially low serum concentrations of DHEA, DHEAS, androstenedione, and testosterone into the normal range. DHEA induced a slight increase in serum IGF-I, but only in patients with primary AI, suggesting a growth hormone-mediated effect. DHEA treatment significantly improved overall wellbeing as well as scores for depression, anxiety, and their physical correlates. Furthermore, DHEA significantly increased both sexual interest and the level of satisfaction with sex. DHEA replacement had no influence on the cognitive performance, which was already on a high level at baseline. In conclusion, DHEA replacement improves well-being and sexuality in women with adrenal insufficiency. If this is due to a direct effect of DHEA on the brain, an indirect effect via increased androgen synthesis, or both, remains to be elucidated. Long-term studies in patients of both sexes are needed to further define the role of DHEA in standard replacement for adrenal insufficiency. PMID: 11196420

Ann Intern Med. 1999 Feb 16;130(4 Pt 1):270-7.

Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Study of Osteoporotic Fractures Research Group.

Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W, Cummings SR. Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pennsylvania 15261.

BACKGROUND: The relation between endogenous steroid hormones and risk for breast cancer is uncertain. Measurement of sex hormone levels may identify women at high risk for breast cancer who should consider preventive therapies. **OBJECTIVE:** To test the hypothesis that serum concentrations of estradiol and testosterone predict risk for breast cancer. **DESIGN:** Prospective case-cohort study. **SETTING:** Four clinical centers in the United States. **PARTICIPANTS:** 97 women with confirmed incident breast cancer and 244 randomly selected controls; all women were white, 65 years of age or older, and were not receiving estrogen. **MEASUREMENTS:** Sex-steroid hormone concentrations were assayed by using serum that was collected at baseline and stored at -190 degrees C. Risk factors for breast cancer were ascertained by questionnaire. Incident cases of breast cancer were confirmed by review of medical records during an average period of 3.2 years. **RESULTS:** The relative risk for breast cancer in women with the highest concentration of bioavailable estradiol ($> \text{or} = 6.83 \text{ pmol/L}$ or 1.9 pg/mL) was 3.6 (95% CI, 1.3 to 10.0) compared with women with the lowest concentration. The risk for breast cancer in women with the highest concentration of free testosterone compared with those with the lowest concentration was 3.3 (CI, 1.1 to 10.3). The estimated incidence of breast cancer per 1000 person-years was 0.4 (CI, 0.0 to 1.3) in women with the lowest levels of bioavailable estradiol and free testosterone compared with 6.5 (CI, 2.7 to 10.3) in women with the highest concentrations of these hormones. Traditional risk factors for breast cancer were similar in case-patients and controls. Adjustments for these risk factors had little effect on the results. **CONCLUSIONS:** Estradiol and testosterone levels may play important roles in the development of breast cancer in older women. A single measurement of bioavailable estradiol and free testosterone may be used to estimate a woman's risk for breast cancer. Women identified as being at high risk for breast cancer as determined by these hormone levels may benefit from antiestrogen treatment for primary prevention. PMID: 10068384

Am J Epidemiol. 1997 Jun 1;145(11):1030-8.

Relation of serum levels of testosterone and dehydroepiandrosterone sulfate to risk of breast cancer in postmenopausal women.

Zeleniuch-Jacquotte A, Bruning PF, Bonfrer JM, Koenig KL, Shore RE, Kim MY, Pasternack BS, Toniolo P. Nelson Institute of Environmental Medicine and Kaplan Comprehensive Cancer Center, New York University School of Medicine, NY 10010.

Abstract: The authors examined the relation between postmenopausal serum levels of testosterone and dehydroepiandrosterone sulfate (DHEAS) and subsequent risk of breast cancer in a case-control study nested within the New York University Women's Health Study cohort. A specific objective of their analysis was to examine whether androgens had an effect on breast cancer risk independent of their effect on the biologic availability of estrogen. A total of 130 cases of breast cancer were diagnosed prior to 1991 in a cohort of 7,054 postmenopausal women who had donated blood and completed questionnaires at a breast cancer screening clinic in New York City between 1985 and 1991. For each case, two controls were selected, matching the case on age at blood donation and length of storage of serum specimens. Biochemical analyses were performed on sera that had been stored at -80 degrees C since sampling. The present report includes a subset of 85 matched sets, for whom at least 6 months had elapsed between blood donation and diagnosis of the case. In univariate analysis, testosterone was positively associated with breast cancer risk (odds ratio (OR) for the highest quartile = 2.7, 95% confidence interval (CI) 1.1-6.8, $p < 0.05$, test for trend). However, after including % estradiol bound to sex hormone-binding globulin (SHBG) and total estradiol in the statistical model, the odds ratios associated with higher levels of testosterone were considerably reduced, and there was no longer a significant trend (OR for the highest quartile = 1.2, 95% CI 0.4-3.5). Conversely, breast cancer risk remained positively associated with total estradiol levels (OR for the highest quartile = 2.9, 95% CI 1.0-8.3) and negatively associated with % estradiol bound to SHBG (OR for the highest quartile = 0.05, 95% CI 0.01-0.19) after adjustment for serum testosterone levels. These results are consistent with the hypothesis that testosterone has an indirect effect on breast cancer risk, via its influence on the amount of bioavailable estrogen. No evidence was found of an association between DHEAS and risk of breast cancer in postmenopausal women. PMID: 9169912

J Clin Endocrinol Metab. 1996 Jan;81(1):59-64.

Dehydroepiandrosterone, dehydroepiandrosterone sulfate, obesity, waist-hip ratio, and noninsulin-dependent diabetes in postmenopausal women: the Rancho Bernardo Study.

Barrett-Connor E, Ferrara A. Department of Family and Preventive Medicine, University of California, San Diego, La Jolla 92093.

Abstract: Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) levels were determined in morning specimens from 659 fasting postmenopausal women who were not using estrogen therapy or antidiabetic medication. All women had concurrent oral glucose tolerance tests and measurements of body mass index (BMI) and waist-hip ratio (WHR). DHEA levels were weakly and inversely associated with BMI but not with WHR or glucose tolerance status. DHEAS levels were not associated with BMI but were positively associated with WHR, diabetes, and impaired glucose tolerance. In analyses adjusted for or stratified by WHR, the DHEAS association with abnormal carbohydrate tolerance was reduced but still independent of fat distribution. Because this was a cross-sectional study, it was not possible to determine whether DHEAS levels were raised by central obesity or vice versa. At a minimum, these data strongly suggest that the positive association of DHEAS with both central obesity and abnormal glucose tolerance does not support the thesis that DHEAS protect against diabetes or obesity in older women as had been suggested by animal studies. PMID: 8550794

Maturitas. 1995 Apr;21(3):227-36.

Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality.

Davis SR, McCloud P, Strauss BJ, Burger H. Prince Henry's Institute of Medical Research, Clayton, Victoria, Australia.

