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JOURNAL ABSTRACTS

Stem cells

MARROW CELL THERAPIES FOR CARDIOVASCULAR DISEASES.

The nascent field of regenerative medicine has taken root in cardiovascular disease. Preclinical data demonstrating hemangioblast potential of marrow cells and cardioprotective effects of growth factors served as the basis for numerous early phase clinical trials. With the first wave of safety and efficacy trials complete, much is still unknown regarding optimal cell dose and type, timing of injection, route of administration, mechanisms of action, and achievable response measures. The next generation of studies will aim to answer these questions and make way for cellular therapies that result in effective cardiac repair.

Exp Hematol. 2008 Jun;36(6):687-94

INDUCED PLURIPOTENT STEM CELLS GENERATED FROM PATIENTS WITH ALS CAN BE DIFFERENTIATED INTO MOTOR NEURONS.

The generation of pluripotent stem cells from an individual patient would enable the large-scale production of the cell types affected by that patient's disease. These cells could in turn be used for disease modeling, drug discovery, and eventually autologous cell replacement therapies. Although recent studies have demonstrated the reprogramming of human fibroblasts to a pluripotent state, it remains unclear whether these induced pluripotent stem (iPS) cells can be produced directly from elderly patients with chronic disease. We have generated iPS cells from an 82-year-old woman diagnosed with a familial form of amyotrophic lateral sclerosis (ALS). These patient-specific iPS cells possess properties of embryonic stem cells and were successfully directed to differentiate into motor neurons, the cell type destroyed in ALS.

Science. 2008 Aug 29;321(5893):1218-21

STEM CELL TREATMENT IN AMYOTROPHIC LATERAL SCLEROSIS.

Amyotrophic Lateral Sclerosis is a progressive fatal neurodegenerative disease that targets motor neurons. Its origin is unknown but a main role of reactive astrogliosis and microglia activation in the pathogenesis has been recently demonstrated. Surrounding neurons with healthy adjoining cells completely stops motor neuron death in some cases. Hence stem cell transplantation might represent a promising therapeutic strategy. In this study MSCs were isolated from bone marrow of 9 patients with definite ALS. Growth kinetics, immunophenotype, telomere length and karyotype were evaluated during in vitro expansion. No significant differences between donors or patients were observed. The patients received intraspinal injections of autologous MSCs at the thoracic level and monitored for 4 years. No significant acute or late side effects were evidenced. No modification of the spinal cord volume or other signs of abnormal cell proliferation were observed. Four patients show a significant slowing down of the linear decline of the forced vital capacity and of the ALS-FRS score. Our results seem to demonstrate that MSCs represent a good chance for stem cell cell-based therapy in ALS and that intraspinal injection of MSCs is safe also in the long term. A new phase 1 study is carried out to verify these data in a larger number of patients.

J Neurol Sci. 2008 Feb 15;265(1-2):78-83

IN VITRO GENERATION OF A SCAFFOLD-FREE TISSUE-ENGINEERED CONSTRUCT (TEC) DERIVED FROM HUMAN SYNOVIAL MESENCHYMAL STEM CELLS: BIOLOGICAL AND MECHANICAL PROPERTIES, AND FURTHER CHONDROGENIC POTENTIAL.

The purpose of this study was to characterize a tissue-engineered construct (TEC) generated with human synovial mesenchymal stem cells (MSCs). MSCs were cultured in medium with ascorbic acid 2-phosphate (Asc-2P) and were subsequently detached from the substratum. The detached cell/matrix complex spontaneously contracted to develop a basic TEC. The volume of the TEC assessed by varying initial cell density showed that it was proportional to initial cell densities up to 4×10^5 cells/cm².

Assessment of the mechanical properties of TEC using a custom device showed that the load at failure and stiffness of the constructs significantly increased with time of culture in the presence of Asc-2P, while in the absence of

Asc-2P, the constructs were mechanically weak. Thus, the basic TEC possesses sufficiently self-supporting mechanical properties in spite of not containing artificial scaffolding. TEC further cultured in chondrogenic media exhibited positive alcian blue staining with elevated expression of chondrogenic marker genes. Based on these findings, such human TEC may be a promising method to promote cartilage repair for future clinical application.

Tissue Eng Part A. 2008 Jul 17

CHONDROGENESIS FROM IMMORTALIZED HUMAN MESENCHYMAL STEM CELLS: COMPARISON BETWEEN COLLAGEN GEL AND PELLET CULTURE METHODS.

Human mesenchymal stem cells (hMSCs) can differentiate into cells of connective tissue lineages, including cartilage. To overcome the limiting autogenous chondrocyte populations available in cartilage repair, various methods have been developed to maximize chondrogenesis of hMSCs in vitro, most of which use cells derived from primary culture. In this study, we compared chondrogenesis of immortalized hMSCs embedded in collagen gel to those grown in pellet culture. The hMSCs in collagen scaffolds expressed more glycosaminoglycan than those in pellet culture. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis demonstrated that the expression of genes encoding sox-9, aggrecan, and types I and II collagen increased in pellet culture over time. However, in the collagen cultures, only type II collagen and aggrecan expression increased over time, whereas sox-9 expression remained unchanged and type I collagen expression decreased. These results indicate that the immortalized hMSC line is a promising tool for further in vitro chondrogenic studies.

Artif Organs. 2008 Jul;32(7):561-6

STEM-CELL BASED THERAPIES FOR BRAIN TUMORS.

Advances in understanding neural stem cell (NSC) biology have facilitated the development of novel cell-based therapies for brain malignancies. NSCs are the most immature progenitor cells in the nervous system that have the ability to self-renew, differentiate into terminal neural cell types, and extensively migrate to areas of pathology in the central nervous system. Because of their inherent tumor-trophic properties and their capacity to differentiate into all neural phenotypes, NSCs represent a powerful tool for the treatment of both diffuse and localized neurological disorders. Progress has validated the feasibility of using engineered NSCs as cell-based therapeutic agents to eliminate malignant cells in the brain. This review discusses the therapeutic potential of NSCs focusing on brain tumors.

Curr Opin Mol Ther. 2008 Aug;10(4):334-42

DISEASE-SPECIFIC INDUCED PLURIPOTENT STEM CELLS.

Tissue culture of immortal cell strains from diseased patients is an invaluable resource for medical research but is largely limited to tumor cell lines or transformed derivatives of native tissues. Here we describe the generation of induced pluripotent stem (iPS) cells from patients with a variety of genetic diseases with either Mendelian or complex inheritance; these diseases include adenosine deaminase deficiency-related severe combined immunodeficiency (ADA-SCID), Shwachman-Bodian-Diamond syndrome (SBDS), Gaucher disease (GD) type III, Duchenne (DMD) and Becker muscular dystrophy (BMD), Parkinson disease (PD), Huntington disease (HD), juvenile-onset, type 1 diabetes mellitus (JDM), Down syndrome (DS)/trisomy 21, and the carrier state of Lesch-Nyhan syndrome. Such disease-specific stem cells offer an unprecedented opportunity to recapitulate both normal and pathologic human tissue formation in vitro, thereby enabling disease investigation and drug development.

Cell. 2008 Sep 5;134(5):877-86

THE PROBLEM OF DECEPTION IN EMBRYONIC STEM CELL RESEARCH.

