

Comment in: [J Urol. 2003 May;169\(5\):1745-6.](#)

Transdermal estradiol therapy for advanced prostate cancer--forward to the past?

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PURPOSE: Current hormonal therapies for prostate cancer are associated with significant morbidities, including symptoms of andropause and osteoporosis. Oral estrogens prevented many of these problems but were abandoned due to cardiovascular toxicity attributed to hepatic effect. In contrast, parenteral estrogens prevent first pass hepatic metabolism and substantially reduce cardiovascular risk, and long-term transdermal estradiol therapy is believed to be cardioprotective. We report preliminary results of a pilot study using transdermal estradiol therapy to treat men with advanced prostate cancer.

MATERIALS AND METHODS: A total of 20 patients with advanced prostate cancer were enrolled in a before and after study that examined the impact of estradiol patches on hormones, disease, thrombophilia, vascular flow, osteoporosis and quality of life.

RESULTS: Median followup is 15 months. Estradiol levels greater than 1,000 pmol/l. were achieved using 2 patches and higher levels were obtained by increasing the number of patches. All patients achieved castrate levels of testosterone within 3 weeks and had biochemical evidence of disease regression. One patient died of disease at 14 months and 1 cardiovascular complication occurred.

Thrombophilic activation was avoided and vascular flow improved. Bone mineral density was significantly increased. Mild or moderate gynecomastia occurred in 80% of patients but no patient had hot flushes. All other functional and symptomatic quality of life domains improved.

CONCLUSIONS: Transdermal estradiol therapy produced an effective tumor response. Cardiovascular toxicity was substantially reduced compared with that expected of oral estrogen, and other morbidity (gynecomastia) was negligible. Transdermal estradiol therapy prevented andropause symptoms, improved quality of life scores and increased bone density. Transdermal estradiol costs a tenth of current therapy cost, with the potential for considerable economic savings over conventional hormone therapies.

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2: [2004 ASCO Annual Meeting](#)

Category: Genitourinary Cancer

SubCategory: [Prostate Cancer](#)

Effect of high-dose estrogen on memory in men with prostate cancer.

Abstract No: 4650

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Abstract: **Background:** Estrogen replacement in women, and in female animal models, improves memory and changes the structure and physiology of relevant brain regions. Estrogen replacement in women improves long term verbal memory (hippocampal function) but may not affect short term working memory (prefrontal cortex function). Gonadectomy in male rats decreases synapse density in the hippocampus, a region important for long term memory. Testosterone, but not estrogen, replacement restores hippocampal synapse spine density. Testosterone supplementation in older men produces improvements in short term working memory. Little is known about the neural and cognitive effects of androgen suppression or estrogen therapy in men with prostate cancer.

Methods: We compared the long term verbal memory (using the immediate and delayed Paragraph Recall test), and working memory (using Subject Ordered and Trails tests) of androgen-deprived men with androgen-independent prostate cancer before and 1 month after starting second-line hormonal therapy with transdermal estradiol 45.6 mg

(six 7.6 mg patches) applied every 7 days.

Results:

Nineteen men, aged 49-92 were evaluated.			
Test	Pre-treatment	On estrogen	P value
Paragraph Recall (immediate; # correct)	19.2	22.9	.007
Paragraph Recall (delayed; # correct)	14.8	18.8	.019
Subject Ordered (# of errors) (data from 18 subjects)			
8 item	6.4	6.3	NS
10 item	7.2	7.0	NS
Trails (seconds B-A) (data from 15 subjects)	66.0	69.9	NS

Androgen deprived men treated with estradiol had a significant improvement in their paragraph recall performance but no change in working memory.

Conclusions: High dose estradiol may have had beneficial but specific effects on cognitive performance. The mechanism of this effect is not clear. Previous studies have shown beneficial effects of testosterone on the brain and performance in androgen deprived male rats, but effects of estradiol have only been found for recovery of function after brain injury. Thus, the beneficial effects of estradiol in this study may be due to its use in combination with androgen suppression, disease and/or an aging brain. Further studies using additional cognitive measures and control subjects will further elucidate the brain and cognitive effects of estradiol in prostate cancer patients.

3:

Transdermal estrogen therapy improves cholesterol levels and lipid profiles in men with prostate cancer.

Abstract No: 8035

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Abstract:

Background: Hypogonadal men have adverse changes in lipids and body composition that are reversed by testosterone replacement. Studies of testosterone replacement co-administered with aromatase inhibitors show that these benefits are in part mediated through conversion of androgens to estrogenic hormones. Lipid and body composition changes may contribute to the long-term morbidity of androgen deprivation therapy for prostate cancer (PC). Oral estrogen therapy for PC is associated with an increased risk of thromboembolic complications, but parenteral administration may be safer. As part of a study of transdermal estrogen (TDE) in androgen-independent PC (AIPC) patients, we sought to determine the impact of such therapy on serum lipids and body composition.

Methods: We measured serum cholesterol, triglycerides, LDL, HDL (total, HDL₂ and HDL₃), VLDL-C, Apolipoprotein-B, and Lp(a) before and 8 weeks after starting TDE therapy (six 7.6 mg patches applied every 7 days) in androgen-deprived men with AIPC. We examined body composition with whole body DEXA and fat distribution with an abdominal MRI at the same time points.

Results: Mean ± SD for variable that changed are shown in the table.

Lipid and DEXA data were obtained in 18 men, aged 49-92				
	Baseline	8 weeks	% change	p value
Total cholesterol (mg/dL)	191 ± 37	171 ± 35	-10%	<0.001
LDL (mg/dL)	116 ± 31	96 ± 30	-17%	<0.001
HDL (mg/dL)	41 ± 9.7	45 ± 11	+10%	0.01
HDL ₂ (mg/dL)	6.6 ± 1.6	8.9 ± 3.6	+35%	0.002
Apo B (mg/dL)	104 ± 19	91 ± 23	-12%	<0.001

No significant change was observed for HDL₃, triglycerides, VLDL, or Lp(a). MRI data were available for 13 of these men. No change was observed in any of the body composition measures including: % fat, fat mass, lean mass, trunkal fat, intra-abdominal fat, or subcutaneous fat.

Conclusions: Androgen deprived men treated with TDE had significant improvements in LDL and HDL levels without raising triglyceride levels. The observed changes are sufficiently large to have the potential to reduce cardiovascular risk. Longer-term observation is necessary to determine if improvements in body composition changes would follow. Controlled studies are needed to determine the impact of TDE therapy on cardiovascular risk.

4: Urology. 2000 Jan;55(1):97-101.

Transdermal estrogen in the treatment of hot flushes in men with prostate cancer.

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OBJECTIVES: To assess the effectiveness and tolerability of transdermal estrogen in men with hot flushes after hormonal therapy for prostate cancer. **METHODS:** Twelve men with moderate to severe hot flushes were randomized to receive either low-dose (0.05 mg) or high-dose (0.10 mg) estrogen patches applied twice weekly for 4 weeks. After a 4-week washout period in which no treatment was given, each patient received the alternative dose for 4 weeks. Treatment response was assessed by daily logs and questionnaires completed every 4 weeks that included a visual analog assessment. Serum luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol levels were also measured every 4 weeks during the study. **RESULTS:** There was a significant reduction in the overall severity of the hot flushes seen in patients with both the low and high-dose estrogen patch. A significant reduction in the daily frequency of the hot flushes was seen with the high-dose patch only. Overall, 10 (83%) of 12 men reported either mild, moderate, or major improvement in symptoms with either the low or high-dose patch. Mild, painless breast swelling or nipple tenderness was noted in 2 (17%) and 5 (42%) of 12 men treated with the low and high-dose estrogen patch, respectively. FSH levels decreased significantly with both the low and high-dose patch. Estradiol levels increased from 12.1 to 16.4 pg/mL and 26.9 pg/mL with the low and high-dose patch, respectively. There was no significant change in serum testosterone or luteinizing hormone levels. **CONCLUSIONS:** Transdermal estrogen appears to be a promising, well-tolerated therapy for men with hot flushes after endocrine treatment for prostate cancer. Further study in larger groups of patients is necessary to assess the relative effectiveness and morbidity of this treatment.

PMID: 10654902 [PubMed - indexed for MEDLINE]

5: Scand J Urol Nephrol. 2002;36(6):405-13.

Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer, Scandinavian Prostatic Cancer Group (SPCG) Study No.5

Hedlund PO, Ala-Opas M, Brekkan E, Damber JE, Damber L, Hagerman I, Haukaas S, Henriksson P, Iversen P, Pousette A, Rasmussen F, Salo J, Vaage S, Varenhorst E; Scandinavian Prostatic Cancer Group.