Abstract: To investigate the role of androgens in increasing bone density and improving low libido in postmenopausal women, we have studied the long-term effects of estradiol and testosterone implants on bone mineral density and sexuality in a prospective, 2 year, single-blind randomised trial. Thirty-four postmenopausal volunteers were randomised to treatment with either estradiol implants 50 mg alone (E) or estradiol 50 mg plus testosterone 50 mg (E&T), administered 3-monthly for

2 years. Cyclical oral progestins were taken by those women with an intact uterus. Thirty-two women completed the study. BMD (DEXA) of total body, lumbar vertebrae (L1-L4) and hip area increased significantly in both treatment groups. BMD increased more rapidly in the testosterone treated group at all sites. A substantially greater increase in BMD occurred in the E&T group for total body ($P < 0.008$), vertebral L1-L4 ($P < 0.001$) and trochanteric ($P < 0.005$) measurements. All sexual parameters (Sabbatsberg sexual self-rating scale) improved significantly in both groups. Addition of testosterone resulted in a significantly greater improvement compared to E for sexual activity ($P < 0.03$), satisfaction ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$) and relevancy ($P < 0.05$). Total cholesterol and LDL-cholesterol fell in both groups as did total body fat. Total body fat-free mass (DEXA, anthropometry, impedance) increased in the E&T group only. We concluded that in postmenopausal women, treatment with combined estradiol and testosterone implants was more effective in increasing bone mineral density in the hip and lumbar spine than estradiol implants alone. Significantly greater improvement in sexuality was observed with combined therapy, verifying the therapeutic value of testosterone implants for diminished libido in postmenopausal women. The favourable estrogenic effects on lipids were preserved in women treated with T, in association with beneficial changes in body composition. PMID: 7616872

Testosterone & Androgens: For Men

Eur J Endocrinol. 2009 Sep;161(3):443-9. Epub 2009 Jun 19.

Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men.

Mathur A, Malkin C, Saeed B, Muthusamy R, Jones TH, Channer K. Department of Cardiology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK.

INTRODUCTION: In short-term studies, testosterone replacement therapy has been shown to protect male subjects from exercise-induced ischaemia and modify cardiovascular risk factors such as insulin resistance, fat mass and lipid profiles. **METHODS:** This randomised parallel group controlled trial was designed to assess the treatment effect of testosterone therapy (Nebido) compared with placebo in terms of exercise-induced ischaemia, lipid profiles, carotid intima-media thickness (CIMT) and body composition during 12 months treatment in men with low testosterone levels and angina. **RESULTS:** A total of 15 men were recruited but 13 ($n=13$) reached adequate duration of follow-up; seven were treated with testosterone and six with placebo. Testosterone increased time to ischaemia (129 ± 48 s versus 12 ± 18 , $P=0.02$) and haemoglobin (0.4 ± 0.6 g/dl versus -0.03 ± 0.5 , $P=0.04$), and reduced body mass index (-0.3 kg/m² versus 1.3 ± 1 , $P=0.04$) and triglycerides (-0.36 ± 0.4 mmol/l versus 0.3 ± 1.2 , $P=0.05$). The CIMT decreased in the testosterone group more than placebo, but full between group analyses suggested this was only a statistical trend (-0.5 ± 0.1 vs -0.09 ± 0.06 , $P=0.16$). There were no significant effects on serum prostate specific antigen, total or high-density lipoprotein cholesterol; or on mood and symptom scores as assessed by Seattle Angina Score and EuroQol. **CONCLUSION:** The protective effect of testosterone on myocardial ischaemia is maintained throughout treatment without decrement. Previously noted potentially beneficial effects of testosterone on body composition were confirmed and there were no adverse effects. PMID: 19542238

Int J Cardiol. 2009 Nov 16. [Epub ahead of print]

Cardiovascular disease and androgens: A review.

Kaushik M, Sontineni SP, Hunter C. Department of Medicine, Creighton University Medical Center, Omaha, NE.

Abstract: Globally, cardiovascular disease is the single largest cause of mortality. The differences in pattern of cardiovascular disease between the two genders have not been explained properly. The spotlight has largely been focused on estrogens but no conclusive evidence has proven its role in reducing the incidence of cardiovascular disease. Consequently, androgens have attracted significant interest in explaining the gender difference in cardiovascular disease. More studies in last two decades have increased our knowledge about the effects of androgens on cardiovascular disease progression. Evidence for age related fall in testosterone levels in males and increasing cardiovascular events with age had lead to the postulation of idea of 'andropause or male menopause'. Unfortunately, for the last few decades the androgens have been highlighted as agents of abuse among athletes all over the world. There have been multiple reports of their association with sudden cardiac death and adverse cardiovascular outcomes when abused. Contrastingly, there has been an increasing prescription use of testosterone supplementation in various conditions related to androgen deficiency state and for many other off-label indications. Human observational studies have mostly concluded that men with lower testosterone levels tend to have higher incidence of coronary artery disease. Emerging evidence supports that lower androgen levels predict poor

cardiovascular risk profile. Role with supplementation of testosterone for cardiovascular disease is being studied in both primary and secondary prevention stages and its safety being evaluated. This is an appropriate time to review the role of androgens specifically from a cardiovascular standpoint. PMID: 19923015

J Steroid Biochem Mol Biol. 2009 Mar;114(1-2):40-3.

The role of testosterone in the metabolic syndrome: a review.

Saad F, Gooren L. Men's Healthcare, Scientific Affairs Bayer Schering Pharma AG, Berlin, Germany.

Abstract: Over the last three decades it has become apparent that testosterone plays a significant role in the maintenance of bone and muscle mass, in erythropoiesis, and in mental functions. But testosterone is also a key player in glucose homeostasis and lipid metabolism. The metabolic syndrome is a clustering of risk factors predisposing to late onset diabetes mellitus, atherosclerosis and cardiovascular morbidity and mortality. The main components of the syndrome are visceral obesity, glucose intolerance, raised blood pressure and dyslipidaemia (elevated triglycerides, low levels of high-density lipoprotein cholesterol), and a pro-inflammatory and thrombogenic state. Cross-sectional epidemiological studies have reported a direct correlation between plasma testosterone and insulin sensitivity, and low testosterone levels are associated with an increased risk of type 2 diabetes mellitus, dramatically illustrated by androgen deprivation in men with prostate carcinoma. Lower total testosterone and sex hormone-binding globulin (SHBG) predict a higher incidence of the metabolic syndrome. There is now evidence to argue that hypotestosteronaemia should be an element in the definition of the metabolic syndrome. Administration of testosterone to hypogonadal men reverses the unfavorable risk profile for the development of diabetes and atherosclerosis. Testosterone should be regarded as a pivotal hormone for men's health. PMID: 19444934

Front Neuroendocrinol. 2009 Jul;30(2):239-58. Epub 2009 May 7.

Protective actions of sex steroid hormones in Alzheimer's disease.

Pike CJ, Carroll JC, Rosario ER, Barron AM. Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089.

Abstract: Risk for Alzheimer's disease (AD) is associated with age-related loss of sex steroid hormones in both women and men. In post-menopausal women, the precipitous depletion of estrogens and progestogens is hypothesized to increase susceptibility to AD pathogenesis, a concept largely supported by epidemiological evidence but refuted by some clinical findings. Experimental evidence suggests that estrogens have numerous neuroprotective actions relevant to prevention of AD, in particular promotion of neuron viability and reduction of beta-amyloid accumulation, a critical factor in the initiation and progression of AD. Recent findings suggest neural responsiveness to estrogen can diminish with age, reducing neuroprotective actions of estrogen and, consequently, potentially limiting the utility of hormone therapies in aged women. In addition, estrogen neuroprotective actions are also modulated by progestogens. Specifically, continuous progestogen exposure is associated with inhibition of estrogen actions whereas cyclic delivery of progestogens may enhance neural benefits of estrogen. In recent years, emerging literature has begun to elucidate a parallel relationship of sex steroid hormones and AD risk in men. Normal age-related testosterone loss in men is associated with increased risk to several diseases including AD. Like estrogen, testosterone has been established as an endogenous neuroprotective factor that not only increases neuronal resilience against AD-related insults, but also reduces beta-amyloid accumulation. Androgen neuroprotective effects are mediated both directly by activation of androgen pathways and indirectly by aromatization to estradiol and initiation of protective estrogen signaling mechanisms. The successful use of hormone therapies in aging men and women to delay, prevent, and or treat AD will require additional research to optimize key parameters of hormone therapy and may benefit from the continuing development of selective estrogen and androgen receptor modulators. PMID: 19427328

Front Horm Res. 2009;37:32-51.