The field of embryonic stem cell research has been plagued by exaggeration and misrepresentation, as three major journals have had to retract significant claims about progress in this field. This problem is exacerbated by the politicized climate in which the research is conducted and defended; it may also lie deeper, in a utilitarian ethic that in principle could justify unethical actions for admittedly worthwhile long-term goals. Such an ethic risks undermining the credibility of science, which must show a commitment to the facts that is independent of social and political goals.

Cell Prolif. 2008 Feb;41 Suppl 1:65-70

STEM CELL RESEARCH: CLONING, THERAPY AND SCIENTIFIC FRAUD.

Stem cell research has generated intense excitement, awareness, and debate. Events in the 2005-2006 saw the rise and fall of a South Korean scientist who had claimed to be the first to clone a human embryonic stem cell line. From celebration of the potential use of stem cells in the treatment of human disease to disciplinary action taken against the disgraced scientists, the drama has unfolded throughout the world media. Prompted by an image of therapeutic cloning presented on a South Korean stamp, a brief review of stem cell research and the events of the Woo-suk Hwang scandal are discussed.

Clin Genet. 2006 Oct;70(4):302-5

HUMAN CLONING AND STEM CELL RESEARCH: ENGAGING IN THE POLITICAL PROCESS. (LEGISLATION REVIEW: PROHIBITION OF HUMAN CLONING ACT 2002 AND THE RESEARCH INVOLVING HUMAN EMBRYOS ACT).

Committees appointed by governments to inquire into specific policy issues often have no further role when the Committee's report is delivered to government, but that is not always so. This paper describes the activities of members of the Australian Committee on human cloning and embryo research (the Lockhart Committee) to inform Parliament and the community about the Committee's recommendations after its report was tabled in Parliament. It explains their participation in the political process as their recommendations were debated and amending legislation was passed by Parliament. It illustrates a method of communication about scientific and policy issues that explores people's concerns and what they 'need to know' to make a judgment; and then responds to questions they raise, with the aim of facilitating discussion, not arguing for one view. The paper considers whether this type of engagement and communication is appropriate and could be used in other policy discussions.

Med Law. 2008 Mar;27(1):119-30

Atherosclerotic plaque

IDENTIFYING THE VULNERABLE PATIENT WITH RUPTURE-PRONE PLAQUE.

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in the United States, and the obesity epidemic combined with aging of the population seems destined to increase the burden of this disease. Traditional cardiovascular risk assessment accounts for <50% of the variability in risk in the United States. Therefore, better and more effective identification of persons at high cardiovascular risk is needed. Our understanding of atherosclerosis has shifted from a focal disease whose hallmark is symptoms caused by a severe stenosis to a systemic disease characterized by endothelial dysfunction (ED) and plaque inflammation, with the potential for rupture and thrombosis mainly in those with subcritical stenosis. Under the new paradigm, clinicians require updated strategies to better assess the quality of arterial plaque. Effective tools for primary and secondary prevention of heart attack and stroke include intensive lifestyle modification, blood pressure reduction, and lipid-modifying therapies. These interventions are now understood to decrease plaque inflammation and thereby promote plaque stability. Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) appears to be a specific marker of plaque inflammation that may play a direct role in the formation of rupture-prone plaque. In contrast, traditional risk factors, lipid measurement, and most vascular imaging modalities do not directly assess the acute ischemic potential in the arterial wall. Measuring Lp-PLA(2) levels in human serum or plasma is noninvasive and relatively inexpensive. Lp-PLA(2) may provide additional clinically relevant information that shows which patients have a high level of atherosclerotic disease activity as manifested by vascular inflammation, ED, and increased risk for progression toward rupture-prone plaque.

Am J Cardiol. 2008 Jun 16;101(12A):3F-10F

THE MOLECULAR BASIS OF VULNERABLE PLAQUE: POTENTIAL THERAPEUTIC ROLE FOR IMMUNOMODULATION.

PURPOSE OF REVIEW: Athero-sclerosis is a chronic inflammatory/immune disease involving multiple cell types including monocytes-macrophages, T-lymphocytes, mast cells, and endothelial cells. Through recent studies the role of the immune system on development of atherosclerosis and approaches to modulate this response are being elucidated. **RECENT FINDINGS:** The use of statins, PPARgamma agonists or lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitors may play a role in reducing progression of atherosclerosis through immunomodulatory pathways. Oxidized LDL biases development toward the pro-inflammatory T-cell Th1 subset and recruits macrophages into the vascular wall. IFNgamma, produced by Th1 cells, inhibits PPARgamma effects. Lp-PLA2 levels correlate with an increased risk of recurrent ischemic events in patients presenting with acute coronary syndromes or myocardial infarction. **SUMMARY:** Recent research has shown that immune pathways play a major role in the development and progression of atherosclerosis. Commonly used medications, specifically statins and some PPARgamma agonists, have demonstrated anti-inflammatory/immune effects unrelated to their primary mode of action. Treatment of infectious agents has proven elusive in the clinical arena. Novel agents targeting immune and inflammatory pathways may prove beneficial in reducing progression and instability of the atherosclerotic plaque.

Curr Opin Cardiol. 2007 Nov;22(6):545-51

ENHANCED EXPRESSION OF LP-PLA2 AND LYSOPHOSPHATIDYLCHOLINE IN SYMPTOMATIC CAROTID ATHEROSCLEROTIC PLAQUES.

BACKGROUND AND PURPOSE: Circulating lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) has emerged as a novel biomarker for cardiovascular diseases. However, the correlation between the plaque expression of Lp-PLA(2) and plaque oxidative stress, inflammation, and stability as well as the clinical presentation remains poorly defined, especially for cerebrovascular disease. Therefore, this study was performed to test the hypothesis that Lp-PLA(2) expression is higher in symptomatic than in asymptomatic carotid plaques of patients undergoing carotid endarterectomy. **METHODS:** The expression of Lp-PLA(2) in 167 carotid artery plaques was determined by immunoblotting and immunostaining. Plaque oxidative stress, inflammation, and stability were quantified by NAD(P)H oxidase p67phox and MMP-2 immunoblotting, oxidized LDL (oxLDL) immunoreactivity, macrophage and Sirius red collagen staining. Lysophosphatidylcholine 16:0 (lysoPC) concentration was measured in 55 plaques using liquid chromatography tandem mass spectrometry. **RESULTS:** Lp-PLA(2) expression was significantly higher in plaques of symptomatic patients than asymptomatic patients (1.66+/-0.19 versus 1.14+/-0.10, P<0.05) and localized mainly to shoulder and necrotic lipid core areas in colocalization with oxLDL and macrophage content. Similarly, Lp-PLA(2) expression was related to collagen content, which was lower in plaques from symptomatic patients than in plaques from asymptomatic patients (9.1+/-2.2

versus 18.5+/-1.7% of staining/field, $P < 0.001$). LysoPC plaque concentration was significantly higher in plaques of symptomatic than asymptomatic patients (437.0+/-57.91 versus 228.84+/-37.00 mmol/L, $P < 0.05$). **CONCLUSIONS:** Symptomatic carotid artery plaques are characterized by increased levels of Lp-PLA(2) and its product lysoPC in correlation with markers of tissue oxidative stress, inflammation, and instability. These findings strongly support a role for Lp-PLA2 in the pathophysiology and clinical presentation of cerebrovascular disease.

Stroke. 2008 May;39(5):1448-55

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2: A RISK MARKER OR A RISK FACTOR?