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OBJECTIVE: In the mid-1980s, interest in parenteral estrogen therapy for prostate cancer was renewed when it was found that it influenced liver metabolism only marginally and had very few cardiovascular side-effects. In this study high-dose polyestradiol phosphate (PEP; Estradurin) was compared to

combined androgen deprivation (CAD) for the treatment of patients with metastatic prostate cancer. The aim of the study was to compare anticancer efficacy and adverse events, especially cardiovascular side-effects.

MATERIAL AND METHODS: A total of 917 patients with T0-4, NX, M1, G1-3 prostate cancer and an Eastern Cooperative Oncology Group performance status of 0-2 were randomized to treatment with either PEP 240 mg i.m. twice a month for 2 months and thereafter once a month or flutamide (Eulexin) 250 mg t.i.d. per os in combination with either triptorelin (Decapeptyl) 3.75 mg per month i.m. or, on an optional basis, bilateral orchidectomy. A total of 556 patients had died at the time of this analysis.

RESULTS: There was no difference between the treatment arms in terms of time to biochemical or clinical progression and overall or disease-specific survival. There was no increase in cardiovascular mortality in the PEP arm. The PEP group had a higher prevalence of cardiovascular disease prior to the study and a significantly higher incidence of non-fatal ischemic heart events and heart decompensation during the study.

CONCLUSIONS: PEP has an equal anticancer efficacy to CAD and does not increase cardiovascular mortality. Final evaluation of cardiovascular morbidity is awaiting further analysis and follow-up. PEP is considerably cheaper than CAD.

PMID: 12623503 [PubMed - indexed for MEDLINE]

6: Urology. 2000 Mar;55(3):328-33.

Parenteral estrogen versus total androgen ablation in the treatment of advanced prostate carcinoma: effects on overall survival and cardiovascular mortality. The Scandinavian Prostatic Cancer Group (SPCG)-5 Trial Study.

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OBJECTIVES: To compare the effect on overall survival of total androgen ablation (TAA) with that of parenteral estrogen and to pay special attention to cardiovascular mortality. TAA (orchiectomy or a luteinizing hormone-releasing hormone analogue combined with an antiandrogen) has been proposed as superior to other endocrine treatments for patients with prostate carcinoma. Recently, the use of parenteral estrogen has been suggested to reduce or even negate the well-known cardiovascular side effects of oral estrogens. **METHODS:** Nine hundred fifteen patients were randomized to intramuscular injections of 240 mg polyestradiol phosphate (PEP) every second week for the first 8 weeks (5 doses) followed by a maintenance dose of 240 mg every month (n = 458) or to bilateral orchiectomy or triptorelin 3.75 mg every month combined with the antiandrogen flutamide 250 mg three times daily.

The choice between orchiectomy and triptorelin was at the discretion of the clinician and patient. Patients were stratified according to performance status, presence of cardiovascular disease, and alkaline phosphatase level. An observer totally unaware of the treatment given classified all deceased patients.

RESULTS: At a median follow-up of 18.5 months, no signs of a difference in overall survival were found between TAA and PEP (P <0.001). Of 458 patients, 266 (58.1%) had died in the PEP group compared with 269 (58.9%) of 457 patients in the TAA group. Within the TAA group, no difference in overall survival existed between patients who had undergone orchiectomy or who were given triptorelin. Furthermore, no differences in cardiovascular mortality were found (3.5% in the PEP group and 3.1% in the TAA group). **CONCLUSIONS:** The current parenteral estrogen regimen seems to be of comparable efficacy and cardiovascular safety as TAA in terms of overall survival. PEP has by far the lowest drug cost and also the lowest cumulative direct costs and thus has the highest cost-effectiveness. We suggest that parenteral estrogen be included as a therapeutic option in the endocrine management of prostate carcinoma.

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Mortality and morbidity in transsexual subjects treated with cross-sex hormones.

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OBJECTIVE: The optimum steroid hormone treatment regimes for transsexual subjects has not yet been established. We have investigated the mortality and morbidity figures in a large group of transsexual subjects receiving cross-sex hormone treatment.

DESIGN: A retrospective, descriptive study in a university teaching hospital.

SUBJECTS: Eight hundred and sixteen male-to-female (M-->F) and 293 female-to-male (F-->M) transsexuals. **INTERVENTIONS:** Subjects had been treated with cross-sex hormones for a total of 10,152 patient-years. **OUTCOME MEASURES:** Standardized mortality and incidence ratios were calculated from the general Dutch population (age- and gender-adjusted) and were also compared to side effects of cross-sex hormones in transsexuals reported in the literature.

RESULTS: In both the M-->F and F-->M transsexuals, total mortality was not higher than in the general population and, largely, the observed mortality could not be related to hormone treatment. Venous thromboembolism was the major complication in M-->F transsexuals treated with oral oestrogens and anti-androgens, but fewer cases were observed since the introduction of transdermal oestradiol in the treatment of transsexuals over 40 years of age. No cases of breast carcinoma but one case of prostatic carcinoma were encountered in our population. No serious morbidity was observed which could be related to androgen treatment in the F-->M transsexuals.

CONCLUSION: Mortality in male-to-female and female-to-male transsexuals is not increased during cross-sex hormone treatment. Transdermal oestradiol administration is recommended in male-to-female transsexuals, particularly in the population over 40 years in whom a high incidence of venous thromboembolism was observed with oral oestrogens. It seems that in view of the deep psychological needs of transsexuals to undergo sex reassignment, our treatment schedule of cross-sex hormone administration is acceptably safe.

PMID: 9373456 [PubMed - indexed for MEDLINE]

8: J Clin Endocrinol Metab. 1996 Jul;81(7):2545-9.

Comment in: [J Clin Endocrinol Metab. 1997 Feb;82\(2\):702-3.](#)

"Add-back" estrogen reverses cognitive deficits induced by a gonadotropin-releasing hormone agonist in women with leiomyomata uteri.

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Treatment of women with uterine myomas with GnRH agonists results in symptoms of hypoestrogenism which can be prevented by concurrent "add-back" estrogen administration. We took advantage of these induced endocrine changes to investigate their effects on cognitive functioning in young women with myomas. Nineteen women with uterine myomas were tested before treatment. They all received the GnRH agonist, leuprolide acetate depot (LAD), every 4 weeks for 12 weeks and were then randomized to receive LAD plus estrogen or LAD plus placebo every 4 weeks for 8 additional weeks. Levels of all sex hormones decreased after 12 weeks of LAD treatment ($P < 0.01$), and only estradiol (E2) levels increased ($P < 0.01$) following 8 weeks of subsequent treatment in the group that received LAD plus E2. Scores on neuropsychological tests of verbal memory decreased from pretreatment to 12 weeks

posttreatment with LAD ($P < 0.05$). These memory deficits were reversed in the group that received LAD plus E2 for 8 weeks coincident with an increase in plasma E2, whereas memory scores remained depressed in the group that received LAD plus placebo. These findings are consistent with those from studies on surgically menopausal women and strongly suggest that estrogen serves to maintain verbal memory in women. These results provide support for the efficacy of add-back estrogen regimens in women treated with GnRH agonists and also imply that estrogen may be important for maintaining memory in the postmenopause.

PMID: 8675575 [PubMed - indexed for MEDLINE]

9: J Cell Biochem. 2004 Feb 15;91(3):491-503.

Estrogens and anti-estrogens: key mediators of prostate carcinogenesis and new therapeutic candidates.

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Despite the historical use of estrogens in the treatment of prostate cancer (PCa) little is known about their direct biological effects on the prostate, their role in carcinogenesis, and what mechanisms mediate their therapeutic effects on PCa. It is now known that estrogens alone, or in synergism with an androgen, are potent inducers of aberrant growth and neoplastic transformation in the prostate. The mechanisms of estrogen carcinogenicity could be mediated via induction of unscheduled cell proliferation or through metabolic activation of estrogens to genotoxic metabolites. Age-related changes and race-/ethnic-based differences in circulating or locally formed estrogens may explain differential PCa risk among different populations. Loss of expression of estrogen receptor (ER)-beta expression during prostate carcinogenesis and prevention of estrogen-mediated oxidative damage could be exploited in future PCa prevention strategies. Re-expression of ER-beta in metastatic PCa cells raises the possibility of using ER-beta-specific ligands in triggering cell death in these malignant cells. A variety of new estrogenic/anti-estrogenic/selective estrogen receptor modulator (SERM)-like compounds, including 2-methoxyestradiol, genistein, resveratrol, licochalcone, Raloxifene, ICI 182,780, and estramustine are being evaluated for their potential in the next generation of PCa therapies. Increasing numbers of patients self-medicate with herbal formulations such as PC-SPES. Some of these compounds are selective ER-beta ligands, while most of them have minimal interaction with ER-alpha. Although many may inhibit testosterone production by blockade of the hypothalamic-pituitary-testis axis, the most effective agents also exhibit direct cytostatic, cytotoxic, or apoptotic action on PCa cells. Some of them are potent in interfering with tubulin polymerization, blocking angiogenesis and cell motility, suppressing DNA synthesis, and inhibiting specific kinase activities. Further discovery of other compounds with potent apoptotic activities but minimal estrogen action should promote development of a new generation of effective PCa preventive or treatment regimens with few or no side-effects due to estrogenicity. Further advancement of our knowledge of the role of estrogens in prostate carcinogenesis through metabolic activation of estrogens and/or ER-mediated pathways will certainly result in better preventive or therapeutic modalities for PCa. Copyright 2003 Wiley-Liss, Inc.

