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5th INTERNATIONAL SYMPOSIUM ON

WOMEN'S HEALTH AND MENOPAUSE

NEW FINDINGS, NEW STRATEGIES, IMPROVED QUALITY OF LIFE

Florence, Italy
April 21-24, 2004

PALAZZO DEI CONGRESSI

PIAZZA ADUA, 1
FLORENCE, ITALY

ABSTRACT BOOK

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

National Heart. Lung and Blood NIH. USA

Fondazione italiana per il cuore

Ministero della Salute 2004 anno del CUORE

5th International Symposium on

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HORMONES AND BREAST CANCER RISK AFTER THE WOMEN'S HEALTH INITIATIVE TRIAL OF ESTROGEN PLUS PROGESTIN

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The WHI trial of estrogen plus progestin is the largest randomized controlled trial to evaluate breast cancer risk among postmenopausal women using estrogen and progestin. Between 1993 and 1998, the Women=s Health Initiative enrolled 161,809 postmenopausal women who were from 50 to 79 years of age in trials that evaluated low-fat dietary pattern, calcium and vitamin D supplementation and postmenopausal hormone use. The estrogen and progestin trial was stopped in May 2002 mainly because of increased breast cancer risk in the estrogen and progestin group compared with the placebo group. The WHI breast, endometrial and colorectal cancer, venous thromboembolism and fracture outcomes were similar to previous epidemiological study reports and the coronary heart disease, stroke and senile dementia outcomes were at variance with existing epidemiological research.

After an average 5.6 years of follow-up reported in 2003, the relative hazard was 1.24 (95% CI 1.01, 1.54), a marginally significant estimate. The absolute risk was 8 breast cancer cases for every 10,000 women per annum in addition to the 31 cases per 10,000 in the placebo group . Breast cancer incidence became significantly higher in the estrogen and progestin group after four years of exposure. One-fourth of women in the estrogen-progestin and placebo groups used menopausal hormones before the study. Although the difference was not statistically significant, the relative hazards among prior users were higher than in women who had not been prior users. The frequency of in situ breast cancers was not significantly different in the estrogen-progestogen and placebo groups (relative hazard 1.18, 95% CI 0.77, 1.82). Among the invasive cancers, there was no specific association with ductal or lobular types, degree of differentiation and estrogen or progesterone receptor status.

Tumours in the estrogen-progestogen group were 2 mm larger ($p = 0.04$), more likely to be regional or metastatic than localized (25.4% vs 16.0%, $P = 0.04$) and more likely to involve lymph nodes (25.9% vs 15.8%, $P = 0.03$). Although previous epidemiological studies indicated that breast cancer survival was better in hormone users, further follow-up is needed among WHI participants to determine whether these tumour characteristics will be associated with poorer survival in hormone users.

PHYSIOLOGICAL ROLE OF ESTROGEN AND ESTROGEN RECEPTORS IN THE CARDIOVASCULAR SYSTEM: 2004 UPDATE

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Blood vessels express estrogen receptors, and their importance in the vascular injury response and in normal vascular physiology are established. However, much remains to be understood about ER-mediated events in blood vessel and heart cells. New data support that both of the known estrogen receptors, ERα and ERß, regulate vascular contractile function. Endothelial nitric oxide synthase (eNOS) generates the endogenous vasodilator NO, which is necessary for maintenance of normal blood pressure. Estrogen activates eNOS in an ER-dependent manner and causes rapid vascular dilatation. New data support that this occurs by the tethering of a subpopulation of estrogen receptors to plasma membrane caveolae by a specific interaction with a newly identified scaffold protein. Estrogen receptors also influence blood pressure. Hypertension is a major risk factor for cardiovascular disease, with a lower incidence in pre-menopausal women and a higher incidence in postmenopausal women when compared to age-matched men. ERb has an important role in the development and/or maintenance of normal vascular tone and blood pressure. Vascular smooth muscle cells and blood vessels from estrogen receptor ß (ERß)–deficient mice exhibit abnormalities of contractile and ion channel function, and . develop sustained systolic and diastolic hypertension as they age. In humans, estrogen and related hormone replacement therapies (HRT) activate estrogen receptors, which in turn regulate the genes for important cardiovascular disease (CVD) risk factors. However, relatively little is known about the effect of polymorphisms in the ERα gene (ESR1) on the risk for CVD. We recently studied ESR1 gene variation in the offspring cohort of the Framingham Heart Study. After adjustment for covariates (age, sex, body mass index, hypertension, diabetes mellitus, total cholesterol, HDL-cholesterol, alcohol consumption, and cigarette smoking) the c.454-397CC genotype was significantly associated with major CVD, with an odds ratio of 2.2 (95% CI, 1.2 - 3.6; $p = 0.004$) compared to the *TC* or *TT* genotypes. Subjects with this genotype also had a 3.2 fold greater odds of myocardial infarction (95% CI, 1.8 - 5.8; $p = 0.0001$) compared to those with the *TC* or *TT* genotype. Thus, individuals with this common ERα gene variant have a substantial increase in risk of CVD and myocardial infarction. These findings further support the importance of estrogen receptors in cardiovascular function in both men and women, and may provide one explanation for recent conflicting data regarding the effects of HRT on CVD in women.

DO GENES DETERMINE RISK AND BENEFITS OF HRT? NEW DATA FROM HERS AND OTHER TRIALS

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Recent unexpected negative results from randomized clinical trials, including the Women's Health Initiative have completely transformed our understanding of the effect of HRT on cardiovascular disease risk from one of presumed benefit to one of possible harm. This surprising turn of events has made it clear that the effects of HRT on vascular health are far more complex than initially assumed and urgently in need of additional study. Understanding how estrogen, which has favorable effects on intermediate pathways such as lipid metabolism and endothelial function, could nonetheless increase risk for cardiovascular disease events would undoubtedly shed new light on the pathogenesis of atherosclerosis and provide fundamentally important additional information concerning estrogen biology. New evidence from the Estrogen Replacement Atherosclerosis (ERA) and Heart and Estrogen/progestin Replacement Study (HERS) trials suggests that genetic variability in the estrogen receptor may account for some of the recent unexpected findings. These new data will be reviewed in detail.

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DIABETES AND THE METABOLIC SYNDROME IN WOMEN

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In the last decade it has become clear that cardiovascular disease (CVD) is the leading cause of death in women of westernized countries, with more than one in two women dying from CVD. The presence of the metabolic syndrome, which affects 20-30% of the middle-aged population, significantly accounts for the high CVD morbidity and mortality among women. The metabolic syndrome encompasses a range of conditions, including insulin resistance, dyslipidemia (high triglycerides, low HDL-C and small, dense LDL), hypertension, clotting abnormalities, central obesity, and overt diabetes, which predispose an individual to a 4 to 5-fold increased risk of CVD. Many of the features of the metabolic syndrome emerge with estrogen deficiency in postmenopausal women: 1) increased central body fat; 2) a shift toward a more atherogenic lipid profile, with increased low density lipoprotein and triglycerides levels, reduced high density lipoprotein, and small, dense low density lipoprotein particles; 3) and increased glucose and insulin levels. It is estimated that more than half of all cardiovascular events in post-menopausal women are related to the metabolic syndrome. Early manifestations of the metabolic syndrome in women include the polycystic ovary syndrome and, in pregnant women, preeclampsia.

Diabetes is associated with a greater increase in risk for atherosclerosis in women than in men, possibly because of the relatively more severe dyslipidemia seen in women with diabetes compared with men with diabetes. Women with diabetes have greater elevations of triglycerides and LDL-C and lower levels of HDL-C than men with diabetes, whether the diabetes is untreated or treated with diet, sulfonylureas, or insulin. The presence of diabetes eliminates any advantage that premenopausal women may have for CVD risk, making their risk approximately equal to that of men. For women with diabetes or the metabolic syndrome, (and increasingly so for men), it is becoming clear that CVD risk modification should focus not only glycemic control and LDL-C lowering, but also on triglycerides and HDL-C. Moreover, therapy should aim to reduce the risk associated with multiple factors, both lipid and nonlipid.

CARDIOVASCULAR PROTECTION: IS POSTMENOPAUSAL HORMONE THERAPY NO LONGER AN OPTION?

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Estrogen deficiency, related to either natural or surgical menopause, is a risk factor for the development of atherothrombotic disease. Supplementation of estrogens therefore has been suggested to be a plausible strategy to prevent coronary artery disease in postmenopausal women. This hypothesis was supported by a multitude of research papers reporting on epidemiological studies with clinical outcomes as well as surrogate endpoint and animal studies, almost all pointing in the same direction. In contrast to these data, recently published randomized controlled trials in apparently healthy women, as well as women with established coronary artery disease, have shown that oral postmenopausal hormone therapy (PHT) was not cardioprotective and maybe even harmful in the first year of treatment. Also transdermal PHT was not found to be protective. Therefore, doctors are discouraged to prescribe PHT only for the prevention of coronary artery disease.
The question remains however, whether the observations done in these randomized controlled trials should be extrapolated to for instance PHT formulations other than those used in these trials. Maybe even more important than the frequently mentioned controversy between the characteristics of observational and randomized controlled trials, is the remarkable difference between the populations studied. An important potential explanation for the observed differences is the (menopausal) age, and therefore the cardiovascular condition of the study populations. Future trials should therefore focus on the effects of PHT in the population that actually uses PHT, that is young peri- and early postmenopausal women.

OXIDATIVE STRESS CONTRIBUTES TO REDUCED LARGE ELASTIC ARTERY COMPLIANCE IN ESTROGEN-DEFICIENT POSTMENOPAUSAL WOMEN

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The compliance of large elastic arteries in the cardiothoracic region decreases with advancing age and plays an important role in the increased prevalence of cardiovascular diseases in postmenopausal women. We determined if excessive bioavailability of reactive oxygen species, i.e., “oxidative stress”, contributes mechanistically to this reduction in arterial compliance. 17 estrogen-deficient postmenopausal (POST, 53±1 years, mean±SE) and 6 premenopausal (PRE, 23±1) healthy sedentary women were studied during acute intravenous infusions of saline (control-CON) and superphysiological levels of the potent antioxidant ascorbic acid (vitamin C-VIT C). Body fat, waist circumference (WC), waist-to-hip ratio (WHR), arterial blood pressure (BP), fasting glucose, and total and LDL cholesterol were higher in POST compared with PRE ($P<0.05$). Carotid artery compliance was 50% lower (0.8±0.1 vs. 1.6±0.2 mm2/mmHg x 10-1, $P<0.0001$) in POST compared with PRE during CON. Carotid artery compliance increased by 27±6% during VIT C in POST (to 1.0±0.01 mm2/mmHg x 10-1, $P<0.001$ vs CON), but was unchanged in PRE (1.5±0.1 mm2/mmHg x 10-1, $P=0.25$ vs CON). Carotid artery diameter and BP were unaffected by VIT C (both $P>0.21$ vs CON). WC, WHR, fasting glucose, and total and LDL cholesterol were positively related to the absolute and % differences in carotid artery compliance during VIT C vs CON ($r=0.37$-0.68, all $P<0.05$). However, WHR was the only significant independent predictor of the change in arterial compliance during VIT C, explaining 40% of the variance ($P<0.005$). These results suggest that oxidative stress is an important mechanism contributing to the reduced large elastic artery compliance in sedentary estrogen-deficient postmenopausal women compared with premenopausal females. Increased abdominal-to-peripheral body fat storage may be one factor involved in the oxidative stress-associated reduction in large elastic artery compliance in these postmenopausal women.

HEART DISEASE RISK DETERMINES MENOPAUSAL AGE RATHER THAN THE REVERSE

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Women with an early menopause are at an increased risk of cardiovascular disease. Although increased cardiovascular risk has been proposed as consequence of menopause, the alternative hypothesis, that increased premenopausal cardiovascular risk promotes early menopause, needs to be examined.
We used data of the Framingham Heart Study cohort.
Women who were premenopausal at study entry and reached natural menopause after at least two examination rounds were included in the study (n=695). Premenopausal age-independent levels of serum total cholesterol, relative weight, blood pressure and Framingham risk score were determined as well as premenopausal changes in cholesterol, body weight and blood pressure.
A higher premenopausal serum total cholesterol level was statistically significantly associated with an earlier age at menopause, as were increase of total serum cholesterol, relative weight and blood pressure in the premenopausal period. Decrease of total serum cholesterol during premenopause was statistically significantly associated with a later age at menopause. Decreasing blood pressure was associated with a later menopausal age, but this association was not statistically significant. Decrease in relative weight was associated with a significant earlier age at menopause. Each 1% higher premenopausal Framingham risk score was associated with a decrease in menopausal age of 1.8 years (95% CI –2.72, -0.92).
The findings support the view that heart disease risk determines age at menopause. This offers a novel explanation for the inconsistent findings on cardiovascular disease rate and its relation to menopausal age and effects of hormonal replacement therapy.

DIVERGENT EFFECTS OF SYNTHETIC PROGESTINS ON ENDOTHELIAL NITRIC OXIDE SYNTHASE

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The long-standing assumption of protective effects of hormone replacement therapy (HRT) on the cardiovascular system has been recently questioned by large randomized controlled trials. While estrogen’s effects on the vessels have been largely explored, the specific mechanisms of action of progesterone as well as the possible interactions with estrogen signaling are not as clear. Moreover, it is likely that different synthetic progestins will have specific effects, and that these potential differences may be of clinical relevance. Human umbilical vein endothelial cells were exposed to long or short treatments with progesterone (P) or with equimolar amounts of medroxyprogesterone acetate (MPA), levonorgestrel (LNG), megestrol acetate (MEG), cyproterone acetate (CYP) or norethisterone acetate (NETA), alone or in the presence of 17ß-estradiol (E2). We found that P, LNG and CYP induce the expression of endothelial nitric oxide synthase (eNOS) and increase its enzymatic activity, while MPA, MEG or NETA do not. Moreover, these three latter progestins blunt E2-induced eNOS expression. In parallel, P, LNG and CYP (but not MPA, MEG or NETA) potentiate E2-dependent nongenomic activation of eNOS. This action depends on the sequential activation of a MAPK/PI3K/Akt cascade. We show that distinct progesterone receptor ligands induce markedly different signaling events in human endothelial cells. These results help to elucidate the mechanisms of transcriptional and non-transcriptional action of progesterone in vascular cells, and suggest that the clinical effects of the progestins used for contraception or HRT should not be generalized, but each molecule should instead be evaluated singularly.

OPPOSITE MODULATION OF INFLAMMATORY ENZYMES BY ESTROGEN AND RESVERATROL IN VASCULAR SMOOTH MUSCLE CELLS

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Several studies demonstrate that 17ß-estradiol (E_2) has antinflammatory activity by interacting with estrogen receptor (ER) α. Our recent work showed that E_2 loses part of its protective effects in diabetes because ER isoform profile is altered by this disease. Resveratrol (Res) is a phytoestrogen with cardioprotective activities that exhibits different affinity for ER isoforms. In this study we compared the effect of E2 and Res on the regulation of two important enzymes involved in the inflammatory response, inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2), in aortic smooth muscle cells (SMC) from diabetic and non-diabetic rats. After 24h-treatment with a cytokine mixture, E_2 (10^{-11}-10^{-8} M) inhibited the expression of iNOS protein both in control and, to a lesser extent, in diabetic SMC. E_2 also reduced iNOS activity, as measured by nitrite formation in the medium, in control but not in diabetic SMC. By contrast, treatment with Res (10^{-7}-10^{-5} M) increased iNOS protein level and activity in both cell types. This was the case also for another isoflavone phytoestrogen, genistein. In control SMC cytokines reduced the basal expression of COX-2 protein. An U-shaped concentration-response curve to E_2 was observed for COX-2 levels. In diabetic SMC both cytokines and E_2 failed to affect COX-2 expression. COX-2 activity, as evaluated by PGE_2 production in the culture medium, increased after treatment with cytokines and E_2 in diabetic more than in control SMC. In contrast with E_2, Res did not change COX-2 levels in control SMC but induced an U-shaped curve in diabetic SMC. Res increased COX-2 activity in diabetic SMC, but reduced it in control SMC. Our results suggest that E_2 and Res affect iNOS and COX-2 function in an opposite fashion because Res, as well as genistein, may preferentially interact with ERß in our cell model. The different pattern of action of E_2 and Res in control and diabetic SMC may in turn result from the marked alteration of ER expression that occurs in diabetes.

HIGH MW FGF2, BUT NOT LOW MW FGF2 NOR VEGF, MEDIATES THE EFFECT OF ESTRADIOL ON REENDOTHELIALIZATION .

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The acceleration of reendothelialization by 17ß-estradiol (E_2) involves ERa and endothelial nitric oxide synthase, but whether major growth factors as VEGF or Fibroblast Growth Factor-2 (FGF2) are involved remains unclear. FGF2 is in fact expressed under several isoforms : the low molecular weight 18 kDa (FGF2lmw) is secreted and activates tyrosine kinase receptors, whereas the high molecular weight (21 and 22 kD) isoforms (FGF2hmw) remains intranuclear, but their role is mainly unknown. The goal of the present study was to explore the role of VEGF and of FGF2 isoforms on the effect of E_2 in a mouse model of reendothelialization.

Inhibition of VEGF (using VEGF trap) slowed reendothelialization in wild type mice, but did not interfere with the acceleration of this process by E2. The velocity of reendothelialization in mice deficient in all FGF2 isoforms ($Fgf2^{-/-}$) was normal, but the accelerative effect of E_2 was abolished. We observed that E2 increased $FGF2^{hmw}$, but not $FGF2^{lmw}$, abundance in aorta and lung homogenates. To further explore the respective roles of FGF2 isoforms in reendothelialization, we generated mice deficient only in the $FGF2^{lmw}$ ($Fgf2^{lmw-/-}$). We found that the accelerative effect of E2 on reendothelialization was similar in both $Fgf2^{+/+}$ and *Fgf2*lmw-/- mice. E_2 increased $FGF2^{hmw}$ protein abundance in aorta and lung tissues in *Fgf2*lmw-/- mice as it did in $Fgf2^{+/+}$.

In conclusion, E_2 increases specifically the intracellular $FGF2^{hmw}$, which mediates the acceleration of reendothelialization via an intracrine action.

HORMONE THERAPY IN MENOPAUSAL DIABETIC WOMEN?

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Epidemiological evidence for the relationship between deterioration of glucose tolerance and risk of cardiovascular disease (CHD). Diabetes confers appproxmiately a 4 fold increased risk, but its has been demonstrated in a vast number of investigations indicating that not only overt diabetes, but also insulin resistance are independent risk factors. Clinical states of insulin resistance involve blocks in the signalling network at one or more sites. The cluster of metabolic changes associated with insulin resistance has been defined as the 'metabolic syndrome'. Aging per se is associated with an increased incidence of type-2 diabetes and CVD. In the context of sex steroids it is of interest that during the fertile period the insulin sensitivity to glucose is greater in women than in men. After the menopause the effects of estrogens suggest that hormonal replacement therapy (HT) would have the potential to reverse the metabolic changes included in the metabolic syndrome. In the HERS study a significant decrased risk of diabetes was observed among the HT users. In diabetic women HT may also correct some of the metabolic disturbances caused by the disease. The direct effect on the endothelial cell of HT may, however, be comparable or even more pro-thrombotic compared with the effect in non-diabetic women, but the improved glucometabolic control will most probable reduce the risk of atherosclerotic plaque formation. From a theoretical point of view the combined risk of the clinically most important condition i.e. atherothrombosis, may therefore be decreased. Such considerations are supported by several observational studies, but the reports from the most recent epidemiological studies on the association between HT and CVD development in diabetic women give conflicting evidence. In a danish cohort study the risk of MI was 4 fold increased in diabetic HT users compared to non-users. In contrast a large scale US investigation among women with diabetes found a decreased risk of first time MI. Further specific HT studies are needed in diabetic women with proper adjust-ments for confounding factors such as route of HT admini-stration, con-figura-tion of the steroids, blood pressure, lipo-protein levels, exercise, diet and concomitant medication.

MODIFICATION OF GLUCOSE METABOLISM BY POSTMENOPAUSAL THERAPIES.

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Alteration of glucose metabolism leading to diabetes is a major cardiovascular risk factor for postmenopausal women. Accordingly, the possibility to anatgonize this modification represents an important adjunct for any therapy given in the postmenopausal period. The results on HT and glucose metabolism are not univocal, mainly as the consequence of the dose of estrogen employed and the type of progestin administered. Convincing evidence indicate that the effect of estrogens is dose-dependent, high estrogen doses being associated with a deterioration of glucose tolerance. These data were not confirmed with lower estrogen doses, which overall showed an improvement of glucose tolerance, insulin clearance or insulin sensitivity. Adjunct of a progestin to estrogens may have a different effect, depending on the type of progestin administered. Several studies indicate negative effects for medroxyprogesterone acetate, while neutral effects were more frequently reported for norethisterone acetate and dydrogesterone. Recently, HT with conjugated estrogens and low doses of medroxyprogesterone acetate was reported to reduce the onset of diabetes in old postmenopausal women. A limited number of studies have evaluated the effect of tibolone and raloxifene on glucose metabolism. Both molecules are capable to interact with steroid receptors. Tibolone can be considered a continuos combined HT. In spite of conflicting evidence, tibolone seems to improve insulin sensitivity without modifying glucose tolerance. Raloxifene, used for the prevention and treatment of osteoporosis seems to exert a neutral impact on glucose tolerance and insulin sensitivity.

ALTERED ESTROGEN RECEPTOR EXPRESSION IN RAT AORTA IS INVOLVED IN DIABETIC VASCULAR DYSFUNCTION

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Anti-inflammatory effects of 17ß-estradiol (E2) have been reported in several tissues including the vascular wall. In fact, E2 reduces the cytokine-mediated activation of inducible NO synthase (iNOS) in vascular smooth muscle cells (SMC). In view of the inflammatory nature of diabetic vascular dysfunction, the estrogenic control of and the contribution of estrogen receptors (ER) to iNOS function were tested in aortic SMC from diabetic rats. E2 (10 pM -1 nM) down-regulated iNOS protein synthesis and activity in control, but not in diabetic SMC after 24-h stimulation with a cytokine mix, suggesting alterations in the ER expression pattern. Indeed, ERα mRNA was more abundant than ERß mRNA in control SMC. ERα mRNA, and even more so ERß mRNA, significantly increased in diabetic SMC, while their protein content increased by 50% and 2.5-fold, respectively. Cytokines consistently reduced the expression of both ER isoforms. Treatment with E2 in the presence of cytokines restored ERa but further reduced ERß expression. In order to dissect the relative contribution of ER isoforms to iNOS modulation, it was observed that the selective ERα agonist PPT dose-dependently decreased, while the selective ERßb agonist DPN increased iNOS protein levels. In conclusion, the estrogenic control of iNOS and the expression profile of ER in vascular SMC were altered by diabetes. Since the anti-inflammatory effect of estrogen appeared to be mediated by ERα, selective ERα agonists may be promising tools to combat the vascular complications of diabetes and other inflammatory disease.

RELATIONSHIP BETWEEN HOMA AND METABOLIC MARKERS IN PERI- AND POSTMENOPAUSAL WOMEN

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Menopausal transition is accompanied by an increasing risk for impaired glucose tolerance and Diabetes mellitus type 2. A HRT may decrease the insulin resistance and improved carbohydrate and lipoprotein metabolism in postmenopausal women.
388 middle-aged women were studied (53,9±9,3 years, BMI 25,12±4,16 kg/m2). Among them were 50 women at perimenopausal transition and 150 women after natural menopause. 2/3 of the perimenopausal and 1/3 of postmenopausal women used HRT. Anthropometrical measurements were taken and serum glucose, insulin, lipoproteins , CRP, ferritine and HbA1c concentration were determined in fasting blood samples. Insulin resistance was estimated by the homeostasis model assessment (HOMA) method. Among healthy middle-aged Dresden women 5% showed an increased HOMA insulin resistance index (2,82±1,63). BMI and CRP were significant higher and HDL-C significant lower in these subgroup. The HOMA index was significantly correlated with BMI (r=0,280; p<0,001), HbA1c (r=0,337; p<0,001), ferritine (r=0,253; p<0,001) and inversely with HDL-C (r = -0,277; p<0,001). There was no relationship between HOMA and age or FSH- concentration in the whole population, as well as in separate groups of postmenopausal women with or without HRT or non-HRT using perimenopausal women. Among perimenopausal HRT-users a weak FSH- (r=0,291; p<0,05) and age- dependency (r=0,294; p<0,05) was observed. Whereas in the subgroups of non-HRT-users all correlations between HOMA and the metabolic markers were highly significant, in the HRT- groups HOMA correlated significantly with HDL-C only.
Conclusion: Factors affecting the HOMA index may be different in peri- and postmenopause.

SEX HORMONES AND RESTING ENERGY EXPENDITURE

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Resting energy expenditure (REE) plays a significant role in maintenance of body weight. REE decreases with aging and may decrease in women as a result of the menopause. Elevated serum concentrations of estrogen (E) and progesterone (P) in the mid-luteal (ML) phase of the menstrual cycle have been associated with higher REE in premenopausal women, suggesting a role for sex hormones in regulation of REE. The aim of the present study was to determine the effects of reducing E and P on REE. Ten premenopausal women (aged 30 ± 6 years) were studied at baseline (ML) and after 5 days of treatment with a gonadotropin-releasing hormone antagonist (GnRHant). REE was measured via indirect calorimetry (Delta Trac) in the morning, following an overnight stay at the General Clinical Research Center, after a 12-hour fast and 24-hour abstention from exercise. On the same day, REE was measured again, after intravenous infusion of the non-selective beta-adrenergic antagonist propranolol, to determine sympathetic nervous system (SNS) "support" of REE in each experimental condition. There was a significant decrease in REE in response to GnRHant (1404 ± 208 in ML vs. 1331 ± 185 in GnRHant kcal/day, p = 0.01). Additionally, SNS "support" of REE was greater at baseline compared with GnRHant (-37 ± 35 vs. 3 ± 45 kcal/day, p = 0.05). Pharmacologic suppression of sex hormones to postmenopausal levels elicits a reduction in REE in young healthy women. There is a trend for a relation between the change in REE and the change in sympathetic "support" of REE from ML to GnRHant (r = 0.50, p = 0.11). Therefore the lower REE observed after administration of GnRHant may be due, in part, to a decrease in sympathetic nervous system "support" of REE.

APPROPRIATE USE OF LOW DOSE HORMONE THERAPY FOR MENOPAUSAL SYMPTOMS: WOMEN'S HOPE STUDY

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Objectives: To examine the safety and efficacy of lower doses of CE and CE/MPA as measured by relief of vasomotor symptoms, vaginal atrophy, and amenorrhea rates.
Design: A prospective, randomized, double-blind, placebo-controlled, multicenter trial in 2,805 healthy, postmenopausal women (40-65 years) with an intact uterus. Patients received 1 of 8 regimens of CE, CE/MPA, or placebo for 12 months (thirteen 28-day cycles).
Materials and Methods: The 8 daily oral regimens were 0.625 mg CE; 0.625 mg CE + 2.5 mg MPA; 0.45 mg CE; 0.45 mg CE + 2.5 g MPA; 0.45 mg CE + 1.5 mg MPA; 0.3 mg CE; 0.3 mg CE + 1.5 mg MPA; and placebo. Patients also received 600 mg elemental calcium daily. Patients recorded daily frequency and severity of hot flushes, occurrence of vaginal bleeding or spotting, and regimen compliance. Hot flushes were analyzed in 241 patients. Vaginal atrophy was assessed by vaginal maturation index (VMI).
Results: All CE alone and CE/MPA groups had significantly fewer and less severe hot flushes than the placebo group (P<0.05). These effects occurred by Wk 3 of therapy and were maintained over 13 cycles. VMI significantly improved from baseline in all active treatment groups at all cycles (P £ .001), and all active treatment groups at all cycles also differed significantly from the placebo group (P < .001). Rates of cumulative amenorrhea were significantly greater (P<0.05) with lower doses of CE/MPA than with standard dose therapy. Patients in the lower dose CE/MPA groups also experienced significantly more cycles with amenorrhea than patients in the 0.625 CE/2.5 MPA group (P<0.05).
After 1 year, all study groups showed modest weight increases. The largest increase occurred in the placebo group.
Conclusions: Lower doses of CE/MPA were effective in treating vasomotor symptoms and vaginal atrophy, and resulted in higher rates of amenorrhea than standard doses. Lower dose regimens of CE and CE/MPA are not associated with significant weight gain when compared to placebo. These results support 0.45 CE/1.5 MPA and 0.3 CE/1.5 MPA as valuable options for addressing patients' needs with HT.

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ENDOMETRIAL AND SKELETAL EFFECTS OF LOW DOSE HORMONE THERAPY: WOMEN'S HOPE STUDY

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Objectives: Lower than standard doses of estrogen and progestin may expand available options for women considering hormone therapy (HT). To examine the safety and efficacy of lower doses of CE and CE/MPA as measured by endometrial histology and bone density.
Design: A prospective, randomized, double-blind, placebo-controlled, multicenter trial in 2,805 healthy, postmenopausal women (40-65 years) with an intact uterus. Patients received 1 of 8 regimens of CE, CE/MPA, or placebo for 12 mos (thirteen 28-day cycles). In the second year, 749 Seven hundred and forty nine patients who participated in the Osteoporosis and Metabolic substudy of the Women's Health Osteoporosis Progestin Estrogen (HOPE) study continued in the study, for a second year, duringwhich evaluated bone and metabolic endpoints as well as endometrial safety were evaluated.
Materials and Methods: The 8 daily oral regimens were 0.625 mg CE; 0.625 mg CE + 2.5 mg MPA; 0.45 mg CE; 0.45 mg CE + 2.5 g MPA; 0.45 mg CE + 1.5 mg MPA; 0.3 mg CE; 0.3 mg CE + 1.5 mg MPA; and placebo. Patients All women also received calcium carbonate (600 mg elemental calcium daily).(mean age: 52.4 years, mean time since menopause: 4.1 years) who took study medication and who had ≥7 moderate-to-severe baseline hot flushes on each of the last 7 days of screening, or ≥50 total hot flushes on the last 7 days combined. , i.e., the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells in a Papanicolaou smear and the Incidence of endometrial hyperplasia was assessed by endometrial biopsy at incidence of endometrial hyperplasia was assessed by endometrial biopsy. These were assessed at baseline and cycles 6, and13, and in the substudy, additionally at cycles 19 and 26. At enrollment, all patients were within 20% of normal body weight range; women in the substudy were between 1 and 4 years post menopause. At enrollment, women in the substudy were between 1 and 4 years post menopause and were within 20% of normal body weight range. Changes from baseline in spine and total hip bone mineral density (BMD) and total body bone mineral content (BMC) were assessed at cycles 6, 13, 19 and 26 in the substudy.
Results: Increases in BMD ranged from 1.7%-3.9% at the spine and 2.0%-3.1% at the hip, and total body BMC increased from 0.6%-2.3% at 2 years of active treatment; aIncreases in BMD ranged from 1.7%-3.9% at the spine and 2.0%-3.1% at the hip, and total body BMC increased from 0.6%-2.3% at 2 years of active treatment. All doses of CE and CE/MPA produced significant increases (P<.05) in BMD and BMC relative to placebo. Placebo-treated patients lost 2.7 ± 3.3% (mean ± SE) of spine BMD and 0.9 ± 3.4% of hip BMD over 2 years; the loss of total body BMC averaged 2.8 ± 2.8%. The incidence of endometrial hyperplasia ranged from 0% to 0.37% for all CE/MPA regimens during the first year. In the consensus analysis for the substudy, 27 of 518 patients developed endometrial hyperplasia during the 2 years. **Placebo-treated patients lost 2.7 ± 3.3% (mean ± SE) of spine BMD and 0.9 ± 3.4% of hip BMD over 2 years; the loss of total body BMC averaged 2.8 ± 2.8%.**No hyperplasias were recorded in the CE/MPA groups. Hyperplasia rates were 27.3% in the CE 0.625 group, 14.9% in the CE 0.45 group, and 3.2% in the CE 0.3 group. The hyperplasia rates in the CE 0.625 and CE 0.45 groups were significantly greater than the rates observed in the corresponding CE/MPA groups. In the analysis of the individual pathologists' diagnoses, the hyperplasia rates in all CE/MPA groups, including the CE 0.3/MPA 1.5 group, were significantly lower than the rates in corresponding CE alone groups.
Conclusions: Compared to standard doses, lower doses of CE/MPA increased mean BMD from baseline at the spine and hip and resulted in endometrial safety similar to 0.625 CE/2.5 MPA. These results support 0.45 mg/1.5 mg and 0.3 mg/1.5 mg CE/MPA as valuable options for addressing patients' needs with HT.

MINING THE COMPLEXITIES OF ESTROGEN AND PROGESTERONE ACTION FOR PHARMACEUTICAL OPPORTUNITIES

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The classical models of steroid receptor pharmacology held that agonists functioned by binding to their cognate receptors facilitating their conversion from an inactive form to one that was capable of activating transcription. By extrapolation, it was believed that antagonists functioned by competitively inhibiting agonist binding, freezing the receptor in an inactive state. However, as early as 1967 when the biological actions of the "antiestrogen" tamoxifen were first described it was clear that this simple model did not adequately describe estrogen receptor (ER) pharmacology. Tamoxifen is more appropriately classified as a Selective Estrogen Receptor Modulator (SERM), one of a group of compounds whose agonist or antagonist activity can differ between cells. Similarly, tissue selective progesterone, androgen and glucococorticoid receptor modulators have also been identified indicating that the observed complexity of ER action extends to other steroid receptors. Significant progress has been made in defining the molecular mechanism(s) by which cells distinguish between agonists and antagonists and how some receptor modulators can manifest their actions in a cell-selective manner. The most important of these are (1) differences in the relative expression level of receptor isoforms or subtypes, (2) the impact which the bound ligand has on the structure of its cognate receptor, and (3) the complement of coactivators and corepressors in a target cell which can interact with the activated receptor. This presentation will focus on the role of coactivators and corepressors in nuclear receptor pharmacology and how these proteins regulate cellular responses to agonists and antagonists and how perturbations in these regulatory mechanisms can have pathological consequences.

RISK-BENEFIT PROFILE FOR RALOXIFENE: 4-YEAR DATA FROM THE MULTIPLE OUTCOMES OF RALOXIFENE EVALUATION (MORE) RANDOMIZED TRIAL

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Introduction: The Women's Health Initiative (WHI) trial reported overall risks that exceeded benefits from use of estrogen-progestin in healthy postmenopausal women. The objective of this post hoc analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial was to assess the safety profile of raloxifene, a selective estrogen receptor modulator indicated for the prevention and treatment of osteoporosis, using the global index method from the WHI trial.

Methods: 7705 postmenopausal women (mean age, 67 yrs) were enrolled in the MORE osteoporosis treatment trial and randomly assigned to receive placebo or one of 2 doses of raloxifene (60 mg or 120 mg per day) for 4 years. A global index of clinical outcomes, defined as described for the WHI trial (the earliest occurrence of coronary heart disease, stroke, pulmonary embolism, invasive breast cancer, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes) was applied to the MORE trial data. Physicians blind to treatment assignment adjudicated events. Intention-to-treat survival analysis of time-to-first-event was performed using a proportional hazards model.

Results and Conclusions: The annualized rate of global index events was 1.83% in the placebo group and 1.39% in the combined raloxifene dose groups (hazard ratio, 0.75 [95% CI, 0.62-0.92]). Analyzing individual dose groups separately yielded the same results (hazard ratio for 60 mg per day, 0.75 [95% CI, 0.60-0.96]; hazard ratio for 120 mg per day, 0.75 [95% CI, 0.59-0.95]). Subgroup analyses showed no significant interactions between age or hysterectomy status and the effect of raloxifene on the global index (interaction P-values > 0.1), whereas the global index risk reduction appeared to be greater in obese women compared with non-obese women (P-value for interaction = 0.03). The significant 25% reduction in global index is compatible with a favorable risk-benefit safety profile when raloxifene is used for osteoporosis treatment in postmenopausal women. These results require confirmation in ongoing clinical trials.