Multiple cardiovascular biomarkers are associated with increased cardiovascular disease (CVD) risk. Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) appears to be relatively unique in its high specificity for and the causal pathway of plaque inflammation. In both primary and secondary prevention study populations, Lp-PLA(2) was consistently associated with higher cardiovascular risk, and the risk estimate appears to be relatively unaffected by adjustment for conventional CVD risk factors. Risk ratios were similar, whether the mass concentration or activity of the enzyme was measured. The purpose of this article is to review the evidence for the clinical utility of Lp-PLA(2), both as a risk marker and as a risk factor involved in the causal pathway of plaque inflammation and the formation of rupture-prone plaque.

Am J Cardiol. 2008 Jun 16;101(12A):11F-22F

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2: AN INDEPENDENT PREDICTOR OF CORONARY ARTERY DISEASE EVENTS IN PRIMARY AND SECONDARY PREVENTION.

In recent years, atherosclerosis has become recognized as an inflammatory disease whose activity can be assessed by circulating biomarkers. Along with C-reactive protein (CRP), lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) may now be considered as a biomarker with sufficient accumulated evidence to support its application in clinical practice. Lp-PLA(2) is especially appealing because of its vascular specificity, which directly derives from its role in plaque pathophysiology. This article reviews the highlights of the >25 prospective epidemiologic studies now published on Lp-PLA(2) as a risk marker in primary or secondary prevention. These trials demonstrate generally consistent correlations between elevated Lp-PLA(2) levels and the increased risk for cardiovascular events, even after multivariable adjustment for traditional risk factors, with roughly a doubling of risk associated with upper quantile levels. Furthermore, Lp-PLA(2) as a risk predictor has been shown to be independent of and complementary to high-sensitivity CRP. These study results combined with recommendations from the American Heart Association/Centers for Disease Control (AHA/CDC) and the National Cholesterol Education Program III (NCEP III) suggest that Lp-PLA(2) might best be used in current clinical practice to refine risk prediction in those at intermediate cardiovascular risk. An increasingly prevalent group at intermediate risk shown to benefit from Lp-PLA(2) risk modification is the population with the cardiovascular metabolic syndrome, clinically identified as overweight patients with features of mixed dyslipidemia, dysglycemia, and hypertension. An additional application supported by these studies is further risk stratification of high- (often secondary-) risk patients into a group at very high risk, for whom a more aggressive target for low-density lipoprotein of <70 mg/dL (1 mg/dL = 0.02586 mmol/L) is now recommended as a reasonable therapeutic goal.

Am J Cardiol. 2008 Jun 16;101(12A):23F-33F

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 IS AN INDEPENDENT PREDICTOR OF INCIDENT CORONARY HEART DISEASE IN AN APPARENTLY HEALTHY OLDER POPULATION: THE RANCHO BERNARDO STUDY.

OBJECTIVES: Lipoprotein-associated phospholipase A2 (Lp-PLA2) levels predict incident coronary heart disease (CHD) in adults without known CHD, independent of heart disease risk factors. We examined whether the independent association was apparent in older adults. **BACKGROUND:** Serum levels of Lp-PLA2, an enzyme that hydrolyzes oxidized phospholipids to yield potentially proatherogenic particles, have been associated with CHD and may help predict cardiovascular risk. **METHODS:** Participants were 1,077 community-dwelling men and women, median age 72 years, who had no known CHD at baseline (1984 to 1987) when blood samples and risk factor data were collected. Participants were followed for CHD events for a mean of 16 years, through 2002. Cox proportional hazards regression models were used to examine the association of serum Lp-PLA2 with incident CHD (myocardial infarction, angina, or coronary revascularization). **RESULTS:** The Lp-PLA2 levels positively correlated with age ($r = 0.09$), body mass index ($r = 0.11$), low-density lipoprotein ($r = 0.37$), triglycerides ($r = 0.25$), and C-reactive protein ($r = 0.10$), and negatively correlated with high-density lipoprotein ($r = -0.27$) (all $p < 0.05$). During follow-up, 228 participants had incident CHD events. Lipoprotein-associated phospholipase A2 levels in the second, third, and fourth quartiles predicted an increased risk of CHD compared with the lowest quartile (hazard ratios 1.66, 1.80, and 1.89, respectively; $p < 0.05$ for each). This association persisted after adjusting for C-reactive protein and other CHD risk factors. **CONCLUSIONS:** Elevated Lp-PLA2 levels predict CHD events in apparently healthy older adults, independent of CHD risk factors.

J Am Coll Cardiol. 2008 Mar 4;51(9):913-9

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 AND RISK OF STROKE.

Stroke is the second-leading cause of death worldwide and is a disabling disease of both older and younger adults. Stroke is also among the most highly preventable disorders because there are well-defined risk factors and preventatives. The establishment of new risk markers or factors for stroke risk assessment provides a new avenue for stroke prevention. Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) is an enzyme that hydrolyzes oxidized phospholipids, releasing lysophosphatidylcholine, which has proinflammatory properties thought to be involved in the development of atherosclerosis and plaque rupture. In 2005, the Lp-PLA(2) blood test was approved by the US Food and Drug Administration (FDA) for assessing the risk of ischemic stroke and coronary artery disease. In epidemiologic studies, low-density lipoprotein cholesterol and other lipid factors have not been shown to be consistent predictors of stroke risk. Lp-PLA(2) measures, on the other hand, have shown a consistent association with stroke risk, conferring about a 2-fold increase in stroke occurrence. This relation has been studied in both first and recurrent stroke and is reviewed in this article. Importantly, a recent study has now shown that Lp-PLA(2) may increase the area under the curve beyond that of traditional cardiovascular risk factors and C-reactive protein. Therefore, Lp-PLA(2) determination may provide a pivotal opportunity to appropriately classify previously misclassified persons who are actually at high risk of stroke and in need of aggressive stroke intervention.

Am J Cardiol. 2008 Jun 16;101(12A):34F-40F

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2, HIGH-SENSITIVITY C-REACTIVE PROTEIN, AND RISK FOR INCIDENT ISCHEMIC STROKE IN MIDDLE-AGED MEN AND WOMEN IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY.

BACKGROUND: Measurement of inflammatory markers has been reported to identify individuals at increased risk for ischemic stroke. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme secreted by macrophages. We assessed Lp-PLA2 and C-reactive protein (CRP) levels along with traditional risk factors to examine their relation to ischemic stroke. **METHODS:** A proportional hazards model was used in a prospective case-cohort study of 12,762 apparently healthy middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study who were observed for about 6 years. **RESULTS:** Mean Lp-PLA2 and CRP levels adjusted for sex, race, and age were higher in the 194 stroke cases than the 766 noncases, whereas low-density lipoprotein cholesterol (LDL-C) level was not significantly different. Both Lp-PLA2 and CRP levels were associated with ischemic stroke after adjustment for age, sex, and race: hazard ratios were 2.23 for the highest vs the lowest tertile of Lp-PLA2 and 2.70 for CRP level higher than 3 vs lower than 1 mg/L. In a model that included smoking, systolic hypertension, lipid levels, and diabetes, Lp-PLA2 and CRP levels in the highest category were associated with hazard ratios of 1.91 (95% confidence interval, 1.15-3.18; P = .01) and 1.87 (95% confidence interval, 1.13-3.10; P = .02), respectively. Individuals with high levels of both CRP and Lp-PLA2 were at the highest risk after adjusting for traditional risk factors compared with individuals with low levels of both, whereas others were at intermediate risk. **CONCLUSION:** Levels of Lp-PLA2 and CRP may be complementary beyond traditional risk factors in identifying middle-aged individuals at increased risk for ischemic stroke.