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10: Clin Prostate Cancer. 2002 Sep;1(2):81-9.

The evolving role of estrogen therapy in prostate cancer.

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Estrogens, including diethylstilbestrol (DES), were used as the primary medical treatment for metastatic prostate cancer for many years but have been superseded in the past two decades by luteinizing hormone-releasing hormone (LHRH) agonists, primarily because of the cardiovascular toxicity associated with oral estrogen therapy. Recently, a renewed interest in estrogen therapy for prostate cancer in the United States has developed as a result of 3 major issues. First, when measured by declines in prostate-specific antigen of $>$ or $=$ 50%, clinical trials have demonstrated activity of DES, DES-diphosphate, and the estrogenic herbal therapy PC-SPES in 21%-86% of patients treated in phase II trials of androgen-independent prostate cancer patients. Second, the recent description of estrogen receptor (ER)- β has led to a reevaluation of the role of estrogens in normal prostate development and cancer pathogenesis. In contrast to ER- α , ER- β is strongly expressed in normal prostate epithelium. Furthermore, loss of ER- β expression has been demonstrated in prostate cancers, suggesting a possible role for this pathway in the development of cancer. Finally, the issues of cost and safety of estrogens are being reassessed in the current environment of rising health care costs and improved cardiovascular care. In Europe, estrogen therapy is more accepted as a low-cost and effective alternative to LHRH agonists and antiandrogens. Toxicity of DES and other estrogens has also been attenuated by strategies that use lower doses and parenteral routes of administration, thereby avoiding hepatic first-pass metabolism and decreasing the risk of thromboembolism. Nonetheless, there remain many unanswered questions about the role of estrogen therapy in prostate cancer, including differences between specific drugs, optimal dose, timing, and patient selection. Further research is needed.

PMID: 15046698 [PubMed - indexed for MEDLINE]

11: J Am Geriatr Soc. 2004 Feb;52(2):269-73.

Comment in: [J Am Geriatr Soc. 2004 Feb;52\(2\):316-8.](#)

The effect of short-term estradiol therapy on cognitive function in older men receiving hormonal suppression therapy for prostate cancer.

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OBJECTIVES: To determine the effect of estrogen (E) alone (without the influence of testosterone (T)) on cognitive function in older men, using 17-beta micronized estradiol versus placebo in older men rendered hypogonadal (low T and E) by treatment for prostate cancer. **DESIGN:** Short-term double-blind, randomized, controlled trial. **SETTING:** An outpatient General Clinical Research Center. **PARTICIPANTS:** Twenty-seven community-dwelling men aged 65 and older receiving neoadjuvant or established therapy with luteinizing-hormone releasing-hormone agonists for treatment of prostate cancer enrolled in a short-term randomized, controlled trial of 17-beta micronized estradiol versus placebo on the effect on biochemical markers of bone turnover. **MEASUREMENTS:** Hormone levels, including E, T, and sex hormone-binding globulin; standardized neurocognitive tests, including measures of sustained attention, executive function, and memory; and questionnaires to assess subjects' perception of cognitive deficits and symptoms of depression.

RESULTS: There were no significant differences between patients receiving E or placebo on 15 of 17 neurocognitive measures and no significant differences in self-reported cognitive deficits or number of depressive symptoms.

CONCLUSION: Although studies have suggested that E replacement therapy may improve cognitive function, most notably memory performance in postmenopausal woman, there was no evidence in the present study that the addition of short-term E therapy was more beneficial than placebo in tests of cognitive performance in hypogonadal men.

PMID: 14728639 [PubMed - indexed for MEDLINE]

12: Prostate. 1999 Jul 1;40(2):76-82.

**Time for revival of estrogens in the treatment of advanced prostatic carcinoma?
Pharmacokinetics, and endocrine and clinical effects, of a parenteral estrogen regimen.**

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BACKGROUND: The present pilot study tested the clinical performance of a new pharmacokinetically guided dosing regimen of parenteral estrogen in patients with advanced prostatic carcinoma. The aim was to accelerate endocrine effects and to avoid cardiovascular side effects.

METHODS: Seventeen patients were randomized to intramuscular injections of 240 mg polyestradiol phosphate (PEP) every second week for the first 8 weeks (five doses), followed by a maintenance dose of 240 mg every month; and 16 patients were randomized to bilateral orchidectomy. The estrogen dosing was calculated by pharmacokinetic modelling to achieve a rapid increase in serum estradiol and thereby a fast decrease in testosterone.

RESULTS: The predicted increment in serum estrogen was achieved, together with a subsequent decrease in testosterone in the PEP group. In addition, there were no signs of an increased cardiovascular morbidity. This was probably due to a minimal estrogenic influence on the liver and was reflected by unchanged levels of coagulation factor VII. Clinical effects, during the first 2 years of treatment, were similar in the two treatment arms, with 12 patients in the orchidectomy group and 14 patients in the PEP group responding to treatment.

CONCLUSIONS: The present parenteral regimen is an efficient and time-saving estrogen regimen with a favorable side-effect profile. PEP seems to offer a potential for revival of the most cost-effective endocrine treatment of cancer of the prostate, i.e., estrogen.

PMID: 10386467 [PubMed - indexed for MEDLINE]

13: Arterioscler Thromb Vasc Biol. 2000 May;20(5):1396-403.

Oral, but not transdermal, administration of estrogens lowers tissue-type plasminogen activator levels in humans without affecting endothelial synthesis.

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Oral estrogen administration decreases plasma levels of tissue-type plasminogen activator (tPA), which may be explained by a decrease in endothelial tPA synthesis, an increase in its hepatic clearance, or both. In the present study, we determined (1) differences between oral (ie, via the liver) ethinyl estradiol and transdermal (ie, systemic) 17beta-estradiol administration on plasma antigen levels of tPA and plasminogen activator inhibitor type-1 before and after 4 months of hormone administration and (2)

effects on endothelial tPA synthesis, by measuring the local increase in plasma tPA during venous occlusion of the upper extremity. Thirty transsexual males (median age 32 years, range 20 to 44 years) were randomly assigned to either oral ethinyl estradiol (n=15) or transdermal 17beta-estradiol (n=15); both treatments included the antiandrogen cyproterone acetate (CA). Ten males were treated with CA alone. Seventeen transsexual females (median age 27 years, range 18 to 37 years) were treated with intramuscular testosterone esters. Only oral ethinyl estradiol plus CA but neither transdermal 17beta-estradiol plus CA, nor oral CA, nor parenteral testosterone lowered plasma tPA and plasminogen activator inhibitor-1 ($P < 0.001$ for both). tPA release during venous occlusion was not affected by oral ethinyl estradiol plus CA in males ($P = 0.52$) or by parenteral testosterone in females ($P = 0.89$). These data are consistent with a previous observation, in rodents, that the decrease in tPA after oral estrogen administration can be explained by an increase in hepatic tPA clearance, leaving endothelial tPA synthesis unchanged, and suggest that these mechanisms also explain the decrease in tPA in humans.

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14: J Am Coll Cardiol. 2003 Apr 16;41(8):1358-63.

Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women.

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OBJECTIVES: We investigated whether the route of estrogen replacement therapy (ET) is the major determinant of C-reactive protein (CRP) in postmenopausal women. **BACKGROUND:** Recent studies demonstrated that oral ET causes a sustained increase in CRP, implicating a proinflammatory effect. Because CRP is synthesized in the liver, we hypothesized that estrogen-induced CRP elevation is related to first-pass hepatic metabolism.