Advances in testosterone replacement therapy.

Gooren LJ. Department of Endocrinology, VU University Medical Centre, Amsterdam, The Netherlands.

Abstract: The major goal of androgen substitution is to replace testosterone at levels as close to physiological concentrations

as is possible. The mainstay of testosterone substitution are parenteral testosterone esters (enanthate and cypionate) to be administered every 2-3 weeks. A major disadvantage is the strongly fluctuating levels of plasma testosterone which are at least 50% of the time not in the physiological range. A significant improvement is parenteral testosterone undecanoate producing normal plasma testosterone for 12 weeks. Subcutaneous testosterone implants provide the patient, depending on the dose of implants, with normal plasma testosterone for 3-6 months. Its use is, however, not widespread. Oral testosterone undecanoate dissolved in oil bypasses the liver via its lymphatic absorption, but resulting plasma levels are erratic. Transdermal testosterone preparations have already been available for two decades. Transdermal testosterone gel produces attractive pharmacokinetic serum testosterone profiles and offers greater flexibility in dosing. Transdermal gel has been recommended in elderly males. In case of complications its use can be discontinued immediately. Oromucosal testosterone preparations are being developed. Testosterone replacement is usually of long duration, and patient compliance is of utmost importance. Therefore, the patient must be involved in the selection of the type of testosterone preparation.

PMID: 19011287

J Sex Med. 2009 Mar;6 Suppl 3:234-8. Epub 2009 Jan 21.

Androgens and erectile function: a case for early androgen use in postprostatectomy hypogonadal men.

Khera M. Baylor College of Medicine, Department of Urology, Houston, TX, USA.

INTRODUCTION: Erectile dysfunction affects up to 80% of men following a radical prostatectomy (RP) and is a common concern for these patients. Currently, hypogonadal men are not treated with testosterone after a RP for fear of stimulating dormant prostate cancer cells even though there is little evidence to support this hesitancy. There is data, however, to support the use of testosterone to aid in faster and better recovery of erections following RP. **AIMS:** The aim of this article is to explore the relationship between testosterone replacement therapy (TRT) and erectile preservation following RP. **MAIN OUTCOME MEASURES:** The results of findings in the literature on the association between testosterone and its role in preserving erectile function, particularly in men following RP. **METHODS:** This article reviews and evaluates the literature that demonstrates the role of testosterone in obtaining erections and preserving erectile function. Additional articles were reviewed to assess the role of testosterone in erectile preservation following RP. **RESULTS:** This review demonstrates that testosterone does play a role in erectile function, particularly for men who have undergone a RP. Testosterone has been shown to have an effect on nitric oxide synthase release, phosphodiesterase type 5 expression and activity, and in cavernosal nerve function, and to contribute to venoocclusive disease in the penis. All of these effects are of particular importance to men attempting to preserve erectile function following RP. **CONCLUSION:** While the relationship between TRT and improvement in erectile function has been well established, the role of testosterone in men following RP may be of even greater significance. However, further studies are needed to assess the true safety of TRT following RP.

PMID: 19207279

J Sex Med. 2009 Feb;6(2):456-63.

The effects of treating male hypogonadism on couples' sexual desire and function.

Conaglen JV, Conaglen HM. Waikato Clinical School, Faculty of Medical & Health Sciences, University of Auckland, New Zealand.

INTRODUCTION: Hypogonadism is a common endocrine condition characterized by low levels of testosterone (T) and marked by numerous symptoms, one of which is low sexual desire. Studies comparing T delivery systems have suggested that hypogonadal men's partners may be at risk from exposure to T gels. Little other mention is found of the impact of hypogonadism and its treatment on a man's partner and the couple's sexual function. **AIM:** To assess sexual desire and sexual function in hypogonadal men and their woman partners before and after treatment with T replacement therapy. **METHODS:** Twenty-one hypogonadal men and 18 partners were recruited from a tertiary endocrine clinic, and were compared with a control group of 20 eugonadal age-matched men and their partners. All men had baseline blood tests to confirm their status as hypogonadal or eugonadal, and hypogonadal men repeated tests at 3-month intervals. All participants completed the Sexual Desire Inventory (SDI) and sexual function questionnaires at baseline and at 3-month intervals until the hypogonadal men attained normal T levels. **MAIN OUTCOME MEASURES:** Pre- and post-treatment SDI and sexual function questionnaires were compared once T normalization was achieved. Between- and within-group comparisons were carried out. **RESULTS:** Pretreatment hypogonadal men recorded lower levels of sexual desire and function than controls,

but significantly improved once hypogonadism was corrected. Eugonadal controls recorded no significant changes in either sexual desire or function during the study. Partners of the hypogonadal men reported no changes on the SDI, but significant improvements in sexual function as their partners recovered. **CONCLUSION:** SDI and sexual function measures reflect sexual changes that accompany rising serum T levels during correction of male hypogonadism. Women partners reported more satisfaction, less pain, and improved sexual function following the men's treatment. Treatments affecting one partner potentially have important effects on the other. PMID: 19215616

Clin Endocrinol (Oxf). 2009 Nov;71(5):715-21. Epub 2009 Jan 19.

Testosterone stimulates extra-hepatic but not hepatic fat oxidation (Fox): comparison of oral and transdermal testosterone administration in hypopituitary men.

Birzniece V, Meinhardt UJ, Handelsman DJ, Ho KK. Pituitary Research Unit, Garvan Institute of Medical Research and Department of Endocrinology, St. Vincent's Hospital, 384 Victoria Street, Darlinghurst, NSW 2010, Australia.

BACKGROUND: Fat mass is increased in hypogonadal men and the changes are reversed by testosterone replacement. Testosterone administration enhances whole body fat oxidation (Fox). Fat is oxidized in the liver and in extra-hepatic tissues. **OBJECTIVE:** To determine whether the stimulation of Fox by testosterone arises primarily from the liver or from extra-hepatic tissues. **DESIGN/PATIENTS:** This was an open-label cross-over study. Thirteen men with hypopituitarism (age 53.1 +/- 4.1 years) with both growth hormone (GH) and testosterone deficiency were studied sequentially after 2 weeks of treatment with transdermal testosterone (5 mg), no treatment, and stepwise incremental doses of oral crystalline testosterone (10, 20, 40 and 80 mg) in the absence of GH replacement. **MEASUREMENTS:** Serum testosterone, IGF-I, metabolic effects [resting energy expenditure (REE) and Fox], SHBG, and thyroid binding globulin (TBG) as markers of excessive hepatic androgen exposure, were measured at the end of each treatment period. **RESULTS:** When compared to the no-treatment phase, mean blood testosterone levels rose into the physiological range after transdermal testosterone delivery but did not significantly change after 10, 20, 40 or 80 mg oral testosterone treatment. Blood SHBG and TBG fell significantly with 80 mg oral testosterone dose but were unaffected by any other testosterone treatment. Fox increased significantly with transdermal but not with any dose of oral testosterone. Mean plasma IGF-I and REE were unaffected by testosterone, regardless of the route or dose. **CONCLUSIONS:** Short-term testosterone administration does not stimulate hepatic fat oxidation but enhances whole body fat oxidation by acting on extra-hepatic tissues. PMID: 19170715

Urologe A. 2009 May;48(5):516-22.

[Testosterone replacement therapy and prostate cancer. The current position 67 years after the Huggins myth]

Rinnab L, Gust K, Hautmann RE, Küfer R. Abteilung Urologie und Kinderurologie, Universitätsklinikum, Ulm.