Arch Intern Med. 2005 Nov 28;165(21):2479-84

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 PREDICTS PROGRESSION OF CARDIAC ALLOGRAFT VASCULOPATHY AND INCREASED RISK OF CARDIOVASCULAR EVENTS IN HEART TRANSPLANT PATIENTS.

BACKGROUND: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a risk factor for coronary artery disease (CAD) in nontransplant patients. We evaluated the association between Lp-PLA2, cardiac allograft vasculopathy (CAV) assessed by 3D intravascular ultrasound, and incidence of cardiac adverse events in heart transplant recipients. **MATERIALS AND METHODS:** Fasting blood samples were obtained and stored from a cross-section of 112 cardiac transplant recipients attending the Mayo cardiac transplant clinic in 2000 to 2001, mean of 4.7 years after transplant. Lp-PLA2 was measured in plasma aliquots using an enzyme-linked immunoassay. Fifty-six of these patients subsequently underwent two 3D intravascular ultrasound studies in 2004 to 2006 12 months apart. Cardiovascular (CV) events included percutaneous coronary intervention, coronary artery bypass grafting (CABG), reduction in left ventricular ejection fraction (LVEF) \leq 45% secondary to CAV and CV death. **RESULTS:** High Lp-PLA2 level was associated with increase in plaque volume ($r=0.43$, $P=0.0026$) and percent plaque volume ($r=0.45$, $P=0.0004$). The association remained significant after adjusting for clinical and lipid variables. During follow-up of 5.1 ± 1.6 years, 24 CV adverse events occurred in 15 of 112 (13%) heart transplant patients. Lp-PLA2 level >236 ng/mL (higher tertile) identified a subgroup of patients having a 2.4-fold increase of relative risk for combined endpoint of CV events (percutaneous coronary intervention, CABG, LVEF $<45\%$, and CV death; 95% CI 1.16-5.19, $P=0.012$) compared with patients with Lp-PLA2 ≤ 236 ng/mL. **CONCLUSIONS:** Lp-PLA2 is independently associated with progression of CAV and predicts a higher incidence of CV events and CV death in transplant patients. This finding supports the concept that systemic inflammation is an important mediator of CAV. Lp-PLA2 may be a useful marker for risk of CAV and a therapeutic target in posttransplant patients.

Transplantation. 2008 Apr 15;85(7):963-8

ASSOCIATION OF LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2 WITH CORONARY CALCIFICATION AMONG

AMERICAN AND JAPANESE MEN.

BACKGROUND: We have previously reported that the prevalence of coronary artery calcification (CAC) was substantially lower among Japanese than American men despite a less favorable profile of many traditional risk factors in Japanese men. To determine whether lipoprotein-associated phospholipase A2 (Lp-PLA2) levels are related to the difference in the prevalence of CAC between the two populations. **METHODS:** A total of 200 men aged 40-49 years were examined: 100 residents in Allegheny County, Pennsylvania, United States, and 100 residents in Kusatsu City, Shiga, Japan. Coronary calcium score (CCS) was evaluated by electron-beam tomography, Lp-PLA2 levels, nuclear magnetic resonance (NMR) lipoprotein subclasses, and other factors were assessed in 2001-2002. **RESULTS:** Lp-PLA2 levels were higher among American than Japanese men (Mean +/- standard deviation 301.7 +/- 82.6 versus 275.9 +/- 104.7 ng/mL, respectively, $p=0.06$). Among all Japanese men and those with low density lipoprotein (LDL) cholesterol ≥ 130 mg/dL, there was an inverse association of the prevalence of $CCS>0$ with the tertile groups of Lp-PLA2 levels ($p=0.08$ and $p=0.03$, respectively). American men did not have any association between $CCS>0$ with the tertile groups of Lp-PLA2 ($p=0.62$). Although Lp-PLA2 among both populations correlated positively with LDL and total cholesterol, American and Japanese men had different correlations with NMR lipoprotein subclasses. Reported high odds ratio for $CCS>0$ among American compared to Japanese men was not reduced after adjusting for Lp-PLA2 levels. **CONCLUSION:** Lp-PLA2 may have different mechanisms of action among American and Japanese men. Lp-PLA2 levels can not explain the observed CAC differences between the two populations.

J Epidemiol. 2007 Nov;17(6):179-85

CURRENT ANTIPLATELET THERAPIES: BENEFITS AND LIMITATIONS.

Antiplatelet therapy is the current criterion standard for the treatment of patients undergoing percutaneous coronary intervention and patients who have acute coronary syndromes. Clopidogrel in combination with aspirin is the current standard of care for reducing cardiovascular events in these patients. However, patients who receive currently available antiplatelet therapy may still develop atherothrombotic events. In addition, despite the clinical benefits achieved with clopidogrel, significant clinical limitations are associated with its use. This article summarizes the current understanding of the benefits and limitations of the commonly used antiplatelet therapies.

Am Heart J. 2008 Aug;156(2 Suppl):S3-9

VARIABILITY IN RESPONSE TO CARDIOVASCULAR DRUGS.

Cardiovascular drugs are characterized by wide inter-individual variability in dose/plasma concentration/ response (therapeutic and/or toxic) relationships. Therefore, some patients achieve good therapeutic response to their drug therapy, while others do not. Also, some patients experience adverse effects, which vary from mild to life-threatening. The source of variability in patients' response to cardiovascular drugs may be of pharmacokinetic and/or pharmacodynamic origin. Many factors can potentially affect both of them such as genetics, gender, age, disease state, environmental factors like smoking and food, possible drug-drug interactions, and ethnicity (race). Cardiovascular pharmacogenomics is a new field that focus on the roles of genetic polymorphisms in drug metabolizing enzymes and drug targets in development of variable drug response.

Curr Clin Pharmacol. 2006 Jan;1(1):35-46

STATINS AND PERIPHERAL ARTERIAL DISEASE: EFFECTS ON CLAUDICATION, DISEASE PROGRESSION, AND PREVENTION OF CARDIOVASCULAR EVENTS.

Peripheral arterial disease (PAD) of the lower limbs is the third most important site of atherosclerotic disease alongside coronary heart disease (CHD) and cerebrovascular disease (CVD). Best medical treatment is beneficial even in patients who eventually need invasive treatment, as the safety, immediate success, and durability of intervention is greatly improved in patients who adhere to best medical treatment. In recent years, a number of studies have suggested that the ACE-inhibitor ramipril and different statins, together with antiplatelet drugs, reduce cardiovascular morbidity and mortality in PAD. Patients with PAD are really a category of patients with a very high cardiovascular risk burden for fatal and nonfatal cerebrovascular and cardiovascular events; therefore, they need to be treated not only for local problems deriving from arteriopathy (intermittent claudication, rest pain and/or ulcers) but, above all, for preventing vascular events. Statins not only lower the risk of vascular events, but they also improve the symptoms associated with PAD. Statins exert beneficial pleiotropic effects on hemostasis, vasculature and inflammatory markers; there is also evidence that statins improve renal function considering that the plasma creatinine level is considered as an emerging vascular risk factor.

Arch Med Res. 2007 Jul;38(5):479-88

THE SIGNIFICANCE OF LOW HDL-CHOLESTEROL LEVELS IN AN AGEING SOCIETY AT INCREASED RISK FOR CARDIOVASCULAR DISEASE.