RALOXIFENE'S MODULATION OF BONE HOMEOSTASIS: EFFECTS ON HUMAN OSTEOBLASTS *IN VITRO*

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Postmenopausal osteoporosis is a metabolic skeletal disorder characterized by compromised bone strength, which reflects the integration of bone quality and density, which leads to an increased risk of fractures in still active women. Raloxifene (RAL) is largely used for the treatment of osteoporosis since reduces bone loss and prevents fractures. Its skeletal effects are mediated by estrogen receptors and it acts by modulating bone cells activity. We demonstrated that RAL inhibits osteoclastogenesis and osteoclast activity by inhibiting the production of cytokines, such as IL-6, IL-1b, RANKL and OPG in murine osteoblasts. Thus, the present study was carried out to evaluate potential effects of RAL on human osteoblasts as well. To this aim, human fetal osteoblastic cell (hFOB1.19) and primary human osteoblasts were exposed to increasing concentrations of RAL (10^{-11} to 10^{-7}M) for 24 hr. At the end of incubation IL-6, IL-1ß, OPG and RANKL mRNA was assessed by PCR. RAL decreased IL-6 and IL-1ß gene expression in a dose-dependent manner with a maximum effect at 10^{-10} M (-50% and -40% respectively) in both clonal and primary human osteoblasts. As already demonstrated in murine osteoblasts, there was no change in OPG mRNA expression upon RAL exposure. In contrast, RAL (10^{-11} M) induced a dose-dependent reduction in RANKL with a significant decrease in the RANKL/OPG ratio, suggesting that osteoclast activity and osteoclastogenesis is under control of complex mechanism(s), regulated by RAL through, at least in part, osteoblast modulation. Additionally, RAL enhanced osteoblastic differentiation markers, as type 1 collagen (approx 50%), and Bone Morphogenic Proteins 2-4-5-7 with a maximum effect at 10^{-9}M (approx 50%, 180%, 65%, 300% respectively) in hFOB 1.19, suggesting an increase in osteoblast differentiation and function. In conclusion, our above described results might underlie the complex mechanism(s) by which RAL contribute to the maintenance of normal bone tissue and to the prevention of fractures in post-menopausal women.

HMR 3339, A NOVEL SERM, REDUCES TOTAL CHOLESTEROL, LDL-CHOLESTEROL AND HOMOCYSTEINE. A 14-WEEK, RANDOMIZED, PLACEBO-CONTROLLED STUDY IN HEALTHY POSTMENOPAUSAL WOMEN

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Abnormal levels of lipids are a strong risk factor for cardiovascular disease. We investigated the short-term effects of three doses of HMR 3339, a novel SERM, in comparison to raloxifene and placebo, on concentrations of lipids, lipoprotein(a) and homocysteine. In a multi-center, 14-week, randomized, placebo-controlled, double-blind, dose-ranging study, 118 healthy nonhysterectomized postmenopausal women received daily either placebo (N=22), HMR 3339 2.5 mg (N=25), HMR 3339 10 mg (N=24), HMR 3339 50 mg (N=24), or raloxifene 60 mg (N=23). Medication was given orally for 12 weeks, followed by a 2-week washout period. Fasting blood sampling was performed at baseline, and after 2, 4, 8, 12 and 14 weeks. After 12 weeks HMR 3339 compared to placebo revealed a reduction in total cholesterol (HMR 10 mg: -9.7%, P=0.002; HMR 50 mg: -15.2%, P<0.001), LDL-cholesterol (HMR 10 mg: -10.8%, P<0.001; HMR 50 mg: -24.2%, P<0.001) and plasma homocysteine concentrations (HMR 2.5 mg: -3.9%, P=0.03; HMR 10 mg: -10.8%, P=0.01; HMR 50 mg: -13.8%, P=0.01). These effects were already observed after 2 to 4 weeks of treatment. Raloxifene, compared to placebo, decreased total cholesterol (-10.5%, P=0.001), LDL-cholesterol (-15.0%, P<0.001), and triglycerides (-16.9%, P=0.032), but not homocysteine. No significant changes were found in HDL-cholesterol and lipoprotein(a). In conclusion, HMR 3339 exerted anti-atherogenic effects by reducing total cholesterol, LDL-cholesterol and homocysteine concentrations in postmenopausal women.

THE HERBAL ALTERNATIVES FOR MENOPAUSE STUDY: FACTORS ASSOCIATED WITH SELF REPORTED SEVERITY OF BASELINE VASOMOTOR SYMPTOMS

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Background: Studies of menopause therapies frequently employ vasomotor symptom diaries, but few diaries have been carefully evaluated, and accompanying symptoms are rarely reported.
Methods: We enrolled 351 peri and postmenopausal women, aged 45-55, in Washington state, USA, into the Herbal Alternatives (HALT) study, a 5-arm randomized controlled trial comparing 3 herbal therapies for menopause symptoms to hormone therapy and placebo. Entry criteria included at least 2 hot flashes and/or night sweats per day. Women use a diary to record each daytime hot flash and its characteristics, and summarize night sweats on awakening. Instructions for rating intensity of vasomotor symptoms (mild, moderate, severe), include feeling hot, sweating, interference with daytime activities and needing to take action to relieve symptoms at night. We analyzed baseline data from 19,979 hot flashes, and 3,544 nights during which women reported vasomotor symptoms. Descriptive statistics and general estimating equation (GEE) regression models were used to evaluate symptoms associated with hot flashes and night sweats, controlling for within women correlations.
Results: Night sweats were more often rated moderate (58%) or severe (27%) than hot flashes (42%, 13%, respectively). The proportion of hot flashes accompanied by anxiety, palpitations, or chills was 2.9%, 2.3%, and 11.2%, respectively; 96% of hot flashes lasted < 5 minutes. The proportion of night sweats accompanied by anxiety, palpitations, or chills was 5.3%, 4.7%, and 19.5%, respectively; 27% of women reported being awakened and kept awake by their night sweats. Duration, sweating, chills, palpitations and anxiety were positively associated with hot flash intensity (p<.008-0.0001). Number of sweats, feeling hot, sweating and interference with sleep were positively associated with night sweat intensity (p<0.002-0.0001).
Conclusions: Factors associated with self-rated vasomotor symptom intensity appear to differ for night sweats and daytime hot flashes. Anxiety and palpitations rarely co-occur with vasomotor symptoms.

MENOPAUSE FORMULA, A PHYTOESTROGEN CONTAINING SUPPLEMENT, REDUCES HOT FLUSHES. A 12-WEEK RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY IN HEALTHY EARLY POSTMENOPAUSAL WOMEN

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In a multi-center, randomized, placebo-controlled, double-blind study we investigated the effects of Menopause Formula (MF), a phytoestrogen containing supplement, on climacteric complaints in healthy early postmenopausal women. One hundred and twenty-four women, having at least five hot flushes per day, were randomized to receive daily either MF (N=60) or placebo (N=64) for twelve weeks. The modified Kupperman Index, the Greene Climacteric Scale, a Visual Analogue Scale for quality-of-life and the daily number and severity of hot flushes were assessed at baseline and after six and twelve weeks. Changes in these scores over time were calculated. All scores showed a beneficial effect in week six and twelve in both groups, the difference between placebo and MF not being significant. In week twelve, in a subgroup of women (N=81) with at least nine vasomotor symptoms per day at baseline, the percentage reduction in total number of daily hot flushes during MF supplementation was -49.4% ± 6.4% compared with -34.7% ± 6.7% in the placebo group (P=0.056). MF was more effective than placebo in the reduction of daily number of moderate hot flushes (-60.0% ± 10.0% versus -33.9% ± 10.5%; P=0.031), and the reduction in mean severity score of hot flushes (-17.8% ± 4.4% versus -4.2% ± 4.6%; P=0.012). In conclusion, Menopause Formula was more effective than placebo in reducing daily number of moderate hot flushes and the mean severity score of self-reported hot flushes in a subgroup of women with at least nine vasomotor symptoms per day.

ESTROGENS AND GLIAL CELLS

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Glial cells in the central nervous system (CNS) are involved in the actions of estradiol on the regulation of synaptogenesis, synaptic plasticity, neuritic growth and neuroendocrine secretion. Furthermore, glial cells synthethize and metabolize steroid hormones and produce local neuroactive steroids that exert neuromodulatory and neurotrophic actions under physiological and pathological conditions. The enzyme aromatase, that is able to convert androgens into estrogens, is not present in glial cells of the CNS of mammals under normal circumstances, since only neurons possess such an activity. However, aromatase is expressed by astrocytes after brain injury, indicating that the enzyme may be induced de novo in these cells under specific conditions. Furthermore, astrocytes in the proximity of injured neural tissue express estrogen receptors alpha and beta, indicating that brain lesions also increase the sensitivity of these cells to estradiol. Aromatase is neuroprotective, since genetic or pharmacological inhibition of brain aromatase results in marked neuronal loss after different forms of mild neurodegenerative stimuli that do not compromise neuronal survival under control conditions. Furthermore, aromatase mediates neuroprotective effects of precursors of estradiol such as pregnenolone, dehydroepiandrosterone and testosterone. These findings strongly suggest that local formation of estradiol by glial cells in the brain is neuroprotective and that the induction of aromatase and the consecutive increase in the local production of estradiol by glial cells are part of the program triggered by the neural tissue to cope with neurodegenerative insults. Aromatase may thus represent an important pharmacological target for therapies conducted to prevent neurodegenerative disorders.

ESTROGENS AND INFLAMMATION

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We have recently demonstrated that 17ß-estradiol (E2) opposes cytokine-dependent increase of inducible nitric oxide synthetase (iNOS) activity in rat smooth muscle cells and proposed that this effect might be associated to an anti-inflammatory activity of this hormone. In the present study, we examine the E2 effects on a well-known in vivo carrageenan model of inflammation. We show that, in ovariectomized rats, prior exposure to E2 significantly attenuate histological damage and exudate production. The effect was visible with a single injection of a physiological dose of E2 1 hour before the carrageenan treatment and was blocked by co-administration of the oestrogen receptor antagonists ICI 182,780 or Tamoxifen. In hormonally-treated rats there is a decrease in polymorphonuclear cells (PMNs) migration, myeloperoxidase (MPO) measurement, lipid peroxidation (MDA) activity, NO production, iNOS activity with consequent diminished nitrite synthesis and nitrosine accumulation. Finally, estradiol treatment blocked positive immunohistochemical staining for PARS, in lungs from carrageenan-treated rats. In an other set of experiments we have investigated the effect of ovariectomy in genetically-modified iNOS-KO mice. The proximal tibiae of mice with iNOS genotypes revealed that 32 days after ovariectomy bone volume (BV/TV) and bone formation rate (BFR/BS) were significantly decreased and the osteoclast surface (Oc.S/BS) was increased. Conversely, in iNOSKO and in wild type mice treated with a specific inhibitor of iNOS, N-iminoethyl-L-lysine (L-NIL), ovariectomy did not result in bone depletion. Immunohistochemical analysis showed that after ovariectomy iNOS protein accumulates in chondrocytes cells and a significant increase in nitrotyrosine and poly (ADP-ribose) synthetase (PARS) staining was observed in the femur epiphyses. The increase in nitrotyrosine and PARS formation induced by ovariectomy was significantly reduced in section from iNOSKO mice. These data indicate that in wild type mice the observed induction of iNOS has functional relevance because leads to overproduction of NO and accumulation of highly reactive molecules triggering a local inflammatory reaction. In iNOS KO mice the measure of IL-1ß, IL-6 and TNFα plasma levels showed that ovariectomy fails to elicit the increase observed in wild type animals and suggests that iNOS plays a primary role in the protective effects of estrogens. Furthermore we show that estradiol-dependent activation of ERα blocks PMA-induced transcription of iNOS promoter in transfected cells thus demonstrating that the promoter of iNOS is under estrogen negative control.

THE ROLE OF INFLAMMATION IN CARDIOVASCULAR DISEASE AND EFFECTS OF HORMONE REPLACEMENT

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Inflammation is involved in the pathogenesis of atherosclerosis. Thus, recent research has focused on the role of inflammation assessment in helping to define cardiovascular risk. The preponderance of the evidence from clinical studies, including middle aged and older women, suggests that inflammation assessment adds to information gained from assessment of standard cardiovascular risk factors such as hyperlipidemia and hypertension. The most widely studied inflammation marker in clinical studies is C-reactive protein (CRP). Initially healthy patients with CRP levels in the top third of the population distribution have an approximately 2-fold higher risk of subsequent myocardial infarction or stroke. Similar relationships are observed, though less consistently from study to study, for other inflammation markers such as interleukin-6 and adhesion molecules. Counter to previous observational data, and despite lipid lowering effects, postmenopausal hormone replacement with conjugated equine estrogen (CEE) or estradiol, with or without a progestin, does not appear to confer protection against myocardial infarction or stroke, and further, CEE + MPA may increase the risk. Several trials comparing oral HT in various forms to placebo have demonstrated a near-doubling of CRP concentration with HT. This occurs despite stabilization of the age-related rise in fibrinogen and lowering of adhesion molecules. The CRP-raising effect does not appear to be interleukin-6 dependent and may be due to first pass liver metabolism, since this effect dose not seem apparent with transdermal HT. Recent data suggest that low dose estrogen does not have this effect on CRP, and neither do raloxifene or tamoxifen. In ongoing analyses in a subcohort of the Women's Health Initiative trial of CEE + MPA, higher baseline CRP was associated with an increased risk of future MI and stroke, but did not appear to identify women at particularly increased risk from CEE + MPA. Further study is needed to determine whether the rise in CRP with HT is associated with adverse vascular effects.

CLASSICAL AND NON CLASSICAL ESTROGEN RECEPTOR ACTION

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Estrogen receptors are hormone-driven transcription factors known to control reproductive functions. The recent description of their widespread distribution in mammalian tissues suggests a potential role of these receptors and their ligands in most metabolic processes. Genetic ablation of the genes encoding these receptors, however, did not produce major phenotypic alterations. Epidemiological studies aimed at assessing the efficacy of estrogen replacement therapy in cardiovascular and neurological disorders show high variability of response. Thus the significance and the real activity of estrogen receptor in non-reproductive organs still awaits for clarification. By in vivo imaging of transgenic mice carrying a luciferase reporter we have documented the activity of estrogen receptor in adult and immature mice (of both sexes). The study demonstrates that the receptor is transcriptionally active in reproductive and non reproductive organs even in the absence of measurable levels of circulating estradiol providing the first punctual in vivo evidence of the breath of estrogen receptor action and of the reality and relevance of mechanisms activating this receptor in physiological states where the cognate ligand is not synthesised (such as in sexually immature and ovariectomized mice). The novel delineation of estrogen receptor activity reported will impact on the design of safer and more efficacious hormone replacement therapies.

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SELECTIVE ESTROGEN RECEPTOR MODULATORS IN THE MANAGEMENT OF POSTMENOPAUSAL WOMEN

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Selective estrogen receptor modulators are nonsteroidal molecules that bind to the estrogen receptor and trigger either estrogen-like or estrogen-antagonist effects according to the target tissue. The concept is based on the observation that tamoxifen is a potent anti-estrogen on the breast but has partial estrogen agonist effect on the skeleton. Raloxifene is the first SERM to be widely available for the prevention and treatment of postmenopausal osteoporosis. Raloxifene at the dose of 60 mg/day prevents bone loss in early postmenopausal women, but has no beneficial effect on hot flashes. The MORE study performed in 7 700 postmenopausal women with osteoporosis has demonstrated a significant reduction of vertebral fracture both in patients with and without prevalent vertebral fractures. The reduction occurs early (1 year), is sustained (4 years) and occurs also in patients with osteopenia. No significant reduction of nonvertebral fractures was observed in the entire cohort although a reduction was observed in those with the most severe osteoporosis. In the MORE study, raloxifene use was associated with a significant 60% reduction of the risk of breast cancer, and with a reduction of cardiovascular events in the subgroup of patients at high initial risk. This potential beneficial cadiovascular profile is now tested prospectively in the RUTH study.The incidence of DVT is significantly increased, with a relative risk of 1.7 after 4 years. The overall safety profile for raloxifene is favorable, with a global risk/benefit score, calculated in the same way as for the WHI study, which is significantly reduced by 25%. Several other SERMs are currently under development.

In conclusion, SERMs are likely to play a growing role in the prevention and treatment of osteoporosis, given the limitation of the long term use of HRT.

PHYTOESTROGENS, REPLACEMENT FOR HORMONE REPLACEMENT THERAPY?

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There is no doubt that any treatment with common hormone replacement therapy preparations, regardless of whether they contain only estrogens or a combination of estrogens and progestins profoundly reduce climacteric complaints, particularly hot flushes and tachycardiac attacks. The recently published frightening data of the HERS, the WHI and the Million Women study have prompted drug and food additive producing companies to promote the concept that plant-derived estrogens may also alleviate climacteric complaints. There are a number of uncontrolled and only very few placebo-controlled studies to indicate that soy or red clover derived isoflavones have beneficial effects on climacteric complaints. The majority of the well controlled studies demonstrated no effect of isoflavones on hot flushes. The possibility exists that other, non-isoflavonic compounds in soy, possibly small peptides, have health-promoting effects not only on psychosomatic but also on other parameters like the cardiovascular system and the bone. In view of the putatively dangerous effects of pure isoflavones in the mammary gland a European Consensus Conference held in April 2003 in Greece stated that soy or red clover derived isoflavones are no good alternatives as a replacement for hormone replacement therapy.

Another alternative for hormone replacement therapy is treatment with extracts from the roots of Cimicifuga racemosa (Black cohosh). In several open and two placebo-controlled studies these extracts were shown to alleviate climacteric complaints. In postmenopausal mamma-carcinoma patients a Black cohosh preparation, however, was without effects on hot flushes. Other than isoflavones and estrogens, the yet unidentified substances, which alleviate climacteric complaints in Black cohosh preparations, do not have an estrogenic effect in the uterus. Cell biological and animal experimental data appear to indicate that Black cohosh preparations also do not address the mammary gland.

ANDROGENS FOR WOMEN

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The physiology of normal androgen production in women has not been well understood. The definition of an androgen insufficiency state in women, in the absence of adrenal suppression and/or bilateral oophorectomy, has been difficult. Nevertheless there are well-documented beneficial effects of androgen on many organ systems, including bone and the brain. This review includes a discussion of the definition of androgen insufficiency, the anticipated effects of androgen on several parameters of health, and treatment options for women with androgen insufficiency.

PRIMARY RESULTS FROM THE WHI TRIAL OF CONJUGATED EQUINE ESTROGEN ONLY (CEE) AND CONTRASTS WITH THE WHI CEE+MPA TRIAL

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The Women's Health Initiative (WHI) Hormone Trials include the Estrogen plus Progestin (E+P) trial of women with a uterus assigned to conjugated equine estrogens (CEE), @ 0.625 mg/day, combined with medroxyprogesterone acetate (MPA), @ 2.5 mg/day or placebo; and the Estrogen-Alone (E-Alone) trial of women who had a hysterectomy prior to baseline, assigned to CEE @ 0.625 mg/day or placebo. The E+P trial was stopped 3.3 years early because the NIH determined that the risks of CEE+MPA outweighed the benefits. Results for an average of 5.2 years of follow-up were reported (JAMA 2002; 288: 321-333) and updated, detailed analyses of major outcomes for 5.6 years of follow-up will be presented. The E-Alone trial was stopped March 1, 2004 after nearly 7 years of follow-up, because women assigned to CEE had an increased risk of stroke of similar magnitude to that reported for the E+P trial, without a benefit to heart disease, which the NIH believed was unacceptable for healthy volunteers. As reported for CEE+MPA, CEE resulted in reduced hip fractures. Unlike the WHI E+P trial, breast cancer was not increased in women assigned to CEE versus placebo. Primary findings, e.g. absolute risks, hazard ratios, and other analyses, which will be published prior to the meeting, will be presented. Noting that hysterectomy status was the primary study design factor distinguishing the E-Alone trial participants from the E+P cohort, the E-Alone trial included a higher proportion of obese women (mean body mass index was 30.1 kg/m2, compared to 28.5 in the E+P trial) and prior menopausal hormone users (about 49% compared to 26%) and medical and reproductive histories differed between the two trial cohorts, as has been previously published (Ann Epidemiol 2003; 13: S78-S86). With these differences in mind, important contrasts with the WHI E+P trail results will be noted. The finding of no overall benefit of CEE results in the conclusion that CEE should not be recommended for chronic disease prevention in postmenopausal women.

IMPLICATIONS OF WHI FINDINGS FOR RECENTLY MENOPAUSAL WOMEN

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The sex difference in onset of CHD by age is consistent with an effect of female sex steroid hormones in slowing down age-related progression of coronary atherosclerosis. A number of prospective observational studies have found postmenopausal estrogen (and estrogen plus progestin) use to be associated with a lower risk of CHD than in non-users. In cohort studies the use of hormones typically commenced at the age of menopause, while laboratory and animal studies suggest that estrogen may have beneficial effects on the earliest stages of atherosclerosis. These data have suggested to some that exogenous estrogen may extend coronary artery health into the postmenopausal years. At the other end of the spectrum, clinical trials have shown conclusively that exogenous hormones do not protect against progression of established atherosclerosis, and may trigger events in women with complicated lesions. There are arguments for and against the concept that there is a "window of opportunity" in recently menopausal women during which postmenopausal hormones may be beneficial to the heart. A particular problem with the concept is that many (if not most) women do not have normal coronary arteries at the average age of menopause. Though it is a primary prevention trial, it is likely that most women in the WHI trials of estrogen and estrogen plus progestin did have some degree of coronary atherosclerosis. CHD rates in the placebo group go up markedly with age. Analyses of hormone effects on CHD risk by age in the WHI trials are inconclusive. Conclusion: estrogens with or without progestins should not be used for prevention of CHD. However, since hormones will continue to be used for other indications, the issue of whether their effects differ by age (and years since menopause) bears further examination.

WHAT WHI CAN AND CANNOT SAY ABOUT QUALITY OF LIFE (QOL)

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The oldest approved indications for use of hormone therapy (HT) are two QOL issues: vasomotor symptoms and vaginal atrophy. In 2003, health-related QOL data from the estrogen plus progestin arm of the WHI were published1. HT users had a statistically significant improvement in physical functioning, sleep disturbance, and bodily pain, but the effect size was too small to be considered clinically meaningful. No statistically significant differences were found at year 3. Two analyses looked at special subgroups thought to be more likely to benefit from HT. The youngest group, ages 50-59 at baseline, had findings similar to those of the entire group. The second analysis of 574 women 50-54 years old reporting moderate to severe hot flushes at baseline found significant improvement in hot flushes and sleep. The WHI hormone therapy QOL data are consistent with those reported from the PEPI trial and HERS2,3 Results from the WHI indicate that women using HT preventive care are unlikely to experience significant improvement in health-related QOL. These results are a generalization for a large population. Individual symptomatic women may achieve benefits significant to them personally. A recent report indicated that 25% of women in the general population who tried to stop using hormones after July of 2002 requested to restart them.4 The HT QOL benefits may be even more important to the woman who experiences an early menopause. Absolute risk should be lower in women under 50. Further information on gynecologic symptoms and symptoms experienced by the participants discontinuing hormone therapy will be presented in upcoming WHI reports. References: 1Hays N Engl J Med 2003;348:1839.2 Greendale Journal of Women's Health 1996;5:445. 3Hlatky JAMA 2002;287:591-597.4Grady Obstet Gynecol 2003;102:1233.

BONE QUALITY: FROM BENCH TO BEDSIDE.

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The NIH-sponsored Consensus Conference on Osteoporosis in 2000 proposed a new definition of osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture." In this statement, bone density and *bone* quality were cited as primary contributors to bone strength. Whereas a precise definition of bone quality remains elusive, evidence is mounting to support the concept that characteristics independent of bone density, such as trabecular architecture, bone turnover, the organic and inorganic composition of bone matrix, damage accumulation, and cell viability, may be important in the pathophysiology of osteoporosis and in the mechanisms that underlie the anti-fracture effects of osteoporosis therapies. For example, the concept of bone quality has been invoked to explain observations from clinical trials that small changes in BMD result in greater than predicted reductions in fracture risk, that therapy-induced changes in BMD explain only a small proportion of the variance in fracture risk reduction, and that reductions in fracture risk are evident long before changes in BMD are observed. Ultimately, the effect of these potential contributors to bone quality must be reflected in bone strength. This presentation will discuss the factors that contribute to bone strength and the ways in which bone quality may contribute to bone strength. An emphasis will be placed on discussion several plausible mechanisms by which osteoporosis therapies may affect bone strength, and therefore fracture risk, independently or synergistically with their effects on bone density.

CLINICAL USE OF RALOXIFENE IN POSTMENOPAUSAL WOMEN

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Selective oestrogen receptor modulators (SERMs) have been developed with the aim to retain the beneficial effects of hormone replacement therapy (HRT) without some of its side effects. Raloxifene is now available widely. In 602 early postmenopausal women, we showed that raloxifene prevents early postmenopausal bone loss, with a decrease in markers of bone turnover (urinary CTX for bone resorption, serum bone alkaline phosphatase and osteocalcin for bone formation) that fell within 3 to 6 months within the premenopausal range. Serum total and LDL-cholesterol decreased significantly. The treatment was well tolerated and adverse event incidence did not differ between groups, including breast pain and vaginal bleeding. Endometrial thickness assessed every 6 months by transvaginal ultrasonography did not change in either group throughout the study. Results from the MORE study, performed in 7 500 osteoporotic women, indicates a marked reduction (-30% to –50%) in vertebral fracture rate with raloxifene 60 or 120 mg/day for 3 years both in patients with and without prevalent vertebral fractures. Raloxifene 60 mg/d reduces by 50% the risk of the first vertebral fracture. No significant reduction of non vertebral fractures has been demonstrated except in a subgroup of patients at high risk characterized by severe vertebral fractures at baseline. The year by year analysis indicates a 60% reduction at the first year, and a reduction during the 4th year alone, demonstrating an early and sustained efficacy of raloxifene on vertebral fractures. The increase in spine bone mineral density is modest at 3 years and triggers new hypothesis for the mechanism responsible for fracture reduction that will be discussed. The only serious adverse event is an increase of venous thrombo embolism (comparable to that reported with hormone replacement therapy). The rate of new breast cancer was decreased by 60% during 4 years of therapy. Raloxifene has no effect on cardiovascular morbidity and mortality in the overall population but decreases it by 40% in women at high risk, an effect that will be tested prospectively in the RUTH study. In summary, raloxifene represent an interesting alternative for the prevention and for the treatment of postmenopausal osteoporosis. Balancing the effects of Raloxifene on major health outcomes in postmenopausal women allows to better define its role in the management of postmenopausal women.

RALOXIFENE: SHORT AND LONG-TERM CHOICE FOR OSTEOPOROSIS PREVENTION AND TREATMENT.

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Bone remodeling is a physiological process that has developed during the evolution to replace and repair continuously fatigue-microfractures (wear), that happen daily as a result of normal skeletal and muscle work.
Remodeling is roused by like-inflammatory mechanisms, therefore cell-mediated, by the insorgence of stress microfractures , an event that concerns both the trabecular and corticoid bone.
In post-menopausal osteoporosis the lack of estrogens causes an unbalanced increase of remodeling that favors fractures for bone mass loss (quantity) and architectural (quality).
This unbalancement is often opposed with anti-resorptive drugs like bisphosphonates, but they decrease remodeling too much.
High remodeling reduction after the treatment with bisphosphonates delays bone callus resorption and the disappearance of fracture line in several animal models. Similar data have been also observed in patients with osteogenesis imperfecta and osteoporotic patients.
Furthermore the remodeling blockade after the treatment with bisphosphonates can compromise the antifracture efficacy of this molecules in the long term because the process of replacing old bone with mechanically competent new bone is stopped or strongly lowered.
Raloxifene is an interesting alternative to bisphosphonates for its ability to balance the remodeling, it is the only one with a double action on osteoclasts and osteoblasts and guarantees the possibility or remodeling the bone callus further to a fracture.
Raloxifene is one of the SERMs, selective estrogen receptor modulators, a family of compounds that interfere selectively with estrogen receptors by producing an agonist effect on non-reproductive tissues (skeletal and cardiovascular system) and an antagonist effect on the reproductive system (uterus and breast).
Raloxifene is a second-generation SERM with a higher selectivity on the different tissues. It is recommended in the treatment and prevention of postmenopausal osteoporosis.
Clinical studies, undertaken in more than 20000 women in postmenopause (age 50-80 years), allowed to show that treatment with Raloxifene in postmenopausal women: a) prevents bone mass loss, determining a 2-3% mineral bone density increase, after 3-5 years of treatment both on the vertebral spine and on the femur, in postmenopausal women with osteopenia and osteoporosis; b) decreases in a statistically and clinically significant manner, new clinical vertebral fractures incidence (68%) after 1 year treatment; c) has an anti-fracture efficacy that is maintained in the long time, for 4 years, and is significant in patients with osteoporosis with or without vertebral fractures before the treatment; the long-lasting efficacy has been recognized by EMEA that approved the amendment of the technical schedule; and d) has a significant anti-fracture efficacy both in patients with osteopenia and in patients with osteoporosis and severe fractures.
To sum up, data available so far seem to propose Raloxifene as an attractive therapeutic option for the prevention and treatment of postmenopausal osteoporosis.

BONE SPARING COMPOUNDS

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EFFECT OF TIBOLONE ON BIOCHEMICAL MARKERS OF BONE TURNOVER IN LATE POSTMENOPAUSAL WOMEN

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Recent data suggest that HRT should be prescribed more cautiously and preferably in the early post menopause. Tibolone is a synthetic drug with many properties, resembling those of the classical estrogens, but without stimulatory effect in the breast. The aim of this study was to establish the effect of tibolone on some biochemical markers of bone remodeling in women in relatively late postmenopausal state. Sixteen women mean age 56.4±4.6 with mean duration of the postmenopausal period 9.5±5.2 years and BMD < - 1SD, estimated by QCT, were assigned to treatment with tibolone – 2.5 mg plus 600 mg calcium plus 200 U vitamin D per day for a period of 6 months. Exclusion criterion was any known disease, which could significantly affect bone metabolism. Before and after the treatment period bone markers were determined and compared to those of a BMD-, age- and postmenopausal period matched control group, treated only with calcium and vitamin D. Significant decrease in serum phosphate ($p<0.01$) and alkaline phosphatase ($p<0.01$), and deoxypyridinoline ($p<0.01$) and calcium excretion ($p<0.05$), but not in serum calcium were observed in the treatment group, compared to no change in the control group. As an additional benefit a reduction in the Kupperman index and quality of life was found in treated women who still had climacteric symptoms at the beginning of the study. Data of this preliminary study show a decrease of bone turnover with tibolone. This drug could be considered as an alternative of the classical HRT in symptomatic late postmenopausal women with low BMD.

"OUR CLINICAL EXPERIENCE USING ONCE-MONTLY NERIDRONATE IN POSTMENOPAUSAL OSTEOPOROTIC WOMEN"

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In 2002 and 2003 we visited in our Department for Diagnosis and Care of Osteomethabolic Diseases in Venaria Reale (Turin) 1480 women with postmenopausal osteoporosis. Among this group, we selected 30 women, 59-68 years old, to use a new bisphosphonate. 20 were classified as no-responders as they didn't have increase in BM measurements by the lumbar spine DXA after 18 months of anti-resorptive therapy. 10 had severe controindications to every oral treatment. They received a therapy with neridronate 1 fl 25 mg intramuscolar, once-monthly. We identified for each woman the individual risk-score, by studying the familiar, physiological and pathological history, with particulary care for the data about nutrition (particularly the intake of Ca) and physical activity. We measured Ca, Ca regulating hormones and bone biomarkers. The patients had a DXA and a QUS (Quantitative UltraSound with Lunar Achilles) at baseline. For each one we determined the ICF (International Classification of Function, Disability and Health) and the Spitzer Index (scale for Life Quality).
The activity of neridronate on bone methabolism is important like in therapy with others anti-resorptive drugs, as measured by bone markers: for example the urinary deoxypyridinoline (uPDP) decreased for 50 percent of the overflowing. Stiffness increased of 5-6 percent at control with QUS at 12 months. The compliance for this therapy is very good. We had only one drop out, a woman who had a RAF with fever and cutaneous rashes at the first injection. The others women of the group are keeping on the protocol. The increase of Stiffness and the reduction of turn-over demonstrate a good action of this bisphosphonate. A better compliance is assured by the injective way and the monthly rhytm.

COMPLIANCE OF POSTMENOPAUSAL OSTEOPOROTIC PATIENTS WITH DIFFERENT TREATMENT REGIMENS

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Prevention of osteoporotic fractures and consequent chronic disability represents a major public-health challenge, requiring adherence to long-term therapy among postmenopausal women. We have previously assessed adherence to the prescribed fracture prevention treatment with alendronate or raloxifene in Israeli postmenopausal women during six month after treatment initiation (Segal at al. IMAJ 2003;12:859-63).
The initially compliant patient group was revisited after 2 years.
Analysis includes 138 postmenopausal women, aged 67.41±8.52, that were treated with alendronate, 102(74%) and raloxifene 36(24%). In addition all patients (pt) were treated with calcium carbonate (1500 mg/day) and vitamin D (600 IU/day). Adherence was assessed by telephone survey: 79(66%) pt, aged 70±7.09, continued with the initially prescribed treatment; 12(10%), aged 64±7.8, switched to another treatment, 25(21%), aged 68±10.1, discontinued therapy, 22(16%) were lost to follow-up. Previous fractures were reported in 37(47%), 6(40%) and 12(47%) pt respectively. Seven (58%) pt switched from ralixifene to alendronate (mostly due to a decrease in BMD, in 5 (34%) pt), and 5 (42%) vise versa. Seven (58%) pt changed the treatment due to physician's recommendations. In the non adherent group : alendronate treatment was discontinued by 20(75%) pt, mostly due to GI adverse events; raloxifene - by 5(25%) pt mostly due to family physicians' recommendation. Currently 63(69%) are treated with alendronate, 28(31%) with raloxifene.
Conclusion: Two years after the initiation of fracture prevention treatment, it was discontinued by a fifth of the pt. Neither age nor previous fracture history influenced pt/physician decision to adhere to treatment.

CHANGES IN THE HYPOTHALAMO-PITUITARY-OVARIAN AXIS DURING THE MENOPAUSAL TRANSITION

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The menopause is defined as the permanent cessation of menstruation, resulting from the loss of ovarian follicular activity. It is preceded by the menopausal transition, the onset of which is generally marked by the occurrence of menstrual cycle irregularity, though the precise degree of such irregularity is controversial. Although the biology which underlies the transition may include central neuroendocrine changes and changes within the ovary, the most striking change is the decline in ovarian follicle numbers. Cross-sectional studies of regularly cycling women show that follicle stimulating hormone (FSH), an indirect marker of follicular activity, begins to increase slowly some years before the menopausal transition and increases more strikingly during the transition. The rise results from a decline in follicular secretion of inhibin B. Levels of oestradiol are well preserved until shortly before final menses. The menopausal transition is marked by great variability in FSH and oestradiol levels which are thus unreliable guides to menopausal status. Detailed examination of the endocrine characteristics of menstrual cycles with the approach of menopause indicate that two main types are observable: ovulatory cycles, with little change in follicular phase FSH levels, and anovulatory cycles, where FSH levels may rise greatly. The major circulating androgen in women is testosterone. Its concentrations fall during reproductive life, but show little change across the time of the menopausal transition and final menses. The use of longitudinal rather than cross-sectional studies has greatly clarified current concepts of the endocrinology of the menopause.

SKIN AGING: ANATOMICAL, FUNCTIONAL AND CLINICAL ASPECTS

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Skin aging is a continuous process that affects skin function and appearance; however not everybody ages at the same speed.
The critical age is 40 years. Two types of skin aging may be distinguished: an *intrinsic aging* is due to genetic, hormonal and metabolic factors; an *extrinsic aging* is conditioned by photoexposition, smoking, diet, alcohol...
Anatomical modifications of the skin inducing functional and clinical consequences may be so summarized:

- reduction in cohesion among corneocytes with decrease of the barrier function is responsible of dryness and/desquamation
- alteration of the keratinization process favors the formation of actinic keratoses
- decrease of the mitotic activity induces thinning of the skin
- modified production and distribution of melanin pigment expresses itself with the appearance of hypermelanotic and hypomelanotic lesions
- decrease in number of Langerhans cells increases the risk of infections and tumors
- alterations of collagen fibers, elastic fiber and glycosaminoglycans indices loss of elasticity and wrinkles formations
- alteration's of vessel elasticity causes increased vascular fragility

Clinically the ìstigmataî of cutaneous aging are considered the following: dryness of the skin, wrinkles, senile lentigines and seborrheic keratoses but aging represents the only way to have a long life.