Abstract: Hypogonadism is highly prevalent in the elderly and in men with prostate cancer. Symptoms of hypogonadism, such as depression, lack of libido, and decreased bone mineral density, can significantly impair quality of life. In addition, testosterone plays an important role in erectile preservation and in growth and function of the cavernosal and penile nerves. There are compelling data showing that testosterone replacement therapy (TRT) does not increase the risk of prostate cancer. The literature (four published studies) concerning men treated with TRT after definitive therapy for prostate cancer reports only one biochemical recurrence. Based on these data, physicians cannot really justify withholding TRT from symptomatic patients after they have been successfully treated for prostate cancer. This review gives the practising urologist an overview of the latest literature and useful advice on this controversial topic. PMID: 19296069

Postgrad Med. 2008 Sep;120(3):130-53.

Testosterone replacement therapy in hypogonadal men: assessing benefits, risks, and best practices.

Miner M, Canty DJ, Shabsigh R. Warren Alpert School of Medicine, Brown University, Providence, RI 02912.

Abstract: Hypogonadism is a common condition, especially among older men, but often goes undiagnosed and untreated. It can be associated with a number of signs and symptoms that affect health and quality of life, including feelings of low energy and fatigue; decreased sex drive and performance; decreased muscle mass and strength; decreased bone mineral density; and increased body fat, particularly abdominal fat, a putative risk factor for metabolic syndrome and type 2 diabetes mellitus. The evidence supporting testosterone replacement therapy (TRT) in improving these and related conditions is strong and

consistent for body composition and sexual function; moderately consistent for bone mineral density; inconsistent for insulin sensitivity, glycemic control, and lipid profiles; and weak and inconsistent for mood and cognitive function. The concern of some physicians about the potential for TRT to stimulate prostate cancer is not supported by decades of data accumulated to date, though studies of longer duration (eg, 10 years or more) would be even more convincing. Other research needs are discussed. As the front line of health care delivery, primary care physicians need to be vigilant in diagnosing and treating symptomatic hypogonadism. Based on current guidelines, we recommend assessing testosterone levels when an adult man exhibits signs of hypogonadism, and as part of normal medical screening in men starting at age 40 to 50 years, to establish a baseline. A physician should discuss the possibility of TRT with symptomatic patients who have a serum total testosterone level < 300 ng/dL. If TRT is initiated, a patient's response and adverse events should be assessed every 3 to 6 months, and therapy adjusted accordingly. PMID: 18824832

BJU Int. 2008 Nov;102(9):1142-6. Epub 2008 Jun 6.

Clinical practice experience with testosterone treatment in men with testosterone deficiency syndrome.

McLaren D, Siemens DR, Izard J, Black A, Morales A. Department of Urology and Centre for Applied Urological Research, Kingston General Hospital, Queen's University, Kingston, ON, Canada.

OBJECTIVE: To report on a clinical practice series of testosterone-replacement therapy (TRT) in men with testosterone deficiency syndrome (TDS), examining clinical efficacy, biochemical parameters and effects on prostate health over a 2-year period. **PATIENTS AND METHODS:** A retrospective review of 85 patients with symptoms of TDS and at least a 3-month trial of TRT was performed in this single-centre, clinical practice setting. Three domains of symptomatology were evaluated: libido, erectile function and energy levels. Symptoms were assessed by a combination of patient reporting, physician's assessment and validated symptom assessment scores. Total testosterone (TT), calculated bio-available testosterone (BT) and prostate-specific antigen (PSA) levels were continuously measured and effects on prostate health were examined. **RESULTS:** Only 38 (45%) patients in this cohort remained on TRT for >2 years. The most common reason for discontinuing treatment was lack of clinical response but those remaining on TRT had continued improvement in libido, erectile function and energy levels. During treatment, the average TT and calculated BT values significantly increased compared with the baseline values at most of the evaluated time points, with no significant change in average PSA values. In all, 15% of this cohort had some degree of progression of lower urinary tract symptoms. Seven patients had eight 'for-cause' prostate biopsies either during supplementation or at any date after completion, with an only three positive for cancer. **CONCLUSIONS:** Only 45% of men on TRT remained on treatment for >2 years in this clinical practice experience of men with TDS. Those remaining showed persistent improvement in their symptoms. The average TT and BT values increased significantly with no significant change in PSA levels. PMID: 18540933

Cancer. 2007 Feb 1;109(3):536-41.

Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy.

Sarosdy MF. South Texas Urology and Urologic Oncology, San Antonio, Texas 78229.

BACKGROUND: Controversy and a notable paucity of published clinical data best characterize the current knowledge of testosterone-replacement therapy (TRT) for hypogonadism after treatment for early, localized prostate cancer. The objective of this study was to assess the risk of biochemical failure with TRT after treatment of early prostate cancer with permanent transperineal brachytherapy with or without external beam therapy in patients with low serum levels of testosterone and clinical symptoms of hypogonadism. **METHODS:** Patients who underwent prostate brachytherapy from 1996 to 2004 and received subsequent TRT for symptomatic hypogonadism were reviewed to detail cancer characteristics and treatment as well as pre- and post-TRT serum testosterone and prostate-specific antigen (PSA) values. **RESULTS:** Thirty-one men received TRT after prostate brachytherapy for 0.5 to 8.5 years (median, 4.5 years), with a follow-up that ranged from 1.5 years to 9.0 years (median, 5.0 years) postbrachytherapy. TRT was started from 0.5 years to 4.5 years (median, 2.0 years) after brachytherapy. Serum total testosterone levels ranged from 30 ng/dL to 255 ng/dL (median, 188 ng/dL) before TRT and rose to 365 ng/dL to 1373 ng/dL (median, 498 ng/dL) on TRT. Transient rises in PSA were observed in 1 patient. The most recent PSA level was <0.1 ng/mL in 23 patients (74.2%), <0.5 ng/mL in 30 patients (96.7%), and <1 ng/mL in 31 patients (100%). No patients stopped TRT because of cancer recurrence or documented cancer progression. **CONCLUSIONS:** For patients with low serum testosterone levels and symptoms of hypogonadism, TRT may be used with caution and close follow-up after prostate brachytherapy. (c) 2007 American Cancer Society. PMID: 17183557

Aging Male. 2006 Dec;9(4):201-6.

Testosterone and erectile physiology.

Guay AT. Center for Sexual Function/Endocrinology, Lahey Clinic Northshore, Peabody, MA.

Abstract: The role of testosterone deficiency in sexual dysfunction is an important aspect of aging, because it affects such a large proportion of men over 50 years old. A number of age-related factors can cause sexual dysfunction (in particular erectile dysfunction) and testosterone deficiency, such as chronic illness and multiple medications, and the causative link between hypogonadism and erectile dysfunction is still debated. However, studies in castrated animals have proven that addition of testosterone, and its conversion to dihydrotestosterone, can restore erectile function. It appears that testosterone achieves this by peripheral mechanisms (endothelial dependent and independent) and central mechanisms. Testosterone replacement therapy is therefore effective for erectile dysfunction in men with hypogonadism, with success rates of 35-40%. Testosterone supplementation is also important in men who fail on phosphodiesterase type-5 inhibitors, because a minimum plasma concentration of testosterone is required for the successful restoration of erectile function with these agents. Testosterone gels are now the preferred formulation for testosterone supplementation and they can be highly beneficial in a proportion of men with erectile dysfunction. PMID: 17178555

Int J Clin Pract. 2006 Sep;60(9):1087-92.

The evolving role of testosterone in the treatment of erectile dysfunction.

Shabsigh R, Rajfer J, Aversa A, Traish AM, Yassin A, Kalinchenko SY, Buvat J. Department of Urology, Columbia University, New York, NY 10032.