In most developed and developing countries, the proportion of the population aged 60 years or more is growing faster than any other age group. Given that the vast majority of cardiovascular events occur in older individuals, new thinking is needed to reduce their risk. Epidemiological studies have shown an increasing prevalence of the metabolic syndrome with age, driven by nutrition inappropriate for a modern sedentary lifestyle. A low level of high-density lipoprotein (HDL)-cholesterol, a component of the atherogenic dyslipidaemia of the metabolic syndrome, has been shown to be an important determinant of coronary risk, which rises in prevalence with increasing age. Thus, raising HDLcholesterol, in addition to lowering the level of low-density lipoprotein (LDL)-cholesterol, seems a plausible approach to reduce cardiovascular risk in an ageing population. Clinical studies have shown that adding nicotinic acid, which raises HDL-cholesterol by 20-25%, to a statin enhances the reduction in progression of atherosclerosis. Results of the ongoing Atherothrombosis Intervention in Metabolic syndrome with low HDL/High triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study are awaited with interest to see whether such theoretical benefit translates

into clinical outcome.

Diab Vasc Dis Res. 2007 Jun;4(2):136-42

STATINS FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN OLDER ADULTS: A REVIEW OF THE EVIDENCE.

BACKGROUND: Although statins have been demonstrated to be beneficial for secondary prevention in the elderly, their use for primary prevention has not been well described. **OBJECTIVE:** In this review, we summarize data regarding the efficacy, safety, and current recommendations for statins for the primary prevention of cardiovascular events in older adults. **METHODS:** This review is based on a computerized literature search of the PubMed database for articles published in the English language from January 1980 to June 2006. Key words searched individually and cross-referenced included: statins, HMG-CoA reductase inhibitors, cholesterol, elderly, aged, cardiovascular disease, primary prevention, risk stratification, and C-reactive protein. This search produced 445 citations; reference lists revealed an additional 12 citations, all of which were screened for relevance to the topic. **RESULTS:** The existing evidence suggests, but does not confirm, benefit from the use of statins for primary prevention in the elderly subgroup (ie, those aged >65 years). Of the 6 published trials of statins for primary prevention, only 3 included subjects aged >75 years, and subgroup results in older adults are unavailable. Current guidelines recommend statins for individuals based on their assessed cardiovascular risk. **CONCLUSIONS:** Extension of treatment guidelines should consider an individual's global risk of coronary heart disease. However, due to the prevalence of subclinical disease in older adults, risk may be higher or otherwise differ with age. In addition, tolerance for and barriers to adherence with long-term medical therapy are important treatment considerations in older adults. Prospective, randomized controlled trials that better define the tolerability, safety, and efficacy of statin therapy in older adults with elevated cholesterol levels and intermediate cardiovascular risk are needed.

Am J Geriatr Pharmacother. 2007 Mar;5(1):52-63

ANTI-INFLAMMATORY AGENTS AND ANTIOXIDANTS AS A POSSIBLE "THIRD GREAT WAVE" IN CARDIOVASCULAR SECONDARY PREVENTION.

There are 3 important factors that predispose patients to plaque rupture or recurrent events: plaque burden or multiple arterial plaques, the presence of persistent hyperreactive platelets, and ongoing vascular arterial inflammation. Successful therapeutic strategies focus on these predisposing factors, and the use of low-density lipoprotein-lowering medications (principally statins) and antiplatelet agents (principally aspirin) has had a major impact on the occurrence of cardiovascular outcomes and overall mortality over the last 2 decades. However, despite these interventions, a significant number of patients experience recurrent events or progression of disease. Novel compounds are being studied to determine, for example, whether an increase in high-density lipoprotein will provide additional risk reduction; to date, this has not proved to be sufficiently effective. Although early invasive management has been proved to be superior to medical therapy in patients with plaque rupture producing acute coronary syndromes, its superiority in patients with clinically stable obstructive disease has been questioned. Thus, the search for additional agents to improve the outcomes of patients with atherothrombotic disease continues. The importance of inflammation, a potentially critical element in the initiation, progression, and rupture of plaque, has become increasingly evident. In this supplement, the role of inflammation and its principal cause, oxidative stress, are analyzed as potential targets of pharmacologic therapy. The history of anti-inflammatory and antioxidant therapy in cardiovascular disease is critically examined. Finally, the whole process of contemporary drug discovery and development from lead rationale and identification through biologic screening and testing in animals and then humans is explored, using as an example the xanthophyll carotenoids, a class of potent antioxidants currently under investigation.

Am J Cardiol. 2008 May 22;101(10A):4D-13D

RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS: FUNDAMENTAL ROLES IN THE INFLAMMATORY RESPONSE: WINDING THE WAY TO THE PATHOGENESIS OF ENDOTHELIAL DYSFUNCTION AND ATHEROSCLEROSIS.

The multiligand receptor for advanced glycation end products (RAGE) of the immunoglobulin superfamily is expressed on multiple cell types implicated in the immune-inflammatory response and in atherosclerosis. Multiple studies have elucidated that ligand-RAGE interaction on cells, such as monocytes, macrophages, and endothelial cells, mediates cellular migration and upregulation of proinflammatory and prothrombotic molecules. In addition, recent studies reveal definitive rules for RAGE in effective T lymphocyte priming in vivo. RAGE ligand AGEs may be formed in diverse settings; although AGEs are especially generated in hyperglycemia, their production in settings characterized by oxidative stress and inflammation suggests that these species, in part via RAGE, may contribute to the pathogenesis of atherosclerosis. In murine models of atherosclerosis, vascular inflammation is a key factor and one which is augmented, in parallel with even further increases in RAGE ligands, in diabetic macrovessels. The findings that antagonism and genetic disruption of RAGE in atherosclerosis-susceptible mice strikingly reduces vascular inflammation and atherosclerotic lesion area and complexity link RAGE intimately to these processes and

suggest that RAGE is a logical target for therapeutic intervention in aberrant inflammatory mechanisms and in atherosclerosis.

Ann N Y Acad Sci. 2008 Apr;1126:7-13

REGULATION OF SMOOTH MUSCLE CELLS IN DEVELOPMENT AND VASCULAR DISEASE: CURRENT THERAPEUTIC STRATEGIES.

Vascular smooth muscle cells (SMCs) exhibit extensive phenotypic diversity and rapid growth during embryonic development, but maintain a quiescent, differentiated state in adult. The pathogenesis of vascular proliferative diseases involves the proliferation and migration of medial vascular SMCs into the vessel intima, possibly reinstating their embryonic gene expression programs. Multiple mitogenic stimuli induce vascular SMC proliferation through cell cycle progression. Therapeutic strategies targeting cell cycle progression and mitogenic stimuli have been developed and evaluated in animal models of atherosclerosis and vascular injury, and several clinical studies. Recent discoveries on the recruitment of vascular progenitor cells to the sites of vascular injury suggest new therapeutic potentials of progenitor cell-based therapies to accelerate re-endothelialization and prevent engraftment of SMC-lineage progenitor cells. Owing to the complex and multifactorial nature of SMC regulation, combinatorial antiproliferative approaches are likely to be used in the future in order to achieve maximal efficacy and reduce toxicity.

Expert Rev Cardiovasc Ther. 2006 Nov;4(6):789-800

PARAOXONASES AND CARDIOVASCULAR DISEASES: PHARMACOLOGICAL AND NUTRITIONAL INFLUENCES.