PELVIC FLOOR FUNCTION

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The pelvic organs are supported by the pelvic diaphragm, the endopelvic fascia and the vagina. The pelvic diaphragm is made up of a bilaterally paired group of three striated muscles, the pubococcygeus, the iliococcygeus and the ischiococcygeus. The levator ani (pubo-coccygeus and ilio-coccygeus muscles) separate anteriorly to form the levator hiatus. Through it pass, anteriorly to posteriorly, the urethra, vagina, and the rectum.
Posterior to the rectum, the paired muscles of the pelvic diaphragm join in the midline to form the levator plate. This portion acts much like a trampoline, receiving and resisting sudden increases in intra-abdominal pressure. Normally the levator ani is in a state of tonic contraction, and its tone increases in response to stress.
The endopelvic fascia ia a loose matrix of collagen, elastin and smooth muscle fibers. Along lines of tension, the endopelvic fascia develops supportive thickenings referred to as ligaments (e.g. uterosacral, cardinal). These ligaments are for visceral support. The vagina has a supportive function with respect to other pelvic organs. The supportive role of the pelvic floor is altered when conditions adversely affect its muscles or nerves. Weakening of the levator ani may cause enlargement of the levar hiatus and descent of the central portion of the pelvic diaphragm. The resultant loss of support to the pelvic organs places tension on their fascial supports and predisposes to breaks, separations and attenuations within the endopelvic fascia. This in addition to direct (e.g. trauma) and indirect (e.g. hypoestrogenism) damage to the vaginal wall results in bulges into and out the vaginal canal.
Vaginal childbirth can contribute to pelvic support defects by direct damage to the endopelvic fascia and vaginal wall and by direct and indirect damage to the muscles and nerves of the pelvic floor.
Progressive deterioration of connective tissue may occur as a result of estrogen deficiency, being responsible for the development of pelvic organ prolapse (POP) in postmenopausal women.
Moreover chronic and repetitive increases in intra-abdominal pressure are major factors in the development of POP. Obesity, chronic respiratory diseases occupational and recreational activities may predispose to pelvic floor defects.

THE EFFECT OF A SOY-RICH DIET ON UROGENITAL ATROPHY : A RANDOMIZED, CROSSOVER TRIAL

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Objective : To evaluate the effect of a soy-rich diet on urogenital symptoms, vaginal health index, vaginal pH, and vaginal cytology in perimenopausal and postmenopausal women.
Methods : Thirty-six perimenopausal and postmenopausal women (mean age 52.5 ± 5.1 years) participated in a randomized, crossover trial with two 12-wk diet period and a 4-wk washout period before and between treatments. The study diet consisted of a control diet (soy-free diet) and an isocaloric soy-rich diet (25 g soy protein in various forms of soy foods containing more than 50 mg/day of isoflavones substituted for an equivalent amount of animal protein). Subjects were assessed for urogenital symptoms, vaginal health index, vaginal pH, and vaginal cytology. The single physician and the single cytopathologist were blinded with regard to onset, period and randomization number. Statistical significance was performed using paired t-test or Wilcoxon Signed Ranks Test, significance was set as $p < 0.05$.
Results : Good compliance to the diet was shown by the significant elevation of serum levels of daidzein and genistein during the soy-rich diet period. The symptoms of urge incontinence and vaginal dryness significantly increased after 12-wk of soy-free diet. All other urogenital symptoms did not change in both periods. The vaginal health index, the vaginal pH, the karyopyknotic index, and the maturation value were not significantly changed in both periods.
Conclusion : A soy-rich diet did not relieve the urogenital symptoms, restore the vaginal epithelium, and improve the vaginal health in perimenopausal and postmenopausal women. However, it might prevent the worsening of urge incontinence and vaginal dryness in this study.

ACUTE CORONARY SYNDROMES IN WOMEN

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Chest pain is the major presenting symptom of acute coronary syndromes (ACS) for both women and men. Women presenting with acute coronary syndromes, compared with their male peers, are older and are more likely to have diabetes, hypertension, and prior heart failure. Elevated troponin levels equally predict mortality risks for women and men, but better predict an increased risk of nonfatal MI for women. There are gender-based differences in clinical profiles, presentation, and outcomes of ACS between women and men. Women are more likely to have unstable angina than enzyme or ECG documented acute myocardial infarction. They have greater delay than men in seeking emergency care after symptom onset. Women have an increased occurrence of complications during the hospitalization, as well as increased hospital mortality. Mortality appears to depend predominantly on age and baseline characteristics rather than on sex per se. There are conflicting data regarding the benefits of acute revascularization procedures in women; it appears that only in higher-risk women does the benefit of an aggressive strategy balance the early procedural risk. A review of catheter-based revascularization strategies for women with ACS showed that women are at increased risk for hemorrhagic complications. Women with documented acute myocardial infarction are less likely to receive early beneficial therapies in the Emergency Department, likely due to lack of recognition of myocardial infarction. There is also less use of aspirin, beta blocking drugs, and statin therapy at hospital discharge. In particular, women younger than age 70 had higher inhospital mortality than their male counterparts. Whether this reflects the contribution of sex per se or the comorbidities that characterize women remains to be ascertained, although the latter appears more likely. Depression following MI is almost twice as common in women and may influence excess mortality rates. The contemporary increased application of appropriate diagnostic, therapeutic, and interventional managements has favorably altered the prognosis for women, particularly when the data are adjusted for baseline characteristics.

HYPERTENSION: PECULIAR FEATURES IN POST-MENOPAUSAL WOMEN

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Hypertension is the major risk factor in post-menopausal women for incidence, prevalence and risk to develop future events. Regarding pathophysiology, it is the result of different factors: increase in body mass index, stop in menstruation, loss of estrogen, age and mainly endothelial dysfunction (ED) responsible for the decrease in vascular reactivity and increase in Pulse Pressure, acceptable surrogate for vascular stiffness or cyclic stress. In relations to estrogens, we have demonstrated in the past that hormonal replacement therapy added to antihypertensive therapy can be helpful in reversing left ventricular hypertrophy. We investigated moreover the effects of transdermal 17β-estradiol on the modification of global cardiovascular risk profile, and particularly glucose intolerance, in hypertensive postmenopausal women (HPmW). Menopause can be the cause of hypertension through the induction of ED, which itself represents the mean for development of hypertension associated disease and target organ damage. Particularly our group tested if there is a blood pressure lowering agent superior to others in improving endothelial function in HPmW. We observed that ACE-inhibitors, more then beta-blockers and diuretics, are able to improve endothelial function. We tried therefore to test the prognostic value of ED reversibility in a group of HPmW. In this study we demonstrated that a significant improvement of ED after 6 months of antihypertensive therapy identifies patients with more favorable outcome. HPmW represent a complex model of mechanism and interaction, which needs further research.

REPRODUCIBILITY OF THE MEASUREMENT OF THE ANKLE-ARM INDEX IN POSTMENOPAUSAL WOMEN; INFLUENCE OF LOCATION AND DEVICE

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The measurement of the ankle-arm index (AAI) is widely used as an objective measure for the diagnosis of peripheral arterial disease. However, the AAI is not well standardized. In this study we investigated which method of AAI measurement in terms of selected arteries and device yields the best reproducibility.

The study population comprised of 336 women. In all subjects duplicate AAI measurements were performed. The systolic ankle pressure was measured at the left and right posterior tibial artery and the right and left dorsalis pedis artery using a hand-held 8 MHz Doppler probe and sphygmomanometer. The blood pressure in the arm was measured in the right and left brachial artery using two types of device: a hand-held 8 MHz Doppler probe plus sphygmomanometer and the Dinamap *XL*. Repeatability of duplicate blood pressure measurements, inter-arm differences, agreement between the posterior tibial artery and the dorsalis pedis artery in each leg and agreement between the Doppler method and the Dinamap method in each arm was examined. All analyses were done according to the methods of Bland and Altman.[1]

The mean age of the subjects was 65.5 (± 5.7) years. For the right and left posterior tibial artery, the coefficients of repeatability (CR) were 11.2 mmHg and 11.2 mmHg and for the right and left dorsalis pedis artery the CR's were 14.0 mmHg and 14.4 mmHg, respectivily. With respect to device, the CR's for Doppler were 13.0 mmHg (right arm) and 11.8 mmHg (left arm) and for Dinamap these were 18.2 mmHg (right arm) and 17.4 mmHg (left arm). The mean inter-arm blood pressure difference was -1.0 (-2.0;0.05) mmHg when using the Dinamap. When measuring with Doppler, the mean inter-arm difference was 3.0 (2.0;4.0) mmHg. The mean blood pressure difference between posterior tibial artery and the dorsalis pedis artery at the right foot is 2.3 (1.4;3.3) mmHg and at the left foot this is 3.9 (2.9;4.9) mmHg. With respect to device, the mean blood pressure difference between Dinamap and Doppler in the right arm was 5.7 (-6.9;-4,5) mmHg. In the left arm the mean difference between the two methods was -1.8 (-2.7;-0.8) mmHg.

Recommendations for measurement of the AAI in epidemiological studies will be presented.

1. Bland et al. The Lancet 1986;1:307-10.

A COMPARATIVE STUDY OF 2 MG ESTRADIOL/ DYDROGESTERONE AND 2MG ESTRADIOL/ TRIMEGESTONE ON FACTORS INVOLVED IN THE VENOUS HAEMOSTATIC BALANCE

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In order to explore the mechanisms involved in the potential risk of thrombosis due to estrogens a subset of data of a more complete study compared changes in inhibitors and activation markers of the thrombin activation and fibrinolytic systems in healthy postmenopausal women taking a high dose of 2mg estradiol (E2) combined with dydrogesterone or trimegestone. 184 women were randomised to six months therapy with either 2mg E2 + trimegestone (0.5mg) or 2mg E2+ dydrogesterone (10mg). Antithrombin and Protein S activity was significantly decreased and APC resistance, prothrombin fragment 1.2 and FDP (D-Dimer) were increased significantly in both groups on treatment. The increase in plasmin-antiplasmin complex and FDP, markers of the fibrinolytic system were significantly greater after 6 cycles of treatment in the trimegestone group compared with the dydrogesterone group. Although increased thrombin production may contribute to the increased risk of venous thrombosis, this may be counteracted by the greater fibrinolytic activation found in women taking 2mg E2 combined with trimegestone. More recent studies with lower doses have shown a further reduction of the activation of both systems.

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EFFECT OF LONG-TERM HORMONE REPLACEMENT THERAPY ON COAGULATION FACTOR VII: A RANDOMIZED CONTROLLED STUDY IN HEALTHY POSTMENOPAUSAL WOMEN

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In subgroups of post-menopausal women hormone replacement therapy (HRT) seems to increase the risk of cardiovascular disease (CVD). Differential effects of HRT on CVD risk markers caused by genetic and environmental interactions may to some extent explain this. Since coagulation factor VII (FVII) is a marker of CVD, where inconsistent HRT-effects have been reported, we decided to investigate the effect of long-term HRT on FVII and to determine whether common polymorphisms in the FVII gene and/or smoking modulate this effect.
Healthy postmenopausal women (n=719) were randomized to HRT (n=357, opposed (n=290) or un-opposed (n=67)) or no substitution (n=362). After 5 years follow-up we measured activated FVII (FVIIa), FVII protein concentration (FVII:Ag), and the following polymorphisms in the FVII gene: FVII R/Q353, FVII –323ins10 and FVII intron7(37bp)$_n$.
No effects of opposed HRT on FVII:Ag and FVIIa were found. Unopposed HRT caused elevated FVII:Ag concentrations both compared with opposed HRT (P=0.01) and controls group (P=0.04). This effect was solely found in non-smokers and in women homozygeous for the common P0 allele of the FVII –323ins10 polymorphism, the R353 allele of the R/Q353 polymorphism, or the H6H6 genotype of the FVII intron7(37bp)$_n$ polymorphism.
The observed elevated FVII:Ag concentrations associated with unopposed HRT may increase CVD risk in subgroups of post-menopausal women.

EXERCISE AND AGING

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Lifestyle of developed countries is characterized by sedentary and excess of caloric intake, with consequent high prevalence of overweigh, obesity, metabolic diseases such as diabetes and dislipidemias. People are not acquainted with the knowledge of the significative relationship between sedentary lifestyle and all causes of disease and death: cardiovascular, cancer, osteoarticular, lung, neurological diseases (dementia, depression).
Until now attention was focussed mainly on obesity.
However we have lot of evidence from recent literature that exercise, even if started in adult or old ages, can be powerful in preventing: all-cause mortality, cardiovascular mortality, cancer, as well as diabetes, dislipidemias, hypertension, osteoporosis, and sarcopania.
We will review all data recently published on this topic giving strong evidence that it is mandatory a change of lifestyle of the population at all ages in order to avoid disability and/or death for all age-related diseases.
It is important to insert in the day/night biorhythms of each individual at all ages time for physical exercise and on the basis of all physical possibilities. Media campaign should be focussed on this goal.

THE IMPACT OF EXERCISE WITH OR WITHOUT HORMONE REPLACEMENT THERAPY (HRT) ON CARDIOVASCULAR RISK IN PERIMENOPAUSE.

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In Malaysia, heart disease comprised 14.1% of total mortality with the mortality rate in women rising more rapidly than men. Almost all myocardial infarcts occur in postmenopausal women. This study involved 339 disease free women above 45 years old who were followed up for 12 months. On recruitment, they were randomly allocated into three groups i.e. control (I), exercise intervention (II) and exercise intervention with HRT (III). The intervention groups were taught a series of exercise and reinforcement undertaken every six months. The BP, BMI, blood sugars and lipid profile were assessed every 6 months and the ECG after 12 months in all groups. The sample population comprised of mainly urban women, three quarters having completed secondary or tertiary education. The average age of menarche and menopause was 13.6$\pm$1.7 and 50.1$\pm$2.8 years respectively. In all groups, the 2 hour postprandial blood sugar increased and HDL-C decreased significantly over 12 months despite a reduction in fasting blood sugar values. Group II showed improved triglyceride and total serum cholesterol with group III having the least increase in LDL-C despite a significant worsening of the 2 hour post prandial sugar ($p<0.0005$).
Regarding BMI, all groups showed a reduction but group I had an increased waist circumference. Group II showed a reduced waist circumference, systolic and diastolic BP and in group III there was a significant reduction of the waist circumference ($p<0.01$) and diastolic BP ($p<0.05$) On ECG, 29.2% of all subjects had at least one abnormality. Group II after exercise showed a reduction in heart rate with 23 subjects achieving normality after an abnormal baseline ECG ($p<0.0005$) e.g. elimination of all right bundle branch block and T wave inversion. In group III, 60% of right bundle branch block at baseline became normal after 12 months. Over a 12 months follow-up, this study demonstrated that exercise intervention with or without HRT improved the cardiovascular risk profile i.e. blood sugars, BMI, BP, and cardiac abnormalities. In conclusion, exercises is a cheap, effective therapeutic tool for perimenopausal women to improve their cardiovascular health. As an option, HRT regime may be used to reduce central obesity.

HORMONES AND CANCER RISK: INTERPRETING EPIDEMIOLOGICAL RESULTS.

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Although the effects of menopausal hormones on cancer risk have been the subject of much debate, several recent findings have suggested the need for re-thinking old concepts. This presentation will review evidence regarding hormone effects on three major cancer sites of importance to women, namely endometrial, breast and ovarian cancers. Endometrial cancer has been most extensively linked with estrogen use, with users having 10-20 increased risks compared with non-users. To counteract the proliferative effects of estrogens on endometrial tissue, it has become commonplace to prescribe estrogens in combination with progestins, particularly for women with intact uteri. However, whether this regimen entirely eliminates the excess risk associated with hormone use has yet to be resolved. Several studies suggest persistent elevations in risk among certain subgroups of combination therapy users, including those with long-term usage. For breast cancer, there has been increasing acceptance that estrogen use can lead to increases in risk, particularly if used recently, suggesting possible promotional effects. Less definitive information has been available on effects of combined therapy, although *in vitro* data showing that mitogenic effects of progestins on breast tissue suggest that combination therapy may have detrimental effects. Although results from several epidemiologic studies have supported this notion, recent confirmatory data from a large intervention trial have raised the level of concern. Ovarian cancer has been less well studied than the other sites with respect to hormone use. Early studies provided reassuring findings, but more recent investigations assessing long-term effects have found moderate risk increases. Much less is known regarding effects of combination therapy for this tumor. This presentation will discuss these recent findings in light of additional unresolved issues. Interactive effects of other risk factors for these tumors on hormone-associated risks will also be discussed.

INTERPRETING EPIDEMIOLOGICAL RESULTS IN DIFFERENT POPULATIONS: THE EXAMPLE OF PROGETTO MENOPAUSA ITALIA (PMI).

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The publication of the preliminary results of the Women Health Initiative (WHI) study and of the Million Women Study has suggested that the use of hormonal replacement therapy (HRT) may increase the risk of cardiovascular diseases as well as breast cancer. These studies, however, have been conducted in Northern American and European populations, which differ from Southern European ones for lifestyle habits and HRT use as well as breast cancer and cardiovascular diseases prevalence. We compare the characteristics of women who entered the WHI study and of those who attend the Italian menopause clinics, using data collected in the framework of a large prospective observational cross sectional study: "PMI". This study started in 1997. Women consecutively observed during the study in 268 centres were eligible. Up to September 2003, a total of 109.793 women (mean age 53 years) entered the study. The large number of subjects considered offers a reasonable picture of characteristics of Italian women attending menopause clinics. Italian women were younger, in pre menopause, less educated, reported less frequently regular physical activity, were less frequently smokers than women who entered the WHI. These data indicate that the characteristics of women who entered the WHI Randomised Trial and the PMI markedly differ in terms of baseline risk profile for breast cancer and cardiovascular disease.

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AGE AT MENOPAUSE, MORTALITY AND LIFE EXPECTANCY

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A later menopause has been associated with a decreased cardiovascular risk, but with an increased risk for breast and endometrial cancer. The net effect on mortality is, however, unclear.
In a large prospective cohort study we set out to determine the association of age at menopause with longevity. The average follow-up was 17 years and we studied the balance between cardiovascular and cancer mortality.
A total of 12,134 postmenopausal women, who did not use HRT, contributed to 204,024 person-years of follow-up and 2,607 deaths occurred: 963 due to cardiovascular diseases and 812 due to cancer. With a later menopause ischemic heart disease risk decreased: HR 0.98 per year (p.y.) (95% confidence interval (CI): 0.96; 0.99), but the risk of fatal uterine or ovarian cancer increased: HR 1.07 p.y. (95% CI: 1.01; 1.12). A later menopause was associated with longevity: age-adjusted hazard ratio (HR) for total mortality: 0.98 p.y. (95% CI: 0.97; 0.99). Life expectancy in women with menopause >55 years was 1.98 years longer compared to those with menopause <40 years. Adjustment for potential confounders did not materially change the results.
From this study we conclude that each year menopause occurs later the age-adjusted mortality is reduced with 2%, in particular, ischemic heart disease mortality is 2% lower. Furthermore, although the risk of death from uterine or ovarian cancer is increased by 5%, the net effect of a later menopause is an increased life span.

ALLELIC VARIANTS IN CYTOKINE GENES AMONG AFRICAN-AMERICAN AND WHITE WOMEN

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Racial disparities in health are ubiquitous. African-American women, for instance, experience higher rates of diabetes mellitus, hypertension, heart disease, breast cancer, and endometrial cancer. Inflammation is thought to mediate all of these diseases. We sought to determine whether African-American women were more likely to carry allelic variants in cytokine genes that up-regulate the inflammatory response. 463 White, non-Hispanic and 186 African-American, healthy women seeking prevention care were enrolled from gynecology clinics in Pittsburgh, PA, USA. SNP's with functional relevance on the pro-inflammatory cytokines IL-1α, IL-1β, and TNF-α, and the immune-regulatory cytokine IL-10, were assayed using standard TaqMan protocols. Positive and negative controls confirmed validity of genotyping. Allele frequencies were generated and shown to be in Hardy-Weinberg equilibrium using the chi square goodness-of-fit statistic. Two genotypes known to increase IL-10 production, -819 C/C and -1082 G/G were 3.5 times (95% CI 1.8, 6.5) and 3.0 times (95% CI 1.7, 5.3) more common in White than African-American women. On the IL-1α gene, the functionally down-regulating -4845 T/T and –M889 C/C genotypes were 4.6 (95% CI 1.8, 12.1) and 2.0(95% CI 1.1, 3.5) times more common in Whites. Finally, the down-regulating IL-1β -3957 T/T and –M511 G/G genotypes were 3.5 times and 4.7 times more common in Whites than African-Americans. Allelic variants were not differently distributed by race for TNF-α. Thus the genotypes that reduced the cytokine suppressant effect of IL-10 and increased the pro-inflammatory effects of IL-1α and IL-1β were substantially more common in African-American women. African-American women had allelic variants that predisposed them to cytokine expression that is hyper-responsive to inflammatory stimuli. This may be one mediating influence in their greater risk for cardiovascular disease and cancer.

ERβ – A MULTIFUNCTIONAL REGULATOR OF WOMEN'S HEALTH

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Since its discovery in our lab in 1995, ERβ has caused a paradigm shift in our understanding of estrogen signaling. It has become apparent that this ligand activated transcription factor regulates a surprisingly large number of physiological processes as a reflection of its widespread tissue distribution. Possibly, the central role played by ERβ in so many contexts might reflect its phylogenetically ancient nature, being one of the first steroid receptors appearing during evolution. Accordingly, deletion of the ERβ gene results in a plethora of phenotypes, some of which are particularly exciting. For instance, mice with ERβ deletion develop a syndrome reminiscent of chronic myeloid leukemia, mice with ERα deletion develop Systemic Lupus Erythematosus Disseminatus (SLE), whereas mice with deleted aromatase gene suffer from Sjogren´s disease. All these observations indicate that estrogen signaling is of paramount importance for regulating the immune system. The mentioned rodent models will aid in generating a better understanding of the mechanisms behind the well known sexual differences in autoimmune disease, hopefully paving the way for a rational treatment of these debilitating diseases. Another unanticipated recent finding is that aging ERβ mice show signs of grossly impaired hearing, consistent with a complete loss of the organ of Corti in the inner ear as well as a total degeneration of the neurons in the spiral ganglion. Needless to say, these findings might support the notion that treatment with ERβ agonists might delay age dependent hearing loss.

MENOPAUSE, MEMORY, AND DEMENTIA

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Sex steroids have the potential to affect brain function and neurological disease. After the menopause, loss of ovarian estrogen and progesterone, and conversely, exogenous estrogens and progestins administered as hormone therapy might influence memory skills or development of severe memory impairment characteristic of dementia. Laboratory research generally suggests that estrogen could enhance memory or protect against dementia due to Alzheimer's disease, and memory complaints are common during the menopausal transition and early postmenopause. However, cross-sectional findings from the Melbourne Women's Midlife Health Project suggest that memory is not adversely impacted by menopause (Henderson et al., Neurology 2003;60:1369-71). Considerable observational data associate hormone therapy with reduced Alzheimer risk, but clinical trial evidence from the Women's Health Initiative Memory Study (WHIMS) indicates that estrogen plus progestin in the older postmenopausal woman increases dementia risk (Shumaker et al., JAMA 2003;289:2651-62). In the WHIMS trial, one can infer that enhanced risk probably included Alzheimer's disease, developed rapidly, and preferentially affected women with low cognitive scores. Bias or confounding in observational studies is one important possibility for discrepant results compared to WHIMS. Other theoretical possibilities include timing of hormone exposure (the so-called "critical window" theory; e.g., Resnick & Henderson, JAMA 2002;288:2170-2) or type of exposure (e.g., unopposed estrogen versus estrogen plus progestin). Until mechanisms of demonstrated harm and putative cognitive benefit are better understood, it appears unwise for clinicians to recommend menopausal hormone therapy to prevent memory decline or reduce dementia risk. However, important questions remain unanswered concerning long-term consequences of menopause and hormone therapy.

SLEEP DISORDERS IN WOMEN - DOES MENOPAUSE HAVE A SPECIAL IMPACT

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Sleep disorders are more common in women than in men and their incidence increases with age. There are two distinct mechanisms, how menopause is known to affect sleep quality: menopausal insomnia, which can be considered as part of the climacteric symptomatology, and sleep-disordered breathing, where impairment of sleep quality is secondary to nocturnal breathing problems. The former is effectively controlled with conventional hormone therapy (HT), whereas the latter could potentially be improved with progestins.

Insomnia is reported by 25% of women and severe insomnia by 15% between 50 and 64 years of age. There are two aspects of sleep disturbance, the subjective and the objective ones, which do not always overlap. Subjective sleep disturbance is a self-reported complaint of nonrestorative sleep, whereas objective sleep disturbance means reduced sleep efficiency or abnormalities in sleep architecture, which can be measured with all-night polygraphic recordings.

The clinical picture of menopausal insomnia is undistinguishable from common insomnia, which manifests as difficulty of falling asleep, frequent awakenings or awakening too early from sleep in the morning. Women typically have complaints of fatigue and tiredness in the daytime. Menopausal insomnia may be primary or secondary to other climacteric symptoms. Frequent awakenings may suggest that insomnia is secondary to vasomotor events inducing awakenings, whereas early awakening evokes suspicion of menopausal depression. In the age group of 40-59 years, including both pre- and postmenopausal women, the frequency of sleep apnoea is about 2.5%. A study in 65 healthy postmenopausal women revealed a significant latent partial upper airway obstruction during sleep in 17 % of the subjects. Since progestins are potent respiratory stimulants, they have been speculated to protect women from the condition until menopause.

THE CLINICAL PHARMACOLOGY OF OSTEOPOROSIS IN POSTMENOPASUAL WOMEN

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The diagnosis of osteoporosis, the most common metabolic sease is commonly made after fractures occur. However, the effects of intervention with pharmacologic agents to reduce the risk of fractures may be compromised at this time, because the excess fracture risk from the first fracture cannot be eliminated by the drugs we use. Therefore, earlier diagnosis becomes important. This will need to be achieved by developing an algorithm that can reliably be used to establish an individual's absolute risk of fracture. Several such algorithms may be required, since likely they will be population specific, and perhaps also fracture specific. These would allow intervention at a level of risk accepted by community standards, and by individual physicians and patients. Bisphosphonates are currently the standard of care for osteoporosis, generally reducing overall fracture risk by about 50%, and producing this effect remarkably rapidly. The data tend to support the concept that much of the effect is produced by reduction in bone remodeling, rather than any change in mass. In contrast, 1-34hPTH (teriparatide) produces marked effects on mass, and likely induces sufficient effects on cancellous bone to repair at least some of the architectural abnormalities of osteoporosis. The mechanisms of the PTH effects on bone are incompletely understood, but are transient and virtually gone after 2 yrs of daily injections. The consequence is that we need to consider whether further intervention with an antiresorptive agent would be necessary in all patients who are given PTH. At present this is still unclear.

DISSOCIATION OF SKELETAL FROM REPRODUCTIVE EFFECTS OF SEX STEROIDS BY ACTIVATION OF NONGENOTROPIC SIGNALS: NOVEL INSIGHTS INTO BONE ANABOLISM AND A SAFER HRT

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Estrogens and androgens decrease the number of bone remodeling cycles by attenuating the birth rate of osteoclasts and osteoblasts from their respective progenitors. These effects result, in part, from the transcriptional regulation of genes responsible for osteoclastogenesis and mesenchymal cell replication and/or differentiation, and are exerted through interactions of the ligand-activated receptors with other transcription factors. Estrogens and androgens also exert effects on the lifespan of mature bone cells: pro-apoptotic effects on osteoclasts, but anti-apoptotic effects on osteoblasts and osteocytes. These latter effects stem from a heretofore unexpected function of the classical "nuclear" sex steroid receptors outside the nucleus and result from activation of a Src/Shc/ERK signal transduction pathway probably operating within preassembled scaffolds, such as caveolae. Strikingly, ER a or b or the AR can transmit anti-apoptotic signals with similar efficiency irrespective of whether the ligand is an estrogen or an androgen. These nongenotropic, sex-nonspecific actions are mediated by the ligand binding domain of the receptor and can be functionally dissociated from transcriptional activity with synthetic ligands. Moreover, synthetic ligands that can dissociate ER or AR signaling through kinases from the classical transcriptional activity of these receptors in the nucleus increase bone mineral density (BMD) and bone strength in both females and males, significantly more than

SEX HORMONES IN THE REGULATION OF BONE AND CARTILAGE METABOLISM: AN OLD PARADIGM AND A NEW CHALLENGE

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The effects of estrogen on tissues such as bone, endometrium and breast have been extensively studied, but cartilage is not generally viewed as an estrogen responsive tissue. However, Epidemiological studies supports that estrogen may have a role in OA, and recent animal studies further suggests that estrogen may be involved in regulation of cartilage turnover. In order to assess this issue, we investigated the effects of ovariectomy (OVX) on cartilage erosion rats using histology and a bioassay of cartilage-specific collagen type II degradation (CTX-II). Furthermore, we investigated whether estrogen and levormeloxifene, a selective estrogen receptor modulator (SERM), can prevent the OVX-induced changes in cartilage degradation. The clinical relevance was assessed in postmenopausal women by measuring the changes in CTX-II during 12-month treatment with levormeloxifene.

We subjected 6-month-old female rats to sham or OVX, followed by treatment with vehicle, estradiol or levormeloxifene. The rats were treated for nine weeks with bi-weekly blood and urine sampling for measurement of bone resorption and cartilage turnover. After 9 weeks, knee-joints were analyzed for erosion by histology. The effect of levormeloxifene in postmenopausal women was assessed by measuring CTX-II in samples from 301 subjects participating in a phase II study of this SERM.

OVX rats showed significant increases in the urinary excretion of CTX-II. After 9 weeks this was manifested as increased surface erosion of knee articular cartilage compared to sham operated rats. Treatment with estrogen or levormeloxifene prevented the OVX-induced changes. There was a significant correlation between the 4-week changes in CTX-II and cartilage erosion at week 9 ($r=0.64$, $p<0.001$). In postmenopausal women treated with levormeloxifene, the urinary excretion of CTX-II decreased by approximately 50% and restored CTX-II to premenopausal levels.

This study is the first to demonstrate that a SERM suppress cartilage degradation in both rodents and humans, suggesting potential clinical benefits in the prevention of destructive joint diseases such as OA

GENETICS OF OSTEOPOROSIS

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Understanding the genetic base of multifactorial diseases represents the future task for scientists in order to explain new physiopathological aspects of complex traits. One of these-diseases is represented by osteoporosis (OP).

OP is a common disorder associated with reduced bone mineral density, affecting up to 40% of women and 12% of men at same point during life. Osteoporotic fractures are an increasing health care burden in all aging communities. A major determinant of fracture risk is represented by bone mineral density (BMD), independent of other factors such as aging per se and falls. BMD depends upon both the peak bone mass achieved in adolescence and the subsequent bone loss. However, peak bone mass is the major determinant of bone mineral density for up to 10-20 years after menopause, until age-related factors become relatively more important in determining bone mass loss. Although OP is a multifactorial trait, genetic factors play an important effects on peak bone mass and in the pathogenesis of OP. The development in advanced techniques for measuring BMD made possible to have available a quantitative trait for segregation analysis. In fact, quantitative traits are defined as characters that everyone has, that are measurable and that exhibit a normal distribution in the population. Up to 75% of variation in BMD has been suggested to be under genetic influences. However, the inclusion of OP in the list of genetic disorders is still debatable. Twin studies have shown a strong genetic effect of BMD at both peripheral and axial sites. The largest genetic influence was observed at sites of high trabecular bone content. Although twin studies have been powerful tools for studying genetic effects, they show some limitations and can only imply but not prove genetic influence. A variety of experimental models for establishing genetic background of OP have been proposed, such as linkage analysis, allele sharing methods, association studies and experimental crosses.

Family studies suggest a significant effect of genetic factors on peak bone mass. For example, using the early approach of metacarpal/cortical bone thickness, parent-offspring correlations indicated that bone mass was for a large portion genetically determined. In addition sib-pair studies, in premenopausal daughters of women with OP, have also shown modest but significant reductions in lumbar spine, femoral neck and femoral shaft BMD compared to premenopausal women without a family history of OP.

In the last five years association studies gave origin to several novel information with considerable controversies. They consist of comparing allele frequencies for a particular polymorphism or candidate gene in diseased population with that in non-diseased population. Despite of linkage analysis, where a physical connection between trait and marker locus must exist, an allele can be considered associated with a trait when it occurs more frequently in individuals with the trait than those without the trait, conferring an increased risk for disease to individuals carrying the associated allele. These studies have been using the candidate gene approach and given the number of factors that are likely to be involved, there is a seemingly unlimited supply of candidate genes for OP.

Discrepancy among studies can be explained on the basis of the quantitative polygenic nature of this disorder, where the effect of a given gene can easily be modified by epistatic and/or pleiotropic effects of other genes. It is likely that interactions between different genes could, at least in part, explain the discrepancy among the studies. To date, association studies have represented the more frequently used approach for the identification of genetic effects in OP.

HRT: DOES THE PROGESTOGEN MAKE THE DIFFERENCE?

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Progestogens are added to oestrogen in hormone replacement therapy (HRT) for endometrial protection. However, they have different potencies, different side-effect profiles and different metabolic effects, depending on the type of progestogen. In general terms, progestogens are classified according to whether they are derivatives of testosterone or progesterone. Classically, the 19 nor-testosterone derivatives such as levo-norgestrel and norethisterone acetate, are regarded as being androgenic, yet certain C-21 steroids, such as medroxyprogesterone acetate, may also have androgenic activity. It is now realised that, within the broad groups, progestogens may differ considerably; they have differing affinities for various steroid receptors, including oestrogen, androgen and glucocorticoid receptors, and also varying agonist and antagonist effects.

The side-effect profile of progestogens varies according to their androgenic or progestogenic properties, but there is considerable overlap of these side-effects between individuals. Of more importance, the metabolic effects of various progestogens may differ quite substantially, with important consequences for certain disease risks. Metabolic effects mainly impact on cardiovascular disease risk, and thus the choice of progestogen in HRT regimens may be quite crucial in this respect. Although recent randomised clinical trials have suggested that there is no beneficial effect of HRT with respect to coronary heart disease (CHD), this is probably due to inappropriate doses of the hormones used, rather than to the types of hormones. Nevertheless, there is clearly potential benefit to be obtained for CHD risk when considering the choice of hormones, oestrogens and progestogens, if appropriate doses are used. This makes the different metabolic effects between progestogens very important when considering CHD benefits and risks.

Oestrogen lowers cholesterol, by lowering levels of LDL. They also increase levels of HDL, and overall this is a beneficial effect. These effects vary according to the type of oestrogen used and their route of administration. Reductions in LDL cholesterol are achieved with all forms of HRT. Oral oestrogen increases HDL cholesterol more than transdermal oestradiol. The addition of an androgenic progestogen, such as norgestrel, prevents this increase, whilst non-androgenic progestogens such as dydrogesterone have little impact. Oral oestrogens result in increases in triglycerides, whilst transdermal oestradiol decreases them. The addition of androgenic progestogens decreases triglycerides, whilst the non-androgenic do not prevent an increase. In older women with established CHD, the use of low-dose continuous combined oestradiol/norethisterone results in a reduction in triglycerides but also an increase in HDL cholesterol.

Oestrogens also affect glucose and insulin metabolism. Insulin resistance is a pivotal metabolic disturbance underlying CHD development. Oestradiol increases pancreatic insulin secretion, insulin sensitivity and insulin elimination. Androgenic progestogens may oppose these effects but non-androgenic progestogens do not.

We now have an increasing number of progestogens that can be used in HRT. The metabolic effects of these progestogens need to be considered, particularly in terms of their impact on cardiovascular risk.