Abstract: Hypogonadism may play a significant role in the pathophysiology of erectile dysfunction (ED). A threshold level of testosterone may be necessary for normal erectile function. Testosterone replacement therapy is indicated in hypogonadal patients and is beneficial in patients with ED and hypogonadism. Monotherapy with testosterone for ED is of limited effectiveness and may be most promising in young patients with hypogonadism and without vascular risk factors for ED. A number of laboratory and human studies have shown the combination of testosterone and other ED treatments, such as phosphodiesterase type 5 (PDE5) inhibitors, to be beneficial in patients with ED and hypogonadism, who fail PDE5 inhibitor therapy alone. There is increasing evidence that combination therapy is effective in treating the symptoms of ED in patients for whom treatment failed with testosterone or PDE5 inhibitors alone. Testosterone replacement therapy has potentially evolved from a monotherapy for ED in cases of low testosterone, to a combination therapy with PDE5 inhibitors. Screening for hypogonadism may be useful in men with ED who fail prior PDE5 inhibitors, especially in populations at risk for hypogonadism such as type 2 diabetes and the metabolic syndrome. PMID: 16939550

J Clin Endocrinol Metab. 2006 Oct;91(10):3908-15. Epub 2006 Jul 18.

Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men.

Fink HA, Ewing SK, Ensrud KE, Barrett-Connor E, Taylor BC, Cauley JA, Orwoll ES. Geriatric Research Education and Clinical Center, Veterans Affairs Medical Center, One Veterans Drive, Box 11G, Minneapolis, MN 55417.

CONTEXT: The clinical value of measuring testosterone and estradiol in older men with osteoporosis and of measuring bone mineral density (BMD) in older men with testosterone or estradiol deficiency is uncertain. **OBJECTIVE:** The objective of the study was to examine the association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. **DESIGN:** This study was a cross-sectional and longitudinal analysis. **Setting:** The study was conducted at six U.S. centers of the Osteoporotic Fractures in Men study. **PARTICIPANTS:** The study population consisted of 2447 community-dwelling men aged 65 yr or older. **MAIN OUTCOME MEASURES:** Total testosterone deficiency was defined as less than 200 ng/dl. Total estradiol deficiency was defined as less than 10 pg/ml. Osteoporosis was defined as femoral neck or total hip BMD T-score of -2.5 or less. Rapid bone loss was defined as 3%/yr or more. **RESULTS:** Prevalence of osteoporosis in men with deficient and normal total testosterone was 12.3 and 6.0% ($P = 0.003$) and 15.4 and 2.8% ($P < 0.0001$) in those with deficient and normal total estradiol. Among osteoporotic men and those with normal BMD, prevalence of total testosterone deficiency was 6.9 and 3.2% ($P = 0.01$), and prevalence of total estradiol deficiency was 9.2 and 2.4% ($P = 0.0001$). Incidence of rapid hip bone loss in men with deficient and normal total testosterone was 22.5 and 8.6% ($p = 0.007$) and in those with deficient and normal total estradiol was 14.3 and 6.3% ($p = 0.08$). **CONCLUSIONS:** Older men with total testosterone or estradiol deficiency were more likely to be osteoporotic. Those with osteoporosis were more likely to be total testosterone or estradiol deficient. Rapid hip bone loss was more likely in men with total testosterone deficiency. BMD testing of older men with sex steroid deficiency may be clinically warranted. PMID: 16849417

Aging Male. 2006 Dec;9(4):195-9.

Testosterone and the brain.

Zitzmann M. Institute of Reproductive Medicine, University of Münster, Münster, Germany.

Abstract: Gender differences in spatial recognition, and age-related declines in cognition and mood, point towards testosterone as an important modulator of cerebral functions. Testosterone appears to activate a distributed cortical network, the ventral processing stream, during spatial cognition tasks, and addition of testosterone improves spatial cognition in younger and older hypogonadal men. In addition, reduced testosterone is associated with depressive disorders. The relationship between depression and testosterone appears to partly depend upon the androgen receptor genotype of the patient, and in appropriate patients with low testosterone levels, testosterone substitution can increase positive mood and decrease negative mood. The much publicized link between testosterone and aggression is probably only of importance in athletes who supplement their testosterone levels to excessively high levels, whereas in hypogonadal men, testosterone supplementation only enhances the positive aspects of aggression such as vigour and energy. Current data suggest that testosterone supplementation in hypogonadal men of all ages will enhance many aspects of mood and cognition.

PMID: 17178554

Treat Endocrinol. 2005;4(5):293-309.

Male hypogonadism : an update on diagnosis and treatment.

Darby E, Anawalt BD. Veterans Affairs Puget Sound Health Care System and University of Washington, Seattle, Washington 98108.

Abstract: Male hypogonadism is one of the most common endocrinologic syndromes. The diagnosis is based on clinical signs and symptoms plus laboratory confirmation via the measurement of low morning testosterone levels on two different occasions. Serum luteinizing hormone and follicle-stimulating hormone levels distinguish between primary (hypergonadotropic) and secondary (hypogonadotropic) hypogonadism. Hypogonadism associated with aging (andropause) may present a mixed picture, with low testosterone levels and low to low-normal gonadotropin levels. Androgen replacement therapy in hypogonadal men has many potential benefits: improved sexual function, an enhanced sense of well-being, increased lean body mass, decreased body fat, and increased bone density. However, it also carries potential risks, including the possibility of stimulating the growth of an occult prostate cancer. The benefits of androgen therapy outweigh the risks in men with classic hypogonadism. However, for men with mild hypogonadism or andropause, the balance between benefits and risks is not always clear. Unfortunately, studies to date have included too small a number of patients and have been too short in duration to provide meaningful data on the long-term risks versus the benefits of androgen replacement therapy in these populations. Several products are currently marketed for the treatment of male hypogonadism. Weekly-to-biweekly injections of testosterone cypionate (cipionate) or testosterone enanthate (enantate) are widely used, as they are economical and generally well tolerated. However, once-daily transdermal therapies have become increasingly popular and now include both patch and gel systems. Intramuscular injection of testosterone undecanoate is an attractive new therapy that can be administered quarterly. To confirm an adequate replacement dosage, assessment of clinical responses and measurement of serum testosterone levels generally suffice. For selected men, serial measurement of bone mineral density during androgen therapy might be helpful to confirm end-organ effects. For men aged >50 years, we advocate measurement of hematocrit for detection of polycythemia and a digital rectal examination with a serum prostate-specific antigen level measurement for prostate cancer screening during the first few months of androgen therapy. Subsequently, a hematocrit should be obtained yearly or after changes in therapy, and annual prostate cancer screening can be offered to the patient after a discussion of its risks and benefits.

PMID: 16185098

Med Hypotheses. 2001 Jun;56(6):702-8.

Aromatase, adiposity, aging and disease. The hypogonadal-metabolic-atherogenic-disease and aging connection.

Cohen PG. 2480 Windy Hill Road SE Suite 200, Marietta, GA 30067.

Abstract: In males, aging, health and disease are processes that occur over physiologic time and involve a cascade of hormonal, biochemical and physiological changes that accompany the down-regulation of the hypothalamic-anterior pituitary-testicular axis. As aging progresses there are relative increases of body fat and decreases in muscle mass. The increased adipose tissue mass is associated with the production of a number of newly generated factors. These include

aromatase, leptin, PAI-1, insulin resistance, and the dyslipidemias, all of which can lead to tissue damage. Fatty tissue becomes the focal point for study as it represents the intersection between energy storage and mobilization. The increase in adipose tissue is associated with an increase in the enzyme aromatase that converts testosterone to estradiol and leads to diminished testosterone levels that favor the preferential deposition of visceral fat. As the total body fat mass increases, hormone resistance develops for leptin and insulin. Increasing leptin fails to prevent weight gain and the hypogonadal-obesity cycle ensues causing further visceral obesity and insulin resistance. The progressive insulin resistance leads to a high triglyceride-low HDL pattern of dyslipidemia and increased cardiovascular risk. All of these factors eventually contribute to the CHAOS Complex: coronary disease, hypertension, adult-onset diabetes mellitus, obesity and/or stroke as permanent changes unfold. Other consequences of the chronic hypogonadal state include osteopenia, extreme fatigue, depression, insomnia, loss of aggressiveness and erectile dysfunction all of which develop over variable periods of time. Copyright 2001 Harcourt Publishers Ltd. PMID: 11399122

Arthritis Res. 2001;3(3):183-8. Epub 2001 Feb 21.