METHODS: In 21 postmenopausal women, we conducted a randomized, crossover, placebo-controlled study to compare the effects of transdermal versus oral ET on CRP and inflammatory cytokines. We measured CRP, interleukin (IL)-1-beta, IL-6, and tumor necrosis factor-alpha before and after eight weeks of transdermal estradiol (E(2)) (100 microg/day), oral conjugated estrogen (CEE) (0.625 mg/day), or placebo. Insulin-like growth factor-1 (IGF-1), a hepatic-derived anabolic peptide, was also measured.

RESULTS: Transdermal E(2) had no effect on CRP or IGF-1 levels. In contrast, eight weeks of oral conjugated estrogens caused a more than twofold increase in CRP and a significant reduction in IGF-1 ($p < 0.01$) in the same women. The magnitude of increase in CRP was inversely correlated to the decrease in IGF-1 ($r = -0.49$, $p = 0.008$). Neither transdermal E(2) nor oral CEE had any effects on the plasma concentrations of cytokines that promote CRP synthesis.

CONCLUSIONS: In postmenopausal women, oral but not transdermal ET increased CRP by a first-pass hepatic effect. An increase in CRP levels is accompanied by a reduction in IGF-1, an anti-inflammatory growth factor. Because CRP is a powerful predictor of an adverse prognosis in otherwise healthy postmenopausal women, the route of administration may be an important consideration in minimizing the adverse effects of ET on cardiovascular outcomes.

PMID: 12706932 [PubMed - indexed for MEDLINE]

15: J Am Coll Cardiol. 1997 Jun;29(7):1437-44.

Comment in: [J Am Coll Cardiol. 1997 Jun;29\(7\):1445-6.](#)

Long-term estrogen therapy improves vascular function in male to female transsexuals.

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OBJECTIVES: This study sought to examine the effects of long-term estrogen therapy on vascular function in male to female transsexuals and to compare the findings with those observed in men and premenopausal women.

BACKGROUND: Gender differences in coronary artery disease have largely been attributed to the beneficial effects of estrogen on vascular function and plasma lipids in women. However, the effects of estrogen on the male vasculature have not been widely studied.

METHODS: We compared the effects of estrogen on vascular function in 14 male to female transsexuals, 14 age-matched men and 15 premenopausal women. Flow-mediated vasodilation and response to nitroglycerin were assessed in the brachial artery using noninvasive ultrasound.

RESULTS: Flow-mediated vasodilation was similar in transsexuals and women but greater than that in men ([mean +/- SE] 11.5 +/- 1.3% and 9.4 +/- 1.1% vs. 5.2 +/- 1.0% respectively, $p < 0.005$). Responses to nitroglycerin were also greater in transsexuals and women than in men (21.6 +/- 1.7% and 21.0 +/- 0.9% vs. 14.5 +/- 1.2%, respectively, $p = 0.0005$). These differences persisted even after adjusting for vessel size. Despite similar total cholesterol levels, transsexuals had high density lipoprotein cholesterol levels similar to those in women and greater than those observed in men (1.76 +/- 0.12 and 1.82 +/- 0.11 mmol/liter vs. 1.35 +/- 0.07 mmol/liter, respectively, $p < 0.005$). Moreover, triglyceride levels were greater in transsexuals than in men and women, and low density lipoprotein cholesterol (LDL-C) particle size was smaller (25.7 +/- 0.2 nm vs. 26.2 +/- 0.1 and 26.6 +/- 0.1 nm, respectively, $p = 0.0001$). Serum testosterone (an index of estrogen therapy in transsexuals) was markedly suppressed in transsexuals and similar to that in women. Univariate analysis revealed that there was a strong inverse correlation between serum testosterone and flow-mediated vasodilation ($r(s) = -0.48$, $p < 0.005$). Multivariate analysis revealed that the best combination of predictors of flow-mediated vasodilation was serum testosterone, vessel size and LDL-C ($R^2 = 0.3$, $p < 0.005$).

CONCLUSIONS: Long-term estrogen therapy appears to improve vascular function in male to female transsexuals and occurs despite higher triglyceride levels and the presence of small, dense LDL-C. The beneficial effects of estrogen are not gender specific or solely mediated through endothelium-derived nitric oxide.

PMID: 9180101 [PubMed - indexed for MEDLINE]

16: J Urol. 2000 Mar;163(3):802-5.

Dramatic suppression of plasma and urinary prostate specific antigen and human glandular kallikrein by antiandrogens in male-to-female transsexuals.

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PURPOSE: Prostate specific antigen (PSA) and human glandular kallikrein (hK2) are mainly produced by the prostate and their genes are regulated by androgens through the androgen receptor. We determine whether PSA and hK2 change significantly in plasma and urine after antiandrogen treatment in male-to-female transsexuals.

MATERIALS AND METHODS: Plasma and urine PSA and hK2 were measured with highly sensitive immunofluorometric procedures capable of detecting within 1 or 6 ng./l. PSA or hK2, respectively.

Study groups consisted of 10 men treated with cyproterone acetate only (group 1), 15 transdermal estradiol plus cyproterone acetate (group 2) and 31 ethinyl estradiol plus cyproterone acetate (group 3). Plasma and urine samples were collected before initiation of treatment as well as after 4 months of hormonal therapy. For a subset of group 3 patients blood and urine samples were also obtained after 12 months of treatment.

RESULTS: Cyproterone acetate, a steroidal antiandrogen, alone or with estradiol was able to suppress greater than 90% of plasma and urinary PSA and hK2 concentration after 4 or 12 months of therapy.

CONCLUSIONS: Cyproterone acetate therapy causes dramatic suppression of plasma and urinary PSA and hK2 in men without prostate cancer. Since cyproterone acetate is used for prostate cancer treatment, suppression of PSA after hormonal therapy may not accurately reflect therapy success in reducing tumor burden.

PMID: 10687981 [PubMed - indexed for MEDLINE]

17: World J Urol. 2003 May;21(1):31-6. Epub 2003 Feb 14.

Antiestrogens and selective estrogen receptor modulators reduce prostate cancer risk.

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The development of chemoprevention strategies against prostate cancer would have the greatest overall impact both medically and economically against prostate cancer. Estrogens are required for prostate carcinogenesis. Estrogenic stimulation through estrogen receptor alpha in a milieu of decreasing androgens contributes significantly to the genesis of benign prostatic hyperplasia, prostate dysplasia, and prostate cancer. The ability of antiestrogens and selective estrogen receptor modulators (SERMs) to delay and to suppress prostate carcinogenesis is supported by preclinical, clinical, and epidemiological studies. SERMs have many features that make them attractive candidates for prostate cancer chemoprevention including their favorable safety profile and efficacy in preclinical prostate cancer models. The true clinical benefits of SERMs for chemoprevention to prevent prostate cancer, however, should continue to be investigated through human clinical trials. A phase IIb/III human clinical trial is currently evaluating safety and efficacy of toremifene, a SERM, in men who have high-grade prostatic intraepithelial neoplasia.

PMID: 12756492 [PubMed - indexed for MEDLINE]

18: Clin Endocrinol (Oxf). 1999 Oct;51(4):517-24.

Role of oestrogen in male sexual behaviour: insights from the natural model of aromatase deficiency.

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OBJECTIVE: In order to evaluate the role of oestrogens on human male sexual behaviour, the gender-identity, psychosexual orientation and sexual activity of a man with a congenital lack of oestradiol resulting from an inactivating mutation of the aromatase P450 gene was investigated. The psychosexual and sexual behavioural evaluations were performed before and during testosterone treatment and before oestradiol treatment, during three phases of different dosages of oestradiol treatment.

DESIGN: The study was performed before (phase A) and during (phase B) testosterone enanthate treatment (250 mg i.m. every 10 days, for 6 months), during testosterone withdrawal (phase C), and during each of the following transdermal oestradiol treatments: 50 microg twice a week for 6 months (phase D); 25 microg twice a week for 9 months (phase E), and 12.5 microg twice a week for 9 months (phase F).

MEASUREMENTS: Sexual behaviour was investigated by a sexological interview and by a 2-month self-reported daily diary performed during each phase of the protocol study. Furthermore, during each oestradiol treatment (phase C, D, E and F), a study of depression, anxiety trait and sexual behaviour was performed by the Beck Depression Inventory (BDI), the Spielberger Trait Anxiety Inventory (STAI) and the Golombok-Rust Inventory of Sexual Satisfaction (GRISS), respectively. Sexual orientation and gender-identity were evaluated by the BEM Sex Role Inventory (BSRI). Serum testosterone and oestradiol were measured during each phase of the study. **RESULTS:** Before oestradiol treatment (phase C), serum oestradiol was undetectable, while it rose to 356.1, 88.1 and 55.1 pmol/l during phases D, E and F, respectively. Before any oestradiol treatment, during phase D, phase E and phase F serum testosterone was 18.13, 0.72, 14.3 and 18.51 nmol/l, respectively. The patient's gender-identity as assessed by BSRI and by the sexological interview was clearly male. The psychosexual orientation evaluated by BSRI, by the sexological interview and by the analysis of the self-filled diary was heterosexual. Relevant modification of the patient's sexual behaviour occurred only during oestrogen treatment. This was more evident during both phase E and phase F, and concerned the behavioural parameters with an increase of libido, frequency of sexual intercourse, masturbation and erotic fantasies. A reduction of BDI and STAI scores was detected during the oestrogen phases.

