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Journal ABSTRACTS

Vitamin D

HIGH PREVALENCE OF VITAMIN D INADEQUACY AND IMPLICATIONS FOR HEALTH.

During the past decade, major advances have been made in vitamin D research that transcend the simple concept that vitamin D is important for the prevention of rickets in children and has little physiologic relevance for adults. Inadequate vitamin D, in addition to causing rickets, prevents children from attaining their genetically programmed peak bone mass, contributes to and exacerbates osteoporosis in adults, and causes the often painful bone disease osteomalacia. Adequate vitamin D is also important for proper muscle functioning, and controversial evidence suggests it may help prevent type 1 diabetes mellitus, hypertension, and many common cancers. Vitamin D inadequacy has been reported in approximately 36% of otherwise healthy young adults and up to 57% of general medicine inpatients in the United States and in even higher percentages in Europe. Recent epidemiological data document the high prevalence of vitamin D inadequacy among elderly patients and especially among patients with osteoporosis. Factors such as low sunlight exposure, age-related decreases in cutaneous synthesis, and diets low in vitamin D contribute to the high prevalence of vitamin D inadequacy. Vitamin D production from cutaneous synthesis or intake from the few vitamin D-rich or enriched foods typically occurs only intermittently. Supplemental doses of vitamin D and sensible sun exposure could prevent deficiency in most of the general population. The purposes of this article are to examine the prevalence of vitamin D inadequacy and to review the potential implications for skeletal and extraskeletal health.

Mayo Clin Proc. 2006 Mar;81(3):353-73

THE PREVALENCE OF HYPOVITAMINOSIS D AMONG US ADULTS: DATA FROM THE NHANES III.

OBJECTIVE: Several epidemiologic and mechanistic studies suggest that 25(OH) D₃ levels should be maintained above 70 nmol/L for a positive effect on the health of adults. Prior studies have noted low 25(OH) D₃ levels in subsets of minority populations. The objective of this study is to examine the prevalence of adequate 25(OH) D₃ levels among US adults. **METHOD:** Using data from the third National Health and Nutrition Examination Survey (NHANES III), we evaluated serum levels of 25(OH) D₃ (nmol/L) among 15,390 adult participants \geq 18 years of age. Racial/ethnic grouping was by self-identification as White, Black or African American, and Hispanic. **RESULTS:** The mean levels of 25(OH) D₃ were lower among the female than male participants (71.1 vs 78.7; $P=.003$) and among the elderly (\geq 65 years of age vs 40-59 and 18-39) than young participants. White men and women (83.0 and 76.0) had higher mean levels of vitamin D than Hispanic men and women (68.3 and 56.7; $P<.0001$) and than Black men and women (52.2 and 45.3; $P<.0001$), respectively. The prevalence of both mild-moderate and severe deficiency of vitamin D is higher among women ($P<.0001$) and minority populations ($P<.0001$). However, even among White men, 34% had low vitamin D levels. **CONCLUSION:** Serum levels of 25(OH) D₃ are below the recommended levels for a large portion of the general adult population and in most minorities. Need exists for a critical review and probable revision of current recommendations for adult vitamin D intake to maintain adequate 25(OH) D₃ levels.

Ethn Dis. 2005 Autumn;15(4 Suppl 5):S5-97-101

VITAMIN D DEFICIENCY AND SEASONAL VARIATION IN AN ADULT SOUTH FLORIDA POPULATION.

Hypovitaminosis D is associated with impaired neuromuscular function, bone loss, and fractures. If a person is not taking a vitamin supplement, sun exposure is often the greatest source of vitamin D. Thus, vitamin D deficiency is not uncommon in the winter, particularly in northern latitudes. Our goal was to establish the prevalence of vitamin D deficiency in south Florida (US), a region of year-round sunny weather. At the end of the winter, 212 men and women attending an internal medicine clinic at a local county hospital were enrolled for measurements of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D, and PTH; 99 participants returned at the end of summer. The mean (\pm sd) winter 25(OH)D concentration was 24.9 \pm 8.7 ng/ml (62.3 \pm 21.8 nmol/liter) in men and 22.4 \pm 8.2 ng/ml (56.0 \pm 20.5 nmol/liter) in women. In winter, the prevalence of hypovitaminosis D, defined as 25(OH)D less than 20 ng/ml (50 nmol/liter), was 38% and 40% in men and women, respectively. In the 99 subjects who returned for the end of summer visit, the mean 25(OH)D concentration was 31.0 \pm 11.0 ng/ml (77.5 \pm 27.5 nmol/liter) in men and 25.0 \pm 9.4 ng/ml (62.5 \pm 23.5 nmol/liter) in women. Seasonal variation represented a 14% summer increase in 25(OH)D concentrations in men and a 13% increase in women, both of which were statistically significant. The prevalence of

hypovitaminosis D is considerable even in southern latitudes and should be taken into account in the evaluation of postmenopausal and male osteoporosis.