PURPOSE OF REVIEW: To summarize the new articles published in the last year on paraoxonases, including their expression in cardiovascular diseases, and regulation by pharmacological and nutritional means. **RECENT FINDINGS:** The elucidation of the crystal structure of the paraoxonase 1 (PON1) gene, obtained by directed evolution, shows that it consists of a six-bladed beta-propeller with a unique active site. PON1 is present in HDL but also in lipoprotein-deficient serum, in VLDL and in chylomicrons. PON1 protects lipids in lipoproteins, in macrophages and in erythrocytes from oxidation. Cellular PON2 and PON3 were also shown to reduce oxidative stress. Beyond its antioxidative properties, PON1 possesses additional antiatherogenic properties against macrophage foam cell formation: attenuation of cholesterol and oxidized lipids influx, inhibition of macrophage cholesterol biosynthesis and stimulation of macrophage cholesterol efflux. The PON1 gene is regulated by Sp1 and protein kinase C, whereas the PON2 gene in macrophages is regulated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. PON1 activity and mass are both reduced in cardiovascular diseases and the hypocholesterolemic drugs, statins, increase serum PON1 activity (by reducing oxidative stress, or by upregulating hepatic PON1 expression). Expression of cellular PON2, like PON1, was upregulated by statins. Nutritional antioxidants, such as polyphenols, increase PON1 mRNA expression and activity, by an aryl hydrocarbon receptor-dependent mechanism. **SUMMARY:** The elucidation of PON1 structure and its active center has enabled a better understanding of its mechanism of action, including its physio-pathological substrate(s). Some drugs and nutrients including dietary antioxidants and polyphenols considerably increase the activities of paraoxonases which, in turn, can reduce oxidative stress and atherosclerosis development.

Curr Opin Lipidol. 2005 Aug;16(4):393-9

DIETARY APPROACH TO ATTENUATE OXIDATIVE STRESS, HYPERTENSION, AND INFLAMMATION IN THE CARDIOVASCULAR SYSTEM.

Imbalance between production and scavenging of superoxide anion results in hypertension by the inactivation of nitric oxide, and the increased oxidative stress from the resultant peroxynitrite that is produced promotes inflammatory processes such as atherosclerosis. Induction of phase 2 proteins promotes oxidant scavenging. We hypothesized that intake of dietary phase 2 protein inducers would ameliorate both hypertension and atherosclerotic changes in the spontaneously hypertensive stroke-prone rat. For 5 days/week for 14 weeks, we fed rats 200 mg/day of dried broccoli sprouts that contained glucoraphanin, which is metabolized into the phase 2 protein-inducer sulforaphane (Group A), sprouts in which most of the glucoraphanin was destroyed (Group B), or no sprouts (Group C). After 14 weeks of treatment, no significant differences were seen between rats in Groups B and C. Rats in Group A had significantly decreased oxidative stress in cardiovascular and kidney tissues, as shown by increased glutathione (GSH) content and decreased oxidized GSH, decreased protein nitrosylation, as well as increased GSH reductase and GSH peroxidase activities. Decreased oxidative stress correlated with better endothelial-dependent relaxation of the aorta and significantly lower (20 mm Hg) blood pressure. Tissues from Groups B and C had considerable numbers of infiltrating activated macrophages, indicative of inflammation, whereas animals in Group A had few detectable infiltrating macrophages. There is interest in dietary phase 2 protein inducers as means of reducing cancer incidence. We conclude that a diet containing phase 2 protein inducers also reduces the risk of developing cardiovascular problems of hypertension and atherosclerosis.

Proc Natl Acad Sci U S A. 2004 May 4;101(18):7094-9

Estrogen

ESTROGENS AND VASCULAR THROMBOSIS.

PIP: The incidence of thromboses among young women has increased with widespread use of oral contraceptives (OCs) due to the significant thromboembolic risk of estrogen. Estrogens intervene at the vascular, platelet, and plasma levels as a function of hormonal variations in the menstrual cycle, increasing the aggregability of the platelets and thrombocytes, accelerating the formation of clots, and decreasing the amount of antithrombin III. Estrogens are used in medicine to treat breast and prostate cancers and in gynecology to treat dysmenorrhea, during the menopause, and in contraception. Smoking, cardiovascular disease and hypertension, hypercholesterolemia, and diabetes are contraindicators to estrogen use. Thrombosis refers to blockage of a blood vessel by a clot or thrombus. Before estrogens are prescribed, a history of phlebitis, obesity, hyperlipidemia, or significant varicosities should be ruled out. A history of venous thrombosis, hyperlipoproteinemia, breast nodules, serious liver condition, allergies to progesterone, and some ocular diseases of vascular origin definitively rule out treatment with estrogens. A family history of infarct, embolism, diabetes, cancer, or vascular accidents at a young age signals a need for greater patient surveillance. All patients receiving estrogens should be carefully observed for signs of hypertension, hypercholesterolemia, hypercoagulability, or diabetes. Nurses have a role to play in carefully eliciting the patient's history of smoking, personal and family medical problems, and previous and current laboratory results, as well as in informing the patients of the risks and possible side effects of OCs, especially for those who smoke. Nurses should educate patients receiving estrogens, especially those with histories of circulatory problems, to avoid standing in 1 position for prolonged periods, avoid heat which is a vasodilator, avoid obesity, exercise regularly, wear appropriate footwear, and follow other good health practices.

Soins Gynecol Obstet Pueric PEDIATR. 1982 Sep;(16):39-41

SERUM ESTRADIOL AND RISK OF STROKE IN ELDERLY MEN.

OBJECTIVE: To determine if levels of serum estradiol and testosterone can predict stroke in a population-based sample of elderly men. METHODS: Serum 17beta estradiol and testosterone were measured in 2,197 men aged 71 to 93 years who participated in the Honolulu-Asia Aging Study from 1991 to 1993. All were free of prevalent stroke, coronary heart disease, and cancer. Participants were followed to the end of 1998 for thromboembolic and hemorrhagic events. RESULTS: During the course of follow-up, 124 men developed a stroke (9.1/1,000 person-years). After age adjustment, men in the top quintile of serum estradiol ($> \text{or} = 125 \text{ pmol/L}$ [34.1 pg/mL]) experienced a twofold excess risk of stroke vs men whose estradiol levels were lower (14.8 vs 7.3/1,000 person-years, $p < 0.001$). Among the lower quintiles, there were little differences in the risk of stroke. Findings were also significant and comparable for bioavailable estradiol and for thromboembolic and hemorrhagic events. After additional adjustment for hypertension, diabetes, adiposity, cholesterol concentrations, atrial fibrillation, and other characteristics, men in the top quintile of serum estradiol continued to have a higher risk of stroke vs those whose estradiol levels were lower (relative hazards = 2.2; 95% CI = 1.5 to 3.4, $p < 0.001$). Testosterone was not related to the risk of stroke. CONCLUSIONS: High levels of serum estradiol may be associated with an elevated risk of stroke in elderly men.

Neurology. 2007 Feb 20;68(8):563-8

ESTRADIOL IN ELDERLY MEN.