CONCLUSIONS: The study of the sexual behaviour in this man with aromatase deficiency suggests that oestrogens in humans do not affect gender-identity and sexual orientation but could have a role in male sexual activity.

PMID: 10583321 [PubMed - indexed for MEDLINE]

19: Br J Urol. 1998 Jul;82(1):63-8.

Parenteral polyoestradiol phosphate vs orchidectomy in the treatment of advanced prostatic cancer. Efficacy and cardiovascular complications: a 2-year follow-up report of a national, prospective prostatic cancer study. Finnprostate Group.

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OBJECTIVE: To evaluate the clinical efficacy and cardiovascular complications of orchidectomy or polyoestradiol phosphate (PEP) in the treatment of advanced prostatic cancer.

PATIENTS AND METHODS: In a prospective, randomized study 444 patients (mean age 73 years, range 45-91) with T3-4 M0 or T1-4 M1 prostatic cancer were treated either by orchidectomy (group 1, n = 217) or parenteral PEP (group 2, n = 227; 240 mg/month). The patients were examined at 3 and 6 months after start of the therapy and thereafter every 6 months; they were also assessed whenever they had symptoms indicating progression. Possible cardiovascular complications included myocardial infarction, cerebrovascular accident, pulmonary embolism and deep vein thrombosis.

RESULTS: After a follow-up of 2 years there was no statistically significant difference between the groups in progression-free time; 65 of 217 (30%) patients in group 1 showed evidence of progression, including seven (3%) who died from prostate cancer. In group 2, 64 of 227 (28%) patients showed progression and eight (3.5%) died from prostatic cancer. There were 10 (5%) cardiovascular complications in patients in group 1, including five (2%) cardiovascular deaths; in group 2 there were 24 (11%) and 14 (6%), respectively. During the first year of treatment there were three (1.4%) cardiovascular complications in group 1 and 14 (6%) in group 2 (P < 0.05), and during the second year, seven (4%) and 10 (6%), respectively.

CONCLUSION: Parenteral PEP (240 mg/month) seems to be as efficient as orchidectomy in inhibiting disease in patients with advanced prostatic cancer (T3-4 M0 and T1-4 M1). There were more cardiovascular complications in patients treated with PEP than after orchidectomy; the difference was statistically significant during the first year of treatment.

PMID: 9698663 [PubMed - indexed for MEDLINE]

20: Tidsskr Nor Laegeforen. 1993 Mar 10;113(7):833-5.

[Endocrine treatment of prostatic cancer. A renaissance for parenteral estrogen]

[Article in Norwegian]

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The standard treatment for advanced cases of cancer of the prostate is castration. Oestrogens, administered per os may have serious side effects, in particular thrombosis and cardiovascular complications. If the oestrogens are administered parenterally, changes in liver function can be avoided and risk of side effects markedly reduced. 38 patients have been treated at Huddinge Hospital in Stockholm, and 14 patients at Aker Hospital in Oslo, with polyoestradiol phosphate (Estradurin) 240 mg injected intramuscularly every 4th week (initial dose 320 mg). We can sum up our own experience as follows: Plasma testosterone is reduced to castration level after 2-3 weeks. Liver function, evaluated by the sexual hormone binding globulin level in plasma, remains unchanged. Morbidity and mortality from cancer are the same as may be achieved by surgical orchidectomy. The only side effect of significance is gynaecomastia. Follow-up of the patients does not indicate any increased risk of thrombosis or cardiovascular disease. The treatment is fairly cheap compared with other alternative methods of endocrine treatment.

PMID: 8480286 [PubMed - indexed for MEDLINE]

21: Br J Urol. 1990 Mar;65(3):282-5.

Effect of parenteral oestrogen on the coagulation system in patients with prostatic carcinoma.

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Patients with prostatic carcinoma on oral oestrogen therapy have an altered coagulation system and suffer cardiovascular side effects. Oestrogens--especially oral oestrogens--are potent inducers of liver synthesised proteins, including coagulation factors. We have assessed the effect of non-oral oestrogen on the coagulation system in patients with prostatic carcinoma. Twelve patients were given monthly intramuscular injections of 320 mg polyoestradiol phosphate (PEP). No additional oestrogens were given. No change was found in any of the coagulation factors, including factor VII, with the exception of a significant decrease in antithrombin III. No patient, including 38 patients treated with PEP, had any cardiovascular complications after a mean follow-up period of 12.9 +/- 0.7 months; 76% of the patients responded to treatment. Parenteral administration of oestrogen caused a less marked change in the coagulation system than oral administration and should be the treatment of choice for prostatic carcinoma.

PMID: 2110842 [PubMed - indexed for MEDLINE]

22: Br J Urol. 1989 May;63(5):512-4.

High dose polyoestradiol phosphate with and without acetosalicylic acid versus orchiectomy in the treatment of prostatic cancer. Finnprostate Group.

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The clinical efficacy of high dose (160 mg) polyoestradiol phosphate (PEP) was compared with that of orchiectomy in a prospective randomised multicentre study including 200 prostatic cancer patients. The effect of daily low dose (75 mg) acetosalicylic acid (ASA) on possible cardiovascular complications during the first 6 months of therapy was also evaluated. Oestrogen-treated patients had more progressions, but follow-up was too short to draw any definite conclusions on the efficacy of treatment. There was no cardiovascular mortality and there were no thromboembolic complications in any treatment group. It was concluded that parenteral high dose PEP is not associated with an increased risk of cardiovascular complications and there is no need for daily low dose ASA.

PMID: 2659136 [PubMed - indexed for MEDLINE]

23: J Urol. 2003 Nov;170(5):1703-8.

The nonsteroidal effects of diethylstilbestrol: the rationale for androgen deprivation therapy without estrogen deprivation in the treatment of prostate cancer.

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PURPOSE: During the last 2 decades there has been an increase in the number of men with prostate cancer placed on luteinizing hormone releasing hormone (LH-RH) agonist therapy. In addition, the duration of individual therapy has extended from what was once only a few months to, in many cases, several years. As a result there has been an increase in the incidence of side effects, including osteoporosis, decreased cognitive abilities, vascular stiffness and fatigue. We explored the use of estrogen in the form of diethylstilbestrol (DES) as an alternative treatment for men with prostate cancer, and introduce the concept of androgen deprivation without estrogen deprivation. In doing so we hope to elucidate some of the nonhormonal nonsteroidal effects of DES. Furthermore, we hope to define the mechanisms by which DES can be useful when LH-RH agonist therapy or orchiectomy has failed.

MATERIALS AND METHODS: We comprehensively reviewed the literature from 1935 to the present regarding estrogen and antiandrogen therapy. Our search focused on issues pertaining to side effects, efficacy and nonsteroidal effects of antiandrogens and estrogens.

RESULTS: It is readily apparent from the literature that androgen deprivation with DES can achieve effective prostate cancer control with demonstrable benefits compared to conventional LH-RH agonist therapy. In particular, rates of bone resorption and osteoporosis are less with the use of estrogen therapies. Estrogen has a clear beneficial effect on cognitive function. The estrogen metabolite 2-methoxyestradiol has significant antiangiogenic and pro-apoptotic effects. These effects give estrogens an added anticancer effect not otherwise seen in conventional LH-RH agonist therapy.

CONCLUSIONS: The efficacy of 1 mg DES extends well beyond its androgen suppressive effects. Androgen deprivation without estrogen deprivation is a concept that deserves further attention in the urological community.

PMID: 14532759 [PubMed - indexed for MEDLINE]

24: *Curr Opin Pharmacol*. 2003 Dec;3(6):650-4.

The use of estrogen therapy in men.

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Men make estrogen throughout their lives through the bioconversion of androgens by the aromatase enzyme in gonadal, as well as peripheral, tissues. The role of estrogen in men is not well understood; however, recent research interest has focused on this intriguing question. In some areas, such as the bone and cardiovascular systems, insights are beginning to be gained. Nevertheless, the clinical use of estrogen in men is limited.