J Clin Endocrinol Metab. 2005 Mar;90(3):1557-62

VITAMIN D AND DISEASE PREVENTION WITH SPECIAL REFERENCE TO CARDIOVASCULAR DISEASE.

Circulating 25-hydroxyvitamin D [25(OH)D] is the hallmark for determining vitamin D status. Serum parathyroid hormone [PTH] increases progressively when 25(OH)D falls below 75 nmol/l. Concentrations of 25(OH)D below 50 nmol/l or even below 25 nmol/l are frequently observed in various population groups throughout the world. This paper highlights the relationship of vitamin D insufficiency with cardiovascular disease and non-insulin dependent diabetes mellitus, two diseases that account for up to 50% of all deaths in western countries. There is evidence from patients with end-stage renal disease that high PTH concentrations are causally related to cardiovascular morbidity and mortality. Activated vitamin D is able to increase survival in this patient group significantly. Moreover, already slightly enhanced PTH concentrations are associated with ventricular hypertrophy and coronary heart disease in the general population. Experimental studies have demonstrated that a lack of vitamin D action leads to hypertension in mice. Some intervention trials have also shown that vitamin D can reduce blood pressure in hypertensive patients. In young and elderly adults, serum 25(OH)D is inversely correlated with blood glucose concentrations and insulin resistance. Sun-deprived lifestyle, resulting in low cutaneous vitamin D synthesis, is the major factor for an insufficient vitamin D status. Unfortunately, vitamin D content of most foods is negligible. Moreover, fortified foods and over-the-counter supplements usually contain inadequate amounts of vitamin D to increase serum 25(OH)D to 75 nmol/l. As a consequence, legislation has to be changed to allow higher amounts of vitamin D in fortified foods and supplements.

Prog Biophys Mol Biol. 2006 Sep;92(1):39-48

PREVALENCE OF CARDIOVASCULAR RISK FACTORS AND THE SERUM LEVELS OF 25-HYDROXYVITAMIN D IN THE UNITED STATES: DATA FROM THE THIRD NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY.

BACKGROUND: Results of several epidemiologic and clinical studies have suggested that there is an excess risk of hypertension and diabetes mellitus in persons with suboptimal intake of vitamin D. **METHODS:** We examined the association between serum levels of 25-hydroxyvitamin D (25[OH]D) and select cardiovascular disease risk factors in US adults. A secondary analysis was performed with data from the Third National Health and Nutrition Examination Survey, a national probability survey conducted by the National Center for Health Statistics between January 1, 1988, and December 31, 1994, with oversampling of persons 60 years and older, non-Hispanic black individuals, and Mexican American individuals. **RESULTS:** There were 7,186 male and 7902 female adults 20 years and older with available data in the Third National Health and Nutrition Examination Survey. The mean 25(OH)D level in the overall sample was 30 ng/mL (75 nmol/L). The 25(OH)D levels were lower in women, elderly persons (≥ 60 years), racial/ethnic minorities, and participants with obesity, hypertension, and diabetes mellitus. The adjusted prevalence of hypertension (odds ratio [OR], 1.30), diabetes mellitus (OR, 1.98), obesity (OR, 2.29), and high serum triglyceride levels (OR, 1.47) was significantly higher in the first than in the fourth quartile of serum 25(OH)D levels ($P < .001$ for all). **CONCLUSIONS:** Serum 25(OH)D levels are associated with important cardiovascular disease risk factors in US adults. Prospective studies to assess a direct benefit of cholecalciferol (vitamin D) supplementation on cardiovascular disease risk factors are warranted.

Arch Intern Med. 2007 Jun 11;167(11):1159-65

MINERAL METABOLISM AND ARTERIAL FUNCTIONS IN END-STAGE RENAL DISEASE: POTENTIAL ROLE OF 25-HYDROXYVITAMIN D DEFICIENCY.