HRT: IMPROVING QUALITY OF LIFE
IMPACT OF HRT ON BONE, CLIMACTERIC SYMPTOMS AND BODY WEIGHT IN EARLY POSTMENOPAUSAL WOMEN

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Postmenopausal estrogen deprivation in mid age women leads to an increased bone turnover along with a decrease in bone mineral density (BMD). In addition, postmenopausal ovarian failure often brings along a series of changes and symptoms, which may greatly affect quality of life. Hormone replacement therapy (HRT) has been used for decades to relieve vasomotor symptoms and maintain bone mineral density (BMD) in postmenopausal women. This presentation will review the evidence for the beneficial effect of HRT on bone, climacteric symptoms, and quality of life. Normal postmenopausal women were recruited and randomly treated with low dose hormonal replacement therapy. Young postmenopausal women (£56 years) were treated with low HRT doses (LD-HRT) (Activelle®, oral 1 mg 17 beta-estradiol combined with 0.5 mg norethisterone acetate) and the actions on bone (spine and femur bone density ,BMD, Lunar DPX), bone metabolism (serum BGP and OHP/Cr urinary excretion), vasomotor symptoms, body weight changes, and quality of life were evaluated in 3-year, open-label trial conducted in 90 symptomatic women, 45 to 56 years of age. All women were supplemented with 1g of calcium/day, and compared to women treated with 1g of calcium/day alone (n=15). The Women's Health Questionnaire, a validated quality-of-life instrument for perimenopausal and postmenopausal women, was administered at baseline and after 6 and 12 weeks of treatment in both groups. At baseline no significant differences in Women's Health Questionnaire scores were present in the two groups. In the control group the scores in all different areas showed no significant modification either after 6 and 12 weeks of observation. Conversely, the LD-HRT group showed a significant decrease in the scores of vasomotor symptoms, somatic symptoms, anxiety/fear, depressed mood and sleep problem items. No effects on memory/concentration and menstrual symptoms areas were evident. LD-HRT is effective for symptom relief, minimizing side effects (weight gain) in early postmenopausal women. In addition, LD-HRT in addition to a proper calcium supplementation can provide effective protection against activation of bone turnover and postmenopausal osteopenia. Although quality of life is also and may be mainly influenced by socio-economic and cultural factors, LD-HRT definitively can improve not only vasomotor symptoms, but also more general aspects of physical and psychological well-being of symptomatic postmenopausal women.

VAGINAL ERT AFTER BREAST CANCER

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Breast cancer may deeply affect women's sexuality. Sexual identity, sexual function and sexual relationship are variably impaired by the diagnosis itself and treatment-related side-effects. Age (25% of breast cancers affects fertile women), lymphedema, side-effects of surgery, radio or chemotherapy, pregnancy-related problems during or after breast cancer, infertility, iatrogenic premature menopause with its cohort of damages secondary to the chronic loss of estrogens on the brain, on the sensory organs, on the pathophysiology of sexual response and on the function of the pelvic floor are discussed. The vulnerability to genital arousal disorders, secondary to the estrogen loss, leading to vaginal dryness, dispareunia and/or post-coital cystitis, with secondary loss of sexual desire increases with time after surgery, affecting personal and couple's lifes. Unfortunately, the general concern about HRT has prevented the appropriate treatment of local genital symptoms in breast cancer survivors. New evidence from the Million's Women Study shows that topical vaginal treatment does not affect the risk of breast cancer (R.R.0.67). Even more important, the RHW Breast cancer study suggests that treatment with 17-beta estradiol does not increase the risk of recurrences after breast cancer (R.R. 0.65). Implications for management are analyzed. Medical and psychosexual suggestions to ease the physical and emotional healing process of breast cancer survivors will be discussed.

VAGINAL ERT: THE THERAPEUTIC STANDARD FOR UROGENITAL AGING

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Urogenital aging (UGA) is a complex cascade of symptoms involving the lower urinary tract, the genital tract and the pelvic floor caused by hypoestrogenism in the postmenopausal woman. Decreased estrogen levels result in lower urogenital tract changes which adversely influences the quality of life. Although systemic hormone replacement therapy is frequently used for the treatment of UGA symptoms, recent attention has been focused on local delivery of estrogen to the affected urogenital tissue which can minimize side effects and achieve satisfactory therapeutic effect. The aim of the study was to determine the efficacy and safety of low dose (25 μg) micronized 17 ß-estradiol administered vaginally in the management of patients with urogenital symptoms. A total of 1612 patients with urogenital complaints were randomized to receive 25 μg of micronized 17ß-estradiol (828) or placebo (784) in a multicenter double-blind placebo controlled study running for 12 months. The women were treated once a day for two weeks, and then twice a week for the rest of the twelve months with the active or placebo tablet. The assessment included full history-questionnaire, micturition diary, gynecological and cystometric examination, transvaginal ultrasound and serum 17-ß estradiol level determination. It was carried out at the beginning, and after four and twelve months of treatment. The overall success rate of micronized 17-ß estradiol on subjective and objective symptoms of postmenopausal women with vaginal atrophy was 85.5%, and the effect of placebo was 41.4%. A significant improvement of urinary atrophy symptoms was determined in vaginal ERT group comparing with the beginning of the study (51.9% vs 15.5%, p=0.001). Maximal cystometric capacity (290 mL vs 200 mL, p=0.023), the volume of the urinary bladder at which patients first felt urgency (180 vs 140, p=0.048) ,and strong desire to void (170 vs 130, p=0.045) were significanlty increased after micronized 17-ß estradiol treatment than before it. The number of patients with uninhibited bladder contractions significantly decreased after micronized 17-ß estradiol compared with the values before the treatment (17/30, p=0.013). Side effects were observed in 61 (7.8%) patients treated with low dose micronized 17-ß estradiol. We found that 25 μg of micronized 17-ß estradiol do not raise serum estrogen level and do not stimulate endometrial growth.

Local administration of 25 μg of micronized 17-ß estradiol is effective and safe treatment option in the management of women with urogenital complaints.

INTERMITTENT LOW DOSE HRT TO MAINTAIN QUALITY OF LIFE

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In September 2003, NAMS convened a panel of 14 experts in the field of the perimenopause and menopause and presented a position paper which suggested the direction one should follow in the pursuance of hormone replacement therapy (HRT) in perimenopausal and postmenopausal women. The position statement focused on the use of government-approved prescription estrogen therapy and estrogen-progestin therapy products available in the USA and Canada, not custom HRT prepa-rations, selected estrogen receptor modulations or hormones available without a prescription. One of the concluding statements and one which was approved by the members of the panel stated "use of EPT (estrogen-progestin therapy) and ET (estrogen therapy) should be limited to the shortest duration consistent with treatment goals, benefits and risks for the individual woman taking into account symptoms and domains, i.e. sexuality, sleep, that may have an impact on quality of life" and secondly "lower than standard doses of ET and EPT should be considered, daily doses of 0.3 mg conjugated estrogen tablet, 0.25-0.5 mg micronized 17-ß estradiol and 0.25 mg 17-ß estradiol patch or the equivalent." However, lower doses have not been tested for outcomes including endometrial safety in long-term trials. At the McGill University menopause clinic, we have pursued these suggestions and will eventually come to some kind of conclusion as to their efficacy and reliability for the treatments of bona fide symptoms of menopause that require treatment. In addition to using lower doses of HRT we also proceeded with the extrapolation of work that had been completed about one year ago and published in which we tested the clinical assessment and quality of life of postmenopausal women treated with an intermittent progestagen combination hormone replacement therapy – a placebo controlled study. In lowering the dose of the estrogen, the progestin component also in low dose was added for 3 days out of 6, i.e. estrogen continuously and every 3 days the progestin was added. This achieved another approach to low-dose therapy and the results of the study will be discussed and the extrapolation of these results and further assessment of low-dose therapy will be determined.

MENOPAUSE, SURGICAL MENOPAUSE AND SEXUAL FUNCTIONING

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This study was designed to compare sexual functioning of women who have undergone surgical menopause (SM) with that of women in age appropriate reproductive phases. **Methods:** The study utilizes a nested control design. 1685 women were selected from a cross-sectional survey of 2467 European women aged 20 – 70 years and resident in France, Germany, Italy and U.K. For this analysis women were selected for experience of SM or age matched control groups of regularly menstruating women aged less than 50 or naturally postmenopausal women aged 50 years or more. Female sexual functioning was measured by the Profile of Female Sexual Function (PFSF), Personal Distress Scale (PDS), and the Sexual Activities measure. Hypoactive Sexual Desire Disorder (HSDD) was defined as women who were below the cut-off scores on both the PFSF and PDS. **Results:** Significantly more of the younger SM women had low sexual desire than did the regularly menstruating control group. Older SM women had similar levels of low sexual desire to that of the postmenopausal women. Younger women who had low desire were more likely to be distressed by it. Surgical menopause women of any age group were more likely to have HSDD. Women with low desire were less sexually active and report less arousal, orgasm, and sexual pleasure, and satisfaction with sexual life. **Conclusion:** Surgically menopausal women are at risk for HSDD.

THE ROLE OF ANDROGENS IN FEMALE SEXUAL FUNCTIONING.

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The right of a woman to maintain her individuality and the possibility to express herself in all aspects of life, including her sexual life has become apparent and accepted. Much work and scientific research has been performed in recent years regarding both the classification of female sexual dysfunctions and potential therapeutic approaches.

Hormones, in particular estrogens and androgens, play an integral role in maintaining the general health and well being of all women, including sexuality. Whilst estrogens play a 'permissive' role in female sexual functioning i.e. assisting with vaginal lubrication, it is androgens that act as the 'drivers of desire'. The decline in circulating bioavailable testosterone either as part of the natural aging process or following surgical menopause may often manifest itself as low desire/libido. When this low desire is associated with distress, a diagnosis of Hypoactive Sexual Desire Disorder (HSDD) may be made.

The acceptance of the role of androgens in female sexual functioning has made them a focus of clinical research and often used treatment approach for HSDD. Typically given as an adjunct to estrogen therapy after menopause (surgical or natural), androgens have a variety of potential therapeutic uses. Although the focus of this presentation will be in the role of androgens in female sexual functioning, their other potential applications including: improvement of vitality, well-being and mood, adjunctive therapy for vasomotor symptoms, and in improving bone and muscle strength will also be discussed.

DO DEPRESSIVE AND ANXIOUS SYMPTOMS INCREASE DURING OR AFTER THE MENOPAUSAL TRANSITION? RESULTS FROM THE FIRST FIVE YEARS OF THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

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Available studies suggest that negative mood increases during the perimenopause. Herein we report results of longitudinal analyses of depressive and anxiety symptoms during five years of follow-up of 3176 women enrolled in SWAN. SWAN is a US 7-site, multiethnic longitudinal study of women's health and menopause. It is one of the largest, most comprehensive studies of menopause in the world. Eligibility included age 42-52; having menses within the previous three months; having a uterus and at least one ovary; not pregnant; and no use of reproductive hormones or birth control pills within the previous three months. Women were evaluated annually. Menopausal status was classified according to self-reported bleeding criteria as premenopausal, early perimenopausal, late perimenopausal, and postmenopausal. Significant depressive symptoms were defined as a score $\geq$ 16 on the Center for Epidemiological Studies Depression Scale (CES-D), a standardized 20-item measure of depressive symptoms. Anxiety was determined based on frequency of 4 anxiety symptoms present in the previous 2 weeks, coded 0 (none) to 4 (daily); ratings were summed to create a summary anxiety score. The top 20% of scores were defined as indicating significant anxiety. Covariates included hot flashes, stress, health measures, age, SES, ethnicity, and weight. Repeated measures logistic regression models (censoring women at the start of hormone use) showed that compared to being premenopausal, becoming early or late perimenopausal was significantly associated with depression: early peri, odds ratio (OR)=1.20, p=.005, and late peri, OR=1.36, p=.006; and becoming early perimenopausal was associated with anxiety: OR=1.28, p=.0001. Postmenopausal status was not associated with elevated anxiety or depression compared to premenopausal status. These unique data clearly show that significant depressive and anxious symptoms increase during the perimenopausal transition.

PSYCHOSOCIAL BEHAVIORAL AND HEALTH FACTORS RELATED TO MENOPAUSE SYMPTOMATOLOGY

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Menopause has long been considered a turning point in women's lives associated with biological and psychological changes affecting health and working capacity. Menopause is also a developmental phase associated with a potential for growth and personal development. Results from our longitudinal study showed that the majority of women (56%) had a neutral attitude to menopause, 31% were negative and 13% were positive. However, the women became increasingly more positive over time and by the end of the fifth year the pattern had changed: 67% were positive, 16% were neutral and 17% only were negative. Vasomotor symptoms were unaffected by attitude, instead mood change, memory problems and sleep-related symptoms were significantly more frequent in the negative group. The aim of an ongoing population-based study was to analyze the health profile of perimenopausal women in relation to psychosocial factors and perceived quality of work role. 2000 women aged 48 to 53 were recruited through the Swedish Population Registry and received a health questionnaire. Among the 950 responders, 150 women were recruited for a biannual follow up study involving a psychological and a biological part. A semi-structured interview focused on health and psychosocial factors and perception of work role. Factor analyses of the symptom ratings yielded five independent factors: burnout, anxiety, musculoskeletal symptoms, vasomotor symptoms and decreased sexual desire. Vasomotor symptoms were related to job strain, physically demanding work, having been born in a country outside Scandinavia and being postmenopausal. Burnout was related to low social support, low job control and poor self-rated health. In conclusion, attitude to menopause, psychosocial factors and perceived quality of work role are important contributors to women's health during transition to menopause. Improving the psychosocial work environment and increasing social support in the workplace may be critical steps in promoting well-being among women at midlife.

SEASONAL VARIATIONS OF OXIDATIVE STRESS PARAMETERS IN WOMEN

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Oxidative stress and its accumulation is caused to be one of the major reasons for preterm ageing and civilisation diseases. It has clearly been observed that circadian rhythm is followed. In our department patients of both gender routinely undergo laboratory analysis of oxidative stress parameters (POX-Act, TAS and oLAb). We were able to demonstrate that oxidative stess not only follows a circadian, but also a seasonal rhythm. Both gender showed higher peroxide levels in springtime and autumn than in winter and summer. Especially women showed up to four times higher levels than men all over the year.

We conclude by this observations that women have a higher risk of diseases caused by oxidative stress than men. Fortunately women show a better behaviour in nourishing, therefore their compensative antioxidative mechanisms seems to prevent them of severe damage – by the moment. Changing the lifestyle behaviours to more smoking, more alcohol, more stressful work will lead to reduced lifespan too. Therefore oxidative stress parameters should also be a remarkable factor in diagnosis of ageing processes.

MEETING THE NEEDS OF WOMEN FOR HEALTHCARE INFORMATION

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The paper highlights the work of a women's health charity. The service operates a Helpline and Internet service run by a team of nurses, backed up by medical staff. The charity provides information on all aspects of gynaecological healthcare, with over a third of enquiries menopause related. The work of the charity has increased by up to one third following reports in the last 2 years regarding HRT and the negative press it receives. This often leaves both the public and professionals unsure of the best way to meet the health needs of women and their families.
The charity was originally set up to enable women to have access to authentic and evidence based information regarding HRT and nearly 33 years on the work is still providing a valuable resource for both women, their families and healthcare practitioners.

Hormone Therapy and Cognition in WHISCA: The Women's Health Initiative Study of Cognitive Aging

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Some observational studies of hormone therapy (HT) and Alzheimer's disease (AD) suggest that HT is associated with a reduced risk for AD. These findings have been challenged by the recent report (Shumaker et al, 2003) from the Women's Health Initiative Memory Study (WHIMS), a large randomized clinical trial conducted as an ancillary study to the Women's Health Initiative. WHIMS investigators reported a 2-fold increase in the risk for all-cause dementia in women aged 65 and older who were assigned to combination estrogen plus progestin (E + P) therapy compared with placebo. Studies of the effects of HT on memory and other cognitive abilities in women without dementia also have yielded inconsistent results. The Women's Health Initiative Study of Cognitive Aging (WHISCA), an ancillary study to WHIMS, was developed to investigate the effects of E + P and estrogen alone on age-related changes in cognition in women without dementia within the context of a large randomized trial. It tests a broad range of specific cognitive functions, using measures that have been shown to be sensitive to the effects of age and hormonal modulation in previous studies in the Baltimore Longitudinal Study of Aging. The rationale, design and current status of the WHISCA study will be described. The presentation will emphasize what WHISCA can and cannot tell us about the effects of hormone therapy on cognitive aging and will highlight open questions for further investigation.

References: Shumaker et al. JAMA 2003; 289:2651-62.

EFFECTS OF ESTROGEN PLUS PROGESTIN ON PROGRESSION TO DEMENTIA IN POSTMENOPAUSAL WOMEN: RESULTS FROM THE WOMEN'S HEALTH INITIATIVE MEMORY STUDY (WHIMS)

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WHIMS is a randomized, double-blind, placebo-controlled clinical trial of women 65-80 years of age in the Estrogen + Progestin (E+P) trial of the Women's Health Initiative. WHIMS participants received either one daily tablet containing 0.625 mg of conjugated estrogen with 2.5 mg of medroxyprogesterone acetate (N = 2,229) or a matching placebo (N = 2,303). They completed a Modified Mini-Mental Status Examination yearly; women who scored below a set cutpoint were further evaluated with standardized interviews, physician assessments, and clinical/laboratory testing, as warranted. A blinded panel of central adjudicators reviewed cases assessed by local WHIMS site clinicians to determine the presence of dementia or Mild Cognitive Impairment (MCI). Overall, 61 women were diagnosed with probable dementia, 40 (66%) in the E+P group and 21 (34%) in the placebo group. The hazard ratio (HR) for probable dementia was 2.05 (95% Confidence Interval [CI], 1.21-3.48; 45 vs 22 per 10,000 person-years, P = 0.01). Alzheimer's disease was the most common classification of dementia in both study groups. Treatment effects on MCI did not differ between groups (HR, 1.07; 95% CI, 0.74-1.55; 63 vs 59 cases per 10,000 person-years; P=0.72). E+P therapy increased the risk of probable dementia in postmenopausal women aged 65 years and older and did not prevent MCI in these women. These findings, coupled with previously reported WHI data, support the conclusion that the risks of long-term use of E+P among older women outweigh the benefits.

ESTROGEN ACTIVITY IN MICROGLIA AS A POTENTIAL PHARMACOLOGICAL TARGET FOR AD THERAPY

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Several lines of evidence demonstrated that estrogens have beneficial effects on Alzheimer's Disease (AD) onset and progression; however, the mechanism underlying this effect is still poorly elucidated. It has been shown that estrogens prevent neuron loss induced by diverse insults by activating specific metabolic and signalling neural pathways. A relevant inflammatory reaction has been observed in AD brains and several lines of evidence suggest that a chronic activation of the inflammatory response may be detrimental for neurons. Based on our demonstration that the inflammatory cells of the brain, i.e. microglia, are targeted by hormone action, we proposed to use the APP23 transgenic mice, a genetic model of AD (expressing the Swedish mutated form of amyloid precursor protein associated with the early AD onset)[1] and study whether the activation of microglia associated with Aβ plaques could be modulated by estrogen (17β-estradiol, E_2). To this aim we first assessed whether hormone modulates the inflammatory response in wild-type animals, by inducing acute brain inflammation with i.c.v. injections of LPS. The results showed that E_2 strongly inhibits LPS-induced microglia activation and monocyte infiltration and that this effect is mediated specifically by estrogen receptor-alpha[2]. These results provide the first evidence for an *in vivo* anti-inflammatory activity of E_2 in the brain and point to the involvement of a specific intracellular receptor. In agreement with these findings, our preliminary results in APP23 mice showed that E_2 may limit the inflammatory reaction associated with brain pathology. In fact, chronic estrogen replacement therapy in ovariectomized female APP23 mice at 12 months of age reduced the number of activated microglia cells associated with Aβ deposits; accordingly with a negative effect of hormone on microglia activation, ovariectomy alone increased the activation of microglia as compared to sham-operated animals. Further results and ongoing experiments will be discussed.

[1] Sturcheler-Pierrat et al. Proc Natl Acad Sci USA 1997;94:13287-92.
[2] Vegeto E et al. Proc Natl Acad Sci USA 2003;100:9614-19.

ERα MEDIATES THE ANTI-INFLAMMATORY ACTIVITY OF 17ß-ESTRADIOL ON MICROGLIA

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Several studies have shown that 17β-estradiol (E_2) participates in neuron metabolic and survival pathways. However, we have shown that blood and brain-derived macrophages are also targets for E_2 action in the brain.[1,2] We previously reported that 6 h E_2 treatment is able to protect rats from acute brain inflammation induced through LPS injection in the third cerebral ventricle. Here we show that E_2 effect is maintained for up to 7 days, when LPS effect disappears, and that chronic replacement with E_2 is effective in preventing activation of microglia, the resident macrophages of the brain. To identify the molecular mechanism of E_2 *in vivo* anti-inflammatory activity in brain, we used estrogen receptor ? (ERα) and ? (ERß) knock-out mice, together with their wild-type (wt) littermates, injected with LPS in the third cerebral ventricle. After 24 h, reactivity of microglia was observed mainly in the hippocampus, as revealed by the increase in complement C3 expression. In wt mice, a 6 h treatment with E_2 prevented both the morphological and the biochemical activation of microglia, as well as in rats. Moreover, E_2 pre-treatment can prevent microglia from expressing important inflammatory mediators, such as iNOS, MMP-9 and MIP-2. Surprisingly, while E_2 effect in ERβKO mice was superimposable to that in wt mice, E_2 was not able to prevent microglia activation in ERβKO mice, suggesting a key role for ERα in mediating E_2 anti-inflammatory action. In fact, genetic disruption of the ERα gene leads to spontaneous activation of microglia in cingulated, parietal and rhinal cortices, hippocampus and amigdala, which is detected as ERα-null mice age, while it does not occur in wild-type or in ERβ-null littermates. Our results therefore point to ERβ as the molecular target of estrogen protective role in inflammation-based neurodegenerative diseases.

1 Vegeto et al. FASEB J. 1999;13:793-803.

2 Vegeto et al. J Neurosci. 2001;21:1809-18

OSTEOPOROSIS IN PREMENOPAUSAL WOMEN

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Osteoporosis is a systemic disease of bone characterized by decreased bone mass and changes in the microarchitecture of bone tissue followed by brittleness of bones and increased risk of fractures. It is commonly a disease of postmenopausal women, but can also occur in young adults. There are only few studies on the pathophysiology of premenopausal osteoporosis; in addition to idiopathic forms, it can be caused by glucocorticoid treatment, smoke, anorexia nervosa, eating or menstrual disorders, low body weight and low body mass index at menarche, cancer chemotherapy and genetic factors. Whether the negative impact of excess glucocorticoids on the skeleton is due to direct effects on bone cells, indirect effects on extraskeletal tissues, or both is unknown, but it has been demonstrated that excess glucocorticoids directly affect bone forming cells in vivo. Smokers have significantly reduced bone mass compared with nonsmokers: it is estimated that smoking increases the lifetime risk of developing a vertebral fracture by 13% in women. Reduced bone density is observed in over half of women with anorexia nervosa and is critically dependent upon nutritional factors in addition to the degree of duration of estrogen deficiency. Low bone density in the premenopausal female may reflect attainment of a lower peak bone mass. Menstrual status is an important determinant of peak bone mass; subclinical decreases in circulating gonadal steroids may be associated with a lower peak bone mass as well as progressive bone loss in otherwise reproductively normal women. 60% to 80% of bone mass is suggested to be under polygenetic control, but the role of individual genes seems to be modest. Further studies are needed to better know the role of genetic factors. Heredity and age at menarche are unmodifiable factors and attention should therefore be directed to more amenable factors. Amenorrhea, low body weight, disordered eating, physical inactivity and smoking are modifiable risk factors and should be corrected. This suggests that a simple risk factors assessment can identify most premenopausal women with low bone mass density. Early intervention in this group of women may reduce the risk of osteoporosis.

SELF REPORTED ARTHRITIS AND THE MENOPAUSE

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AUSTRALIA

ABSTRACT

OBJECTIVE :

To determine the prevalence of self-reported arthritis in the Melbourne Women's Mid-life Health Project cohort of mid-aged women and to identify health, social and lifestyle factors associated with self-reported arthritis.

DESIGN

Cross-sectional community-based survey by telephone interview of Australian-born women between 45-55 years old and residing in Melbourne in 1991. Information was collected on age, weight, height, medical history, health and lifestyle factors including moods scores, smoking history, hormone use and menopausal status. Arthritis was defined by answering yes to the question: Have you been diagnosed with arthritis?"

RESULTS

51.7% of women reported they suffered from aches and stiff joints. This was the most commonly reported symptom in this cohort. 34.4% of participants reported they had been diagnosed with arthritis and this was the most common chronic disease reported. More postmenopausal women (38.8%) reported they were diagnosed with arthritis compared to pre-menopausal women (27.36%; $p<0.001$). Logistical regression analysis found that women who reported arthritis were more likely to: be older (50.86 Vs 49.86); have a higher body mass index (24.6 Vs 23.7); be postmenopausal (38.8% Vs 27.4%); have a lower overall wellbeing score (1.60 Vs 1.45) and report a decrease interest in sex (44% Vs 30%).

CONCLUSIONS

Aches and stiff joints are the most frequently reported symptom of mid-aged women. Reported arthritis is associated with postmenopausal status, age, body mass index, less interest in sex and lowered mood. Further longitudinal research is needed to determine the role of these factors in the development of arthritis.

"OSTEOPOROSIS IN POSTMENOPAUSE: EXPERIENCE OF ASL 6, VENARIA"

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Dott. Pasquale Rosiello

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Postmenopausal osteoporosis is a disease characterized by skeleton fragility, related to reduced bone mass and density and to modification of bone microarchitecture, with high risk of fractures. The estrogen deficiency causes principally an imbalance in bone remodeling, between resorption and neophormation. The aim of the present study was to evaluate the correlation between risk factors for osteoporosis in a group of our postmenopausal population, recruited and followed during 2002 and 2003, and the Stiffness Index and T-score, measured with calcaneal quantitative ultrasound.During 2002 we recruited 1480 women under 65, followed for two years.The first evaluation consisted in a careful study of mean anamnes data (family and personal history).The physical activity and the diet intake of calcium were calculated by a detailed self-administrated questionnaire. All the women were also studied through specific lab-test for metabolic bone diseases and had QUS measurements at the calcaneus (with Lunar Achilles), executed in our Institute. We carefully provided to stress the message about the importance of modifie the lifestyle with the counselling. During the follow up, every six months, we noted the changes in patients life style. There is a relation between the lifestyle and a low Stiffness.The 35% of the women in postmenopause (518 subjetcs) had risk-factors (reduced intake of Ca and physical activity) associated. In the 20% of our women (296) the Stiffness indicated an osteopoenia.In these women the correction of the factors by the counselling increased the Stiffness for a 4% in the QUS control at 12 months.In 222 patients with osteoporosis the correction of risk factors, by an adeguate increase of the generic physical activity or specific individual programs, associated with the assumption of Ca and vitD and the use of antiresorptive drugs, improved the Stiffness about of a 10%.

OSTEOPOROSIS AND VERTEBRAL FRACTURES INCIDENCE IN CLINICALLY HEALTHY MENOPAUSAL WOMEN

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750 women who attended our divisional service for the relief and prevention of menopausal symptoms underwent a calcaneal QUS (quantitative ultrasonometry) for determination of their bone mineral density (BMD).
In order to find out the actual amount of patients affected by vertebral fractures in menopausal bone mineralization disorders, 110 patients with a definitive diagnosis of osteoporosis or osteopenia also underwent a vertebral computerized morphometry by X ray film, evaluating quantitative and semi-quantitative height of each single lumbar and thoracic soma. 64% out of the women enrolled in the study (71) resulted to be properly osteoporotic (T score ranged from –2.51 to –6.56 SD, mean value –3.2; Z score ranged from –0.63 to –5.06 SD, mean value –1.75). 42% of women in the osteoporotic group had at least one vertebral fracture, with a reduction of vertebral height ranged from 15.12 to 43.51%. Ill-shaped vertebrae were mostly located at thoracic level with an incidence twice as much as lumbar spine. Fractures were especially found at D7 and D9 level, while among lumbar soma the most frequent localization was L5. Moreover, a positive correlation between fracture severity and T and Z scores degree has been found. A very impressive result emerged from the analysis of data from the patients classified as osteopenic (36%, n= 39): 31% out of these women already had minimal vertebral fractures, with a percentage reduction of vertebral height comprised between cut-off value (>15%) and 21.66% in the worse case.
These data highlight the relevance of preventing vertebral accidents by life style modifications and/or an adequate therapy even in osteopenic patients.

RISK OF LOWENERGY FRACTURE IN THE YEARS AFTER DISCONTINUATION OF HORMONE REPLACEMENT THERAPY (HRT)

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In this study we have evaluated the effect of oestrogen alone and oestrogen in combination with progestin on low-energy fractures years. Specifically, we have examined to what extent duration of use, previous use, as well as recency of discontinuation of HRT influences the risk of fracture.
The study is a prospective cohort study and is based on questionnaire data from 7082 female nurses aged 50-69.
Compared to never users, current users of hormone replacement therapy, either oestrogen alone or combined with progestin, had a lower risk of low-energy, non-spinal fractures (hazard ratio 0.60, 0.39 to 0.93 and hazard ratio 0.44, 0.30 to 0.66, respectively). The protective effect of hormone replacement therapy appeared to be statistically significant only in users who had used the therapy for ten years or more (hazard ratio 0.27, 0.14 to 0.51). Women who had discontinued HRT experienced no protective effect on fracture risk regardless of duration of therapy and recency of discontinuation.
Only long-term hormone replacement therapy (ten years or more) offers a protective effect against low energy, non-spinal fractures.

ESTROGEN DEFICIENCY ALTERS TRABECULAR MICROARCHITECTURE OF MANDIBLE AND TIBIA

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Early detection of osteoporosis (OP) at the time of dental examination might be a useful practice if a technique to detect microarchitectural changes of mandibular bone existed. The purpose of this study was to investigate effects of estrogen deficiency on microarchitecture of the trabecular bone in the mandible and tibia, and to test the correlation of the microarchitectural alterations between the two bones. Twenty-four sexually mature age-matched Lewis-Brown Norway rats were randomly assigned to sham (SOVX, n=12) and ovariectomy (OVX, n=12) groups. Sixteen weeks later, the left side of the mandibles and tibias were scanned with high-resolution Micro-CT. The Bone Volume/Tissue Volume (BV/TV), Trabecular Thickness (Tr.Th.), Trabecular Separation (Tr.Sp.), and Structure Model Index (SMI) were obtained for morphological calculations. OVX group had significantly decreased BV/TV and Tr. Th., while significantly increasing Tr.Sp. and SMI in the mandible ($p < 0.005$) and the tibia ($p < 0.005$). There were significant positive correlations between the mandible and the tibia for Tr.Sp. ($r = 0.68$, $p < 0.0125$) and SMI ($r = 0.60$, $p < 0.0125$). There were no significant correlations for BV/TV ($r = 0.468$, $p > 0.0125$) and Tr. Th. ($r = 0.471$, $p > 0.0125$) although moderate levels of correlation were determined. Estrogen deficiency results in microarchitectural alterations of trabecular bone in both the mandible and the tibia. The size of the marrow spaces and the shape of trabeculae in the mandible are correlated with osteoporotic changes in the long bone. These data suggest the potential utility of oral trabecular bone pattern for the detection of OP.

MOLECULAR MECHANISMS OF FEMALE SEX HORMONE ACTION ON PROLIFERATION

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Female sex hormones (E and P) are direct mitogens for a subset of their target tissues, including the mammary gland where they induce growth of normal and transformed cells *via* specific intracellular receptors (ERs and PRs) and act as tumor promoters. In hormone responsive human breast cancer (hBC) cells these steroids promote G_1 progression by inducing expression of the cyclin D1 gene (*CCND1*) and phosphorylation of pRb. The mechanism by which E and P control *CCND1* expression, a key process in both normal mammary gland physiology and breast carcinogenesis, still awaits elucidation. The region conferring responsiveness of the *CCND1* gene to E in hBC cells binds *in vivo* the c-*Jun*/c-*Fos* heterodimer, which targets the ER to the promoter. In this way, E promotes formation of a multi-protein complex on the *CCND1* promoter that enhances transcription within 15 min of hormone challenge. These early events are followed by recruitment of the $p36^{D1}$/cdk4 holoenzyme to promoter *via* a constitutively bound E2F/pRb complex. This kinetic transcription factors interplay, which reflects the early cell cycle changes resulting from timed gene expression induced by E in hBC cells, characterizes *CCND1* as the first known primary and secondary response gene. Interestingly, progesterone triggers similar regulatory events through its own NRs, suggesting that the gene regulation cascade uncovered here represents a cross-road for transcriptional control of G_1 phase by different classes of NRs.
Genome-scale gene expression profiling analyses of hBC cells response to estrogens identifies discrete patterns of hormone-dependent gene activation and inhibition and uncovers multiple hormone specific gene regulation events. Interestingly, E target genes are not randomly distributed in the genome as, for example, chromosome 17 is particularly rich in hormone-activated gene clusters. These results suggest a higher level of regulation of genome activity by female sex steroids.
Research supported by grants RBNE0157H_001 and 2002067514_002 from MIUR and by a research grant from AIRC.

MENOPAUSE, HORMONE THERAPY AND BREAST CANCER RISK

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Most data on menopause, hormone therapy (HT) and breast cancer risk available until the mid 1990's, were included in a Collaborative Re-analysis of individual data from 51 epidemiological studies, based on over 52,000 women with breast cancer and 108,000 without breast cancer. HT increased breast cancer risk by about 2.3% per year of use. However, the increased breast cancer risk associated with HT declines within a few years after stopping use. At least 5 case-control and 4 cohort ones were subsequently published. They confirmed that breast cancer risk is elevated in current and recent (but not past) HT users, that the relative risk (RR) is higher for users of combined estrogen-progestin treatment than for users of estrogen only, but is seen with various types of preparations (including tibolone) and routes of administration. With reference to intervention studies, relevant information on cancer risk in users of combined HT derives for the Women's Health Initiative (WHI), including 8,506 women aged 50 to 70 treated with combined HT estrogen/progestogen and 8,102 untreated women. At 7 years follow-up, 166 breast cancer cases were registered in the HT group versus 124 in the placebo group, corresponding to a RR of 1.24. Data from two other smaller randomized studies are available, one (HERS) with combined therapy, and one (WEST) with estrogen only. In a combined analysis of the three randomized trials, 205 cases of breast cancer were observed in the treated groups versus 154 in the placebo ones, corresponding to a pooled RR of 1.27. The results from the WHI did not confirm the suggestion that breast cancers in women using HT have a more favourable prognosis. Likewise, in the Million Women study, there was no consistent suggestion that prognostic indicators were more favourable among women who had ever used HT.

THE BIOLOGICAL BASIS FOR THE DETECTION OF EARLY STAGE OVARIAN CANCER

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QUALITY OF LIFE THROUGH AND BEYOND MENOPAUSE – DEFINITION AND EVALUATION

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Quality of Life (QOL) is an outcome variable requiring measurement in clinical care or pivotal regulatory research. Until recently, all menopause-related QOL measures have predominantly been life phase or disease symptom inventories or scores. These will be reviewed. The latest generation of instruments validated for quantifying sense of well-being in a perimenopausal population is represented by the Utian Quality of Life Scale (UQOL). Details will be presented of the domains and value in clinical care or research. Utilization of such instruments in clinical care will be elaborated, and the value of combining pure QOL instruments with symptom scores will be considered.

Utian WH, Janata JJ, Kingsberg S, et al. The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. *Menopause* 2002;9:402-410.