PMID: 14644018 [PubMed - indexed for MEDLINE]

25: *Arterioscler Thromb Vasc Biol*. 2004 Jul 29 [Epub ahead of print]

Contrasting Effects of Oral Versus Transdermal Estrogen on Serum Amyloid A (SAA) and High-Density Lipoprotein-SAA in Postmenopausal Women.

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OBJECTIVE: Previous studies indicated that oral estrogen increased C-reactive protein by a first-pass hepatic effect. In this study, we determine whether the route of estrogen administration influences serum amyloid A (SAA), another acute-phase protein produced by the liver, and the SAA content of the high-density lipoprotein (HDL-SAA) in postmenopausal women.

METHODS AND RESULTS: In 29 postmenopausal women without coronary heart disease, we conducted a randomized cross-more than placebo-controlled study to compare effects of transdermal versus oral estrogen on SAA and HDL-SAA. SAA, apolipoprotein A-I, HDL, and HDL-SAA were measured before and after 8 weeks of transdermal estradiol (100 micro g per day), oral-conjugated estrogens (0.625 mg per day), or placebo. We found that oral estrogen significantly increased levels of SAA, HDL, and HDL-SAA, whereas transdermal estrogen reduced SAA and HDL-SAA but had no effect on HDL in the same women.

CONCLUSIONS: Oral estrogen increased SAA and altered HDL composition to contain a higher level of SAA by a first-pass hepatic mechanism. Because elevated SAA levels predict adverse prognosis in healthy postmenopausal women, and elevated HDL-SAA levels have been shown to interfere with HDL function, the administration route may be an important consideration in minimizing side effects of estrogen replacement therapy on cardiovascular outcomes.

PMID: 15284085 [PubMed - as supplied by publisher]

26: *Rev Infirm*. 2004 Apr;(100):23-30.

[Patches: the success of transdermal administration]

[Article in French]

Derrien E.

PMID: 15222181 [PubMed - indexed for MEDLINE]

27: Diabetes Care. 2004 Mar;27(3):645-9.

Transdermal 17-beta-estradiol and risk of developing type 2 diabetes in a population of healthy, nonobese postmenopausal women.

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OBJECTIVE: Various observational and randomized studies have demonstrated a reduction in the incidence of type 2 diabetes in postmenopausal women who received estrogen orally. No studies have been performed on the incidence of type 2 diabetes in postmenopausal women treated with transdermal 17-beta-estradiol. The purpose of our study was to assess the influence of transdermal 17-beta-estradiol on the incidence of type 2 diabetes in a population of healthy, nonobese postmenopausal women.

RESEARCH DESIGN AND METHODS: Between January 1998 and December 2002, 673 healthy, nonobese postmenopausal women (mean age 54 +/- 5 years) were enrolled: 144 (21.4%) of these took transdermal 17-beta-estradiol and 529 (78.6%) had never taken hormones during their postmenopausal period. Final elaboration of the data took place in July 2003, with a mean follow-up of 3.7 +/- 0.7 years (ranging from 0.5 to 5 years).

RESULTS: Type 2 diabetes developed in 60 patients during the follow-up period, which is the equivalent of 22 cases per 1,000 women-years. In the "hormones nonusers" group, diabetes developed in 10% (54 of 529 women; equivalent of 26.5 cases/1,000 women-years), whereas in the "hormones users" group, diabetes developed in 4.16% (6 of 144 women; equivalent of 12.1 cases/1,000 women-years). Transdermal 17-beta-estradiol emerged as a treatment that significantly reduced the risk of developing diabetes (RR 2.19, 95% CI 1.79-3.56; P=0.006).

CONCLUSIONS: Our results suggest a significant reduction in the incidence of type 2 diabetes in our population of nonobese, healthy postmenopausal women who used transdermal 17-beta-estradiol. This could suggest that, in some women, the estrogen deficiency that occurs after menopause could represent a fundamental step in the process of diabetogenesis.

PMID: 14988279 [PubMed - indexed for MEDLINE]

28: J Clin Endocrinol Metab. 2003 Dec;88(12):5723-9.

Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people.

Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, Rosing J.

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The incidence of venous thrombosis associated with estrogen treatment in male-to-female (M-->F) transsexuals is considerably higher with administration of oral ethinyl estradiol (EE) than with transdermal (td) 17-beta-estradiol (E(2)). To find an explanation for the different thrombotic risks of oral EE and td E(2) use, we compared the effects of treatment of M-->F transsexuals with cyproterone acetate (CPA) only, and with CPA in combination with td E(2), oral EE, or oral E(2) on a number of

hemostatic variables [activated protein C (APC) resistance and plasma levels of protein S, protein C, and prothrombin], all of which are documented risk factors for venous thrombosis. APC resistance was determined by quantification of the effect of APC on the amount of thrombin generated during tissue factor-initiated coagulation; plasma levels of total and free protein S were determined by standard ELISA; and levels of prothrombin and protein C were determined with functional assays after complete activation of the zymogens with specific snake venom proteases. CPA-only, td-E(2)+CPA, or oral E(2)+CPA treatment produced rather small effects on hemostatic variables, whereas oral EE treatment resulted in a large increase in APC resistance from 1.2 +/- 0.8 to 4.1 +/- 1 (P < 0.001), a moderate increase in plasma protein C (9%; P = 0.012), and a large decrease in both total and free plasma protein S (30%; P < 0.005). The large differential effect of oral EE and oral E(2) indicates that the prothrombotic effect of EE is due to its molecular structure rather than to a first-pass liver effect (which they share). Moreover, these differences may explain why M-->F transsexuals treated with oral EE are exposed to a higher thrombotic risk than transsexuals treated with td E(2). Testosterone administration to female-to-male transsexuals had an antithrombotic effect.

PMID: 14671159 [PubMed - indexed for MEDLINE]

29: Am J Obstet Gynecol. 2003 Nov;189(5):1221-7.

Effects of low-dose oral and transdermal estrogen replacement therapy on hemostatic factors in healthy postmenopausal women: a randomized placebo-controlled study.

Post MS, van der Mooren MJ, van Baal WM, Blankenstein MA, Merkus HM, Kroeks MV, Franke HR, Kenemans P, Stehouwer CD.

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OBJECTIVE: This study was undertaken to investigate the effect of transdermal and oral estrogen replacement therapy in healthy postmenopausal women on markers of coagulation and fibrinolysis associated with coronary artery disease.

STUDY DESIGN: In a randomized, placebo-controlled, double-blind study, healthy hysterectomized postmenopausal women received daily either placebo (n=49), transdermal 17beta-estradiol (E(2)) 50 microg (tE(2) group, n=33), oral E(2) 1 mg (oE(2) group, n=37), or oral E(2) 1 mg combined with gestodene 25 microg (oE(2)+G group, n=33) for thirteen 28-day treatment cycles. Hemostatic variables were measured in blood samples collected at baseline and in cycles 4 and 13.

RESULTS: No significant changes versus baseline and placebo were found in the tE(2) group, except for plasminogen activator inhibitor type-1 (PAI-1) in cycle 13 (-32.4%, P=.01). In the oE(2) group, significant percentage changes from baseline versus placebo in cycle 13 were found in fibrinogen, -5.4% (P<.05); factor VII, -7.3% (P<.05); thrombin-antithrombin III complexes, -13.3% (P<.05); tissue-type plasminogen activator (t-PA), -17.3% (P<.001); and PAI-1, -54.3% (P<.001). In the oE(2)+G group, respective changes were factor VII, -17.6% (P<.001); t-PA, -14.5% (P=.01); PAI-1, -36.4% (P<.01); and D-dimer, +21.8% (P<.05). No significant changes were observed in prothrombin fragment 1+2 and plasmin-alpha(2)-antiplasmin complexes.

CONCLUSION: Low-dose oral estradiol therapy was associated with an increase in fibrinolysis and small decreases in procoagulant variables. Transdermal therapy had minor effects.

PMID: 14634544 [PubMed - indexed for MEDLINE]

30: Urology. 2003 Dec 29;62 Suppl 1:87-94.

Role of secondary hormonal therapy in the management of recurrent prostate cancer.

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Androgen ablation remains the cornerstone of the systemic management of prostate cancer. After initial androgen deprivation, clinical outcomes vary considerably. For the patient with progressive disease after androgen deprivation, multiple therapeutic options are available and include antiandrogen withdrawal, chemotherapy, and secondary hormonal agents. Multiple secondary hormonal agents have clinical activity and the sequential use of these agents may lead to prolonged periods of clinical response. In addition to the use of oral antiandrogens, active secondary hormonal therapies include adrenolytic agents such as ketoconazole and aminoglutethimide, corticosteroids and estrogenic compounds. This article reviews the clinical trial data for these various agents and discusses their role in the management of patients with advanced prostate cancer.