The role of estrogens in male physiology has become more evident, as a consequence of the discovery of human models of estrogen deficiency such as estrogen resistance or aromatase deficiency. In males, testosterone is the major source of plasma estradiol, the main biologically active estrogen, only 20% of which is secreted by the testes. Plasma estrone, 5% of which is converted to plasma estradiol, originates from tissue aromatization of, mainly adrenal, androstenedione. The plasma concentration of estradiol in males is 2-3 ng/dl and its production rate in blood is 25-40 micrograms/24 h; both of these values are significantly higher than in postmenopausal women. Plasma levels of estradiol do not necessarily reflect tissue-level activity as peripherally formed estradiol is partially metabolized in situ; thus, not all enters the general circulation, with a fraction remaining only locally active. Of the factors influencing plasma estradiol levels, plasma testosterone is a major determinant. However, the age-associated decrease in testosterone levels is scarcely reflected in plasma estradiol levels, as a result of increasing aromatase activity with age and the age-associated increase in fat mass. Free and bioavailable estradiol levels do decrease modestly with age as does the ratio of free testosterone to free estradiol, the latter testifying to the age-associated increased aromatization of testosterone. Estradiol levels are highly significantly positively related to body fat mass and more specifically to subcutaneous abdominal fat, but not to visceral (omental) fat. Indeed, aromatase activity in omental fat is only one-tenth of the

activity in gluteal fat. Estrogens in males play an important role in the regulation of the gonadotropin feedback, several brain functions, bone maturation, regulation of bone resorption and in lipid metabolism. Moreover, they affect skin metabolism and are an important factor determining sex interest in man.

Aging Male. 2002 Jun;5(2):98-102

LOW SERUM TESTOSTERONE AND HIGH SERUM ESTRADIOL ASSOCIATE WITH LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE IN ELDERLY MEN. THE MROS STUDY IN SWEDEN.

OBJECTIVES: This study sought to determine whether serum levels of testosterone and estradiol associate with lower extremity peripheral arterial disease (PAD) in a large population-based cohort of elderly men. **BACKGROUND:** Few studies have explored the relationship between serum sex steroids and lower extremity PAD in men. **METHODS:** The Swedish arm of the MrOS (Osteoporotic Fractures in Men) study (n = 3,014; average age 75.4 years) assessed ankle-brachial index (ABI) and defined lower extremity PAD as ABI <0.90. Radioimmunoassay measured serum levels of total testosterone, estradiol, and sex hormone-binding globulin, and we calculated free testosterone and free estradiol levels from the mass action equations. **RESULTS:** A linear regression model including age, current smoking, previous smoking, diabetes, hypertension, body mass index, free testosterone, and free estradiol showed that free testosterone independently and positively associates with ABI (p < 0.001), whereas free estradiol independently and negatively associates with ABI (p < 0.001). Logistic regression analyses showed that free testosterone in the lowest quartile (vs. quartiles 2 to 4; odds ratio [OR] 1.65, 95% confidence interval [CI] 1.22 to 2.23, p = 0.001) and free estradiol in the highest quartile (vs. quartiles 1 to 3; OR 1.45, 95% CI 1.09 to 1.94, p = 0.012) independently associate with lower extremity PAD. **CONCLUSIONS:** This cross-sectional study shows for the first time that low serum testosterone and high serum estradiol levels associate with lower extremity PAD in elderly men. Future prospective and interventional studies are needed to establish possible causal relationships between sex steroids and the development of lower extremity PAD in men.

J Am Coll Cardiol. 2007 Sep 11;50(11):1070-6

ENDOGENOUS SEX HORMONES AND C-REACTIVE PROTEIN IN HEALTHY POSTMENOPAUSAL WOMEN.

Background. Oral oestrogen replacement therapy increases levels of C-reactive protein (CRP). CRP is an established strong predictor of cardiovascular events. It is unknown whether endogenous oestrogen levels are associated with CRP. We therefore studied the relationship between endogenous sex hormones and CRP in healthy postmenopausal women emphasizing the role of body composition as peripheral fat is both a main source of oestrogen production after menopause and an endocrine tissue with inflammatory activities. **Subjects and methods.** The study population comprised 889 women participating in the PROSPECT study, an ongoing population-based cohort study. Information on risk factors was collected by questionnaires and clinical examination. Endogenous sex hormone levels and CRP were measured with double antibody radio immuno assay (RIA) from fasting plasma samples. In this cross-sectional study, associations between risk factors and lnCRP were studied using linear regression models. **Results.** Increases in oestrone and free oestradiol levels and the free androgen index were related to an increase in lnCRP of 1.19, 1.23 and 1.21 mg dL(-1) respectively. Body mass index (BMI), waist circumference and physical activity were strongly related to CRP levels, independent of age and other cardiovascular risk factors. Levels of all sex steroids but dehydroepiandrosterone decreased with age. In age-adjusted analyses, an increase in waist circumference or BMI by one quartile was associated with a 1.28-fold and 1.26-fold increase in CRP. The relationship between endogenous hormones and CRP was modestly attenuated but remained highly significant after adjustment for body composition, physical activity and other traditional cardiovascular risk factors. **Conclusions.** Our findings show that in postmenopausal women high levels of endogenous oestrogenic and androgenic sex steroids coincide with high CRP levels. This was only explained in part by markers of body composition or intra-abdominal fat.

J Intern Med. 2008 Mar 12

A POTENTIAL PARADOX IN PROSTATE ADENOCARCINOMA PROGRESSION: OESTROGEN AS THE INITIATING DRIVER.

One in 10 men in the developed world will present with prostate cancer (CaP), and in an ageing population developing strategies for its chemoprevention or treatment is of significance. For decades, androgen ablation has remained the frontline treatment for CaP that is no longer organ-confined and thus deemed surgically inoperable. Orchidectomy or drug-induced reduction of serum testosterone levels with the consequent removal of growth-promoting effects in the prostate is the driving rationale for this regimen. However, resistance often develops within a few months to years and androgen-insensitive tumours develop. In recent years, there has been an increasing focus on chemoprevention with agents such as finasteride being employed to reduce the risk of developing CaP. Significantly, such chemoprevention strategies are also based on 5alpha-reductase inhibition thus reducing intraprostatic dihydrotestosterone levels. Although there may be an overall reduction in CaP incidence in cohorts using such chemoprevention, in a subset of users who do develop this pathology there results a more aggressive, higher-grade disease. There have also been suggestions regarding the protective role of androgens against high-grade CaP. This leads to the intriguing

notion that 17beta-oestradiol (E2) may be an initiating driver of CaP; in fact, in old studies in which CaP was induced in rodents, E2 often accelerated the effect of the carcinogen. Might certain chemoprevention strategies or androgen ablation result in a systemic feedback loop in hormone synthesis or metabolism? If so, elevated serum E2 levels could result in its increased conversion to genotoxic catechol oestrogens in target tissues such as the prostate. Paradoxically, if E2 were to be an initiating factor in CaP, anti-oestrogens might be an overlooked treatment or chemoprevention strategy.

Eur J Cancer. 2008 May;44(7):928-36

CATECHOL QUINONES OF ESTROGENS IN THE INITIATION OF BREAST, PROSTATE, AND OTHER HUMAN CANCERS: KEYNOTE LECTURE.