EXERCISE EFFECTS ON TOTAL BODY FAT, INTRA-ABDOMINAL FAT, INSULIN, LEPTIN, AND THE METABOLIC SYNDROME IN MENOPAUSE

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The increasing prevalence of obesity in women is a major public health concern around the world, since obesity is associated with several chronic diseases including coronary heart disease, diabetes mellitus, hypertension, stroke, and certain cancers, particularly colon, postmenopausal breast, endometrial, esophageal, and kidney cancers. Metabolic Syndrome ($\geq$ 3 of the following characteristic: waist circumference > 88 cm, serum triglycerides > 150 mg/dL, HDL cholesterol < 50 mg/dL, blood pressure $\geq$ 130/85, fasting glucose $\geq$ 110 mg.dL) increases in prevalence with menopause and aging in women, and markedly increases risk of several of these chronic diseases. Previous research indicates that lifestyle dietary and physical activity change to produce weight loss significantly improves these correlates of obesity, and reduces risk of developing diabetes. We conducted a 12-month randomized controlled trial in 173 overweight postmenopausal women aged 50-75 years in Seattle, WA. Exercisers completed an average 171 minutes/week (vs. goal 225 min/week) of moderate-intensity aerobic activity such as brisk walking. 170 women completed the trial, and 6 exercisers dropped the intervention. Caloric intake did not change in exercisers or controls. We observed statistically significant differences in exercisers vs. controls in: DEXA-measured % body fat (-1.0%, $p<0.01$), intra-abdominal fat (-8.6 cm^2, $p<0.05$), fasting insulin (-2.8 U/mL, $p=0.0002$), and leptin (-3.3 ng/mL, $p=0.04$). Fasting glucose and triglycerides did not change differently in exercisers vs. controls. Physical activity promotes loss of body fat, particularly the highly metabolic intra-abdominal fat, and may reduce the incidence and severity of Metabolic Syndrome and its related biomarkers.

OESTROGENS AND THE LOWER URINARY TRACT

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Oestrogen is known to have an important role in the function of the lower urinary tract throughout adult life, with oestrogen receptors demonstrated in the vagina, urethra, bladder and pelvic floor musculature. Lower urinary tract symptoms are common in postmenopausal women attending menopause clinic. Oestrogen deficiency following the menopause causes atrophic changes within the urogenital tract and is associated with urinary symptoms such as frequency, urgency, nocturia, incontinence and recurrent infection. These may also co-exist with symptoms of vaginal atrophy. Oestrogens may affect continence by increasing urethral resistance and raising the sensory threshold of the bladder. On urodynamic testing, postmenopausal women have been found to have reduced flow rate, increased urinary residuals, higher filling pressures, reduced bladder capacity and lower maximum voiding pressures.

When considering urinary urgency, frequency and urge incontinence, oestrogen therapy is commonly of benefit, although this may simply represent reversal of urogenital atrophy rather than a direct effect on the lower urinary tract. Oestrogens have not been shown to significantly improve urodynamic stress incontinence.

HORMONE REPLACEMENT THERAPY (HRT) AND COLORECTAL CANCER: NEW EVIDENCE FOR AN UNSPECTED FINDING

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Colorectal cancer is the most frequent neoplasm in non-smokers of both sexes combined in Western countries. Similar incidences in men and women are seen for colon cancer, whereas a male predominance is found for rectal cancer. During the last few decades, mortality trends from colorectal cancer have been consistently more favourable in women than in men in Europe. This may be due to healthier dietary and lifestyle patterns in women, but also to a potential protective effect of exposure to exogenous female hormones in women (i.e. hormone replacement therapy [HRT] and perhaps oral contraceptives). The effects of the menopause and age at menopause on the risk of colorectal cancer are unclear[1].

Many cohort and case–control studies have reported on HRT use and the risk of colorectal cancer. Cohort studies with a total of over 2400 cases have reported on HRT use and the risk of colorectal cancer. Most showed relative risks (RRs) around or below unity. A significant inverse association was found in two (including the largest one), focusing on fatal colon cancers. A short-term improvement in survival among HRT users after a colon cancer diagnosis has also been suggested[1,2].

Among 12 case–control studies including over 5000 cases, five reported significant risk reductions, of 20–40%, among those who had ever used HRT. Although these observational studies support a possible inverse association between colorectal cancer and HRT, prevention and surveillance bias cannot be excluded. Thus, data from randomized controlled trials are of extreme importance.

Data from randomized studies including over 4000 healthy women followed up for almost 5 years on average also indicate a lower incidence of colorectal cancer among HRT users. The, evidence from observational and randomized studies is consistent in showing a reduced risk of colorectal cancer among women who had ever used HRT. Open questions include the quantification of the role of duration of HRT use, time since first or last use, type of menopause and route of administration of HRT, and interactions with lifestyle factors.

1. Franceschi et al. Eur J Cancer Prev 1998;7:427-38
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MOLECULAR CHARACTERIZATION OF BREAST CANCER AGGRESSIVENESS

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Breast cancer (BC) is a very composite disease, with clinical outcomes ranging from complete cure to early relapse and death. Clinical variability is due to the diversity of genetic changes occurring in individual tumors. A modern way for monitoring the activity of genes and the effects of structural changes at the genome level is the molecular profiling of gene expression, by measuring the relative mRNA levels of thousands of genes at once on DNA microarrays (MA). Retrospective analysis of frozen BC tissues has already proven to be extremely informative, since tumors from patients relapsing at short time have a very distinctive gene expression signature. The set of genes showing optimal prognostic power can be computationally restricted to few tens. This will permit routine analysis of all BCs by cheaper methods, such as real-time RT-PCR. Identification of a set of relapse-associated genes was also performed by directly comparing small pools of poor-prognosis *versus* good-prognosis BCs, with oligonucleotide MA. Among the subgroup of genes showing association with BC aggressiveness, there are both known genes, i.e. genes whose role in cancer is well-defined or suspected, and completely new genes, e.g. a number of splicing factors. Investigating the functions of these genes will give clues not only to additional molecular mechanisms of cancer development and progression, but also to new potential drug targets. A second, important point to address is BC sensitivity to chemo- or hormone therapies. A metanalysis of MA data in the public databases was performed, showing that a subset of genes, among those responding to estrogen treatment of BC cells in culture, was sufficient to correctly classify hormone-dependent BCs. MA analysis of BCs responding to chemo- and hormone therapy is currently under way in several laboratories. In conclusion, molecular profiling will provide in the near future reliable predictors of BC outcome and response to treatment, as well as new targets for innovative drug development.

COMBINED ADMINISTRATION OF INDOMETHACIN, ANASTROZOLE AND VINORELBINE EXERT ANTIANGIOGENIC, ANTIMITOTIC AND ANTIAROMATASE ACTION AGAINST INVASIVE DUCTAL CA (IDC) METASTASIZED TO AXILLARY LYMPH NODES OF A POSTMENOPAUSAL PATIENT CHARACTERISED BY OVEREXPRESSION OF HER-2/NEU, COX-2,RAS,BCL-2 AND ER

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HER-2/neu stimulates COX-2 to enhance the levels of PGE2 which is an inducer of aromatase (CYP19) gene activity,increasing intracellular cAMP levels which stimulates estrogen biosynthesis.

HER-2/neu stimulated COX-2 transcription via the Ras/Raf/MAPK pathway.We have obtained from the patient breast tumoral tissue pre- and post-treatment for analysis with IHC,Western Blotting and RT-PCR.Pre-treatment,we observed upregulation and overexpression of HER-2/neu,COX-2,bcl-2, Ras,CD31(endothelial cell marker of proliferation), Ki67 (proliferation marker), PGE2,CYP19 and ER.

The tumor was of large size with high histological grade and axillary node metastasis.Post-treatment,

we observed downregulation of COX-2,bcl-2,CD31,Ki67,PGE2,CYP19 and ER. More analytically,

indomethacin as COX-2 inhibitor blocked PGE2 and acted synergistically on aromatase inhibition which blocked conversion of C19 steroids to estrogen. Furthermore,inhibition of COX-2 inhibited angiogenesis. Vinorelbine blocked cell cycle at G2/M according to flow-cytometry after microtubule depolymerization and downregulated bcl-2 after phosphorylation. MTT and BrdU assays exhibited inhibition of metabolic activity and DNA synthesis of tumor cells compared to controls. Also, the

proliferation marker Ki67 was reduced. TEM exhibited irreversible D2 stage of apoptosis forming apoptotic bodies which were phagocytosed by adjacent tumor cells indicating a bystander killing effect.

TUNEL and AnnexinV-FITC confirmed the morphological results. Concluding,chemosuppression of

HER-2/neu (+) breast tumor with indomethacin,anastrozole and vinorelbine is associated with antiangiogenicity.

THE D327N VARIANT OF HUMAN SEX HORMONE-BINDING GLOBULIN (SHBG) IS LINKED TO BREAST CANCER GOOD PROGNOSIS.

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Sex Hormone-Binding Globulin (SHBG) binds and transports estradiol in the blood, regulating thus its bioavailable fraction. By interacting with a specific cell membrane binding site, SHBG also inhibits the proliferation of breast cancer cells. A variant form of human SHBG (D327N SHBG) resulting from a point mutation in exon 8 of *shbg* coding gene, has been reported to occur with a significantly higher frequency in breast cancer patients with estrogen receptor positive tumours diagnosed in post-menopause. The association between the variant SHBG and two favourable prognostic factors induced us to analyze a brand new group of breast cancer patients (n=81) and to evaluate the distribution of the D327N SHBG in relationship with a number of prognostic factors: The variant SHBG was significantly more frequent in estrogen receptor positive cancer and in cancer diagnosed after menopause, confirming also in this new group our previous finding. Moreover, the variant SHBG was also more frequent in erb2 and p53 negative tumours. In conclusion, the variant form of SHBG is more frequent in breast cancers characterized by favourable prognostic factors. We, thus, suggest that women carrying the D327N SHBG, in case unfortunately develop in their life breast cancer, are likely to be affected by a neoplasm with a god prognosis.

MICROARRAY AND PROTEOMICS ANALYSES OF TIBOLONE, MEDROXIPROGESTERONE ACETATE AND 17β-ESTRADIOL IN BREAST CANCER CELLS IN VITRO

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Recent evidence suggests that hormone therapy, estrogen (E2) alone or estrogen combined with a synthetic progestin, increase the incidence of breast cancer. Tibolone (Tib), a selective tissue estrogenic activity regulator (STEAR), has been used for many years for osteoporosis prevention and relief of postmenopausal symptoms. Tib and its metabolites have been demonstrated to have a proapoptotic and antiproliferative effect and to reduce the formation of E2 in the breast, in vitro. We designed our study to investigate the effect of Tib, its metabolites (3αOH-Tib, 3βOH-Tib and Δ^4-Tib), medroxyprogesterone acetate (MPA), and E2, using microarray and proteomic technology, in T47-D and MCF-7 breast cancer cell lines. Microarray analysis in MCF cells revealed that 248 genes were altered by E2. Angiogenic (VEGF, FGF) and prooncogenic genes (Sp2) were upregulated by E2. 3αOH-Tib and 3βOH-Tib, both estrogenic metabolites of Tib, modulated 47 genes. Antiangiogenic (BAI) and proapoptotic (ubiquitin-6; BCL-2 protein) genes were upregulated, whereas cell cycle regulators genes were downregulated by these OH-metabolites. These results indicate a different effect of Tib-OH metabolites in comparison with E2 in breast cells. In T47-D cells, 84 genes were significantly changed by Δ^4-Tib. Proapoptotic (BCL2 protein, IP3), inhibitors of cell cycle (cyclin-kinase 4 inhibitor) and antiangiogenic genes (TSP-2) were upregulated, whereas angiogenic genes (TNF) and cell cycle regulators (Sp2) were downregulated. Overall, MPA treatment upregulated angiogenic genes and cell cycle regulators, whereas proapoptotic genes downregulated. Finally, using proteomic technology we compared the effect 3αOH-Tib and E2 in MCF cells. We have observed a different "proteomic-fingerprint" (protein expression pattern) in the proteomic analysis when comparing 3αOH-Tib and E2.
Gene expression combined with proteomic information,
provides a more detailed picture of the different effect of Tib in the breast in comparison to E2 and MPA.

ENDOMETRIOSIS AND ENDOMETRIOSIS-RELATED MORBIDITY IN A LARGE COHORT

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Endometriosis has been linked to autoimmune conditions and hormonally-responsive cancers. We asked whether endometriosis treatments may alter the risk for co-morbidities. 3711 women with laparoscopically-diagnosed endometriosis responded to a self-administered survey. Treatments for endometriosis were queried as were physician diagnosed co-morbidities including autoimmune diseases (systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and Sjögren's syndrome); hypothyroidism; fibrocystic breasts; fibroid uterus; and breast or ovarian cancers. Danazol use was more frequently reported by women with endometriosis plus autoimmune disorders (OR 1.5, 95% CI 1.0, 2.2) than among women with endometriosis alone, after adjustment for age, parity, and other treatments. Progestin use was more commonly reported by women with each of the co-morbidities studied including autoimmune diseases, hypothyroidism, fibrocystic breasts, fibroid uterus, and cancers (ORs 1.2-2.3) than by those with endometriosis alone. Combined oral contraceptive use was less common among women with endometriosis plus breast/ovary cancers (OR 0.3, 95% CI 0.1, 0.6). Danazol and progestin, used to treat endometriosis, elevated the risk for related co-morbidities. Endometriosis-associated cancers developed less commonly among women taking combined oral contraceptives. These data, if replicated, favor the use of some endometriosis treatments over others.

ENDOMETRIAL CANCER IN POSTMENOPAUSAL WOMEN

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Background: The endometrial cancer's sick rate among women in economy developed countries increases at last 20-30 years. Sick rate in postmenopausal women is at 10 times more than in premenopausal women. The influence of the age and menopause on the endometrial cancer's prognosis is discussed [Alektiar KM et al. Cancer. 2003; 98:2368-77; Mangili G Eur J Gynaecol Oncol. 2002; 23: 216-20]. Purpose: Studying the clinical and morphological peculiarities of endometrial cancer in postmenopausal women. Methods and materials: Data of 1559 primary patients with endometrial cancer I-IV stages (1233 of postmenopausal age and 326 of premenopausal age) who were treated at the N.N. Petrov Search Institute's department of oncological gynaecology in the period from 1960 to 1995 inclusive were examined. The math analysis included: age, menstrual and reproductive functions, parameters of patients' endocrine and immune status, stage, hystological type and depth of invasion, RE, RP. Results: It was determined that fertility's lowering and infertility in anamnesis were rarely (11 and 70 %), and the obesity was often (83 and 62 %) in postmenopausal women in comparing with premenopausal patients. The diabetes, RP- and clear cells carcinomas were detected only in postmenopausal women. The infertility didn't influence on the of the reproductive age patients' survival, and correlated with the negative prognosis of postmenopausal women. Conclusions: Pathogenesis and prognosis of endometrial cancer in postmenopausal and premenopausal patients are different and there should be different ways of looking at the prophylaxis and treatment.

INHIBIN A, INHIBIN B, PRO-ALPHAC AND ACTIVIN A – VALID MARKERS FOR OVARIAN AGING?

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The ovary produces growth factors that are involved in the regulation of follicle development. Among these, inhibin A, inhibin B, activin A as well as a precursor of the alpha-chain named pro-alphaC are ovarian glycoproteins. The inhibins were first characterized for their inhibitory effect on pituitary FSH secretion, whereas avtivin A shows an equipotent capacity to increase FSH release. We performed a study to evaluate serum levels of inhibin A and B, pro-alphaC and activin A in healthy premenopausal women at different age and to compare them with levels in healthy postmenopausal women. Material and Methods: The study design included three groups of women: group 1 consisted of 29 women, age range 20-25 years; group 2 consisted of 27 women, age range 38-43; group 3 consisted of 85 postmenopausal women. Within the fertile period the serum concentrations of all four ovarian glycoproteins were measured at three different days of the menstrual cycle (early follicle phase, time of ovulation, middle of the luteal phase). Inhibin A and B, pro-alphaC were measured in all serum samples using specific two-site ELISAs purchased from Serotec (Oxford, UK). A complete medical history was obtained and a physical examination was performed from each women. Serum FSH, LH, estradiol, testosterone and progesterone were measured with the use of specific assays. Results: The inhibin A and B as well as pro-alphaC serum levels of the young fertile women were significantly higher than those of the postmenopausal women ($p< 0.1$). The activin A level did not change significantly between all three groups. Inhibin A and B serum levels decreased before FSH and LH rised up at the beginning of the perimenopausal period. Within the fertile groups the inhibin A and B serum levels of the younger women were significantly higher compared to the results of the elder regularly menstruating fertile women. Conclusion: Inhibin A and B and less pronounced pro-alpha C but not activin A are valuable markers for the ovarian function and may reflect the ovarian age.

GENETIC MECHANISMS IN PREMATURE OVARIAN FAILURE: IMPLICATION OF X CHROMOSOME

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Premature Ovarian Failure, premature menopause, or early menopause, is a condition generally characterized by amenorrhea and impaired fertility with or without hypoestrogenism and elevated serum gonadotropin levels in women younger than 40 years. Although often used as synonyms, POF is not equivalent to menopause and reproductive capacity can sometimes be succesfully reverted. As expected, POF proved to be a multifactorial determined condition: genetic, immunologic, iatrogenic and infectious factors were incriminated in the pathophysiology of this disease.

Ovarian functioning is closely linked to proper coordination between se- veral compartments including endocrine, immunologic, cellular and gross anatomic systems. Hormone structure and production, receptor structure, antibody response, cell division cycle, gametogenesis, follicle recruit-ment and development, ovarian gross structure share the same trait: they all have a genetic determinant. Recent genetic studies have revealed nu- merous genetic mechanisms that lead to POF including: pure or mosaic aneuploidy (Turner monosomy), Xq/Xp deletions, balanced X-autosome translocations, isochromosome i(Xq), GpC islands methylation (FRAXA permutation), histone acetilation and point mutation of several genes encoding: hormone receptors (FSH, LH receptor encoding gene), tyrosine kinase receptors (KIT gene), hormones (Inhibin A gene), metabolic enzymes (Gal-1-PUTgene - in galacto-semia), steroidogenic enzymes (cytochrome P450c17 - CYP 17), mem- branar transport components (DIA gene), transcription factors (AIRE gene - Autoimmune polyendocrinopathy syndrome APS1), trans-acting factors (FOXL2 - in resulting in blepharophimosis-ptosis-epicanthus inversus syndrome BPES type I), adhesion molecules (KALIG1- in Kallmann syndrome), etc.

The topic of the present workout is to review current knowledge on genetic mechanisms of improper ovarian function and to report our results upon a prospective study regarding genetic determination of POF. The study was carried out in a non-randomised fashion, including female subjects under age 40 with amenorrhea and/or serum FSH over 40 UI/l.

Genetic studies included kariotyping, PCR amplification, Denaturating Gradient Gel Electrophoresis (DGGE) and DNA sequence analysis.

OSTEOPROTEGERIN AND RANKL: WHAT IS THEIR ROLE IN THE OSTEOPOROSIS MANAGEMENT AND DIAGNOSIS (POST-MENOPAUSAL)?

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Most of the molecular biology studies confirm the important and valid role played by two new bone markers: OSTEOPROTEGERIN (OPG) and RANKL. Bone resorption is a very complex process characterised by a series of events which contribute to form mature osteoclastic cells. This process is greatly influenced by a variety of factors (e. g. interleukin-1β, interleukin-6, prostaglandin E2, PTH, etc) which act through the OPG-RANK-RANKL system. The osteoclastic precursors and osteoclasts themselves present a membrane receptor, known as RANK, which, once activated by its RANKL ligand (produced by osteoblasts in response to external stimuli) induces a series of events that leads to the formation of mature osteoclasts and, then, to bone resorption. OPG is a molecule belonging to the super family of TNF receptors which presents a marked inhibitory activity on osteoclastogenesis, mediated by its link with RANKL. The delicate balance of this system is very fondamental in order to guarantee correct osteoclastic recruitment. Recently we've examined some talassemic patients even affected by secondary osteoporosis, to find out a significant statistic variation of OPG serum concentration and bone densitometer (DEXA) in comparison with a group of the same age, sex healthy people (1,2). We have started a research in order to valuate OPG and RANKL serum concentration in a post-menopausal female group, who followed an hormonal therapy and non ormonal, verifying the contemporary variation of the bone density through the Unigamma X-Ray Plus densitometer at the beginning of the study and after twelve months. The final goal is to verify the modifications of these two new bone markers, related to the densitometer variations and the employed therapies, in order to use these new markers as affective in bone resorption.

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PROBABILITY OF DEVELOPING PREMATURE OVARIAN FAILURE (POF) AT DIFFERENT CUMULATIVE DOSES OF INTRAVENOUS CYCLOPHOSPHAMIDE (IV CYC) THERAPY.

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Ovarian toxicity is a known secondary effect of IV CYC. However, the probability of developing POF at different cumulative doses is unknown. Aim: To determine the probability of developing POF at different cumulative doses of IV CYC. Methods: 26 premenopausal women suffering from systemic lupus erythematosus were followed prospectively since the beginning of intermittent pulse IV CYC therapy up to the development of POF or last IV CYC pulse. At baseline, demographic and gynecological variables and disease related factors were recorded. Before each pulse, a standardized form was filled where information about the dose of IV CYC, disease activity (SLEDAI), and concurrent medications was documented. In addition, blood samples were drawn at -60, -30 and 0 minutes before IV CYC pulse to determine FSH, LH and estradiol in serum. Statistical analysis: descriptive statistics, Mann Whitney U test, Fisher exact test, logistic regression, Kaplan Meier Curves; p value was set at <0.05, two-tail. Results: Mean (±SD) age at start of CYC treatment was 26.3±5.3 yrs (17-37), number of pulses 7.1±4.6 (2-19), CYC dose/body surface area 663.5±102.6 mg/m^2 (535-950), total accumulated CYC dose 7.61±5.82g (2.0-24.25). Five women developed POF after an accumulated dose of 5.5, 8.0, 9.95, 13.85 and 23.8g, respectively. In the multivariate analysis, accumulated dose of CYC and age were the only variables that significantly predicted POF. In two of the five affected patients POF was temporary. Conclusion: Young women who receive intermittent pulse IV CYC therapy are free of developing POF with accumulated doses <5g. The probability of developing POF rises proportionally to the accumulated dose. Whether those women who did not develop POF are at increased risk of developing menopause at an earlier age than expected is pending to be determined.

THE ATP-SENSITIVE POTASSIUM CHANNEL OPENER ZM226600 IMPROVES MICTURITION PARAMETERS IN FEMALE RATS WITH PARTIAL URETHRA OBSTRUCTION

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Detrusor overactivity, which is characterized by involuntary bladder contractions and loss of urine, is a major cause of urinary incontinence, a common health problem in both sexes. Its treatment, despite advances in pharmacotherapy, still remains unsatisfactory. Nowadays, some new drugs such as the ATP-sensitive K^+-channel openers may represent a possible alternative to muscarinic antagonists. Unfortunately, for most of them (pinacidil and cromakalim) the clinical utility is dampered by an unacceptable level of hypotension at effective doses. The aim of the present work was to investigate the activity of a new ATP-selective potassium channel opener ZM226600 compared with that of pinacidil, on female rats with partial outflow obstruction. The proximal urethra of female rats was partially obstructed for 6-8 wk and bladder function was compared with that of age-matched controls. Bladder weight (102±9 vs 462±93 mg) and capacity (0.91±0.10 vs 4.14±0.46 ml) increased significantly in rats with urethra obstruction. Accordingly, resting pressure, pressure threshold, maximal contraction, contraction interval, contraction time, expulsion time, micturition volume, residual urine and voiding per hour, were also significantly altered compared to controls. Bladder instillation of ZM226600 (10^{-9} - 10^{-7} M, 30 min) almost completely blocked detrusor overactivity during the filling phase and reduced residual urine, increased contraction interval and micturition volume, altering blood pressure by only 5% in operated rats. Conversely, bladder instillation of pinacidil, at the same doses, reduced detrusor overactivity but also reduced blood pressure by about 25%. In conclusion, ZM226600 improved cystometric parameters in rat with urethra obstruction showing only slight effects on blood pressure, at the doses used. To the reason, it might be taken into consideration for new preclinical studies which might promote its use as a pharmacological tool for treatment of urinary incontinence.

UROGENITAL ATROPHY AND URINARY TRACT INFECTIONS

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Objective: To evaluate the occurrence of urinary tract infections in women over 50 years old , with symptoms of urogenital atrophy and their responses to hormone therapy.
Materials & Methods: We evaluated 3000 ambulatory women between 30 and 70 years old ; presenting to our medical Center , from January 2002 to June 2003. They were asked regarding: symptoms of vaginal dryness, history of urinary tract infections (diagnosed by the clinic, pathologic urine sediment and positive urine culture), and concomitant hormone therapy (estrogen therapy/estrogen-progestin therapy).
Results: Over the course of eighteen months , 7% of the women under the age of 50 and 12% (p<o,oo5) of the women over 50 presented urinary tract infections, with 16% of the latter group presenting a recurrent urinary tract infection. 8% of the women over 50 receiving hormone therapy for more than 6 months (systemic or vaginal) presented urinary tract infection.
In 78% of the cases, *Escherichia coli* was the pathogen isolated.
With respect to hormone therapy for clinical symptoms of repeated urinary tract infections, 60% of the women would prefer local and 30% would prefer systemic hormone therapy (oral or percutaneous administration in the majority of cases).
Conclusions: The incidence of urinary tract infections within the group of menopausal women over 50 years old , was lower for those women receiving more than 6 months of hormone therapy, with an incidence almost equivalent to that observed in the group of women under the age of 50.

COMBINED VAGINAL ESTRIOL AND SYSTEMIC ALPHA ADRENERGIC AGONIST THERAPY – EARLY EFFECTS ON UROGENITAL COMPLAINTS IN POSTMENOPAUSAL WOMEN WITH NON INSULIN DEPENDENT DIABETES MELLITUS NIDDM.

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The aim of the study was to evaluate the early effects of combined treatment of vaginal estriol and alpha adrenergic agonist compared to vaginal estriol only in postmenopausal women with NIDDM.We studied 21 women aged 42-62 years, with natural (N=11) and surgical (N=10) menopause, mean years since menopause 6,6. We included in the study women with controlled NIDDM (mean HbA1c 5,8mg/dl). 19 of the patients had a history of NIDDM of less than 8 years, except of two patients with more than 8 years. Exclusion criteria were: prior hormonal replacement therapy, signs of pelvic relaxation, such as cystocele, rectocele, and/or uterine prolapse, urinary or vaginal infection and history of pelvic surgery. The subjects were evaluated clinically for history of symptoms related to urogenital atrophy, gynecological examination with a vaginal smear and cytological examination (maturation index). The most common symptoms were vaginal dryness, burning, pruritus (45%), dyspareunia (21%), vaginal discharge (11%), vaginismus (1 case), dysuria (29%), urinary frequency (42%), stress incontinence (57%), nocturia (30%), voiding difficulty (2 cases). Peak incidence of urinary stress incontinence occurred in the first 5 years postmenopause. In 9 women we administered vaginal estriol plus systemic alpha adrenergic agonist, and in 12 women we administered only vaginal estriol (3 weeks 0,5mg daily, and after twice/week). We evaluated both study groups at 1 month for symptoms and 3 months for symptoms and with vaginal smear. Results: at 1 month the group with combined treatment had a better improvement of dysuria, nocturia, urinary frequency (33% compared to 28%); reduction in dyspareunia, pruritus, vaginal dryness had no differences between groups, with significant improvement at 1 month of treatment (60%). Cure rates were obtained at 3 months in 72% of patients for symptoms related to vaginal atrophy. On gynecological exam objective improvement at 3 months of treatment was observed in 64% of cases - amelioration of vaginal cytology, increased vaginal fluid secretions and mucosa thickness. Absence of dysuria and stress incontinence were noted in 6 of 9 women in the combined treatment group, and in 6 of 12 women in the estriol only group. In 2 cases with NIDDM of more than 8 years there were no signs of improvement regarding voiding difficulties. In conclusion: combined vaginal estriol with systemic alpha adrenergic agonist in diabetic postmenopausal women provide effective relief of utinary symptoms, as early as 1 month of treatment.

LOWER URINARY TRACT SYMPTOMS AMONG MALAYSIAN WOMEN 45 YEARS AND ABOVE AND ITS IMPACT ON THEIR QUALITY OF LIFE

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OBJECTIVES: To evaluate the prevalence of lower urinary tract symptoms in Malaysian women age 45 years and above and to assess the influences of these symptoms on their quality of life.
METHODS: We randomly sampled all women age 45 years and above attending general gynaecology and menopause clinics at a large teaching hospital in an urban population. The women were successfully interviewed using a 2-part questionnaire consisting of Part 1: Demographic Data and Part 2: **Bristol Female Lower Urinary Tract Symptoms (BFLUTS)** Questionnaire.
RESULTS: A total of 250 women were recruited into this cross-sectional study. The mean age was 53.2 years. 82.4% of them received secondary education and above and 40.8% are career women. Majority of them (81.2%) are married. 71.6% have reached menopause, either naturally or surgically. Of the women sampled, 42.4% (106 women) perceived that they have urinary problems. However, only 34.9% of these women actually seek medical services for treatment. Commonest reason for not seeking treatment was that urinary symptoms are minor problem and not a disease requiring treatment (52%). Of the women who perceived problems with their bladder, 78.3% had stress incontinence and 65.1% claimed to have urge incontinence. As for symptoms of overactive bladder, 47.2% had urgency, 39.6% experienced urinary frequency, 23.6% complained of dysuria, 20.8% had nocturnal enuresis and 15.1% had nocturia. 28.3% of the women reported some form of voiding dysfunction. Interestingly, working women reported more urinary symptoms compared to those who were not (p=0.032). The occurrence of urinary symptoms were not significantly influenced by the menopausal status (p=0.345) but menopause women who took hormone replacement therapy experience less urinary symptoms compared to those who did not (p=0.024). Approximately one-third of those affected by the urinary symptoms had restricted their social activities and of those who are sexually active (67.9%), more than one-third reported an affected sexual life.
CONCLUSION: Urinary symptoms are common among Malaysian women above 45 years of age but majority of them did not seek treatment as they perceived these symptoms as minor problems with increasing age. These symptoms were more common among working women with stress incontinence being the most predominant symptom.

Urinary infection associated with pregnancy

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The study made on a number of 4.000 pregnant women showed that, during pregnancy, urinary infection takes different forms between asymptomatic becteriuria and septicemia (3,4%).

The most common clinical form they have met was the chronic pyelonephritis (60 % of the cases). The most frequently isolated bacterial organism was Escherichia Coli (80 %), but there are some ather bacterial organism implied (enteroccus, staphylococcus, mycoplasma).

The authors have found an increasing frequency of the urinary infection at pregnant women suffering from vaginitis or vaginal infection and those suffering from bowel infections. These locations represent the original spot of bacterial organisms.

The persistence of bacterial organisms în the mucosa of the urinary bladder predisposes to recurrent infections. It was found an unfavorable evolution of the pregnancy for 28 % of the cases (preterm delivery, abortion, low birth weight).

The efforts to establish again the vaginal and intestinal biocenosis, by using probiotics like lactobacillus, represent a therapeutical alternative of the urinary inferction.

Key words
– urinary infection
– pregnancy

CLINICAL EFFECTS OF FINASTERIDE, A 5-α-REDUCTASE INHIBITOR, IN POST MENOPAUSAL WOMEN WITH HAIR LOSS

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It has been shown that the estrogen-receptor pathway regulates the telogen-anagen follicle transition under the influence of estrogen. In many women, hair loss has been associated with the onset of menopause a particular form of hair loss (frontal fibrosing alopecia, a variant of lichen planopilaris) has been associated with the post-menopausal period. The hormonal treatment for this condition has been tried, however, hair loss seems to persist despite hormonal therapy. A kind of hair loss as androgenic alopecia may occur in genetically susceptible women during post-menopausal period. In this placebo-controlled trial, we demontrate the efficacy of a low-dose of finasteride, a 5-α-reductase inhibitor, in the long-term treatment of post-menopausal hair loss in 25 affected women. Patients were randomized to receive orally finasteride, 1 mg/day (Group A, 13 patients) or placebo (Group B, 12 patients), for 12 months. All the patients were treated with hormonal replacement therapy. Clinical and dermatologic evaluations were performed at baseline and during cycles 3-9 and 12. The occurrence of adverse events was recorded at each visit. An unexpected, no serious, drug-related adverse events occurred during the study. Our study, finasteride tratment has been shown the possibility to reverse, either partially or completely, hair loss in all patients treated (Group A) ($P < 0.01$) vs baseline, on the contrary no significative differences were revealed in placebo group (Group B). ($P < 0.01$ vs Group A). Furthermore, our study, confirms that hair loss seems to persist despite hormonal therapy. In conclusion, finasteride was effective in reducing hair loss in post-menopausal affected women.

AGING HANDS – THE SECOUND COSMETIC TARGET ON SENIORS

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The main goal of cosmetic surgery is to modifie (as possible it is) a physical envelop of the body. Menopause implies modification of skin complexe-skin aging- with brown spots, visible veins and cutaneous laxity. Hand skin suffers the same-sometimes more phenomenon of aging. Cosmetic surgery of the face and body is not complete without the treatment of aging skin of hand. Today hands are considered the second cosmetic target on seniors. We present our method of treatment of brown spots and cutaneous laxity of hands using a new formula of peeling.

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CONSIDERATIONS CONCERNING THE DIAGNOSIS OF DYSFUNCTIONAL UTERINE BLEEDINGS IN PREMENOPAUSE

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The dysfunctional uterine bleeding (DUB), in the premenopause period, represent in the first time a problem of diagnosis. It must exclude other ethyology of uterine bleeding as uterine carcinoma, blood dyscrasias, benign local disease etc. Investigatins such as (hysteroscopy, hormonal doses, hematological investigations, hystopatological examinations and hystochemistry doses) must exclude these diseases. So the diagnosis of dysfunctional uterine bleeding is made by excluding the other ethyology. Our study made in the period 1999 – 2003 considered a group of 825 subjects which were in premenopause period. After a carefuly investigation we decided a dysfunctional ethyology of bleedings in 81 cases which represent 9.58 %.

FUNCTIONAL HYPOTALAMIC AMENORRHOEA: A SEXUOLOGICAL EVALUATION

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Functional hypotalamic amenorrhoea, well known as stress-related amenorrhoea, is a neuro-endocrine pathology treated by gynecologists and neurologists. Particularly "Minnesota Multiphasic Personality Inventory" and "Eisenk Personality Inventory" tests showed that patients affected by functional hypotalamic amenorrhoea have neurological disturbances.Psychodynamic evaluation considered secondary amenorrhoea as the refusion of sexual maturity and maternal rule with infant regression.Thirtysix patients affected by functional hypotalamic amenorrhoea were submitted to diagnostic examinations at the Universitary Department of Gynecological, Obstetric and Reproductive Sciences of the Second University of Naples.Twentyone patients (58.3%) answered the questions. Sixteen patients showed hypotalamic hypogonadotropic amenorrhoea (HH) (76.2%) and 5 patients (23.8%) were affected by Policystic Ovarian Syndrome (PCOS).Mean age: 40.4±4.5 years; amenorrhoea time: 26.2±20.1 months; Body Mass Index: 22.4±4.5 kg/m2 (values are expressed as M±DS).Sexual symptoms consent to examinate two kinds of hypogonadotropic hypogonadism:without vaginism and with vaginism.Our data suggest the necessity to have a complete diagnostic characterization of functional hypotalamic amenorrhoea to obtain a valid therapeutical programmation.

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SUBCLINICAL HYPOTHYROIDISM AMONG SUBJECTIVE AND OBJECTIVE SYMPTOMS IN MENOPAUSE TRANSITION: PREVALENCE AND INCIDENCE

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There are few studies on thyroid status and the menopause transition, althought the prevalence of thyroid disease, particularly hypothyroidism, increase with advancing age. This condition, affects from 8 to 10% of the general adult population and is especially prevalent in menopausal women. Thyroid status may contribute to the variation in symptom frequency and intensity during the menopausal period. Disturbance in menstrual pattern, urogenital atrophy, osteoporosis, psychological symtoms, including anxiety, increased tension, loss of libido, increase in body weight are common manifestations in both the conditions. The aim of our study was to identifies the incidence and the role of "subclinical hypothyroidism" in 480 menopausal transition women. We evaluated clinical, metabolic, endocrine and ultrasonographic parameters in all patients. Subclinical hypothyroidism was detected in 48 (10%) patients, while 3 (0,6%) patients were identified as affected by hyperthyroidism and were positive for either TgAb or TPOAb. Twentyeight (58,3%) women belonging of the hypothyroidism sample were treated or had been receiving previously for 12 consecutive months HRT regimen, while 20 (41,7%) were escluded to the study for controindications to HRT therapy. All the patients, based on took into consideration their TSH mean plasma concentrations, were submitted to receive L-tiroxina for 12 months. At the follow-up, respect to basal evaluation, a significant reduction on subjective and objective simptomatology ($P < 0,001$) was observed. Total and low-density lipoprotein cholesterol was significantly reduced ($P < 0,01$) unlikely to the patients treated only with HRT regimen. Based on these findings, we recommend the screening for thyroid status on all women reporting symptoms associated with menopausal transition.