Hyposecretion of the adrenal androgen dehydroepiandrosterone sulfate and its relation to clinical variables in inflammatory arthritis.

Dessein PH, Joffe BI, Stanwix AE, Moomal Z. Department of Rheumatology, Johannesburg Hospital, University of the Witwatersrand, Johannesburg, South Africa.

Abstract: Hypothalamic-pituitary-adrenal underactivity has been reported in rheumatoid arthritis (RA). This phenomenon has implications with regard to the pathogenesis and treatment of the disease. The present study was designed to evaluate the secretion of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) and its relation to clinical variables in RA, spondyloarthropathy (Spa), and undifferentiated inflammatory arthritis (UIA). Eighty-seven patients (38 with RA, 29 with Spa, and 20 with UIA) were studied, of whom 54 were women. Only 12 patients (14%) had taken glucocorticoids previously. Age-matched, healthy women (134) and men (149) served as controls. Fasting blood samples were taken for determination of the erythrocyte sedimentation rate (ESR), serum DHEAS and insulin, and plasma glucose. Insulin resistance was estimated by the homeostasis-model assessment (HOMAIR). DHEAS concentrations were significantly decreased in both women and men with inflammatory arthritis (IA) ($P < 0.001$). In 24 patients (28%), DHEAS levels were below the lower extreme ranges found for controls. Multiple intergroup comparisons revealed similarly decreased concentrations in each disease subset in both women and men. After the ESR, previous glucocorticoid usage, current treatment with nonsteroidal anti-inflammatory drugs, duration of disease and HOMAIR were controlled for, the differences in DHEAS levels between patients and controls were markedly attenuated in women ($P = 0.050$) and were no longer present in men ($P = 0.133$). We concluded that low DHEAS concentrations are commonly encountered in IA and, in women, this may not be fully explainable by disease-related parameters. The role of hypoadrenalism in the pathophysiology of IA deserves further elucidation. DHEA replacement may be indicated in many patients with IA, even in those not taking glucocorticoids. PMID: 11299059

J Clin Endocrinol Metab. 2000 Dec;85(12):4500-10.

Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men.

Swerdlow RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Longstreth J, Berman N. Divisions of Endocrinology, Departments of Medicine/Pediatrics, Harbor-University of California-Los Angeles Medical Center, Torrance, California 90509.

Abstract: Transdermal delivery of testosterone (T) represents an effective alternative to injectable androgens. Transdermal T patches normalize serum T levels and reverse the symptoms of androgen deficiency in hypogonadal men. However, the acceptance of the closed system T patches has been limited by skin irritation and/or lack of adherence. T gels have been proposed as delivery modes that minimize these problems. In this study we examined the pharmacokinetic profiles after 1, 30, 90, and 180 days of daily application of 2 doses of T gel (50 and 100 mg T in 5 and 10 g gel, delivering 5 and 10 mg T/day, respectively) and a permeation-enhanced T patch (2 patches delivering 5 mg T/day) in 227 hypogonadal men. This new 1% hydroalcoholic T gel formulation when applied to the upper arms, shoulders, and abdomen dried within a few minutes, and about 9-14% of the T applied was bioavailable. After 90 days of T gel treatment, the dose was titrated up (50 mg to 75 mg) or down (100 mg to 75 mg) if the preapplication serum T levels were outside the normal adult male range. Serum T rose rapidly into the normal adult male range on day 1 with the first T gel or patch application. Our previous study showed that steady state T levels were achieved 48-72 h after first application of the gel. The pharmacokinetic parameters for serum

total and free T were very similar on days 30, 90, and 180 in all treatment groups. After repeated daily application of the T formulations for 180 days, the average serum T level over the 24-h sampling period (C(avg)) was highest in the 100 mg T gel group (1.4- and 1.9-fold higher than the C(avg) in the 50 mg T gel and T patch groups, respectively). Mean serum steady state T levels remained stable over the 180 days of T gel application. Upward dose adjustment from T gel 50 to 75 mg/day did not significantly increase the C(avg), whereas downward dose adjustment from 100 to 75 mg/day reduced serum T levels to the normal range for most patients. Serum free T levels paralleled those of serum total T, and the percent free T was not changed with transdermal T preparations. The serum dihydrotestosterone C(avg) rose 1.3-fold above baseline after T patch application, but was more significantly increased by 3.6- and 4.6-fold with T gel 50 and 100 mg/day, respectively, resulting in a small, but significant, increase in the serum dihydrotestosterone/T ratios in the two T gel groups. Serum estradiol rose, and serum LH and FSH levels were suppressed proportionately with serum T in all study groups; serum sex hormone-binding globulin showed small decreases that were significant only in the 100 mg T gel group. We conclude that transdermal T gel application can efficiently and rapidly increase serum T and free T levels in hypogonadal men to within the normal range. Transdermal T gel provided flexibility in dosing with little skin irritation and a low discontinuation rate.

PMID: 11134099

Urology. 2000 May;55(5):755-8.

Serum dehydroepiandrosterone sulfate concentrations in men with erectile dysfunction.

Reiter WJ, Pycha A, Schatzl G, Klingler HC, Märk I, Auterith A, Marberger M. Department of Urology, University of Vienna, Vienna, Austria.

OBJECTIVES: In 1994, the Massachusetts Male Aging Study presented the finding of an inverse correlation of the serum levels of dehydroepiandrosterone sulfate (DHEAS) and the incidence of erectile dysfunction (ED). Prompted by the positive results of a pilot study on the treatment of ED with dehydroepiandrosterone (DHEA), we performed a detailed investigation on the serum DHEAS levels in men with ED according to age category. **METHODS:** Inclusion criteria included a history of ED for more than 6 months, a body mass index less than 30, and a state of good general health. Serum DHEAS concentrations were determined in 309 patients with ED and 133 healthy volunteers. All participants were carefully screened to assess medical factors known or suspected to alter endocrine function. Questions 3 and 4 of the International Index of Erectile Function were used to evaluate erectile function. **RESULTS:** The mean serum levels of DHEAS in patients with ED were lower than in healthy volunteers until 60 years of age. The shape of the curve of the patients with ED indicated a quadratic decrease of DHEAS with age in contrast to a more linear decrease of DHEAS with age in the control group. **CONCLUSIONS:** Our results suggest that until the age of 60 years, the mean serum level of DHEAS is lower in patients with ED than in healthy volunteers. PMID: 10792095

Med Hypotheses. 1999 Jan;52(1):49-51.

The hypogonadal-obesity cycle: role of aromatase in modulating the testosterone-estradiol shunt--a major factor in the genesis of morbid obesity.

Cohen PG. 2480 Windy Hill Road SE Suite 200, Marietta, GA 30067.