PMID: 14747046 [PubMed - indexed for MEDLINE]

31: Urology. 2002 Sep;60(3 Suppl 1):87-92; discussion 93.

Secondary hormonal therapies in the treatment of prostate cancer.

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Patients with androgen-independent prostate cancer demonstrate progression of disease, despite chemical or surgical castration, and have a poor prognosis. Cancer progression may be manifest as an asymptomatic increase in serum prostate-specific antigen (PSA) or may be accompanied by symptomatic and/or radiographic evidence of tumor growth. Observation remains a reasonable choice for asymptomatic patients. However, many patients remain anxious about withholding further treatment and, although studies have not demonstrated a survival benefit with second-line hormonal therapy, it may be appropriate to consider these therapies. In patients who have radiographic and/or symptomatic progression, the use of second-line hormonal therapy is more easily justified. Treatment options include: (1) secondary use of antiandrogens (eg, high-dose bicalutamide), (2) therapies targeted against adrenal steroid synthesis (eg, ketoconazole, aminoglutethimide, and corticosteroids), and (3) estrogenic therapies (eg, diethylstilbestrol). Symptomatic improvement and PSA-level decreases of > or =50% have been reported in approximately 20% to 80% of patients with androgen-independent prostate cancer who receive such second-line hormone therapies, with a typical response duration of 2 to 6 months. Toxicity is generally mild for these oral therapies, although serious side effects, including adrenal insufficiency, liver toxicity, and thrombosis, may occur. In conclusion, secondary hormonal therapies have a significant role in the treatment of patients with androgen-independent prostate cancer. Further research is needed to understand their optimal use.

PMID: 12231058 [PubMed - indexed for MEDLINE]

32: Hinyokika Kyo. 2000 Jan;46(1):9-14.

[Endocrine therapy of stage D2 prostate cancer--comparison of drugs used for total androgen blockade]

[Article in Japanese]

Tanaka M, Murakami S, Suzuki N, Hamano S, Kinsui H, Oikawa T, Shimazaki J.

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Patients with Stage D2 prostate cancer were treated with surgical or medical (LHRH analog) castration combined with either estrogen, chlormadinone acetate or flutamide as initial therapy. The effect of each medication was compared. The overall survival, cause-specific survival and relapse-free survival were not different among the three medications. Patients given each medication were divided into two groups each according to grade, extent of diseases on bone metastases, and levels of tumor marker. Survivals of the corresponding two groups were compared with each other among different medications. No differences were revealed with any medication. There were no serious side effects in whole patients, except that grade 2 liver dysfunction was accompanied in 12% of flutamide-treated group. It is concluded that the three drugs used with castration did not make any difference in the survival of stage D2 patients, and differences between medications were seen in the frequency of side effects.

PMID: 10723657 [PubMed - indexed for MEDLINE]

33: Eur J Clin Invest. 1996 Dec;26(12):1186-8.

Profound decrease of in vivo formation of thromboxane during oestrogen therapy.

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Oestrogen has been proposed to influence platelet activity and formation of the vasoactive eicosanoids thromboxane and prostacyclin. Previous studies have been based on ex vivo techniques with well-known artifacts during blood sampling and ex vivo conditions. The present study is the first to assess in vivo formation through gas chromatographic/mass spectrometric analysis of the major urinary metabolites 2,3-dinor-thromboxane B2 and 2,3-dinor-6-keto-PGF1 alpha. Ten consecutive male patients with prostatic carcinoma participating in a randomized study comparing the effects of parenteral oestrogen therapy (n = 5) with orchidectomy (n = 5) were included. Oestrogen was given as polyestradiol phosphate 240 mg i.m. every month, 2,3-dinor thromboxane B2 and 2,3-dinor-6-keto-PGF1 alpha were analysed with the help of tetradeuterated internal carriers/standards. We found a consistent decrease of in vivo formation of thromboxane by approximately 40% during parenteral oestrogen therapy (P = 0.008) and a doubling after surgical castration. The ratio of prostacyclin to thromboxane increased by approximately 50% (P = 0.023) during oestrogen therapy. In conclusion, oestrogen induced a marked decrease of in vivo formation of thromboxane and a marked increase in the ratio of prostacyclin to thromboxane formation in all patients. According to current knowledge this should be beneficial for the cardiovascular system. Furthermore, thromboxane formation increased after surgical castration. The latter fact should direct attention to the influence of androgens on thromboxane synthesis. Our findings discloses a marked sex-hormone sensitivity of the thromboxane-forming system.

PMID: 9013098 [PubMed - indexed for MEDLINE]

34: Prostate. 1996 Oct;29(4):209-18.

Expression of transforming growth factor-beta 1 in rat ventral prostate and Dunning R3327 PAP prostate tumor after castration and estrogen treatment.

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BACKGROUND: In normal prostate, TGF-beta 1 is associated to castration induced apoptosis. Combined castration and estrogen treatment, but not castration alone, induces apoptosis in the Dunning R3327 PAP adenocarcinoma.

METHODS: TGF-beta 1 expression in rat ventral prostate (VP) and Dunning R3327 PAP tumor was studied after castration and estrogen treatment, using competitive RT-PCR, in situ hybridization and immunohistochemistry.

RESULTS: TGF-beta 1 mRNA level was 6 times higher in the tumor than in the VP. Combined castration and estrogen treatment increased TGF-beta 1 mRNA levels in the tumor from day 3, while castration did not. The TGF-beta 1 expression was located in the epithelial cells.

CONCLUSIONS: The Dunning R3327 PAP tumor contains high levels of TGF-beta 1, which are further increased by combined castration and estrogen treatment. However, since this increase is not apparent until day 3, TGF-beta 1 probably does not contribute to the known induction of apoptosis in the tumor at day 1 after combined castration and estrogen treatment.

PMID: 8876704 [PubMed - indexed for MEDLINE]

35: JAMA. 1996 Apr 17;275(15):1153.

Estrogen therapy for prostate carcinoma.

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PMID: 8609673 [PubMed - indexed for MEDLINE]

36: Oncologist. 2003;8(5):474-87.

Andropause: symptom management for prostate cancer patients treated with hormonal ablation.

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Andropause, or the age-related decline in serum testosterone, has become a popular topic in the medical literature over the past several years. Andropause includes a constellation of symptoms related to lack of androgens, including diminished libido, decreased generalized feeling of well-being, osteoporosis, and a host of other symptoms. The andropause syndrome is very prominent in men undergoing hormonal ablation therapy for prostate cancer. Most significant in this population are the side effects of hot flashes, anemia, gynecomastia, depression, cognitive decline, sarcopenia, a decreased overall quality of life, sexual dysfunction, and osteoporosis with subsequent bone fractures. The concept of andropause in prostate cancer patients is poorly represented in the literature. In this article, we review the current literature on the symptoms, signs, and possible therapies available to men who cannot take replacement testosterone.

PMID: 14530501 [PubMed - indexed for MEDLINE]

37: J Clin Endocrinol Metab. 2002 Nov;87(11):4907-13.

The effect of micronized estradiol on bone turnover and calciotropic hormones in older men receiving hormonal suppression therapy for prostate cancer.

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To examine the effect of estradiol (E(2)) without the confounding effect of hypothalamic-pituitary feedback, we studied men with prostate cancer in whom gonadotropin secretion was suppressed by LH-releasing hormone agonists (LHRH-A). Fourteen men over 65 yr of age and receiving established LHRH-A treatment (EST group) without bony metastases and 12 men who received LHRH-A as neoadjuvant therapy for locally advanced prostate cancer (NEO group) were randomized (double blind) to receive either 1 mg/d micronized E(2) (n = 12) or placebo (PL; n = 13) for 9 wk. E(2), estrone, testosterone, SHBG, PTH, and 25-hydroxy- and 1,25-dihydroxyvitamin D levels as well as markers of bone resorption [N- and C-telopeptide cross-links (NTX and CTX) and deoxypyridinoline] and bone formation (bone-specific alkaline phosphatase, osteocalcin, and N-terminal type I collagen) were measured before LHRH-A in the NEO group, before [baseline (BL)] and after 9 wk of E(2) or PL in all patients, and 6 wk after E(2) treatment in the EST group. In the NEO group, hormone levels fell 3 wk after the initial LHRH-A injection, and deoxypyridinoline increased significantly (P = 0.006). At BL, the EST group had higher bone turnover due to the longer duration of LHRH-A treatment. With E(2) treatment, E(2) levels rose into the normal male range, and two resorption markers decreased significantly from BL by 33% for NTX (P < 0.001) and 28% for CTX (P = 0.009). Bone formation markers did not change. PTH increased by 43% from BL (P < 0.01) in the E(2) group and decreased 16% from BL in the PL group (P < 0.01). Ionized calcium did not change in the E(2) group, but increased in the PL group by 2.3% (P < 0.01). NTX and CTX increased 6 wk after E(2) withdrawal in the EST group. We conclude that E(2) inhibits bone resorption in hypogonadal men through a direct skeletal effect that is independent of PTH. Low dose estrogen may be an option for the prevention and/or treatment of bone loss in this population.