MENOPAUSAL SYMPTOMS ; NOT ALWAYS REFLECT BODY STATUS

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Menopausal symptoms often start before menstruation ends.Most common symptoms are hot flushes,night sweats, palpitations,mood swings,aches, pains .in extremities and lomber areas .The severity and frequency of the symptoms is variable according to patients education, character, mood and other accompanying health disorders (1,2,3).
Objective: We investigated if musculoskeletal pains; one of the symptoms of menopause is associated with bone loss.
Design: 94 post menopausal women having hot flushes,sweats, sleep disorders and musculoskeletal pains as symptoms of menopause were included in this randomized study. Women were divided into 2 groups. First group consisted of 74 women having the menopausal symptoms of hot flushes,sweats, sleep disorders and other mood disorders. Second group consisted of 20 women having musculoskeletel pains, back pains and aches as a symptom.Bone mineral densities of spine, femur ,humerus,radius were measured to all patients (4).Exercise,Ca intake in diet,genetic risk factors for osteoporosis, sort of dressing and lactation period after birth were checked.
Results: Mean ages, Body Mass Indexes,duration of postmenopause, exercise habit,Ca intake in diet,genetic risk factors for osteoporosis, sort of dressings and lactation period after birth were similar in two groups. Mean Bone mineral densities (N,osteopenia,osteoporosis) were not stastistically significant in two groups.
Conclusion: Our menopausal patients'complaints of back and extremity pains did not reflect their bone mimeral densities. Menopause creates depression in women and patients may exaggerate the symptoms. Menopausal symptoms must be assessed and treated carefully as they may change according to patients' mood and education.
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USEFULNESS OF EXPERIMENTAL MODELS TO UNDERSTAND THE EFFECTS OF OESTROGENS ON ATHEROSCLEROSIS

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Hormonal replacement therapy does not prevent cardiovacular events in postmenopausal women. In contrast, the incidence of cardiovascular disease is higher in men than in premenopausal women but increases in postmenopausal women, and all animal studies demonstrate a prevention of fatty streak deposit by estradiol. Although estradiol improves the lipoprotein profile, this effect can account for only a minor part of the protective effect. Endothelium appears to be an important target for estradiol, because this hormone potentiates endothelial NO production, thus promoting the beneficial effects of NO as vasorelaxation and inhibition of platelet aggregation. Estradiol accelerates endothelial regrowth, thus favoring vascular healing, and prevents apoptosis of endothelial cells. Estradiol prevents fatty streak deposit through a mechanism which is clearly independent of NO. The immuno-inflammatory system appears to play a key role in the development of fatty streak deposit as well as in atherosclerotic plaque rupture. Mice deficient in either in monocyte-macrophage or in lymphocytes are partially protected against fatty streak deposit. Interestingly, the atheroprotective effect of estradiol is absent in mice deficient in T and B lymphocytes. Most of these effects of estradiol are mediated by estrogen receptor α, and are independent of estrogen receptor β. Thus, the inflammatory-immune system appears to be also a major target of estrogens. However, the effects of estrogens on the immuno-inflammatory system appear ambiguous, as in some models, estradiol rather promotes inflammation (by increasing interferon γ which could elicit plaque destabilization). A better understanding of the mechanisms of estrogens on the normal and atheromatous arteries is required and should help to optimize the prevention of cardiovascular disease after menopause.

THE EFFECT OF CHRONIC ESTROGEN DEFICIENCY ON KEY DETERMINANTS OF LV MASS

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The best index for assessment of LV growth relative to body size is one which correlates with the physiologic demands of the body and changes in proportion to heart size. In animal models where intervention significantly alters the indices used for normalization, this relationship is lost. We sought to understand the impact of estrogen deficiency (ED) on 4 of the key determinants of LV mass; lean body mass (LBM), tibial length (TL), body weight (BW), and systolic blood pressure (SBP).We used sexually mature age-matched Lewis-Brown Norway rats randomly assigned to sham (SOVX, n=9) and ovariectomy (OVX, n=12) groups. Animals were followed for 12 months. Prior to sacrifice, SBP was measured using a tail cuff. LV mass and BW were obtained. The tibias underwent standardized x-ray imaging using Scion Image software. LBM was derived, using underwater weighing and compared to fat free mass. Results are expressed as the mean ± SEM. A p value < 0.05 was significant. After 1 year of ED, the OVX group had an increase in BW(grams) compared to SOVX (301.6 ± 8.7 vs. 220 ± 6.5, p < 0.005). There was a trend of an increase in LBM in OVX group compared to SOVX. LV mass/LBM or BW yielded significant regression in LV mass. However, LV mass/TL (grams/centimeters) in OVX and SOVX were similar (0.174 ± 0.003 vs. 0.179 ± 0.002, p=0.74) suggesting no difference in LV mass. No differences in SBP were noted at 1 year. Autopsy derived LV mass confirm similar rates of growth between SOVX and OVX up to one year of ED. Prior to the onset of senescence; ED is not associated with significant regression of LV mass when appropriately indexed.

THE ESTROGEN REGULATED MYELOPEROXIDASE ENZYME'S INHIBITORS AFFECT AORTIC INTIMA-MEDIA THICKNESS IN NEW-ZEALAND RABBITS

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Background: Some in vitro and in vivo data concerning the significant role of certain sex steroids in the regulation of granulocyte myeloperoxidase (MPO) enzyme activity and release are already known. Oxygen derived free radicals such as superoxide anion are responsible for LDL-oxidation, the highly important key factor in atherogenesis. Recently we managed to prove the superoxide anion inhibiting i.e. antioxidant effect of myeloperoxidase in a human in vitro model. According to our previous study MPO plasma levels are significantly lower in postclimacterial people and MPO inhibitors increase superoxide release. MPO-deficient mice are known to develop increased atherosclerosis. Aim: We intended to investigate how MPO-inhibitors affect the preclinical phase of atherosclerosis, namely intima-media thickness. **Method:** New Zealand white male adult rabbits were fed with lipid rich (cholesterol: 1.3%, peanut oil: 8%) food for 8 weeks. During this period the animals were also given orally administered MPO-inhibitors (4-aminobenzoicacid-hydrazide/ABAH/ 40 mg/day or indometacin 15 mg/day). After dissection of anaesthetized and exsanguinated animals media thickness was measured on cross-sections of logitudinally cut proximal aortas by using light microscopy following hematoxylin-eosin staining. Measurements were carried out on plaque-free areas of the vessels. Results: Media thicknesses: control (cholesterol feeding alone): 189.2 ± 31.7µm; cholesterol+ABAH: 230.5 ± 37.1µm, p<0.05; cholesterol+indometacin: 271.5 ± 75.7µm, p<0.05 (means±SD; n= 5/group; data are averages of two measurements). Conclusions: Inhibitors of MPO seem to promote the development of the preclinical grade of atherosclerosis in our animal model. According to our previous observations i.e. sex steroids increase MPO release from human granulocytes, and plasma MPO concentrations decrease with age, MPO inhibits production of atherogenic free radical superoxide anion and MPO-inhibitors enhance superoxide production, the antiatherogenic effect of sexual hormones might be realized through the impact on MPO metabolism.

HYDROPHOBIC DERIVATIVES OF ESTRADIOL INHIBIT HIGH DENSITY LIPOPROTEIN OXIDATION

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The risk of cardiovascular disease in women increases markedly after menopause. Endogenous estrogens are considered protective against atherosclerosis, but the exact mechanisms remain unclear. One possible mechanism is inhibition of the oxidation of lipoproteins. There is indirect evidence that to act as antioxidants in low density lipoprotein estrogens need to be converted to their hydrophobic derivatives, estrogen fatty acyl esters. This reaction is catalysed by lecithin:cholesterol acyltransferase (LCAT) which is an enzyme in high density lipoprotein (HDL). To find direct evidence that estradiol (E2) esters formed by LCAT and incorporated in HDL increase the antioxidant potential of HDL we incubated ultracentrifugally isolated HDL from healthy donors with different amounts of radioactive and non-radioactive estradiol with and without purified LCAT. After purification on gel chromatography, E2 ester-containing HDL was used in copper-induced oxidation experiments to measure the formation of conjugated dienes. The ester nature of HDL-associated radioactivity was confirmed by chromatographic methods.
The results demonstrated that after estradiol esters were formed by LCAT and incorporated in HDL, this lipoprotein became significantly more resistant to oxidation. In addition, when E2 was present in the incubation mixture, there was a significant correlation between LCAT-activity and HDL oxidation resistance.
Our experiments provided an *in vitro* model using isolated HDL, exogenous E2 and purified LCAT to produce E2 ester –containing HDL particles for studies on the oxidation resistance of HDL. Our previous studies indicate that E2 esters are generated in HDL and transported to low density lipoprotein. This could explain part of the protective effects of estrogens on lipoproteins.

NO EFFECT OF LONG-TERM HORMONE REPLACEMENT THERAPY ON FIBRINOGEN LEVEL IN SMOKING WOMEN: A RANDOMIZED CONTROLLED STUDY

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Elevated plasma fibrinogen is a strong marker of cardiovascular risk modulated by genetic and environmental factors. Smokers have higher fibrinogen level than non-smokers and since smoking reduces the efficacy of orally administered estrogens it may counteract the fibrinogen lowering effect of hormone replacement therapy (HRT).
Healthy post-menopausal women (n=719) were randomized to HRT (n=357) or no substitution (n=362). Plasma fibrinogen concentration, fibrinogen ß –455G/A, and fibrinogen α 6638ins28 polymorphisms were measured after 5 years follow-up. Plasma fibrinogen concentration was lower in the HRT than in the control group (P=0.001). This difference was restricted to non-smoking women (P<0.001). The fibrinogen β –455G/A polymorphism was associated with fibrinogen level. The fibrinogen lowering effect of HRT in non-smoking women showed similar pattern within all –455G/A genotypes, but significant difference was only reached in individuals with the GG genotype. No effect of fibrinogen β 6638ins28 polymorphisms on plasma fibrinogen was found. Both intention-to-treat and per-protocol analyses yielded similar results.
In conclusion we present evidence that long-term treatment with HRT in non-smoking healthy women lowers fibrinogen levels, whereas no effect of HRT on fibrinogen was found in smoking women. The fibrinogen lowering effect of HRT only reached statistical significance in non-smoking women homozygous for the G allele of the fibrinogen β –455G/A polymorphism.

CHANGES IN THE LIPID STATUS AND HAEMOSTASIS SYSTEM DURING HORMONE REPLACE

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Introduction:Postmenopausal status is associated with increase of risk for cardiovaskular disease,in part because of detrimental changes in plasma lipoproteins and endothelial function.
Objective:To determine the effects of HRT on plasma lipids and haemostasis system.
Study method:Our propose was to examine the plasma concentracion of total cholesterol (TC),triglicerides (Tg),LDL cholesterol (LDL-C),HDL cholesterol (HDL-C),as well as coagulation status (PT,aPTT,TT and fibrinogen),protein C activity,antithrombin III activity and protein S activity in 45 healthy postmenopausal women on HRT, after six months of therapy, in compare with 30 postmenopausal women on placebo.
Results:Total cholesterol and triglyceride concentrations decreased by 8% and 22%,respectively,in those receiving hormone replacement therapy (P< 0,05 relative to change in placebo group after adjustment for baseline concentrations).There was not a trend toward a reduction in HDL cholesterol concentration, but LDL cholesterol concentration significantly decreased in group on HRT.On the other side there were some significantly changes in coagulation status :PT,aPTT were reduced in group on HRT,as well as decreased of antithrombin, protein S and protein C levels.
Conclusion:The observed changes may increase the early thrombotic risk associated with HRT use,but HRT has beneficial effects on plasma lipids.

DOSE-DEPENDENT RISES IN SERUM C-REACTIVE PROTEIN TO INCREASING DOSES OF ORAL BUT NOT TO TRANSDERMAL ESTRADIOL: EVIDENCE OF NO ROLE OF PROGESTIN AND A HISTORY OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Liver dysfunction may affect the production and release of C-reactive protein (CRP). We compared the responses of CRP to increasing doses of oral and transdermal estradiol followed by oral progestin in a double-blind prospective crossover study in women with or without a history of intrahepatic cholestasis of pregnancy (ICP). In a randomized order, the women started using estradiol either orally (estradiol 2mg, 14 days; 4mg 14 days with concomitant placebo patches) or transdermally (estradiol 50μg/day, 14 days; 100μg/day 14 days with concomitant placebo tablets). After the completion of the last estradiol alone treatment, the women continued with the same estradiol dose in combination with oral medroxyprogesterone acetate (MPA)(10mg/day 14 days). After 4 weeks wash-out the regimens were switched over and the procedures repeated.
Both regimens were accompanied by significant rises in estrone and estradiol; the former were 16 times higher during oral than transdermal regimen. Oral but not transdermal estradiol increased CRP dose-dependently by a median of 39-51% at 2 weeks, by 87-95% at 4 weeks and79-108% at 6 weeks from baseline, and this response was unaffected by MPA or by a history of ICP. The activities of liver transaminases varied but stayed in the normal range.
The synthesis of CRP is readily and dose-dependently stimulated by oral but not by transdermal estradiol already in 2 weeks and progestin had no effect. ICP is not characterized by any effect on the baseline or estrogen stimulated CRP.

THE INFLUENCE OF NORETHISTERONE ACETATE ON INFLAMMATORY MARKERS IN POSTMENOPAUSAL WOMEN RECEIVING ESTRADIOL

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Oral estrogen replacement therapy increases C-reactive protein (CRP), an independent predictor of coronary events in apparently healthy women. This proinflammatory effect could be one possible mechanism for the increased cardiovascular risk in the first year of hormonal replacement therapy. Androgenic progestins such as norethisterone acetate (NETA) may inhibit proinflammatory effects of estrogen. We compared the effects of oral estradiol and estradiol combined with NETA on markers of inflammation in a randomised double-blind study.
Methods: Fifty one healthy women were randomised to receive 28 weeks of oral treatment, either with estradiol (2 mg E2) or estradiol combined with NETA (2 mg E2 plus 1 mg NETA). At baseline and after 28 weeks of hormonal replacement therapy, levels of CRP, serum amyloide A (SAA), fibrinogen and cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) were determined.
Results: E2 significantly increased CRP from 2.15 (0.71-4.05) to 3.41 (1.12-5.92) mg/l (p=0.04), while the addition of NETA inhibited the increase in CRP. E2 significantly decreased fibrinogen levels: from 3.58 (2.81-3.77) to 2.58 (2.47-2.80) g/l (p= 0.002) while E2 combined with NETA showed no effect. The levels of SAA, Il-6 and TNF-α did not change significantly after both modes of hormonal replacement therapy.
Conclusion: The addition of NETA to E2 diminished the proinflammatory effect of E2, but it also attenuated the favourable effect od E2 on fibrinogen, an independent predictor of cardiovascular disease.

HEMODYNAMIC AND METABOLIC CHANGES IN HYPERTENSIVE PERI- AND POSTMENOPAUSAL WOMEN.

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Epidemiology studies suggest a higher blood pressure and cholesterol level in postmenopausal women. However, hemodynamic and metabolic changes in hypertensives are less studied. The aim of the study was to evaluate effect of menopause on hemodynamics and metabolic parameters in peri- and postmenopausal women with hypertension.
One hundred and twenty two women aged 45-59 (mean age 52.4±3.7) with hypertension and amenorrea more than 6 months were enrolled. Height, weight, SBP, DBP, heart rate, ECG and echocardiography were recorded. Climacteric syndrome using Kupperman index, total cholesterol (Ch), fasting glucose were evaluated. Women with last menstrual cycle 6-24 months back were classified as perimenopausal (n=62), women with menopause more than 24 months – as postmenopausal (n=60). Statistical analysis was performed using SAS. All comparisons were age-adjusted.
Mean SBP was 157.0±20.0 mm Hg, DBP 98.3±10.9 mm Hg. Obesity was present in 62%, Ch>200 mg/dl – in 76%. Presence of climacteric syndrome (63% of women) was positively associated with heart rate independent of age and menopause duration. SBP was significantly higher in perimenopausal women compared to postmenopausal (161.6±2.7 vs 152.3±2.7 mm Hg). DBP and heart rate were similar between the groups. Stroke volume, cardiac output and cardiac index tended to be higher in perimenopausal women. High cardiac output (>5.5 l/min) was significantly more prevalent in perimenopausal women (46.8 vs 28.6%. Ch tended to increase with duration of menopause (230.2 ± 6.0 vs 244.0 ±6.1 mg/dl, p<0.01). Postmenopausal women had a higher glucose level (102.8±2.3 vs 94.0±2.3 mg/dl).
Thus, in hypertensive women menopause transition is associated with higher SBP level and hyperkynetic hemodynamic pattern, while duration of estrogen deficiency contributes to metabolic abnormalities.

ISCHEMIC HEART DISEASE IN PRE-MENOPAUSE WOMEN (CLINIVAL ANGIOGRAPHIC STUDY)

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All in all 69 women 40 to 55 years-old with ischemic heart disease were investigated. Women were divided by 2 angiography groups on the basis of results of angiography. First group consisted of 51 women (73.9%) with pathologically changed coronary vessels. Second group consisted of 18 women (26.1%) that had angiographically normal vessels. 23 (45.1%) of women in the first group experienced myocardial infarction (MI) in the past and 28 (54.9%) had angina pectoris (AP). Out of women of the second group 9 (50.0%) had MI and 9 (50.0%) had AP. Comparison of prevalence of risk factors in both groups showed that women from the second group were more likely to report stress than women in the first group – 80.0% and 36.6% respectively (p=0.03). The prevalence of arterial hypertension, obesity, serum lipids disorders, blood glucose levels and gynecological disorders didn't differ significantly between the groups. Women with MI (n=32) had higher levels of blood glucose in comparison with women with AP (n=37) – 39.3% and 6.5% (p=0.002) and gynecological diseases were also registered less frequently – 31.8% vs. 71.4% (p=0.01). MI women in the first group (n=23) smoked higher that AP women in the first group (n=28) – 30.8% vs. 0% (p=0.05) and had increased blood glucose level – 46.2% vs. 8.3% (p=0.035), they also had lesser prevalence of gynecological diseases – 20.0% vs. 66.7% (p=0.04). MI women in the second group (n=9) had higher blood glucose levels than women with AP (n=9) – 55.6% and 11.1% (p=0.045).

HORMONE REPLACEMENT THERAPY AND ITS RELATIONSHIP TO GLUCOSE METABOLISM IN NON-DIABETIC POSTMENOPAUSAL WOMEN

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Our purpose was to examine the relationship of Hormone Replacement Therapy (HRT) with glucose metabolism, in non-diabetic women seeking consultation for menopausal symptoms.
We studied 92 women aged 44-51 years that were divided in two groups. In group A 46 women with mean age 48,56 years that received HRT for 24 months were included, and in group B 46 women with mean age 48,89 years that did not receive HRT were included. All the women in both groups were tested with oral glucose tolerance test (OGTT) at their initial visit, 12 months later and 24 months later. All the women in the study had normal fasting glucose levels when they entered the study. The period of the study was from July 1999 to December 2002.
In group A mean fasting glucose levels were 89,69 mg/dl, 89,52 mg/dl (12 months later), and 90,93 mg/dl (24 months later). In group B mean fasting glucose levels were 89,82 mg/dl, 90,82 mg/dl (12 months later), and 91,54 mg/dl (24 months later). In group A 3 women were diagnosed with impaired glucose tolerance, and in group B 7 women were diagnosed with impaired glucose tolerance.
Non-diabetic HRT users seem to have better glucose metabolism compared with non-diabetic postmenopausal women that do not use HRT.

MENOPAUSE ACCELERATES OXIDATIVE STRESS IN POSTMENOPAUSAL MIDDLE AGED FEMALES.

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Slovak females exhibit high level of classical risk factors contributing to the third highest cardiovascular mortality level in Europe, however, association of oxidative stress with the homocysteine (Hcy) and other risk factors for cardiac events has been not studied.
Patients and methods: We investigated 76 randomly selected females with stable IHD (27 pre- and 46 post-menopausal) (preM resp. postM groups) in age between 35-75 years, who were compared according to their menopausal status for oxidative stress parameters: total antioxidant status (TAS), oxidized LDL cholesterol (oLDL), Schiff base substance (SBS), oxidized glutathione (GSSG). Total glutathione (tGSH), Hcy and lipid spectrum were analyzed as non oxidative stress risk factors.
Results: As expected, postmenopausal females had worse lipid spectrum (TCH, LDL, TG and Apo B) and substantially higher level of Hcy (11.9±5.20 vs 7.9±2.68 umol/l; p<0.001). Parameters of oxidative stress also worsened in postM group [(GSSG: 21.9±18.50 vs 37.2±28.7 umol/l, P<0.001); (SBS: 23.76±5.39 vs. 19.35±5.09 ummol/l, p<0.001)]. TAS was same in both groups (1.41±0.17 vs. 1.44±0.19 umol/l, NS). Hcy did not correlate with any of analyzed parameters, but PostM group shown correlation between oLDL and TAS (r=0.34; p<0.02) as well as negative correlation between peroxidation (SBS) and oxidation of lipids (oLDL) (r=-.46; p<0.001) in contrary to lack of the analogical association in preM group (r=0.05; NS) resp. (r=-0.16; NS).
Conclusion: Postmenopausal females with stable IHD have increased a level of oxidative stress, which is related also to oxidation and peroxidation of lipids.

SEX HORMONE-BINDING GLOBULIN (SHBG) MODULATION OF ESTROGEN-REGULATED GENE EXPRESSION IN BREAST CANCER

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SHBG is the plasma carrier for androgens and estradiol and in addition it recognizes a specific binding site on membranes. Estradiol-induced growth of breast cancer cells is inhibited by the interaction SHBG/receptor. However, the mechanism by which SHBG inhibits the growth effect of estradiol is not known. The aim of the present study was to evaluate the modulation exerted by SHBG on the expression of estrogen regulated genes in MCF-7 breast cancer cells. Total RNA was extracted from cells treated for 72 hours with 10 nM estradiol, in the absence or in the presence of 50 nM human recombinant SHBG. RNA was used as a template to synthesize biotinylated cDNA probes. The cDNAs were hybridized on GEArray membrane (Super Array Inc. Bethesda MD, USA). The array we used was composed of 23 different genes associated with estrogen signaling pathway and 2 house-keeping genes (actin and GAPDH). Hybridization took place overnight at 68°C. After the appropriate washing and blocking, the chemiluminescent signals were detected and spot intensity analyzed with the Kodak 1D Science software. We observed that estradiol up-regulated 11 genes out of 23 (bcl-2, PR, BRCA1, cathepsinD, pS2, EBAG-9,cox7RP, cyclin D, EFP, keratin 19, EGF-R) and down-regulated the estrogen receptor α gene. SHBG counteracted estradiol effect only on selected genes, reducing the expression of PR, bcl-2, EGF-R, EBAG-9, and increasing ERa. Our data support that in breast cancer SHBG inhibits selected estradiol-regulated genes that are involved in tumor cell growth.

RELEVANCE OF THYROID DISORDERS IN BREAST CANCER.

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Literature data reported an association between breast cancer (BC) and thyroid diseases. Iodine deficiency and the presence of autoimmune thyroid illnesses seem to influence BC incidence and prognosis but this relationsheep is debated. The aim of our study was to verify the prevalence of thyroid disease in breast cancer patients (pts). One hundred eighty- eight consecutive BC pts, aged 36-79 years (mean 57 ys), were examined; 153 (80%) of them were postmenopausal. All of them were from mild iodine deficiency areas. Modified radical mastectomy was performed in 96 pts (51%), quadrantectomy in 92 pts (49%) for infiltrating ductal carcinoma or lobular carcinoma. Six out 188 (4 %) pts had bilateral BC and 128/188 (68%) axillary lymphnodes involvement. After surgery 118 (63%) underwent to radiotherapy, 117 (62%) to chemotherapy and 73 (39%) received hormonal therapy (tamoxifen or anastrazol with or without LHRH analogs). All subjects were submitted to serum FT3, FT4, TSH, Tg, Tg and TPO antibodies determination and thyroid ultrasonography. Fine needle aspiration biopsy (FNAB) was performed in all suspect thyroid nodules. The prevalence of Hashimoto's thyroiditis was 35 in 188 pts (19%) (27 pts were hypothyroid, 77%) and Graves's disease was found in 3%. Both groups of pts had TPO Ab and Tg Ab titles persistently high. One hundred and twenty seven pts (67.5%) showed nodular nontoxic goiter; 17 of them had thyroid autoantibodies (13%). A multinodular toxic goiter was found in 5 (3%) pts. In 35 (19%) cases was necessary histological confirmation: 6 out 35 pts (17%) had a differentiated thyroid carcinoma (papillary histotype). Eighteen-eight (63%) of 188 pts were treated with levothyroxine to substitutive or TSH-suppressive goal. In conclusion, in this study the overall prevalence of thyroid disorders was increased in pts with BC. Nodular nontoxic goiter and autoimmune disorders, especially Hashimoto's thyroiditis, accounted to a large extent for the increased prevalence of thryoid diseases in these pts. The present findings call attention to the usefulness of screening for thyroid disease in any patient with breast cancer.

OESTROGEN REGULATED GENE EXPRESSION IN NORMAL AND MALIGNANT ENDOMETRIAL TISSUE

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The aim of this study was to examine the expression of oestrogen regulated genes in premenopausal and postmenopausal normal and malignant endometrial specimens. The molecular mechanisms and the role of these genes in endometrial carcinogenesis are poorly understood. Normal and malignant endometrial specimens were collected from patients undergoing hysterectomy (n=60). Real time TaqMan PCR was used to examine the mRNA expression of oestrogen receptor α (ERα) and β (ERβ), progesterone receptor (PGR), insulin like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF). ERα was more predominantly expressed in the endometrial samples than ERβ. Normal pre and postmenopausal tissue expressed higher levels of ERα, PGR and IGF-1 than malignant tissue. ERα and PGR expression were significantly higher in the proliferative phase endometrium compared to the secretory phase. PGR mRNA expression was significantly correlated with ERα in all tissue types suggesting ERα plays an important role in the regulation of PGR in normal and malignant endometrium. IGF-1 may not play a role in endometrial cancer as previously thought but insulin like growth factor binding proteins (IGFBP) may contribute to endometrial carcinogenesis.

GENOME WIDE ANALYSIS OF DNA IN ENDOMETRIAL CANCER USING COMPARATIVE GENOMIC HYBRIDISATION MICROARRAYS.

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The aim of this study was to identify amplified oncogenes in endometrial cancer using array based comparative genomic hybridisation (array CGH). Despite its prevelance, the molecular mechanisms of endometrial carcinogenesis are still poorly understood. The selected array CGH allows the simultaneous examination of 58 oncogenes commonly amplified in human cancers and is capable of achieving increased mapping resolution compared with conventional CGH. A subset of 8 specimens from a bank of 60 malignant and normal specimens was selected for array analysis to identify potential genes of interest. TaqMan PCR was carried out on the 60 specimens to examine if aberrations at the genomic level correlated with gene expression and to compare expression in normal and malignant samples. Oncogenes amplified in the endometrial cancers included AR, PIK3CA, MET, HRAS, NRAS, D17S1670, FGFR1, CTSB, RPS6KB1, LAMC2, MYC, PDGFRA, FGF4/FGF3, PAKI, and FGR. Three genes were examined at the mRNA level. AR and PIK3CA were higher in normal specimens and MET was higher in malignant samples suggesting a role for MET in endometrial cancer.

GENOME WIDE ANALYSIS OF DNA IN ENDOMETRIAL CELLS TREATED WITH PHYTOESTROGENS USING COMPARATIVE GENOMIC HYBRIDISATION MICROARRAYS.

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The aim of this study was to identify genomic alterations in endometrial cells treated with the phytoestrogens Tectorigenin, Irigenin, Apigenin and extracts of Silybum marianum (Milk Thistle) using array based comparative genomic hybridisation (array CGH). A novel array CGH allows the simultaneous examination of 287 targets that are commonly altered in human cancers and is capable of achieving increased mapping resolution compared to conventional CGH. Endometrial biopsies were cultured using an explant technique and treated with various concentrations of phytoestrogens and β-estradiol. An endometrial cancer cell line (Ishikawa) was also treated. Array results were validated using Taqman PCR. Some of the extracts are found to decrease the expression of hepatocyte growth factor receptor (MET), which may suggest a beneficial role for these plant-derived extracts in the treatment of endometrial cancer. Genes involved in insulin metabolism (insulin (INS), insulin receptor (INSR), protein kinase c, zeta form (PRKCZ) and protein-tyrosine phosphatase, nonreceptor-type, 1 (PTPN1)) were altered by the extracts, which may suggest a role in cardiovascular disease.

OVEREXPRESSION OF P53 AND P53 POLYMORPHISM IN HPV RELATED CERVICAL CARCINOMA.

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Cervical cancer is the second commonest cancer in women worldwide. Human papillomavirus (HPV) infection has been shown to be an important causative factor in the development of cervical carcinoma. E6 oncoprotein of HPV binds to the cellular tumour suppressor p53 protein and directs its degradation through the ubiquitin pathway. A recent study suggested that p53 polymorphism affects the susceptibility of p53 protein to HPV E6 oncoprotein and individuals homozygous for p52Arg are seven times more susceptible to HPV-assosciated carcinogenesis of the cervix than heterozygotes. The objective of this study is to detect the expression of protein p53 and p53 polymorphism in HPV-related cervical carcinoma. DNA of six fresh tumour tissues were extracted using Kit Dneasy Tissues (Qiagen, Germany) followed by PCR amplification of gene p53 and HPV. ABI Prism 3100 Genetic Analyser is used to confirm the polymorphism of p53 gene and the genotype of HPV. Immunohistochemistry was used to determine the expression of the p53 protein. Samples analysed showed positivity for HPV infection. In addition, sequence analysis showed five individuals were homozygous for p53Arg and one individual was homozygous for p53Pro. Individuals homozygous for p53Arg genotype appear to be more susceptible to HPV infections. Overexpression of p53 protein is a significant characteristic in HPV-related cervical cancer.

THE COMBINED TREATMENT OF LOCAL-SPREAD CERVIX CANCER BY USING EMBOLIZATION AND CHEMOEMBOLIZATION

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Cervix cancer (CC) is very dangerous disease for women's life and health. The main reason of mortality is reappear of CC, which is registered from 37% to 50% among treated patients. The problem of increasing the effect of radial treatment CC patients is very important.
The local-spread CC is often complicated by acute bleeding and pain. To control these symptoms we often use surgical ligation of internal iliac artery (IIA). This operation is traumatic and developing of collaterals after it leads to bleeding again.
One of the modern methods of CC treatment is the selective embolization and chemoembolization of anterior branches of IIA under X-ray control.
At present time we have performed embolization of anterior branch of IIA on 9 patients with CC, 2 of them had severe form of the disease (profuse bleeding, pronounced pains). Bilateral embolization of anterior branch of IIA was performed urgently in severe cases. After supporting and medical treatment bilateral embolization with doxorubicin 40mg/m? was performed on 7 patients. After perfomance antibacterial immuno-potentiative and infusion supporting treatment were used. Bleeding, decreasing of pains were observed after it.
In a short time the regress of tumor (20-50%) was observed and it made possible to do radial therapy.
This method of treatment of CC patients is being used in our Center successfully.

USEFULNESS OF MORPHOLOGICAL AND DOPPLER ULTRASONOGRAPHIC INDICES IN DIFFERENTIATION OF OVARIAN TUMORS IN POSTMENOPAUSAL WOMEN

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Purpose: The aim of this study was to estimate the clinical value of transvaginal grayscale and color Doppler ultrasonography in early prediction of ovarian tumors malignancy in postmenopausal women. Patients and Methods: 159 postmenopausal patients with ovarian tumors (125 malignant and 34 benign) were investigated between 1994 and 2002. A morphological index based on seven ultrasonographic features of ovarian tumors was developed. Tumor volume, wall structure, wall thickness, structure of septa, echogenicity, localization and ascites were analyzed. Doppler analysis involved data obtained in evaluation of 101 ovarian tumors (74 malignant and 27 benign). Doppler Index concerning five half-amount characteristics was created. Evaluation involved: number of vessels, their location and arrangement, shape of velocity waves as well as presence of the protodiastolic notch in the arterial vessels of the tumor. Ultrasonographic devices Aloka 2000 and 5500 with color Doppler technique and transvaginal probes were used. Cut-off levels and diagnostic values of analyzed indices were defined using ROC. Prognostic values were also calculated. Results: The cut-off value in distinguishing malignant from benign ovarian tumors of the morphological index in postmenopausal women was 7 points and for Doppler index 4 points. Morphological Poznan Index created in this way was useful with sensitivity of 92%; specificity 50%, accuracy 83%; negative and positive predictive values of 63% and 87% respectively. Prognostic values calculated for Doppler index were: sensitivity 92%; specificity 100% and accuracy 94%; negative and positive predictive values 82% and 100% respectively. Area under ROC for Doppler index was bigger then for morphological ultrasonographic estimation: 0.978 versus 0.788. Conclusions: Clinical application of both created indices allows quite precise and early evaluation of ovarian tumor malignancy in postmenopausal women. They also make possible proper decisions making concerning manner of surgical treatment. In analyzed group of women after menopause Doppler Index was especially useful.

CLINICAL VALUE OF CA 125 AND TPS ASSESSMENT IN OVARIAN TUMORS MALIGNANCY PREDICTION IN POSTMENOPAUSAL WOMEN

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Clinical value of two biochemical markers of ovarian tumors malignancy were compared. Evaluation involved serum CA 125 and TPS concentration. Blood samples were obtained from 89 postmenopausal patients undergoing laparotomy for ovarian masses. 60 of operated tumors were malignant. CA 125 was tested in all cases. TPS concentration was tested in 54 of our cases (25 malignant). The cut off level of CA 125 in ovarian tumor malignancy prognosis for postmenopausal women was 33.4 IU/ml. Prognostic values for this test were: specificity – 80.3%, positive and negative predictive values - 87.5% and 63.4% respectively. It has a sensitivity of 71.7% and accuracy of 76.4%. Estimation of TPS concentration for the best cut-off level at 73.0 U/l in our group of postmenopausal patients revealed specificity of 74.2%, positive and negative predictive values of 69.2% and 79.3% respectively. It has a sensitivity 75.0% and accuracy of 74.5%. Comparison of prognostic values of analyzed markers in group of postmenopausal patients based on the area under ROC has shown that there are no statistically significant differences between diagnostic value of CA 125 and TPS (0.844 vs. 0.801). Using this methods alone it is very difficult to make a precision prognosis of ovarian tumor malignancy, but they have practical value as additional tests for supporting decision making concerning tumors malignancy especially in postmenopausal women.