Abstract: Massive obesity in males is associated with decreased total and free testosterone levels as well as elevated estradiol levels. The decrease in testosterone occurs without the compensatory increases in gonadotropin and a progressive hypogonadotropic hypogonadal cycle develops. During the hypogonadal state, there is a preferential deposition of abdominal adipose tissue. With the increasing fatty-tissue accumulation, there is an increase of aromatase activity that is associated with a greater conversion of testosterone to estradiol (testosterone-estradiol shunt). This results in further depression of testosterone concentrations and leads to the increased preferential deposition of abdominal fat that, in turn, leads to a progressive hypogonadal state. Testalactone, an aromatase inhibitor, interrupts this cycle and repairs the depressed testosterone concentrations and decreases estradiol levels. This increases the testosterone levels and reverses the preferential deposition of abdominal fat, while increasing muscle protein and fat-free mass. PMID: 10342671

Int J Androl. 1999 Oct;22(5):300-6.

Testosterone replacement therapy in older adult men.

Tenover JL. Wesley Woods Center of Emory University, Atlanta, GA 30329.

Abstract: Serum testosterone levels decline slowly with normal ageing in men and, although all men are not destined to become hypogonadal as they age, the prevalence of androgen deficiency in the older male is not insignificant. Over the past several decades, there has been an increasing interest in evaluating whether testosterone therapy (male HRT) might be beneficial for certain older men in preventing or reversing some aspects of ageing. The major androgen target organs of interest with regard to beneficial effects of male HRT include bone, muscle, adipose tissue, the cardiovascular system and the central nervous system (libido and aspects of mood). At the same time, potential adverse effects of male HRT on target organs such as the prostate continue to be evaluated. It is the purpose of this review to summarize the information to date with regard to testosterone replacement therapy in the older man and to discuss areas where more research and clinical information need to be forthcoming. Hormonal replacement therapy (HRT) for post-menopausal women has been studied and discussed for many years. The idea of male HRT, however, is a relatively recent development, with increasing interest in this area occurring only over the past two decades. Reasons for this nascent enthusiasm include burgeoning evidence that testosterone levels decline with normal male ageing (and with age-associated diseases) and an interest in preventing age-related dysfunction and prolonging quality life among an ever increasing population of older adults. The decline in testosterone with age often parallels unfavourable changes in organs upon which androgens act and the goal of male HRT would be to prevent, stabilize or even reverse some of these detrimental target-organ changes. PMID: 10509230

J Clin Endocrinol Metab. 1999 Feb;84(2):573-7.

Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study.

Barrett-Connor E, Von Mühlen DG, Kritz-Silverstein D. Department of Family and Preventive Medicine, School of Medicine, University of California, San Diego, La Jolla 92093.

Abstract: A cross-sectional population-based study examined the association between endogenous sex hormones and depressed mood in community-dwelling older men. Participants included 856 men, ages 50-89 yr, who attended a clinic visit between 1984-87. Total and bioavailable testosterone, total and bioavailable estradiol, and dihydrotestosterone levels were measured by radioimmunoassay in an endocrinology research laboratory. Depressed mood was assessed with the Beck Depression Inventory (BDI). Levels of bioavailable testosterone and bioavailable estradiol decreased with age, but total testosterone, dihydrotestosterone, and total estradiol did not. BDI scores increased with age. Low bioavailable testosterone levels and high BDI scores were associated with weight loss and lack of physical activity, but not with cigarette smoking or alcohol intake. By linear regression or quartile analysis the BDI score was significantly and inversely associated with bioavailable testosterone (both P s = 0.007), independent of age, weight change, and physical activity; similar associations were seen for dihydrotestosterone (P = 0.048 and P = 0.09, respectively). Bioavailable testosterone levels were 17% lower for the 25 men with categorically defined depression than levels observed in all other men (P = 0.01). Neither total nor bioavailable estradiol was associated with depressed mood. These results suggest that testosterone treatment might improve depressed mood in older men who have low levels of bioavailable testosterone. A clinical trial is necessary to test this hypothesis. PMID: 10022418

Drugs Aging. 1999 Aug;15(2):131-42.

Risks versus benefits of testosterone therapy in elderly men.

Basaria S, Dobs AS. Division of Endocrinology and Metabolism, Johns Hopkins University, Baltimore, MD 21287.

Abstract: 'Andropause', like menopause, has received significant attention in recent years. It results in a variety of symptoms experienced by the elderly. Many of these symptoms are nonspecific and vague. For this reason, many authors have questioned the value of androgen replacement in this population. Also in dispute is the normal cutoff level for testosterone beyond which therapy should be initiated, and whether to measure free or total testosterone. Testosterone levels decline with age, with the lowest level seen in men older than 70 years. This age-related decline in testosterone levels is both central (pituitary) and peripheral (testes) in origin. With aging, there is also a loss of circadian rhythm of testosterone secretion and a rise in sex hormone binding globulin (SHBG) levels. Total testosterone level is the best screening test for patients with suspected hypogonadism. If the total testosterone concentration is low, free testosterone levels should be

obtained. Prostate cancer remains an absolute contraindication to androgen therapy. Testosterone replacement results in an improvement in muscle strength and bone mineral density. Similar effects are observed on the haematopoietic system. Data on cognition and lipoprotein profiles are conflicting. Androgen therapy can result in polycythemia and sleep apnoea. These adverse effects can be deleterious in men with compromised cardiac reserve. We recommend that elderly men with symptoms of hypogonadism and a total testosterone level <300 ng/dl should be started on testosterone replacement. This review discusses the pros and cons of testosterone replacement in hypogonadal elderly men and attempts to answer some of the unanswered questions. Furthermore, emphasis is made on the regular follow-up of these patients to prevent the development of therapy-related complications. PMID: 10495072

Am J Psychiatry. 1998 Oct;155(10):1310-8.

Age-associated testosterone decline in men: clinical issues for psychiatry.

Sternbach H. Department of Psychiatry, UCLA-Neuropsychiatric Institute, Los Angeles.

OBJECTIVE: The author summarizes current knowledge about the diagnosis and treatment of testosterone decline in healthy aging men and the associated clinical issues for psychiatry. **METHOD:** A MEDLINE search was conducted in which the search terms "male climacteric," "male menopause," "andropause," "viropause," "low-testosterone syndrome," and "testosterone replacement therapy" were used. Literature published before 1966 was identified by reviewing the reference lists of later publications. **RESULTS:** Manifestations of testosterone deficiency have included depression, anxiety, irritability, insomnia, weakness, diminished libido, impotence, poor memory, reduced muscle and bone mass, and diminished sexual body hair. Although testosterone levels decline with age, there is great interindividual variability, and the connection between serum testosterone levels and clinical psychiatric signs and symptoms is not clear-cut, since other hormonal changes are implicated as well. Testosterone replacement therapy may offer hypogonadal men benefit, but long-term studies on its efficacy and safety are lacking. Comprehensive biopsychosocial assessment should be a routine part of the evaluation of complaints of low-testosterone syndrome in men. **CONCLUSIONS:** Testosterone decline/deficiency is not a state strictly analogous to female menopause and may exhibit considerable overlap with primary and other secondary psychiatric disorders.

PMID: 9766760

Hormones & Skin Aging

Menopause. 2008 Nov-Dec;15(6):1193-4.

Changes in skin topography during hormone therapy.

Kaatz M, Elsner P, Koehler MJ. Dept of Dermatology and Allergology, Friedrich Schiller University, Jena, Germany.

Abstract: The influence of female sex hormones on skin aging has repeatedly been investigated with contradictory results. In our study, the skin roughness of eight women receiving hormone therapy decreased significantly by approximately 15% in 12 months. Our results provide new evidence of the antiaging effect of female sex hormones. PMID: 18725866

Climacteric. 2007 Aug;10(4):320-34.

A prospective, randomized, double-blind, placebo-controlled study on the influence of a hormone replacement therapy on skin aging in postmenopausal women.