In ESRD, arterial function is abnormal, characterized by decreased capacitive function (arterial stiffening) and reduced conduit function, shown by diminished flow-mediated dilation (FMD). The pathophysiology of these abnormalities is not clear, and this cross-sectional study analyzed possible relationships among arterial alterations and cardiovascular risk factors, including mineral metabolism parameters, such as serum parathormone, and vitamin D "nutritional" and "hormonal" status by measuring serum 25-hydroxyvitamin D [25(OH)D(3)] and 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] levels. Aortic stiffness (pulse wave velocity), brachial artery (BA) distensibility (echotracking; $n = 42$), BA FMD (hand-warming; $n = 37$), and arterial calcification scores (echography and plain x-rays) were measured in 52 stable and uncomplicated patients who were on hemodialysis. 25(OH)D(3) and 1,25(OH)(2)D(3) serum levels were low and weakly correlated ($r = 0.365$, $P < 0.05$). After adjustment for BP and age, multivariate analyses indicated that 25(OH)D(3) and 1,25(OH)(2)D(3) were negatively correlated with aortic pulse wave velocity ($P < 0.001$) and positively correlated with BA distensibility ($P < 0.01$) and FMD ($P < 0.001$). Arterial calcification scores were not independently associated with 25(OH)D(3) and 1,25(OH)(2)D(3) serum concentrations. These results suggest that nutritional vitamin D deficiency and low 1,25(OH)(2)D(3) could be associated with arteriosclerosis and endothelial dysfunction in patients who have ESRD and are on hemodialysis.

J Am Soc Nephrol. 2007 Feb;18(2):613-20

VITAMIN D AND CALCIUM SUPPLEMENTATION REDUCES CANCER RISK: RESULTS OF A RANDOMIZED TRIAL.

BACKGROUND: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking. **OBJECTIVE:** The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types. **DESIGN:** This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1,179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4 degrees N. Subjects were randomly assigned to receive 1400-1500 mg supplemental calcium/d alone (Ca-only), supplemental calcium plus 1100 IU vitamin D(3)/d (Ca + D), or placebo. **RESULTS:** When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects ($P < 0.03$). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 ($P = 0.01$) and 0.532 ($P = 0.06$), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for the Ca + D group fell to 0.232 (CI: 0.09, 0.60; $P < 0.005$) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk. **CONCLUSIONS:** Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women.

Am J Clin Nutr. 2007 Jun;85(6):1586-91

THE ROLE OF VITAMIN D FOR BONE HEALTH AND FRACTURE PREVENTION.

Vitamin D inadequacy is pandemic in adults. Vitamin D deficiency causes osteopenia, precipitates and exacerbates osteoporosis, causes the painful bone disease osteomalacia, and increases muscle weakness, which worsens the risk of falls and fractures. Vitamin D deficiency can be prevented by sensible sun exposure and adequate supplementation. Monitoring serum 25-hydroxyvitamin D is the only way to determine vitamin D status. Recent recommendations suggest that in the absence of sun exposure, adults should ingest 1000 IU of vitamin D3 per day. The ideal healthy blood level of 25-hydroxyvitamin D should be 30 to 60 ng/mL. Vitamin D intoxication occurs when 25-hydroxyvitamin D levels are greater than 150 ng/mL. Three recent reports suggesting that vitamin D and calcium supplementation does not decrease the risk of fracture will be put into perspective in light of the vast literature supporting increasing vitamin D and calcium intake as an effective method for decreasing risk of vertebral and nonvertebral fractures. Curr Osteoporos Rep.

2006 Sep;4(3):96-102

ASSOCIATION BETWEEN SERUM 25(OH)D CONCENTRATIONS AND BONE STRESS FRACTURES IN FINNISH YOUNG MEN.

Low vitamin D level may predict rickets, osteomalacia, or osteoporosis. We examined serum 25(OH)D concentration as a predisposing factor for bone stress fracture in 756 military recruits. The average serum 25(OH)D concentration was significantly lower in the group with fracture, suggesting a relationship between vitamin D and fatigue bone stress fracture. **INTRODUCTION:** Low vitamin D level may predict rickets, osteomalacia, or osteoporosis. Fatigue bone stress fracture is one of the most frequently seen types of overuse injuries in athletes and military recruits. An association was recently shown between vitamin D and BMC. A correlation has also been found between low femoral BMD and stress fractures. We measured serum 25(OH)D concentration in a population sample of military recruits to determine if vitamin D is a predisposing factor for fatigue bone stress fracture. **MATERIALS AND METHODS:** We prospectively followed 800 randomly selected, healthy Finnish military recruits with a mean age of 19 years for developing stress fractures in homogenous circumstances. Blood for serum 25(OH)D concentration was drawn at entry into military service, and the weight, height, body mass index (BMI), muscle strength, and 12-minute running were measured for all subjects. Serum 25(OH)D concentrations were measured with enzyme immunoassay. At end of the 90-day follow-up, 756 subjects completed the study. Subjects without fracture constituted controls. **RESULTS:** Twenty-two recruits with stress fracture were identified (2.9%), the incidence being 11.6 (95% CI: 6.8-16.5) per 100 person-years. In the final multivariate analysis, the significant risk factor for stress fracture in conscripts was a below median serum 25(OH)D level (75.8 nM), OR being 3.6 (95% CI: 1.2-11.1). No significant associations between BMI ($p = 0.255$), age ($p = 0.216$), or smoking ($p = 0.851$) and bone stress fracture were found in this study population. **CONCLUSIONS:** A lower level of serum 25(OH)D concentration may be a generally predisposing element for bone stress fractures. Considering the obvious need of additional vitamin D in prevention of stress fractures, the effects of vitamin D fortification of foods and supplementation will be subjects of interest for future research.