Estrogens can be converted to electrophilic metabolites, particularly the catechol estrogen-3,4-quinones, estrone (estradiol)-3,4-quinone [E(1)(E(2))-3,4-Q], which react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone repair of this damage leads to the mutations that initiate breast, prostate, and other types of cancer. The reaction of E(1)(E(2))-3,4-Q with DNA forms the depurinating adducts 4-hydroxyE(1)(E(2))-1-N3adenine [4-OHE(1)(E(2))-1-N3Ade] and 4-OHE(1)(E(2))-1-N7guanine(Gua). These two adducts constitute >99% of the total DNA adducts formed. The E(1)(E(2))-2,3-Q forms small amounts of the depurinating 2-OHE(1)(E(2))-6-N3Ade adducts. Reaction of the quinones with DNA occurs more abundantly when estrogen metabolism is unbalanced. Such an imbalance is the result of overexpression of estrogen-activating enzymes and/or deficient expression of deactivating (protective) enzymes. Excessive formation of E(1)(E(2))-3,4-Q is the result of this imbalance. Oxidation of catechols to semiquinones and quinones is a mechanism of tumor initiation not only for endogenous estrogens, but also for synthetic estrogens such as hexestrol and diethylstilbestrol, a human carcinogen. This mechanism is also involved in the initiation of leukemia by benzene, rat olfactory tumors by naphthalene, and neurodegenerative diseases such as Parkinson's disease by dopamine. In fact, dopamine quinone reacts with DNA similarly to the E(1)(E(2))-3,4-Q, forming analogous depurinating N3Ade and N7Gua adducts. The depurinating adducts that migrate from cells and can be found in body fluids can also serve as biomarkers of cancer risk. In fact, a higher level of estrogen-DNA adducts has been found in the urine of men with prostate cancer and in women with breast cancer compared to healthy controls. This unifying mechanism of the origin of cancer and other diseases suggests preventive strategies based on the level of depurinating DNA adducts that generate the first critical step in the initiation of diseases.

Ann N Y Acad Sci. 2006 Nov;1089:286-301

THE ROLE OF ESTROGENS AND ESTROGEN RECEPTORS IN NORMAL PROSTATE GROWTH AND DISEASE.

Estrogens have significant direct and indirect effects on prostate gland development and homeostasis and have been long suspected in playing a role in the etiology of prostatic diseases. Direct effects are mediated through prostatic estrogen receptors alpha (ERalpha) and beta (ERbeta) with expression levels changing over time and with disease progression. The present review examines the evidence for a role of estrogens and specific estrogen receptors in prostate growth, differentiation and disease states including prostatitis, benign prostatic hyperplasia (BPH) and cancer and discusses potential therapeutic strategies for growth regulation via these pathways.

Steroids. 2008 Mar;73(3):233-44

IMPORTANT FUNCTIONS OF ESTROGENS IN MEN—BREAKTHROUGH IN CONTEMPORARY MEDICINE.

Estradiol (E2) is traditionally recognised as the female sex hormone. Since discovery of estrogens in the early forties of XX century it has been believed, that these hormones caused impairment of the gonadal function in men or didn't exert any influence. New studies are contradictory, but indicate also a possible involvement of estrogens in the pathogenesis of some systemic diseases of men. The main source of E2 in men is adipose tissue and the brain. E2 is also produced in adrenals, liver, mammary glands, hair and in male gonads. Daily production and blood level of E2 in men are higher than those in postmenopausal women. In 1988 we were the first to demonstrate that E2 is an important hormonal signal for initiation of spermatogenesis. The traditional view about unimportant or inhibitory role of E2 in male physiology was finally refuted thanks to discovery of the estrogen receptors in males. In the middle 90ties transgenic mice with the lack of estrogen receptor (ER knockout) or enzyme aromatase, that enable the conversion of testosterone into E2, were produced. Observations of men with inherited mutations of these genes, considerably extended our knowledge about stimulatory role of E2 in men in the formation of bone stroma, inhibition of their linear growth, lipids metabolism and sexual maturation, the effects that were attributed to testosterone action until today. New data indicate role of estrogens and ER in the function of the cardio-vascular system. Their link with development of arteriosclerosis seems, however, to be bipolar. In single reported cases of men with the inactivating mutations of ERalpha or aromatase genes, a precocious arteriosclerosis is noted. From the other site, men homozygous for the most common variant of ERalpha gene (ESR1c.454-397cc) have a significantly increased risk of myocardial infraction. Estrogens are the risk factors in prostatic cancer and their local tissue increase in autoimmune diseases is connected with aggravation of the proliferative complications of these disorders.

ESTROGENS AND BONE HEALTH IN MEN.

It has generally been held that estrogen and testosterone are the major sex steroids regulating bone metabolism in women and men, respectively. However, the description of several "experiments of nature" led to a reconsideration of this notion. Thus, a male carrying homozygous mutations in the ER-alpha gene and two males with homozygous mutations in the aromatase gene had osteopenia, unfused epiphyses, and elevated indices of bone turnover. Though these findings indicated that estrogen plays a role in regulating the male skeleton, they left unresolved the issue of whether estrogen acted on the male skeleton mainly to enhance bone mass acquisition during growth and maturation, or whether it also acted to retard bone loss in aging individuals. To address this issue, several cross-sectional observational studies have related bone mineral density (BMD) to sex steroids in elderly men, and found that estrogen correlated better than testosterone with BMD. In addition, recent longitudinal studies from our group indicate that bioavailable estrogen correlated better than testosterone both with the gain in BMD in young men and with loss of BMD in elderly men. These observational studies do not, however, prove causality, which requires direct interventional studies. Thus, we eliminated endogenous testosterone and estrogen production in 59 elderly men (mean age 68 years), studied them first under conditions of physiologic testosterone and estrogen replacement, and then assessed the impact on bone turnover of withdrawing both testosterone and estrogen, withdrawing only testosterone, only estrogen, or continuing both. We found that estrogen played the major role in regulating bone resorption in these men, and that both estrogen and testosterone were important in maintaining bone formation. Collectively then, these findings indicate that estrogen plays a dominant role in regulating the male skeleton.

Calcif Tissue Int. 2001 Oct;69(4):189-92

ESTRADIOL, TESTOSTERONE, AND THE RISK FOR HIP FRACTURES IN ELDERLY MEN FROM THE FRAMINGHAM STUDY.

BACKGROUND: Low serum estradiol has been more strongly associated with low bone mineral density in elderly men than has testosterone, but its association with incident hip fracture is unknown. We examined whether low estradiol increases the risk for future hip fracture among men and explored whether testosterone levels influence this risk. **METHODS:** We examined 793 men (mean age = 71 years) evaluated between 1981 and 1983, who had estradiol measures and no history of hip fracture, and followed until the end of 1999. Total estradiol and testosterone were measured between 1981 and 1983. Hip fractures were identified and confirmed through medical records review through the end of 1999. We created 3 groups of men based on estradiol levels and performed a Cox-proportional hazards model to examine the risk for incident hip fracture, adjusted for age, body mass index, height, and smoking status. We performed similar analyses based on testosterone levels, and then based on both estradiol and testosterone levels together. **RESULTS:** There were 39 men who sustained an atraumatic hip fracture over follow-up. Incidence rates for hip fracture (per 1000 person-years) were 11.0, 3.4, and 3.9 for the low (2.0-18.1 pg/mL [7-67 pmol/L]), middle (18.2-34.2 pg/mL [67-125 pmol/L]), and high (> or =34.3 pg/mL [> or =126 pmol/L]) estradiol groups, respectively. With adjustment for age, body mass index, height, and smoking status, the adjusted hazard ratios for men in the low and middle estradiol groups, relative to the high group, were 3.1 (95% confidence interval [CI], 1.4-6.9) and 0.9 (95% CI, 0.4-2.0), respectively. In similar adjusted analyses evaluating men by their testosterone levels, we found no significant increased risk for hip fracture. However, in analyses in which we grouped men by both estradiol and testosterone levels, we found that men with both low estradiol and low testosterone levels had the greatest risk for hip fracture (adjusted hazard ratio: 6.5, 95% CI, 2.9-14.3). **CONCLUSION:** Men with low estradiol levels are at an increased risk for future hip fracture. Men with both low estradiol and low testosterone levels seem to be at greatest risk for hip fracture.

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