Sator PG, Sator MO, Schmidt JB, Nahavandi H, Radakovic S, Huber JC, Hönigsmann H. Division of Special and Environmental Dermatology, Dept of Dermatology, Medical University of Vienna, General Hospital, Austria.

BACKGROUND: There is mounting evidence that menopause affects some functions of the skin. Hormone replacement therapy (HRT) appears to limit some of the climacteric aspects of cutaneous aging. **OBJECTIVE:** In the light of a growing interest in the endocrinological influence of skin, we performed a study evaluating the effects of HRT on skin aging in postmenopausal women. **METHODS:** Forty non-hysterectomized, postmenopausal women were included in this prospective, randomized, double-blind, placebo-controlled study on the influence of oral sequential treatment with a combination of 2 mg 17beta-estradiol/10 mg dydrogesterone (Femoston) for seven 28-day cycles. Skin elasticity, skin surface lipids, skin hydration and skin thickness were measured by non-invasive methods, and both adverse-event profile and clinical-dermatological status were evaluated. **RESULTS:** After 7 months of HRT, skin elasticity increased significantly at the right ramus of the

mandible, while skin hydration tended to improve significantly at the right upper arm (inner side); skin thickness improved significantly but skin surface lipids did not. Absolute effects did not differ significantly between HRT and placebo patients. A dermatological evaluation was largely consistent with measurement results. Safety and tolerability of HRT were positive. CONCLUSION: The results showed improvements in the parameters involved in skin aging in the HRT group as compared to baseline. While skin aging is no indication for systemic hormone supplementation, a positive effect on aging skin can be observed. PMID: 17653959

J Cosmet Dermatol. 2006 Mar;5(1):3-8.

Skin climacteric aging and hormone replacement therapy.

Quatresooz P, Piérard-Franchimont C, Gaspard U, Piérard GE. Department of Dermatopathology, University Hospital of Liège, Liège, Belgium.

Abstract: A gender perspective is indispensable for a full understanding of aging. Menopause is a turning point in women's lives. In addition to the effects of chronological aging, sunlight exposure, and other environmental and endogenous stimuli, the climacteric appears to exert some dramatic consequences on skin biology and aspect. The epidermis may become xerotic and exhibit altered functions. The dermis thins out and its elasticity decreases in concert with the decline in bone mass. The skin microcirculation is impaired. These aspects are some of the better worked-out changes of the climacteric, which in turn seem to be stabilized or in part reversible with hormone replacement therapy (HRT). The HRT effect on menopause consequences on hair growth and sebum production is less impressive. This review summarizes some important impacts of the climacteric on skin, and highlights the benefits of HRT that may influence cosmetic dermatology.

PMID: 17173565

Maturitas. 2001 Jul 25;39(1):43-55.

The influence of hormone replacement therapy on skin ageing: a pilot study.

Sator PG, Schmidt JB, Sator MO, Huber JC, Hönigsmann H. Department of Special and Environmental Dermatology, University of Vienna, General Hospital, Währinger Gürtel 18-20, 1090 Vienna, Austria.

OBJECTIVES: We studied the effect of hormonal treatment on skin ageing in menopausal women. METHODS: Twenty-four patients (45-68 years; mean age, 54.9 years) without hormone treatment for at least 6 months were included. Patients were assigned to three therapy groups: 1, oestrogen only (Estraderm TTS 50) (n=6); 2, transdermal oestrogen and progesterone (Estraderm TTS 50 and 0.4 mg progesterone vaginal suppository) (n=7); and 3, oral oestrogen and progesterone (2 mg Progy Nova and 0.4 mg progesterone vaginal suppository) (n=8). One group without therapy was included as a control group (n=3). Treatment was continued for 6 months. Three patients, one from group 2 and two from group 3, discontinued therapy before the study endpoint. The following skin parameters were measured at monthly intervals during treatment: skin surface lipids, epidermal skin hydration, skin elasticity and skin thickness. Concomitant clinical evaluation included a subjective clinical evaluation form, a patient questionnaire and laboratory tests for oestradiol, progesterone and follicle stimulating hormone. RESULTS: Mean levels of epidermal skin moisture, elasticity and skin thickness were improved at the end of treatment based on both subjective and objective evaluation in patients with hormone replacement therapy (HRT). Skin surface lipids were increased during combined HRT, which may reflect stimulatory effects of the progestagen component on sebaceous gland activity, while oestrogen alone has a sebum-suppressive action. In the HRT groups, the questionnaire for climacteric complaints demonstrated significant improvements, while laboratory tests showed increases in oestradiol and progesterone and decreases in FSH. CONCLUSIONS: HRT with the mentioned regimes significantly improved parameters of skin ageing. PMID: 11451620

Int J Dermatol. 1996 Sep;35(9):669-74.

Treatment of skin aging with topical estrogens.

Schmidt JB, Binder M, Demschik G, Bieglmayer C, Reiner A. Department of Dermatology, University of Vienna Medical School, Austria.

BACKGROUND: The coincidence of climacteric symptoms and the beginning of skin aging suggests that estrogen deficiency may be a common and important factor in the perimenopausal woman. Often hormones have been considered important

in endogenous aging of the skin, but their role has not been clearly defined. Therefore, we investigated, whether topical treatment of the skin with estrogen could reverse some of the changes in the aging skin. MATERIAL AND METHODS: The effects of 0.01% estradiol and 0.3% estriol compounds were compared in 59 preclimacteric women with skin aging symptoms. Monthly determinations of estradiol (E2), follicle-stimulating hormone (FSH), and prolactin (PRL) were done and the monthly clinical monitoring was supplemented by measurements of skin hydration by corneometry and profilometry. In 10 patients, skin biopsies were taken for immunohistochemical determination of collagen types I and III. RESULTS: After treatment for 6 months, elasticity and firmness of the skin had markedly improved and the wrinkle depth and pore sizes had decreased by 61 to 100% in both groups. Furthermore, skin moisture had increased and the measurement of wrinkles using skin profilometry, revealed significant, or even highly significant, decreases of wrinkle depth in the estradiol and the estriol groups, respectively. On immunohistochemistry, significant increases of Type III collagen labeling were combined with increased numbers of collagen fibers at the end of the treatment period. As to hormone levels, only those of PRL had increased significantly and no systemic hormonal side effects were noted. PMID: 8876303

Maturitas. 1994 Nov;20(1):25-30.

Treatment of skin ageing symptoms in perimenopausal females with estrogen compounds. A pilot study.

Schmidt JB, Binder M, Macheiner W, Kainz C, Gitsch G, Bieglmayer C. Department of Special and Environmental Dermatology, University of Vienna Medical School, Wien, Austria.

Abstract: A wide range of somatic symptoms of the perimenopausal female is due to the decrease of estrogen at that age. Minor attention has been paid hitherto to the involvement of estrogens in female skin ageing symptoms. In our study, the ageing skin of the face of perimenopausal females was treated with a 0.3% estriol cream (8 patients) or with a 0.01% estradiol cream (10 patients) for 6 months. Dermatologic follow-up was performed monthly. At each follow-up venous blood for radioimmuno assay determination of prolactin (PRL), follicle stimulating hormone (FSH) and estradiol (E2) was sampled. In addition, prior to and after 3 and 6 months of treatment, gynecological examinations for climacteric symptoms, mammary and colposcopic investigations and vaginal smears for cytology were performed. Both treatment groups showed improvement of the various skin ageing symptoms at the end of treatment. The effects of the group treated with topical estriol were slightly superior with regard to their extent and onset. No hormonal side effects were noted either clinically or by hormone monitoring. According to these preliminary results, local estrogen treatment appears to be a promising new approach for the treatment of skin ageing in perimenopausal females. However, for minimizing the risk of systemic hormonal side effects, concentrations and size of application field should be limited. PMID: 7877517

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