REPRODUCTIVE SCREENING STRATEGIES IN THE PERIMENOPAUSE

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This study on 418 disease free women was done to assess the reproductive health status in Malaysian women at perimenopause, to provide local health indices which will enable the clinician to exercise greater selectivity when ordering tests and providing preventive counselling. The study sample comprised of 225 perimenopaused and 193 menopaused women who were 73% Chinese, 22% Malays and 4% Indians. The mean age, height, weight and BMI was 51.43±5.59 years, 1.55±0.05cm, 58.78±9.26kg and 24.37±3.80kg/m^2 respectively. Overall, 21.1% were overweight and 7.7% obese, the premenopausal being significantly heavier than postmenopausal (p=0.04). Haemoglobin value was higher in postmenopause (p<0.001) and anaemia was twice higher in premenopause (p<0.002). Fifty six (13.3%) had an abnormal Pap smear comprising of CIN changes or cervical carcinoma 8 (1.9%), HPV 14 (3.3%) and other infections 34 (8.1%). Postmenopausal women had three fold higher unsatisfactory smear and two fold higher CIN or malignancy changes compared to premenopaused (p<0.0005). Overall, twenty nine (6.8%) had abnormal mammogram with abnormalities being significantly higher (p< 0.017) in postmenopaused women. The incidence of breast cancer was ten fold higher in postmenopaused (0.01) than the premenopaused (0.009). A significant atrophy of the uterus with menopause was demonstrated (p<0.001). Eighty (19.6%) had fibromyoma comprising 27% premenopaused versus 11.4% postmenopaused, also significant (p<0.001). The mean endometrial thickness (ET) was 8.04±3.54mm premenopausal and 4.40±2.89mm postmenopausal (p<0.001). The ET remained fairly constant at 4mm in the postmenopaused and a cut-off of 5.0mm was suggested as clinically acceptable postmenopause. In one fifth (19.6%) of the sample asymptomatic fibroids existed, significantly more common in premenopaused, 27% than postmenopaused, 11.4% (p<0.001) and 2.87% had asymptomatic adnexal enlargement. Although the prevalence of ovarian tumour was not significantly different between pre and postmenopaused, postmenopausal tumours were significantly larger in size (p=0.02). Any enlargement in the ovaries in the post-menopause was considered ominous requiring vigilant follow-up. Screening thus was indicated as a preventive and therapeutic strategy to avoid and detect any pathology early. ET and ovarian volume normogram should be made available for the local population to enable the physician to tailor subsequent counselling and management. BMI, Hb, Pap smear, mammogram and pelvic ultrasound should be used synergistically with clinical judgment after detailed (risk profile) history and physical examination. All women at perimenopause should be offered screening with counselling to ascertain their health status and update their knowledge. This will booster their confidence to enable them to choose appropriate therapy if indicated postmenopause.

INVOLVEMENT OF ESTROGENS IN THE MODULATION OF BEHAVIORAL AND LOCOMOTOR RESPONSE IN RATS

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Clinical and experimental researches have reported the influence of estrogens on the central nervous system, as well as their implications on behavior.
Behavioral and locomotor exploration was initiated in ovariectomized animals with and without estrogen replacement therapy.
Bilateral ovariectomy was performed in all groups (excepting the control group). Results were compared between: the control group, the untreated castrated group, the castrated group in which immediate replacement therapy was initiated, and the group in which therapy was initiated one month after castration. In all animals, the open field locomotor test was performed; results were recorded on a grid. The quantified data represent the level of locomotor activity, orientation, as well as neurosensory disorders as an expression of neurovegetative stress.
It was shown that in castrated animals without hormone replacement therapy, only the stationary index was decreased (expressing orientation disorders). In animals in which immediate estrogen replacement therapy was initiated, all locomotor indices increased compared to the control group, as a result of exaggerated motor activity, while in animals with late initiation of estrogen replacement therapy, a decrease in locomotor indices was found. The results obtained suggest that estrogens play an important role in the maintenance of adequate behavior, castration and estrogen replacement therapy changing these indices.

EFFECT OF RALOXIFENE AND HORMONE REPLACEMENT THERAPY ON SERUM MARKERS OF CHOLESTEROL METABOLISM IN HEALTHY POSTMENOPAUSAL WOMEN

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A relationship between both long-term exposure to endogenous estrogens and lower levels of circulating cholesterol and incident dementia has been reported. This randomized, double-blind, placebo-controlled trial was designed to compare the long-term effects of raloxifene (Rlx) with oral hormone replacement therapy (HRT) on serum markers of brain and whole body cholesterol metabolism. Ninety-five healthy, non-hysterectomized, early postmenopausal women received either daily Rlx 60 mg (N=24), or Rlx 150 mg (N=23), or HRT (conjugated equine estrogens 0.625 mg/medroxyprogesterone acetate 2.5 mg) (N=24), or placebo (N=24). Fasting blood samples were collected at baseline and after 6, 12, and 24 months of treatment. Twenty-four months treatment with Rlx 150 mg was associated with a reduction in serum cholesterol concentration (-10%, P=0.008). The ratio of 24S-hydroxycholesterol to cholesterol decreased with Rlx 150 mg (P=0.001) after a significant increase during the first six months. The ratio of lathosterol to cholesterol, a marker of whole body cholesterol synthesis, increased in both raloxifene groups (Rlx 60 mg, P=0.03 and Rlx 150 mg, P<0.001), as well as with HRT (P=0.006). The ratio of campesterol to cholesterol, a serum marker of cholesterol absorption rate, was reduced with HRT only (P=0.002). In conclusion, long-term treatment with raloxifene or HRT had no influence on brain cholesterol metabolism, while the ratio of lathosterol to cholesterol increased during all therapies.

THE EFFICACY OF ATYPICAL ANTI-PSYCHOTICS IN THE TREATMENT OF AGITATION AND PSYCHOSIS IN ALZHEIMER DISEASE

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Many people over age 65 may worry that any mild forgetfulness is an early indication of Alzheimer Disease, and wonder if anything can be done about it. Alzheimer's Disease begins with forgetfulness and ends with total dementia.Behavioural symptoms commonly occur with dementia. Agitation and psychosis are some of the usual behavioural symptoms in AD that worry everyone around the patient. In our study we use in geriatric patients conventional and non-conventional anti-psychotics to treat this symptoms. Compared with conventional anti-psychotic agents, risperidone, olanzapine and guetiapine appear to be well tolerated in the elderly population. The choice of the atypical anti-psychotics depends on tolerability, efficacy and pharmacoeconomics .Our data indicate that risperidone or olanzapine were the drug of choice for the treatment of psychosis and agitation associated with AD and we note a high treatment compliance.

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MOOD SYMPTOMS IN POSTMENOPAUSAL WOMEN: A PRELIMINARY REPOR.

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Background: Mood symptoms are very often in postmenopausal women. Depresive disorders occur two times more frequently in women than in men.
During postmenopausal period depression is remarkably preevalent and women often attend gyneacological clinics.
While many women present at the menopause with depression wnd anxiety, the reason for these mood disorders cannot be attributed to menopause status alone.
Patients and methods
40 women (age: 47-57) without somatic and endocrynological disorders and natural menopause were included in the study. The patients filled out Beck Depression Juvenory (BDJ) and Hospital Ansiety and Depression Scale – modyficated (HADS). Depression symptoms were assesed according to ICD-10 diagnostic criteria. Patients were divided into two groups: I- 19 women, who scared 20 or more on BDI and on HADS - more than 10 points. They were referred to a psychiatrist for veryfication of depression diagnosis. II – 21 women without depression (less then 19 points on BDI). The two groups compared according to symptoms of depression, irritability, concentration difficulty, anxiety.
Results: Mood disturbances were more intensificated in women, with depression episode. Anxiety and deppharia were less in depression group than in women without depression.
Conclusion: Perimenopausal patients are at higher risk of occuring of depression-rating depressive symptoms in this group seems aimful. Some menopausal symptoms may mask depression.

THE HERBAL ALTERNATIVES FOR MENOPAUSE STUDY: THE ASSOCIATION OF SLEEP DISTURBANCE AND DEPRESSION WITH DIMINISHED LIBIDO

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Background: The prevalence of sexual dysfunction (decreased sexual desire and response) in perimenopausal and early postmenopausal women is estimated to be at least 25-30%. Risk factors that contribute to diminished libido include deterioration in social status, history of sexual assault, dyspareunia, medications, illness, depression, and anxiety. The association of depression and sleep disturbance with diminished libido warrants further examination.
Methods: A total of 351 peri- and postmenopausal women, ages 45-55, were recruited in western Washington state for a randomized placebo controlled trial investigating alternative therapies for menopause. Women were eligible if they had at least 2 hot flashes and/or night sweats per day. Baseline surveys were administered that evaluated sexual function (Index of Female Sexual Function, IFSF), sleep (General Sleep Disturbance Scale, GSDS) and depression (Patient Health Questionnaire, PHQ-9). Frequencies and bivariate analyses between predictor variables (sleep, depression) and libido measures were performed, as well as a correlation matrix to assess colinearity among independent measures. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models.
Results: Criterion for depression were met in 18% of women, 41% had daytime sleepiness at least 3 days per week, and 70% had diminished libido. Depression and sleepiness were highly correlated (r = 0.48). Women who experienced daytime sleepiness at least 3 days per week had diminished frequency of desire, level of desire, and frequency of orgasm, OR = 0.61, 0.54, 0.55, respectively ($p<0.05$). Women who were depressed had diminished levels of desire and frequency of orgasm, OR = 0.45, 0.53, respectively ($p\leq 0.05$).
Conclusions: Daytime sleepiness and diminished libido were common among perimenopausal and early postmenopausal women. Diminished libido in the midlife is complex and is associated with depression and sleep dysfunction.

EFFECTS OF HMR 3339, A NOVEL SERM, ON MARKERS OF COAGULATION AND FIBRINOLYSIS. A 14-WEEK RANDOMIZED, PLACEBO-CONTROLLED STUDY IN HEALTHY POSTMENOPAUSAL WOMEN

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In a multi-center, 14-week, randomized, placebo-controlled, double-blind, dose-ranging study, we investigated the short-term effects of three doses of HMR 3339, a novel SERM, in comparison to raloxifene (Rlx) and placebo, on markers of coagulation and fibrinolysis. One hundred and eighteen healthy nonhysterectomized postmenopausal women received daily either placebo (N=22), HMR 3339 2.5 mg (N=25), HMR 3339 10 mg (N=24), HMR 3339 50 mg (N=24) or Rlx 60 mg (N=23). Medication was given orally for 12 weeks, followed by a 2-week washout period. Fasting blood sampling was performed at baseline, and after 2, 4, 8, 12 and 14 weeks for fibrinogen and at baseline and after 4 and 12 weeks of treatment for the other markers. After 12 weeks of treatment, antithrombin III (AT III), protein C (prot C), both total and free protein S (prot S_t and prot S_f), fibrinogen, tissue-type plasminogen activator (t-PA) and D-dimer revealed significant dose-related changes in all three HMR-groups. The HMR 50 mg group showed the largest mean percentage changes compared to placebo in AT III: -13.0%, $P<0.001$; prot C: -12.2%, P=0.029; prot S_f: +7.2%, P=0.063; and fibrinogen: -20.0%, P=0.001 after 12 weeks and in prot S_t after 4 weeks (-11.2%, P=0.001). A decrease in t-PA after 4 weeks (-9,7 %, P=0.026) and in D-dimer after 12 weeks (-40.3%, P=0.018) was observed in the HMR 2.5 mg group. Compared to placebo, Rlx decreased prot S_t (-4.0%, P=0.009) after 4 weeks and AT III (-4.4%, P=0.034) and fibrinogen (-6.0%, P=0.007) after 12 weeks. In conclusion, HMR 3339 and Rlx lowered fibrinogen levels, but both also impaired the anti-coagulatory potential.

DT56a, A POTENT PHYTO-SERM FOR THE COMBINEDTREATMENT OF MENOPAUSAL SYMPTOMS AND OSTEOPOROSIS

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Post-menopausal osteoporosis and osteoporotic fractures present a serious threat to the aging population. Hormone replacement therapy, although being effective, is not recommended for long duration. Other anti-resorptive agents do not treat menopausal symptoms. These facts lead the patients and the medical community to seek for other safe and effective treatments.
DT56a is a phyto-SERM for the treatment of menopausal symptoms and osteoporosis. DT56a was previously shown to relieve menopausal symptoms. We conducted in vivo, in vitro and clinical studies to prove its safety and efficacy for the treatment of osteoporosis. Data from *in vivo* experiments demonstrated that DT56a displayed selective estrogenic activity: it simulated creatine kinase (CK) specific activity in the skeletal tissues of ovariectomized rats but had no effect on the uterus. Long-term histomorphometric studies showed that DT56a-treated ovariectomized rats had a significant improvement in the trabecular bone volume, cortical width and the growth plate width. In addition, DT56a stimulated cultured human female osteoblasts *in vitro*, measured by DNA synthesis, CK and alkaline phosphatase (ALP) specific activities. In a *clinical study*, patients treated with DT56a for one year had a significant elevation in the bone mineral density compared to the control group. The scientific back-up of DT56a supports the incorporation of Femarelle in treatment regimens for postmenopausal bone loss.

EARLY START OF SEQUENTIAL HORMONE REPLACEMENT THERAPY IN PERIMENOPAUSE HAS NEUTRAL OR POSITIVE EFFECTS ON METABOLIC MARKERS

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Objectives: A group of 43 perimenopausal women was followed during one-year prospective study.
Results and methods: They were assessed for 31 parameters before the beginning, after 6 and 12 months of HRT. Women were treated with 1 mg estriol and 2 mg estradiolvalerate for 21 days and with 0,25 mg levonorgestrel for 10 days of the 28-day treatment cycle. Drugs were administrated daily and orally. Data were evaluated by the Friedman test.
Results: Changes in 10 of the 31 parameters were not significant. Blood pressure , BMI, insulin, transferrin, ferritin, ALT and testosterone levels, as well as INR and APTT did not change significantly after 6 or 12 months. In spite of a significant (p=0,0001) decline of total cholesterol and LDL cholesterol levels conjoined with significant (p=0,0001)enhancement of HDL levels, changes in the atherogenic index were not significant. Moderate decreases in endometrial thickness demonstrate the safety of this treatment on the endometrium. The applicability of the drug to treatment of menopausal syndrome was demonstrate by a significant (p=0,0001) decrease of the Kuppermann index. Bone density significantly (p=0,0001) increased. Possitive changes in bone metabolism are documented also by lowering of calcium levels in urine and increase in serum calcium levels. Glucose levels were significantly (p=0,001) decreased. Changes in hepatic enzymes , iron levels and thrombocytes are also significant, but not of clinical importance.
Conclusions: All changes in markers except the Kupperman index were in the physiological range.
Supported by grant IGA MZ CR NB/7588-3

EFFECTS OF CONTINUOUS COMBINED HORMONE REPLACEMENT THERAPY AND TIBOLONE ON HAEMOSTASIS PARAMETERS

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Objective:To determine the effects of hormone replacement therapy and tibolone on some haemostasis parameters in postmenopausal women.
Study method:This study has included 43 healthy postmenopausal women aged 49-65.Tibolone was prescribed to 23 women and continuous combined HRT (2 mg/d oestradiol and 1 mg norethisteronacetate) was prescribed to 20 women.Effects of this two medicaments on some haemostasis parameters were measured after 6 months of treatment.
Results:Tibolone showed less reduction of protein C and protein S activity and AT-III as well, more reduction of factor VII activity and more increase of aPTT and plasminogen in compare with continuous combined HRT.
Conclusion:Tibolon does not significantly alter coagulation parameters in comparison with continuous combined hormone replacement therapy who affects both fibrinolysis and coagulation parameters.

WEIGHT CHANGE AND ADVERSE EVENT INCIDENCE WITH A DIFFERENT COMBINED ESTRADIOL-PROGESTIN REGIMENS IN POST-MENOPAUSAL WOMEN

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In this study changes in body weight and the incidence of estradiol-progestins regimens in post-menopausal women have not been demonstrated in placebo-controlled trial.This study demonstrates the efficacy of estrogen-progestin replacement therapy for the treatment of subjective menopausal symptoms in 40 post-menopausal women (54 ± 3.8 years old, 63.6 ± 7.4 kg, means ± SD). Patients were randomized to receive (15 women, Group A) 2 mg/day of valerate estradiol plus 10 mg/day of dihydroprogesterone for 28 days/month or (15 women, Group B) 2 mg/day of valerate estradiol plus 0.075 mg/day of levonorgestrel for 28 days/month, or (10 women, Group C) placebo for 12 months.
Body weight was measured from baseline and then constantly during cycles 1-3-6-9 and 12 like at the basic level. The occurrence of adverse events was recorded at each visit. In all patients regression of symptomatology (hot flushes, depression, vaginal dryskin, insomnia, irritability, etc.) was revealed from baseline ($P < 0.01$). Mean changes in weight from baseline were similar in the Group A (0.78 ± 1.75 kg), Group B (0.68 ± 1.90 Kg) and Group C (0.57 ± 1.96 Kg) ($P < 0.05$) for the last measured weight of each patients. Rates of headache, gain in weight, breast pain, side effects, commonly attributed to estroprogestins replacement therapy were also similar between groups ($P < 0.05$).
No serious, unexpected, drug-related adverse events occurred during the study. In summary, the present study demonstrates, in a placebo-controlled trial, that estrogen-progestins replacement therapy is not associated with many of the effects traditionally thought to be attributed to hormonal treatments in post-menopausal women.

TWO-YEAR ADHERENCE IN THE ESTONIAN POSTMENOPAUSAL HORMONE THERAPY TRIAL

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Introduction: This paper compares adherence between a blind and non-blind arm in a randomized postmenopausal hormone treatment (PHT) trial and the reasons for non-adherence within the two first years.
Material and methods: 1,823 postmenopausal women aged 50 to 64 years were recruited into the Estonian Postmenopausal Hormone Prevention trial. They were randomized into four arms: in the blind group the participants received continuous orally administered PHT or a placebo and in the non-blind group open-label PHT or no drugs. This paper examines women who were allocated study medication, (n=1,299) excluding the group with no drugs. A woman was classified as fully adherent if she took at least 80% of the drugs all the time. A Chi-square-test was used to test the statistical significance of the differences.
Results: Adherence is better when women know they are taking active treatment compared with blind treatment: 38% of the women in the open-label PHT arm and 33% in the blind group were adherent. Most women (36%) both in the open-label PHT arm and the blind group discontinued the treatment within the 1st year. During the second year the discontinuation rate declined by less than 10% in both groups. The most common reasons to discontinue were the woman's own decision to stop the treatment (37% of women who discontinued) and experiencing adverse effects (30%). Younger age was associated with a higher degree of adherence ($p<0.001$) but history of using oral contraceptives, level of education and marital status were not statistically significant.
Conclusions: Adherence rates are lower than reported in most other clinical trials. Discontinuation due to adverse effects was comparable with that reported before, but there was a high proportion of women who chose not to continue. The adherence was similar to that found for PHT use in everyday life.

PRESCRIPTION OF HORMONE REPLACEMENT THERAPY IN A MENOPAUSE CLINIC AFTER WHI PUBBLICATION.

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In Italy the use of postmenopausal hormone replacement therapy (HRT) is low, around 8-10%. In Menopause Clinics this percentage is more elevated, around 30%, as they are privileged sites of reception for women suffering menopause disorders, such as hot flushes, depression and vaginal dryness. Up to Women Health Initiative (WHI) study publication, meta-analysis and reviews suggested a risk reduction in cardiovascular disease among postmenopausal women taking HRT. In the scientific community WHI produced a great discussion on the risks and benefits of HRT, causing a drastic reduction in its use. In order to evaluate the impact of WHI publication on our clinical practice, we compared data of 292 postmenopausal women observed in our Menopause Clinic for the first time from 01/01/2002 to 01/06/2002 (I) with 290 postmenopausal women observed from 01/09/2002 to 01/03/2003 (II). The table shows the percentage of HRT prescription and the most important clinical determinants of prescription.

	Tot.	Surgical menopause	Hot flushes	Osteoporosis	Familiar breast cancer
I	50%	70%	83%	63%	48%
II	36%	43%	80%	45%	7%

Data analysis shows that prescription of HRT decreased significantly after WHI publication, from 50% to 36%. As far as clinical determinants of medical prescription, hot flushes emerged as the most important in both periods, and the percentage of prescriptions in the two studied groups is approximately the same. While, when data concerning the type of menopause, osteoporosis and familiar history of breast cancer was analysed, a significant difference in prescription was observed. With regards to estrogen dose, a high dose was used more frequently in the first period; after WHI we prescribed mainly low doses of HRT, independently of women's age and intensity of menopausal disorders.

EFFECT OF HRT BASED ON TRANSDERMAL ESTRADIOL AND TRANSVAGINAL PROGESTERONE ON BLOOD SERUM LIPID PROFILE

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BACKGROUND: Postmenopausal estrogen replacement therapy induces favorable changes in blood lipid profile. Progestins used in the combined HRT regimes may interfere with these changes. There have been few data on the effect of HRT based on transdermal estradiol and vaginal progesterone on the blood lipids. METHODS: This 6-months, single-center, prospective study evaluated changes in blood lipid profile in 15 postmenopausal women receiving transdermal estradiol (40 µg/24h; Estroplast, Adamed) and micronized progesterone in vaginal tablets (50 mg b.d.; Luteina, Adamed) in a continuous regimen. Blood levels of total cholesterol (TC), low-density lipoprotein-cholesterol (LDC-C), high-density lipoprotein-cholesterol (HDL-C) and triglicerides (TG) were evaluated after 3 and 6 months of treatment and compared with the baseline values. RESULTS: TC levels significantly decreased after 3 months of treatment (p=0,015) with further although insignificant decline at 6 months. LDL-C levels did not change significantly throughout the 6 month observation period. HDL-C levels did not change significantly after 3 months of treatment and significantly increased between month 3 and 6 of therapy (p=0,001). The atherogenesis index (TC/HDL-C) decreased significantly after 3 months of treatment (p=0,017) and further declined during the following 3 months of therapy (p=0,002). TG levels significantly declined at month 3 (p=0,004) with further although insignificant decrease during months 4-6 of therapy. CONCLUSION: Continuous combined hormonal replacement therapy based on the application of transdermal of 17-β estradiol (40 µg/d.) and progesterone in vaginal tablets (2x50 mg) resulted in favorable changes in blood lipid profile. Transvaginal progesterone constitutes a metabolically safe option for patients requiring endometrial protection during estrogen supplementation.

IUMPA-2: UTERINE ARTERIES FLOW VELOCIMETRY IN PATIENTS WITH HYPERPLASTIC ENDOMETRIUM AFTER INTRAUTERINE MODROXIPROGESTERONE TREATMENT.

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Aim:
Uterine arteries RI (Resistivity Index) and PI (Pulsatility Index) estimation in women with endometrial hyperplasia simplex before and after treatment by intrauterine medroxiprogesterone acetate system (IUMPA-2).
Method:
Doppler flow velocimetry (transvaginal, 6,5 MHz) performed prior to IUMPA-2 application and after 30 days period of treatment.
Material:
39 postmenopausal women with endometrial hyperplasia simplex treated by IUMPA-2.
Results:
Mean values before IUMPA-2 application: RI 0,95 +/- 0,10, PI 3,17 +/-0,98. Mean values after by IUMPA-2 treatment: RI 0,90 +/- 0,09, PI 3,01 +/- 0,94. There were no statistically significant differences between RI/PI values in two analyzed periods, although slightly lower values of RI/PI were founded after IUMPA-2 treatment.
Conclusion:
Our results may suggest vasodilatation effect of intrauterine medroxiprogesterone acetate appliance in women with endometrial hyperplasia simplex.
Grant of The State Committee of Scientific Research nr 4P05E 058 19.
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IUMPA-2: DOPPLER FLOW IN UTERINE ARTERIES IN WOMEN WITH ENDOMETRIAL HYPERPLASIA SIMPLEX.

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Aim:
Uterine arteries RI (Resistivity Index) and PI (Pulsatility Index) estimation in women with endometrial hyperplasia simplex in comparison to women without endometrial pathology.
IUMPA-2: Intrauterine Medroxiprogesterone Acetate – intracavitary drug delivery system.
Method:
Transvaginal ultrasonography with 6,5 MHz Doppler system.
Material:
39 women with endometrial hyperplasia simplex and 20 women without endometrial pathology were taken to the analysis.
Results:
Mean values of RI 0,95 +/- 0,10, of PI 3,17 +/- 0,98.
No statistical differentiation between the two analyzed groups were found.
Conclusion:
Doppler flow velocimetry is not a useful method of differentiation of endometrial pathology.
Grant of The State Committee of Scientific Research nr 4P05E 058 19.
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IUMPA-2: PHOTODYNAMIC METHOD IN DIAGNOSIS OF ENDOMETRIAL PATHOLOGY - FIRST ANNOUNCEMENT.

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Aim:
Assessment of a new method of local photosensibilisation of endometrium. IUMPA-2: Intrauterine Medroxiprogesterone Acetate – intracavitary drug delivery system.
Method:
2-hour application of intrauterine methylcellulose carrier with 5-ALA (15% dispersion). Hysteroscopic evaluation of photosensibilisation of endometrium after stimulation of luminescence with xenon lamp (430 nm). Obtained pictures were digitally analyzed.
Material:
39 patients with suspected endometrial pathology were included into the study.
Results:
In all analyzed cases positive photosensibilisation focuses with histological verification have occurred.
Conclusion:
Photodynamic diagnosis may be a useful tool in endometrial pathology diagnosis.
Further research results after statistical analysis will be presented.
Grant of The State Committee of Scientific Research nr 4P05E 058 19.
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UTILIZATION OF HEALTH CARE DURING THE FIRST YEAR OF POSTMENOPAUSAL HORMONE THERAPY

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Objective. There is not much data available about the utilization of medical care by women using postmenopausal hormone treatment (PHT).
Methods. 1,027 postmenopausal women aged 50 to 64 years at the time of sampling were recruited into a non-blind group of a randomised trial in Estonia in the period 1999-2001. In the PHT arm, 503 women received 0.625 mg of open-label conjugated oestrogens plus 2.5 mg of medroxyprogesterone acetate daily, and women within 3 years of the menopause received in addition 2.5 mg of open-label medroxyprogesterone acetate daily. In the control arm, 524 women received no treatment. Visits to the physician and selected medical procedures were analysed from Estonian Health Insurance Fund records. Scheduled visits once a year to the trial physician are included, as these would also appear in lay practice. Student's t-test was used to compare the mean number of visits to the physician, gynaecological operations, transvaginal sonograms, mammograms, bone densitometry and Pap-smears between the two arms during the first 12 months of the trial.
Results. In the first 12 months, the adherence rate was 63.2% in the PHT arm. In the control arm 6.7% of women initiated PHT. The mean number of visits to the clinic per year was 2.36 (95% CI: 2.10-2.63) in the PHT arm and 2.10 (95% CI: 1.86-2.34) in the control arm (p=0.144). The mean number of gynaecologic operations was 0.02 (95% CI: 0.01-0.03) in the PHT arm and 0.004 (95% CI: 0.00-0.01) in the control arm (p=0.018). The mean number of transvaginal sonograms was 0.23 (95% CI: 0.19-0.28) in the PHT arm and 0.08 (95% CI: 0.05-0.10) in the control arm (p<0.001). The mean number of mammograms was 0.22 (95% CI: 0.19-0.26) in the PHT arm and 0.16 (95% CI: 0.13-0.19) in the control arm (p=0.016). The mean number of bone densitometry was 0.04 (95% CI: 0.02-0.05) in the PHT arm and 0.05 (95% CI: 0.03-0.07) in the control arm (p=0.281). The mean number of Pap-smears was 0.33 (95% CI: 0.28-0.37) and 0.34 (95% CI: 0.30-0.38) respectively (p=0.667).
Conclusions. Use of PHT increased the utilization of health care, but not for all outcomes studied.

BIOAVAILABILITY OF ISOFLAVONE PHYTOESTROGENS FROM SOYMILK FERMENTED WITH PROBIOTIC BIFIDOBACTERIA

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Isoflavones found abundantly in soybeans are selective and partial oestrogen agonists, amongst other biological properties. Epidemiological and clinical studies suggest beneficial effects with respect to chronic diseases and menopausal symptoms. Isoflavones occur in soyfoods as biologically inactive glucosides. Fermentation of soymilk with probiotic bifidobacteria biotransforms isoflavone glucosides into aglycones and further metabolises daidzein into equol. In order to examine the effect of fermenting soymilk with *Bifidobacterium animalis* on urinary excretion and percentage recovery of isoflavones in post-menopausal women we recruited sixteen post-menopausal women (age: 54.1±4.1 y; BMI: 27.0±5.8 kg/m^2; mean±SD0 in a randomised, double-blind, crossover study with three 14-d soymilk supplementation periods, each separated by a 14-d washout. Subjects were divided into 2 groups, each group ingesting three daily dosages of isoflavone via 200 mL of fermented or non-fermented soymilk. Subjects consumed a restricted self-selected diet and provide a weighed food record and collected 24 h pooled urine specimens on day 0, 4, 13 and 14 of each supplementation period. Soymilks were prepared by reconstituting soy protein isolate (SPI) and soy germ (SG) at different ratios to contain 20, 40 and 80 mg total isoflavones per 200ml, followed by fermentation with *B. animalis* to attain 10^7 to 10^8 viable cells per mL. Isoflavone levels in soymilk and urine were quantified using reversed-phase HPLC.Both groups had similar daily intakes of total energy, protein, carbohydrate, fat and dietary fibre (P>0.05). The non-fermented beverages at 20, 40 and 80 mg per 200ml contained 9%, 8% and 7% of total isoflavones in an aglycone form, respectively, whereas their fermented counterparts contained significantly more aglycone forms (P<0.05), at 69%, 57% and 36% of total isoflavones. Urinary isoflavones were linearly related to dose in fermented, but not with non-fermented soymilks. Fermentation of soymilk with *B. animalis* enhanced the bioavailability of isoflavones in soymilks containing 40 mg total isoflavones (P<0.05). Excretion and urinary recovery of equol was enhanced by the fermentation of soymilk (P>0.05). Therefore increasing the proportion of aglycone forms in soymilk to greater than 50% of total isoflavones by fermentation with bifidobacteria may enhance the bioavailability of isoflavones in post-menopausal women and thus be more effective in preventing chronic diseases associated with menopause.

EFFECT OF THE PHYTOESTROGENS ON ANTI-HEAT SHOCK PROTEIN ANTIBODIES, NITRIC OXIDE, AND VASCULAR REACTIVITY IN MENOPAUSE

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Introduction: Endothelial dysfunction and immune system activation play an important role in the pathogenesis of atherosclerosis. Antibodies against heat shock proteins (HSP) have been found in atherosclerotic lesions and plasma of patients with coronary artery disease and indicate an immune humoral response against these autoantigens. Phytoestrogens may have beneficial effects on reduction of cardiovascular disease risk in menopause. Hypothesis: To evaluate the effect of phytoestrogens on antibodies anti-HSP, nitric oxide metabolites and vascular reactivity in comparison with hormonal replacement therapy in hipercholesterolemic postmenopause women. Methods: The women were treated with phytoestrogens (PE, n=20); 17 beta-estradiol (E, n=17) or 17 beta-estradiol + noretisterone acetate (E+P, n=18), for 3 months, after 1 month of placebo. Plasma concentrations of NOx (nitrite + nitrate), S-nitrosothiols, nitrotyrosine, anti-HSPs antibodies, estradiol, phytoestrogens and brachial artery reactivity were evaluated at baseline and after treatment. Results: There was a reduction of NOx in the 3 studied groups after treatment in relation to placebo (PE, 37 ± 19 to 17 ± 7 µM; E, 32 ± 19 to 12 ± 9 µM; E+P, 32 ± 19 to 11 ± 6 µM; p<0,05) and an increase of S-nitrosothiols (PE, 117 ± 70 to 312 ± 113 nM, p<0,05; E, 140 ± 154 to 177 ± 96 nM; E+P, 88 ± 44 to 218 ± 208 nM, p<0,05). Nitrotyrosine was reduced only in PE group (132 ± 28 to 101 ± 48 nM). Titer of anti-HSP60 antibodies did not change in none of the studied groups. The response of anti-HSC70 antibodies was decreased only in group E (0.282 ± 0.136 to 0.206 ± 0.103), while in FE group a significant reduction of anti-HSP70 was found (0.327 ± 0.117 to 0.228 ± 0.111). The use of phytoestrogens did not change plasma concentration of estradiol (26 ± 38 to 25 ± 37, pg/mL). Brachial artery reactivity was not improved by treatments. Although plasma estradiol concentrations were not correlated with vascular reactivity, a positive correlation between the plasma concentration of phytoestrogens (daizein and genistein) and brachial artery reactivity was found (p =0.04; r=0.88). Conclusion: Phytoestrogens reduce antibodies anti-HSP and increase the bioavaibility of nitric oxide. Financial support: FAPESP and PRONEX.

PHYTOESTROGENS AND HORMONAL REPLACEMENT THERAPY ON CHOLESTEROL OXIDES IN MENOPAUSE

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Atherosclerosis and its complications remains the most common cause of death in postmenopausal women. The low levels of estrogens may promote lipid peroxidation and contribute to atherogenesis. Phytoestrogens and hormonal replacement therapy may have beneficial effects on reduction of cardiovascular disease risk in menopause. Objective: To evaluate the effect of phytoestrogens on formation of cholesterol oxides in comparison with hormonal replacement therapy in hipercholesterolemic postmenopause women. Methods: The women were treated with phytoestrogens (PE, n=20); 17 beta-estradiol (E, n=17) or 17 beta-estradiol + noretisterone acetate (E+P, n=18), for 3 months, after 1 month of placebo. Plasma concentrations of COx (cholesterol oxides), were evaluated at baseline and after treatment. COx were determined by GC-FID after methylation and derivatization to trimethylsilyl derivatives. Results: The total level of COx was reduced after treatment in all studied groups (PE, 89,3 to 67,4 ng/mL; E, 76,6 to 56,5 ng/mL; E+P, 77,9 to 62,8 ng/mL; p<0,05). E+P group showed significative reduction only on 7 α-hidroxicholesterol levels. E group showed significative reduction on 7 α- and 7 β-hidroxicholesterol. Phytoestrogens showed significative reduction on 7 β-hidroxicholesterol, cholestan-5α,6β-epoxy-3β-ol (α-epox) and cholestan-5α,6β-epoxy-3β-ol (β-epox) This result indicate that all studied treatments reduce formation of cholesterol oxides, but with different specificity. Financial support: FAPESP and PRONEX

EFFECTS OF ISOLATED ISOFLAVONOIDS ON LIPIDS, LIPOPROTEINS, INSULIN SENSITIVITY AND GHRELIN IN POSTMENOPAUSAL WOMEN

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The low cardiovascular risk in Asian women has been thought to result from high isoflavonoid intake. In a double-blind randomized placebo-controlled trial we studied the effects of isolated isoflavonoids (114 mg/day) on lipids, lipoproteins, insulin sensitivity and ghrelin in 56 non-diabetic postmenopausal women with a history of breast cancer. Isoflavonoid or placebo tablets were given for 3 months and the treatment regimens crossed over after a 2-month washout period.
The concentrations of total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides, apolipoproteins B and A1, and lipoprotein (a) were not affected by isoflavonoids. However, during the isoflavonoid regimen women with LDL cholesterol level above the median (4.20 mmol/L) showed a rise in it (0.65 ± 0.60 [SD] mmol/L), which was statistically different from the fall during the placebo regimen (-0.45 ± 0.67 mmol/L, p=0.009).
Isoflavonoids did not affect insulin sensitivity as assessed by an oral 2-h glucose tolerance test (75g). Changes in ghrelin levels differed (p=0.048) during the isoflavonoid (-7.1 ± 151 _mol/L) and placebo regimens (+47.9 ± 198 _mol/L).
In conclusion, we found no effects of isolated isoflavonoids on lipids, lipoproteins or insulin sensitivity in postmenopausal women, implying no vascular benefit. Isoflavonoids may reduce ghrelin levels and thus hunger and weight.

EFFECTS OF MENOPAUSE FORMULA, A PHYTOESTROGEN-CONTAINING SUPPLEMENT, ON LIPIDS AND C-REACTIVE PROTEIN. A 12-WEEK RANDOMIZED, PLACEBO-CONTROLLED, STUDY IN POSTMENOPAUSAL WOMEN

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In a multi-center, randomized, placebo-controlled, double-blind study we investigated the effects of Menopause Formula (MF), a phytoestrogen containing supplement, on total cholesterol, low-density lipoprotein (LDL-) and high-density lipoprotein (HDL-) cholesterol, triglycerides and C-reactive protein (CRP) in healthy early postmenopausal women. One hundred and twenty-four women were randomized to receive daily either MF (N = 60) or placebo (N = 64) for twelve weeks. Fasting blood samples were collected at screening and after twelve weeks of supplementation. Total cholesterol and LDL-cholesterol showed a reduction after twelve weeks in the MF group (-0.2 ± 0.5 mmol/L; P = 0.019 and -0.2 ± 0.5 mmol/L; P = 0.011, respectively) whereas no change was observed in the placebo group. HDL-cholesterol was increased in the placebo group (+0.06 ± 0.20 mmol/L; P = 0.020) but showed no change in the MF group. Triglycerides and CRP revealed no significant changes in both groups. The difference between groups in changes observed for any of the parameters did not reach statistical significant. The observed changes were not correlated with plasma concentrations of isoflavones. In conclusion, short-term supplementation with Menopause Formula induced small reductions in total and LDL-cholesterol, and not in CRP. The clinical relevance of these observations needs to be determined.