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38: Atherosclerosis. 1998 Apr;137(2):359-66.

Erratum in: Atherosclerosis 1998 Jun;138(2):403.

Oral estrogen improves serum lipids, homocysteine and fibrinolysis in elderly men.

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The effects of estrogen on cardiovascular risk factors have been less well defined in men than in women. We measured lipid and lipoprotein concentrations, lipoprotein particle size distributions, lipoprotein (a), homocysteine, and markers of thrombosis and fibrinolysis in 18 [corrected] healthy elderly men (age 74 +/- 3 years, mean +/- S.D.) before and after 9 weeks of treatment with 0.5, 1 or 2 mg/day of oral micronized 17beta-estradiol. LDL-C (-6%), apo B (-9%), triglyceride (-5%), and homocysteine (-11%) concentrations decreased with estradiol, whereas HDL-C (+14%) increased. Intermediate-size VLDL subclass concentrations were lowered and LDL and HDL subclass levels altered in such a way as to cause average LDL and HDL particle size to increase. Lipoprotein (a) did not change. Fibrinogen (-13%) and plasminogen activator inhibitor-1 (PAI-1) concentrations (-26%) decreased, but there were no changes in thrombotic markers including thrombin-antithrombin III complex, prothrombin fragment 1.2, D-dimer, antithrombin activity, protein-C and S and von Willebrand factor antigen. Breast tenderness occurred in four men and heartburn in five but did not require discontinuation of treatment. We conclude

that oral estrogen in men reduces homocysteine, fibrinogen, and PAI-1 concentrations and favorably influences VLDL, LDL and HDL subclass levels without increasing markers of thrombotic risk.

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39: BJU Int. 2002 Sep;90(4):427-32.

Comment in: [J Urol. 2003 Apr;169\(4\):1598.](#)

Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial.

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OBJECTIVE: To report the first systematic investigation of the cognitive effects of luteinizing hormone-releasing hormone (LHRH) analogues in male patients, as LHRH analogues have been associated with memory impairments in women using these drugs for gynaecological conditions. **PATIENTS AND METHODS:** Eighty-two men with extraprostatic prostate cancer were randomly assigned to receive either continuous leuporelin, goserelin (both LHRH analogues), cyproterone acetate (a steroidal antiandrogen) or close clinical monitoring. These patients underwent cognitive assessments at baseline and before starting treatment (77), and then 6 months later (65). **RESULTS:** Compared with the baseline assessments, men receiving androgen suppression monotherapy performed worse in two of 12 tests of attention and memory; 24 of 50 men randomized to active treatment and assessed 6 months later had a clinically significant decline in one or more cognitive tests but not one patient randomized to close monitoring showed a decline in any test performance. **CONCLUSION:** Pharmacological androgen suppression monotherapy for prostate cancer may be associated with impaired memory, attention and executive functions.

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40: Drug Saf. 1991 Jan-Feb;6(1):47-53.

Estrogen in patients with prostatic cancer. An assessment of the risks and benefits.

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Estrogen therapy of patients with prostatic carcinoma appears to be at least as effective in antitumour activity as surgical castration: the recent therapeutic alternative of gonadorelin (gonadotrophin-releasing hormone) analogues has not to date been shown to improve patient outcome. Oral estrogen therapy in these patients increases the incidence of arterial ischaemic events, thromboembolic events and congestive heart failure. A plausible mechanism behind the enhanced cardiovascular morbidity is an increase in the formation of proteins synthesised by the liver, including coagulation factors. Oral estrogens induce a 'hypercoagulable state' which can be expected to have an adverse influence on the cardiovascular system. The effect of estrogen on cholesterol metabolism is likely to be beneficial for the cardiovascular system, with decreased levels of the atherogenic low density lipoprotein (LDL) cholesterol and increased levels of the putatively beneficial high density lipoprotein (HDL) cholesterol. The effects of estrogen on platelets and cardiovascular prostanoids are difficult to evaluate at present. A

possible approach to reduce its impact on the liver, and thereby possibly to minimise the risk of cardiovascular side effects, is parenteral administration. The promising results obtained in a pilot study of parenteral estrogen therapy in patients with prostatic carcinoma await confirmation in a randomised study, but where treatment with estrogen is considered for these patients, it may be that parenteral administration would be preferable.

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41: Eur Urol. 1998;34 Suppl 3:7-11.

Orchidectomy and oestrogen therapy revisited.

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Over the past 20 years therapeutic options for prostate cancer have increased. Nevertheless, there may still be a role for long-established treatments such as orchidectomy and oestrogens. Orchidectomy is a simple surgical procedure, and patient survival is comparable with other treatments involving androgen ablation. However, loss of libido and sexual function is an expected outcome and hot flushes occur in about 50% of patients. Osteoporosis, loss of muscle mass, and the psychological impact associated with orchidectomy are of concern, particularly with increasing treatment periods. Nevertheless, orchidectomy is indicated when an immediate reduction of testosterone levels is required, or the patient does not comply with other treatments or objects to the cost of medical therapy. Oestrogen therapy may be superior to castration in terms of efficacy, but orally administered oestrogens are associated with gynaecomastia, loss of sexual function and unacceptable cardiovascular toxicity. Low dose oestrogens in combination with antiandrogens or antithrombotic agents may be better tolerated treatments. The route of administration is a crucial factor in the genesis of cardiovascular toxicity and parenterally administered oestrogens may not entail the same risk. Further research in this area is warranted.

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42: Prostate. 1989;14(4):389-95.

Estrogen therapy and liver function--metabolic effects of oral and parenteral administration.

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Oral estrogen therapy for prostatic cancer is clinically effective but also accompanied by severe cardiovascular side effects. Hypertension, venous thromboembolism, and other cardiovascular disorders are associated with alterations in liver metabolism. The impact of exogenous estrogens on the liver is dependent on the route of administration and the type and dose of estrogen. Oral administration of synthetic estrogens has profound effects on liver-derived plasma proteins, coagulation factors, lipoproteins, and triglycerides, whereas parenteral administration of native estradiol has very little influence on these aspects of liver function.

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Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade.

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OBJECTIVE: To describe the incidence, time to onset and extent of anaemia occurring in patients with prostate cancer receiving combined hormone blockade (CHB) and the timing and extent of recovery from anaemia in those patients where CHB was discontinued. **PATIENTS AND METHODS:** Patients with prostate cancer were evaluated prospectively by physical examination and laboratory tests at baseline and at routine intervals while receiving CHB. Of 142 patients who received CHB, 133 were evaluable for the assessment of anaemia; CHB was discontinued in 76 patients, of whom 64 were assessable for recovery from their anaemia.

RESULTS: Haemoglobin levels declined significantly in all patients from a mean baseline of 149 g/L to means of 139 g/L, 132 g/L and 131 g/L at 1, 2 and 3 months, respectively. Haemoglobin levels continued to decline during CHB to a mean nadir of 123 g/L at a mean of 5.6 months of CHB, representing a mean absolute haemoglobin decline at nadir of 25.4 g/L. In 120 of the 133 (90%) patients, the relative decline in haemoglobin at nadir was $\geq 10\%$ and was $\geq 25\%$ in 17 (13%) others, representing a mean absolute haemoglobin decline in this subset of 42.7 g/L. Significant symptoms related to anaemia occurred in 17 patients (13%). Anaemia and symptoms in these patients were easily corrected with the subcutaneous administration of recombinant human erythropoietin.

CONCLUSIONS: The anaemia associated with androgen deprivation is significant and occurs routinely in men receiving CHB. It is normochromic, normocytic, temporally-related to the initiation of androgen blockade and usually resolves after CHB is discontinued. We suggest that patients receiving CHB undergo haematological testing at baseline, 1-2 months after initiating CHB and periodically thereafter. Patients developing anaemia should be questioned about symptoms reflecting physiological compromise (e.g. angina, dyspnoea on exertion). In the absence of other causes, CHB should be suspected in the development of anaemia in patients receiving this treatment.

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