A HERBAL REMEDY, FEMAL, MADE FROM POLLEN EXTRACTS, REDUCES HOT FLUSHES AND IMPROVES QUALITY OF LIFE, IN MENOPAUSAL WOMEN

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Aim: This study aimed, in a randomised, double blind, placebo-controlled, parallel designed trial, to evaluate whether Femal, a herbal remedy made from pollen extracts, alleviates the symptoms of the menopause, especially hot flushes.
Design: After an initial run-in phase of one month, 64 menopausal woman were randomly given either two Femal tablets a.m., or two identical placebo tablets, for 3 months' treatment. On inclusion, and then at 4-weeks intervals, the patients were asked to evaluate sixteen symptoms of the menopause, on Menopause Rating Scales. Every day during the study, certain menopausal symptoms were recorded in a diary. Blood-samples were taken at the beginning and at the end of the study.
Results: The two treatment groups were identical regarding demographic data, and the initial symptom scores. In the active-treatment group, 65% responded with a reduction in hot flushes compared with 38 % in the placebo group (p<0.006) and in the active treated group the number of hot flushes registered in diaries declined after 3 months by 27 % as compared to the placebo group (p<0.0348).
Menopause Rating Scale evaluation of hot flushes yielded similar results (p<0.0318). Here there was a 26% reduction of hot flushes after 2 and 3 months' treatment, as compared to placebo and on both occasions the inter-group comparison was significantly affected. An overall evaluation of the trend in 15 other "quality-of -life" parameters, was likewise in favour of the pollen extract (p<0.025). No significant change was observed in routine haematology or hormone prophile.
Conclusion: The pollen extract Femal significantly reduces hot flushes and certain other menopausal symptoms when compared to placebo.

CLINICAL EFFICACY AND DRUG SAFETY OF HERBAL REMEDIES IN THE TREATMENT OF CLIMACTERIC COMPLAINTS

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The climacteric syndrome is polysymptomatic: Numerous women suffer from neurovegetative and/or psychic symptoms. Aim of this prospective cohort study is to analyse efficacy and tolerability of herbal remedies in climacteric complaints. A mono-drug preparation of Black Cohosh, Remifemin®, and a fixed combination of Black Cohosh and St. John's Wort, Remifemin® plus, is investigated during a 6-month treatment phase in 2,228 climacteric women (Remifemin®: n = 1,060; Remifemin® plus: n = 1,168). Efficacy is evaluated using the validated Menopause Rating Scale (MRS I). Tolerability is judged with an ordinal scale (4 categories). The dosage is chosen depending on the individual therapeutic needs.
The MRS-Score was reduced from 32.9 to 15.3 ($p < 0.001$) across medication groups. The vasomotor MRS-factor was assessed as "severe" at the beginning of the therapy in both treatment groups. Psychic symptoms are differently distributed: In the Remifemin® group these symptoms are "mild" compared to „moderate" in the Remifemin® plus group. Already after 3 months the intensity of the complaints was reduced ($p<0.0001$). Baseline-adjusted ANCOVA revealed a group difference in the psychic MRS-factor in favour of Remifemin® plus ($p=0.016$). The tolerability of Remifemin® was assessed as "very good" resp. "good" by 92.4 %, and of Remifemin® plus by 92.4 % of the physicians. For mainly neurovegetative symptoms of climacteric complaints the Black Cohosh preparation is the first choice; while in patients with pronounced psychic symptoms the fixed combination of Black Cohosh and St. John's Wort is preferred due to its additional benefit. Both preparations show a favourable benefit-risk-ratio.

THE HERBAL ALTERNATIVES FOR MENOPAUSE STUDY: CHALLENGES IN STUDY DESIGN AND METHODOLOGY

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Background: There are multiple challenges in designing randomized, controlled trials of alternative herbal therapies. Chief among these are control selection and blinding. We describe in detail the study methods for the Herbal Alternatives for Menopause (HALT) Study.
Methods: The HALT study enrolled and randomized 351 peri- and postmenopausal women, living in western Washington state into one of 5 treatment arms: 1) Premarin™ or Prempro™ for women without or with a uterus, respectively; 2) black cohosh; 3) a multibotanical preparation that contained black cohosh; 4) the same multibotanical preparation plus, soy diet counseling and 5) placebo. After a 2-week run-in period, study visits occur at baseline, 3, 6 and 12 months. The primary outcome is vasomotor symptoms. There are 5 secondary outcomes: lipids, vaginal cytology, bone mineral density, serum glucose, and coagulation factors.
Results: Study design challenges included addressing: the natural regression of vasomotor symptoms; appropriate measurement tools for vasomotor symptoms; selection of secondary endpoints; blinding; choice of interventions; recruitment strategies; study power by recruiting women with sufficient number and intensity of hot flashes to detect symptom changes; the impact of the Women's Health Initiative on recruitment and design; the quality assurance of herbal products; retention and compliance. The HALT study will be completed in August 2004; retention is 94%, with only 4% off study drug but continuing follow up.
Discussion: Meticulous attention to study design can maximize successful completion of randomized controlled trials of alternative therapies for menopausal symptoms.

SOY PHYTOESTROGENS REDUCE SPINE BONE LOSS IN POSTMENOPAUSAL WOMEN

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Background: Few randomized trials have tested the hypothesis that soy isoflavone supplementation preserves bone mineral density (BMD).
Methods: We conducted a controlled, parallel-arm, double-blinded intervention study with participants aged 50-80 years. Participants were randomly assigned to consume soy beverage powder daily for 12 months. The active treatment group (+ISO) received soy protein containing 83 mg isoflavones (45.6 mg genistein, 31.7 mg daidzein, and 5.5 mg glycitein), and the comparison group (–ISO) received soy protein containing 3 mg isoflavones. We measured BMD using dual-energy x-ray absorptiometry at the posterior-anterior spine (L1-L4) and total hip at baseline in 22 women (11 +ISO; 11 –ISO), at 6 months in 16 women (9 +ISO; 7 –ISO) and at 12 months in 13 women (8 +ISO; 5 –ISO). We used linear mixed models, adjusted for age and BMD at baseline, to test for an isoflavone effect on percentage change in BMD from baseline values in spine and hip separately.
Results: Baseline age, BMI, fracture history, amount of exercise, calcium intake, and thiazide use were similar in +ISO and –ISO. Levels of adherence (>80% of packets consumed) were 73% in +ISO group and 44% in the –ISO group. Mean percent change in BMD ($\pm$ SE) from baseline in spine was 0.48 $\pm$0.89 in +ISO and –1.95+0.98 in –ISO ($p=0.09$) at 6 months, and 0.58$\pm$0.70 in +ISO and –1.84$\pm$0.86 in –ISO ($p=0.05$) at 12 months. By comparison, percent change in hip BMD was similar in the treatment groups, +ISO and –ISO. Mean percent change in hip BMD ($\pm$ SE) from baseline to 12 months was 0.35$\pm$0.97 in +ISO and 0.23$\pm$1.19 in –ISO ($p=0.93$).
Conclusions: Soy isoflavone supplementation preserved spine, but not hip, bone mineral density in this older population of women in a randomized controlled trial.

THE EFFECT OF SOY CONTAINING ISOFLAVONES ON BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN: A DOUBLE-BLIND RANDOMIZED TRIAL.

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Osteoporosis is a frequent condition, especially among postmenopausal women because of the decrease in estrogen after menopause. As a result, bone becomes fragile and is more prone to fracture. For a long period of time, estrogen replacement therapy (ERT) was considered a good option for preventing postmenopausal bone loss. However, ERT is associated with serious side effects. Some evidence has shown that phytoestrogens may be able to play an important role in the prevention of bone loss after menopause. The objective of our study was to examine the effect of the intake of high amounts of isoflavones for 1 year on bone mineral density of the left proximal femur and the lumbar spine in postmenopausal women. For our double-blind randomized trial we recruited 202 postmenopausal women aged 60–75 years. Subjects were randomly assigned to receive either a soy isolate containing 99 mg isoflavones (phytoestrogens) or casein (placebo) for 1 year. At baseline and at the end of intervention, bone mineral density of the lumbar spine (L1–L4) and the left hip was assessed by dual-energy x-ray absorptiometry. Linear regression was used to study the difference in change in bone mineral density between both groups. For the left hip the placebo group showed a decrease of 0.6% vs. a decrease of 0.05% for the soy group. For the lumbar spine the decreases were 0.27% for the placebo group and 0.39% for the soy group. However, none of the observed changes was statistically significantly different from placebo. Supplementation of soy protein containing 99 mg isoflavones for 1 year had no effect on bone mineral density of the lumbar spine or the left hip in postmenopausal women aged 60–75.

SOY CONTAINING ISOFLAVONES AND PLASMA LIPIDS: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL.

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A meta-analysis comprising 38 intervention studies with soy protein naturally containing isoflavones found a 9.3% decrease in total cholesterol and a 12.9 % decrease in LDL cholesterol, which has resulted in the health claim approved by the U.S. Food and Drug Administration that diets low in saturated fats and cholesterol that include 25 g/d of soy protein may reduce the risk of heart disease. Our goal was to investigate whether the improvement in plasma lipids seen with soy protein containing isoflavones can be extrapolated to postmenopausal women. For our double-blind randomized trial we recruited 202 postmenopausal women aged 60 to 75 y. Subjects were randomly assigned to consume either a soy isolate containing 99 mg isoflavones (phytoestrogens) or casein (placebo) for 1 y. At baseline, 3 mo, and the end of the intervention, we measured plasma lipids [total cholesterol, LDL, HDL, triglycerides, and lipoprotein(a)]. Linear regression was used to analyze the differences in change in plasma lipids between the two groups during the intervention. The randomization was successful: 153 women (75%) completed the intervention. At baseline total cholesterol was 6.3 mmol/L (range 3.0–9.8), LDL 4.2 mmol/L (range 1.9–7.0), HDL 1.6 mmol/L (range 1.0–3.0), triglycerides 1.2 mmol/L (range 0.5–2.7), and lipoprotein(a) 0.22 mmol/L (range 0.02–1.58). At 3 months and 12 months no significant differences in plasma lipid values were seen between the 2 groups. Our results suggest that the positive effects of soy isoflavones on plasma lipids cannot be extrapolated to postmenopausal women.

SOY CONTAINING ISOFLAVONES AND COGNITIVE FUNCTION; A RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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Estrogen replacement (ERT) may improve cognitive function in postmenopausal women. However, ERT does have serious side effects. Phyto-estrogens, estrogen-like compounds naturally occurring in plants, may have similar positive effects on cognitive function and could provide an alternative. In rat-models soy isoflavones stimulate biomarkers important for cognition and improve performance on a radial maze task.

We conducted a double blind randomised placebo-controlled study. 202 postmenopausal women aged 60-75 years were randomised to receive 36.5 g soy protein containing 99 mg of isoflavones or casein (placebo) per day for 12 months. Cognitive function was assessed for several domains: Dementia (Folsteins' Mini Mental State Examination), Memory (Rey Auditory Verbal Learning Test, immediate recall, delayed recall and recognition, the Digit Span forward and reversed, and the Doors test), Complex attention tasks (Digit Symbol Substitution, and Trailmaking A1, A2 and B), and Verbal skills (Verbal Fluency A and N and the Boston Naming Task). Furthermore, the Geriatric Depression Scale and Dutch Adult Reading Test to assess prevalent depression and verbal intelligence quotient.

Linear regression was used to analyze the differences in change between the two groups during the intervention.

The randomisation was successful, 153 (75%) women completed the intervention. After intervention there were no differences in any of the domains of cognitive function between the soy and the placebo group. Our results suggest that phyto-estrogens from soy protein are not able to exert a positive influence on cognitive function of postmenopausal women, when started at the age of 60 or later.

RESULTS ON PHYTOESTROGENS USE IN THE MENOPAUSE MANAGEMENT.

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Aim of the study. To draw an updated profile on the actual trend in menopause management as routinely approached in clinical practice by Italian Gynaecologists, in view of the recent scientific papers.

Methods. Each centre was given individual login and password allowing the protected access to the website www.estronet.net, where the first 10 menopause women (MP) referring to the gynaecologist as outpatients were recorded. Thus the sample was representative of the general population with no bias in selection.

A clinical report form collecting history, life style, diet, past and actual treatments, HRT refusal/withdrawal, symptoms evaluation, rate of visits and exams in the previous three months was realised.

Results The study still in progress collected up to now 1190 cases, of which 1148 menopause women (87.5% spontaneous, 12.5% surgical) and 42 pre-menopause women. MP mean age was 54.8 years. Respectively, estrogens and phytoestrogens were prescribed in 17.1% and 33.4% of MP. Estrogens were used as transdermal (8.8%), oral (2.5%), gel (1.8%) and nasal spray (1.0%). Focusing on phytoestrogen use, the combination of genistein and daidzein (60 mg, 50:50), lactobacilli, calcium, vitamin D_3, and equisetum was given to 312 MP for a mean duration of 117.1 days up to 270 days.

At menopause onset, the symptom rate was: flushing 86.8%, nocturnal sweating 82.1%, vaginal dryness 66.0%, palpitations 46.9%.

In the evaluation referred to the week before the interview, the frequency of improved MP was: flushing 78.7%, nocturnal sweating 75.1%, vaginal dryness 43.2%, palpitations 58.5%. Clinical activity and safety were judged positive in 94.5% and 99.6%, respectively.

Well-being was good in 73.6% of MP, and feeling better was reported by 82.8% referred to the week before the interview.

Discussion. The data show the good activity and safety of a specific titrated phytoestrogen in menopause management.

QUALITY OF LIFE ACCORDING TO DIFFERENT MENOPAUSAL STAGES

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Abstract:

This is a cross sectional, descriptive-analytic study that conducted by aim of "identifying and comparing quality of life according to different menopausal stages and other demographic and medical variables in Tehranian women, 2001". Samples consisting 210 women in 40-60 years of age. Samples selected random frequency and divided in four groups: before menopausal, per-menopausal, menopausal duration less than 5 year, and menopausal duration higher than 5 year. Data collected by researcher made questionnaire that completed at client home by interview. Result showed that there are significant relationship between quality of life and menopausal stages. Women who was not Amenopause have had highest quality of life and lowest quality of life seen in women who ready for menopause or go through first 5 years of menopausal ($p<0.0001$). This relationship affected by factors such as duration of menopause, marital status, and age of participant. There are, however, no significant relationship with factors including duration of menopause, job, educational level, economical status, age of menses, number of children that living with family.

Keywords: **menopause, quality of life**

LIFESTYLE AND QUALITY OF LIFE OF MIDDLE-AGED WORKING WOMEN IN SAPPORO, J APAN

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Objective: To assess the lifestyle and quality of life of middle-aged working women in Sapporo, Japan.
Design: Questionnaires focusing on lifestyle and quality of life were distributed to 1,100 female city officials aged 35 to 65. Quality of life data was collected using WHOQOL-BREF. The Simplified Menopause Index that identifies 10 typical menopausal symptoms of Japanese women was also used. The anonymity and confidentiality of participants was respected. 700 questionnaires were returned (63.3%) and 699 met the strict inclusion criteria and were analyzed using SPSS.
Results: The average age of the participants was 46.4 ± 6.4 years. The average BMI was 21.9 (15.6–36.7). Common symptoms were "have stiff shoulders" and "being fatigued". Concern about diet was seen in 85.5% of the participants, regular exercise was done by 31.7%, smoking was mentioned by 15.2% and drinking by 20.0%. The rate of annual health check-ups was 97.3%, but bone density examinations were done in 28.5% and self breast examinations in 16.2%. The mean scores of WHOQOL-BREF were 2.86 (physical), 3.25 (psychological), 3.36 (social relationships), and 3.41 (environment).

This study was supported by Grant-in-Aid for Scientific Research (B14370806) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

LIFESTYLE OF WOMEN ATTENDING THE MENOPAUSE CLINIC

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Objective : To investigate the lifestyle and associated factors of women attending the menopause clinic.
Methods : A total of 1195 climacteric women attending the menopause clinic, Faculty of Medicine, Mahidol University, Bangkok, Thailand responded to a self-administered questionnaire. The sociodemographic data, menopausal status, and body mass index were recorded. The health-related lifestyle ; alcohol, coffee, and milk consumption, cigarette smoking, and regular exercise were studied and Pearson Chi-Square was used to test the association between lifestyle and those factors. All tests were considered statistically significant at $p < 0.05$.
Results : The percentage of women that consumed alcohol, coffee, and milk were 11.1%, 50.0%, and 62.8%, respectively. Only 0.006% smoked cigarettes. Regular exercise was practiced in 62.8%. Statistical associations were found between milk consumption and educational level, alcohol and coffee consumption and menopausal status. Women from higher educational level consumed milk more than women from lower educational level. Postmenopausal women significantly consumed alcohol and coffee more than premenopausal women. There were no association between marital status, occupation, body mass index and lifestyle differences.
Conclusion : More than half of women attending the menopause clinic consumed milk and exercised regularly. Alcohol consumption and cigarette smoking were not widely practiced. Educational level and menopausal status were associated with differences of health-related lifestyle.

EFFECTS OF HRT ON QUALITY OF LIFE IN POSTMENOPAUSAL WOMEN WITH POSITIVE MODIFIED ATTITUTE TO MENOPAUSE.

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Attitude to menopause, has been reported to have a great influence on climacteric complaints perception. However the onset of menopause marks a withdrawal of estrogens and lead to climacteric syndrome among many woman. The aim of the study was to investigate relationship between attitudes and menopausal distress, describe QoL in women with a positive tested attitude to menopause and compare the effects of HRT in users and non-users .
We followed up a sample of 20 early postmenopausal women aged 45 to 55 years. All the patients underwent a new integrated gynaecological-psychological method with the aim to improve their own attitude to menopause. After the treatment purposely designed questionnaires assessing attitude to menopause were set up to monitor . **Group A**: a sample of 10 patients underwent HRT (transdermal 17-beta- Estradiol 37.5 mcg MX and oral Nomegestrol acetate 2.5mg for 12 days). **Group B** in a sample of 10 patient no hormonal treatment was performed. 24 months after the treatment. ad hoc questionnaires assessing physical, psychological and psychophysical well being , self perception, sexual behaviour, relational, social, and emotional quality of life, with a score intensity scale 1 to 3, were administered .
The main difference between group A and group B appears to be an increased physical well being in the HRT users (60%score 3/ scale 1-3) if compared with non-users (0% score3/scale 1-3). No differences were reported both in group A and B for psychological and psycho-physic well being and sexual behaviour, multifactorial conditions strictly related to the personal menopause attitude.
HRT seems to increase physical health-related QoL in postmenopausal women with a positive attitude to menopause after therapeutic gynaecological-psychological integrated approach to climacteric complaints.

EFFECT OF HORMONE REPLACEMENT THERAPY ON QUALITY OF LIFE IN POSTMENOPAUSAL AFRICAN AMERICAN WOMEN

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In many studies on Hormone Replacement Therapy (HRT), few participants have been African American (AA). This study investigated the effect of HRT on Quality of Life (QOL) in a cohort of AA postmenopausal women. AA women were recruited from a network of community-based clinics. Participants (N=70), ages 45-65 yrs, minimum 1 yr self-reported yrs of menopause were randomized to treatment group (N=52) with daily administration of conjugated equine estrogen, 0.625mg, and medroxyprogesterone acetate, 2.5mg or placebo (N=18). The Menopause Specific QOL instrument (MenQOL) was completed by participants measuring responses to symptoms across 4 domains: Vasomotor, Psychosocial, Physical, and Sexual. The score (1-8) reflected varying levels of perceived QOL with a higher score representing a poorer QOL. Data were collected on 60 of 70 women at all 3 time periods (enrollment, 6 weeks, 12 weeks). No QOL data were collected on 3 subjects (2=treatment group; 1=control group). Across all participants: X Age=52.3yrs; X Age Menopause=46.7yrs; X Yrs Last Cycle=5.6yrs; History HRT use=21%; Household Income <$20,000=66%; Education Status= <HS=27%, HS=28%, >HS=45%; Smokers=35%; ETOH use=50% Planned Exercise=8%; HTN=56%; X BMI=31.75; X Systolic/Diastolic BP=143/84. In treatment group, at 6 & 12 weeks, all 4 QOL domains demonstrated significant (p=.01) improvement in values over enrollment. This study suggests short-term HRT significantly improves perceived QOL variables in AA women.

POSTMENOPAUSAL SEXUAL FUNCTION UNDER HORMONAL TREATMENTS - ANDROGENIC AND VASCULAR CORRELATES.

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We investigated the effects of a 6 months conventional estrogen-progestin therapy (EP) and tibolone (T) in a sample of postmenopausal women with severe sexual dysfunction (SD).
44 women (age range: 52-56 yrs; time since last menstrual bleeding: 12-24 months) with hypoactive desire and arousal disorders (under the lower quartile of distribution of FSFI scores for age) were randomized to receive either EP (1 mg 17-β-estradiol + 0.5 mg NETA, Activelle, Novo Nordisk, A/S, DK) or T (2.5 mg, Livial, NV Organon, NL). Freetestosterone (FT) and DHEA-S were measured before and after 6-months of treatment, as well as clitoral artery blood flow and sexual function. Both HT increased libido and arousal scores following 6 months, but the percent change (Δ%) was significantly higher for T ($p<0.02$ e $p<0.03$, respectively) in comparison with EP. Pain, lubrication, orgasm and satisfaction scores increased under both HT, without significant differences. Interestingly, FreeT and DHEA-S plasma levels significantly increased ($p<0.01$ and $p<0.03$, respectively) in women treated with T, while did not show any significant changes in comparison with baseline following 6 months of EP. In addition, T significantly increased both systolic and diastolic clitoral artery blood flow ($p<0.03$, $p<0.04$, respectively) in comparison with basal values, while EP did not significantly affect clitoral circulation following 6 months. The present study suggests that T, a tissue-specific steroid with estrogenic, progestagenic and androgenic properties, is highly effective in treating postmenopausal SD by influencing androgen plasma levels and clitoral circulation. However, even a conventional EP therapy exerts some positive effects on sexual function, independently from androgens plasma levels.

HORMONE REPLACEMENT THERAPY USE, AMONG GREEK WOMEN, ACCORDING TO THEIR SOCIO-ECONOMIC LEVEL.

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Our purpose was to compare the use of hormone replacement therapy (HRT) among Greek women according to their socio-economic level.
A total of 234 Greek women between 52 and 74 years of age were interviewed in our department. Women were allocated into three groups (H, high; M, medium; L, low), according to their socioeconomic status. Group H consisted of 64 women, Group M consisted of 83 women, and Group L consisted of 87 women. The mean age and percentage of menopausal women were similar in all groups.
Of the interviewed women, 43,59% had taken HRT at some time; marked differences between the three groups were observed (L, 10,34%; M, 55,42%; H, 73,43%;). In group H, the percentage of women who had been advised about HRT was 92,18%, whereas, in group M, the percentage was 86,74%, and in group L, the percentage was only 27,58%. Among the women who were informed about HRT, 67,74% had used it at some time. The percentage of women who used HRT for >2 years was similar in all groups.
Women in the low socioeconomic group who use HRT, are a minority. Medical advice is fundamental to increasing HRT use in this group.

VITAMINS: D, A, E, C STATUS AND BONE MINERAL DENSITY IN HEALTHY POLISH POSTMENOPAUSAL WOMEN.

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Aims: Measurement of serum vitamins concentrations: 25-hydroxy vitamin D ([c] 25OHD) in winter, vitamin A, caroten, tocoferol, ascorbic acid and BMD in postmenopausal women.
Methods: n=42 postmenopausal healthy, untreated (without vitamin supplementation) women (mean aged: 58,80± 4,98). Mean BMD: 0,878±0,18 g/cm2 and T-score: -2,39±1,49 and BMI: 26,3±4,24. BMD was estimated using a dual energy X-ray absorptiometer (Lunar). We measured: [c] 25OHD by radioimmunoassay, vitamin A, caroten, tocopherol, ascorbic acid by colorimetric assay. Serum were collected during winter (January and February).
Results: All women have [c]25OHD belove 40ng/ml (mean value 13,18±7,37). Using a serum [c]25OHD of 10 ng/ml (mean value 7,21±2,01)as a cutoff, 38,1% (16/42) of the subjects were found to be vitamin D deficient. When a serum [c] 25OHD was: 10- 20 ng/ml(mean value 14,44±2,93): 50% (21/42) of the subjects were found to be vitamin D deficient. Only 11,9% (5/42) women have [c] 25OHD: 20-40 ng/ml (mean value 30,47±6,83). Mean value of vitamins[c]: A (normal range: 25-80 ug/dl – 79,65±32,26 ug/dl, caroten (normal range: 80-480 ug/dl)- 129,29±55,68 ug/dl, E (normal range: 0,5-1,6 ug/dl) – 1,91±0,72 ug/dl, C (normal range: 0,4-1,5 mg/dl) - 0,64±0,27 mg/dl.
Conclusions: A low winter serum [c]25OHD is possibly one of the factors for lower BMD among Polish postmenopausal women, but correlation between BMD and [c]25OHD was no significant.
All women have normal range of caroten, vitamin A and C [c] and higher [c] of vitamin E without correlation with BMD.

Effect of body mass index (BMI) on bone mineral density in peri- and postmenopausal women.

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Objective : To assess the effect of body mass index (BMI) on bone mineral density (BMD) in peri- and postmenopausal women.
Method : Cross sectional study on 1,041 peri-and postmenopausal women who attended at the menopause clinic. Body weight and height were recorded. Bone mineral density at ultradistal radius was measured by DEXA. ANOVA test was used for statistical analysis.
Results : The mean bone mineral density was 0.332 ± 0.057 gm/cm^2. The mean BMD in thin women (BMI < 18.5 kg/m^2) was 0.298 ± 0.069 gm/cm^2 and in women with normal weight (BMI 18.5 – 24.9 kg/m^2) was 0.324 ± 0.055 gm/cm^2, that was no statistically significant between both groups. The mean BMD in overweight (BMI 25 - 29.9 kg/m^2) and obese women (BMI ≥ 30 kg/m^2) was 0.342 ± 0.056 gm/cm^2 and 0.381 ± 0.054 gm/cm^2 , respectively. The mean BMD in overweight and obese women were higher than that in thin and normal weight women statistically significant ($P < 0.01$).
Conclusion : The BMD in thin women was the same as in normal weight women. The BMD in thin and normal weight women were significantly less than in overweight and obese women .

CLINICAL STUDY ON LIFESTYLE RELATED DISEASES MET ON MENOPAUSAL PHYSICIANS WOMEN IN ROMANIA

Dr. E. Stuparu[1]; Dr. E. Marincea[1]; Dr. M.A. Ciochirca[2]; Dr. M.R.Stoenescu[2]

Our study underlines the difficulties that a physician in general and a physician woman in particular had to overcome to maintain the cultural accepted position of wise, knowledge and power in the health profession. Also is focused on the diseases related with stress and lifestyle met on medical women especially in pre- and menopausal period of time. The negative consequences of lifestyle and behavioral factors (lack of exercises, unhealthy diet, smoking, lot of caffeine intake, alcohol consumption) are stress-induced diseases like: eating disorders, obesity, high blood pressure, high levels of serum cholesterol and various psychosomatic and minor psychiatric disorders. In our assessment of a 200 lot of women physicians patients with various age we focused on the types of individual physicians behavior. We used standard tests, scales for psychological evaluation and clinical and laboratory examinations. Our results express the high rate of stress related diseases met on physicians women especially on menopausal time. The most frequent problems are binge eating, obesity and disturbed body image and coronary pathology. The conclusions are that social and family pressure on physician women in Romania (expected to be a high professional figure and at the same time to be performant in her other social roles, including being a wife and a mother) puts the physician woman in a double binded position which increases the risks of stress related diseases, especially over 40-50 years.

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ROLE OF BODY IMAGE IN MENOPAUSE OF PHYSICIANS WOMEN IN ROMANIA

Dr. E. Marincea[1]; Dr. E. Stuparu[1]; Dr. Maria-Antoaneta Ciochirca[2]

In the medical field the physician woman is in a way of thinking a public person. The way she looks and dresses influences the establishment of physician-patient relationship. It is well-known that a nice appearance is related with a better compliance of the patient. Our study is focused on the motivations of pre- and menopausal medical women asking aesthetic surgery in this period of time. The objective of this study is to evaluate the correlation of the three parameters body-image-self-esteem and professional-success of medical women during psychiatric assessment before and after surgical intervention. Increasing physical attractiveness represents an important factor on psychosocial adaptation and physician-patient communication.

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AGE-RELATED BONE LOSS IN NORMAL POPULATION OF UKRAINIAN WOMEN : DATA OF ULTRASOUND BONE DENSITOMETRY

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The bone tissue state in the Ukrainian women was studied. The total of 1364 women 20–89 years old were included. Patients with diseases influencing their bone tissue metabolism were excluded from the study. The heel bone examinations were performed by means of an ultrasound bone densitometer «Achilles+» (Lunar Corp., Madison, WI). The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated «Stiffness» index (SI, %) were measured. It was found out that the ultrasound parameters characterising state of spongy bone tissue and its density decrease after the age of 45 years old in Ukrainian women (fig. 1).SI lower than the fracture threshold was found in: 13,4% – women in age group of 50–59 years; 24,6% – women in age group of 60–69; 50,0% – women in age group of 70–79 years, 53,3% – women in age group of 80–89 years.

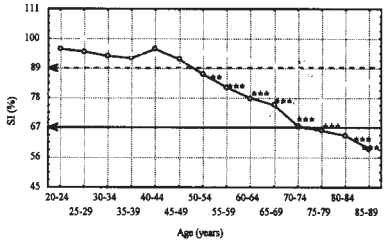

***Fig.* 1.** SI values in population of Ukrainian women associated with age.
Note: * – p < 0,05; ** – p < 0,01; *** – p < 0,001 compared to the age group of 35–39 years old.

Thus, in the process of ageing ultrasound parameters characterising bone tissue state decrease significantly and number of the examined with indices lower than the fracture threshold increases.

PARTICULARITIES THE AGEING OF WOMEN IN POSTMENOPAUSAL PERIOD

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Ukrainian women spend almost one third of the life in postmenopausal period. The quality of their life in this period considerably becomes worse in tie with development of numerous of neuro-vegetative, uro-genital disorders, cardio-vascular diseases and osteoporosis. The early menopausal symptoms (hot flushes, sleep disturbances and others) conduce to bringing down the capacities of women, to increasing the number of hospitalisations, to decreasing the life quality. The aim of the research is to study the ageing speed of Ukrainian postmenopausal women in dependence on anthropometric indexes, peculiarities of actual feeding, time of menopause, concomitant pathology of bone and muscular system. It was inspected 215 women in postmenopausal period in the age 48-69 years (duration of postmenopause put together 1-15 years). It was establish, that in early postmenopausal period (postmenopause's duration is 1-3 of year) augmentation of frequency of neuro-vegetative symptoms (is marked significant increase of modified ?upperman index), is marked a speed-up the ageing of women. In women in late postmenopausal period (postmenopause's duration is 9-15 years) on frequency diminution background and intensity of neuro-vegetative violations is established slowing down of speed ageing, improvement the life quality of women. The speed of ageing was connected with duration of postmenopausal period, Kupperman index, contents of some nutrition (protein, vitamin E), some anthropometric i.

PECULIARITIES OF LEAKING O KNEE OSTEOARTHRITIS IN UKRAINIAN WOMEN IN POSTMENOPAUSAL PERIOD AND THE CONNECTION WITH THE STRUCTURAL-FUNCTIONAL STATE OF BONE LOSS

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Osteoarthritis and osteoporosis are most important diseases of bone and joint system, however tempos of their development in postmenopausal period have some peculiarities. In many researches it was founded the deficit role of sexual hormones and menopause in development of osteoarthritis and osteoporosis. In the order to study the peculiarities of the knee osteoarthritis and structural-functional state of bone mass in elder women we inspected 97 women by age of 50-79 years, which were in postmenopausal period (his duration composed from 2 to 34 years) with the knee osteoarthritis (I-III stages). A diagnosis of osteoarthritis it was determined for criterions of American rheumatology association (1995), its stage - for Kellgren-Lourenz classification. The heel bone examinations were performed by means of an ultrasound bone densitometer. The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated «Stiffness» index (SI, %) were measured.

We founded the peculiarities of structurally-functional state of bone loss in depend of the of knee osteoarthritis' stage, duration of postmenopausal period (Tabl.1) and coming time of menopause. Also we definite the role of surplus body weight in development of knee osteoarthritis and in beginning of structural-functional violations of bone mass in women in postmenopausal period.

Tabl.1. Structural-functional state of bone mass of women in depend of the duration of postmenopausal period and stage of knee osteoarthritis

Data of ultrasound densitometry	Stage of knee osteoarthritis		P
	I	II	
Duration of postmenopausal period: 1-9 years			
SOS, m/s	1534,5±6,0	1523,0±24,8	>0,05
BUA, dB/MHz	115,5±1,3	108,0±8,8	>0,05
SI, %	86,5±2,2	76,2±9,9	>0,05
Duration of postmenopausal period: 10-19 years			
SOS, m/s	1534,6±5,3	1510,2±9,2	<0,05
BUA, dB/MHz	112,0±1,9	107,4±3,0	>0,05
SI, %	84,1±2,0	74,3±4,4	<0,05
Duration of postmenopausal period: more than 20 year			
SOS, m/s	1525,9±11,4	1503,1±3,7	>0,05
BUA, dB/MHz	110,8±3,6	99,9±2,5	<0,05
SI, %	81,4±5,4	68,5±2,6	<0,05

HYPOACTIVE SEXUAL DESIRE IN MENOPAUSAL WOMEN IN EUROPE

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Objectives: To determine in four European (EU) countries: (1) the proportion of menopausal women classified as having low or hypoactive sexual desire (HSD), (2) the proportion of these women with HSD who are distressed by their loss of desire and are classified as having hypoactive sexual desire disorder (HSDD), (3) sexual activity levels and behaviour as a function of level of sexual desire, and (4) the relationship of sexual desire and satisfaction with sex life or relationship with partner.

Methods: The Women's International Sexuality and Health Survey (WISHES) was a mail survey conducted among 2467 pre-, peri, and postmenopausal women in France, Italy, Germany, and the UK.

The survey contained the Profile of Female Sexual Function (PFSF), a validated instrument designed to measure hypoactive sexual desire in women, and the Personal Distress Scale (PDS), a scale developed to measure distress due to lost desire. Respondents were also asked questions about how often they engaged in sexual activities, and how satisfied they were with their sex lives and/or their relationships with their partners. Cut-off scores were obtained for the desire domain of the PFSF and the PDS from the results of validation studies with the instruments. These cut-off scores have now been applied to the WISHES data to determine the proportion of women with low desire in larger, national, populations.

Results: Across the four countries, the percentage of the total population of menopausal women classified as having HSD ranged from 21 to 36% and about 20% of these women with HSD were classified as having hypoactive sexual desire disorder (HSDD), i.e., low sexual desire accompanied by distress due to lack of desire. Many menopausal women with low desire endorsed statements expressing negative psychological or emotional states related to their own sexual function, sexual identity, and sexual relationships with their partners. Low sexual desire was associated with significantly less frequent sexual activities including low frequency of initiation of activity by the woman respondent, and low frequencies of orgasm and intercourse. Menopausal women with lower sexual desire were significantly less satisfied with their sex lives than women with higher sexual desire. Menopausal women with low satisfaction with their sex lives were significantly less satisfied with their relationships than those women with higher sexual desire.

Conclusions: HSDD is prevalent in menopausal women in Europe and is accompanied by personal distress. Women with low desire are more likely to experience low satisfaction with their sex lives and their partner relationships.

INDEX OF ABSTRACT CONTRIBUTORS

(The number refers to the Abstract Book page)

IN GRATEFUL APPRECIATION

The Organizing Committee is grateful to all the contributors that have generously supported the Symposium:

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Wyeth Pharmaceuticals

The Organizing Committee gratefully acknowledges Aboca S.p.A. and Ferrero S.p.A. for offering their products during the coffee breaks.

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Finito di stampare nel mese di aprile 2004
presso Ialitotipo s.r.l.
via Enrico Fermi, 17 - Settimo Milanese (MI)

Lorenzini Foundation Symposium: 298