J Bone Miner Res. 2006 Sep;21(9):1483-8

CARDIOVASCULAR PROTECTIVE EFFECTS OF RESVERATROL.

Resveratrol (3,4',5-trihydroxy-trans-stilbene), a phytoalexin found in grape skins, peanuts, and red wine, has been reported to have a wide range of biological and pharmacological properties. It has been speculated that at low doses (such as consumed in the common diet) resveratrol may have cardioprotective activity. In this article we describe recent *in vitro* and *in vivo* studies in animal models. The results of these studies suggest that resveratrol modulates vascular cell function, inhibits LDL oxidation, suppresses platelet aggregation and reduces myocardial damage during ischemia-reperfusion. Although the reported biological data indicate that resveratrol is a highly promising cardiovascular protective agent, more studies are needed to establish its bioavailability and *in vivo* cardioprotective effects, particularly in humans.

Cardiovasc Drug Rev. 2004 Fall;22(3):169-88

WINE INGESTION HAS NO EFFECT ON LIPID PEROXIDATION PRODUCTS.

OBJECTIVE: Moderate alcohol consumption has been associated with beneficial effects on coronary heart disease. This positive effect has been partly attributed to the flavonol contents which promote vasodilatory, anti-aggregatory and antioxidative effects and protect low-density lipoprotein (LDL) cholesterol from oxidation. Thus, the present study was carried out to determine the acute effects of different wines on LDL oxidation in healthy volunteers. **METHODS:** Healthy male and female subjects (15/group) on a flavonol-restricted diet were randomly assigned to drink 300 ml wine from one of four different grapes and fermentation processes. Conjugated fatty acid dienes and thiobarbituric acid reactive substances (TBARS) were determined as a measure of LDL oxidation in serum at baseline and up to 96 h after wine ingestion. **RESULTS:** At baseline, mean conjugated dienes in serum were 12.5+/-6.2 micromol/l and mean TBARS in serum were 15.7+/-8.1 micromol/l. There were no differences between the groups and no effect of any wine type on conjugated dienes ($p=0.15$) or TBARS ($p=0.38$) over time. 96 h following wine ingestion, the mean conjugated dienes were 12.1+/-4.12 micromol/l and mean TBARS were 16.4+/-8.8 micromol/l (pooled data, $n=60$). **CONCLUSION:** Ingestion of 300 ml wine does not protect LDL from oxidation *in vivo* in healthy subjects. However, this does not exclude an effect of habitual wine consumption on LDL plasma oxidation.

Pharmacology. 2005 Nov;75(3):152-6

RED WINE REDUCES OXIDATIVE STRESS IN PATIENTS WITH ACUTE CORONARY SYNDROME.

BACKGROUND: Moderate red wine consumption improved endothelial function in normal volunteers. Herein we explored the effects of moderate red wine consumption in endothelial function and in oxidative stress in patients with an acute coronary syndrome. **METHODS:** 20 patients treated with percutaneous coronary interventions after an acute coronary syndrome were randomized to a red-wine group ($n=9$, 250 ml daily, Cabernet Sauvignon) or to a control group ($n=11$, abstinence from alcoholic beverages). Studies were performed at baseline and after 2 months. Endothelial function was estimated by flow-mediated vasodilatation of the brachial artery. Plasma antioxidant capacity was measured by total antioxidant reactivity and ferric reducing antioxidant power. Oxidative damage was evaluated by measurements of 8-OH deoxyguanosine content in leukocyte deoxyribonucleic acid. **RESULTS:** The endothelium dependent/independent dilatation ratio significantly improved compared to baseline in both groups. The 8-OH deoxyguanosine content decreased significantly in both groups; this effect was more pronounced with wine ($p<0.002$ vs. control). Oxidative deoxyribonucleic acid damage in controls decreased from 13.1+/-1.1 to 10.0+/-1.0 ($p<0.003$); with wine from 13+/-0.8 to 5.6+/-0.7 per 10(5) guanosines ($p<0.001$; $p<0.002$ vs. control). Total antioxidant reactivity increased from 240+/-18 to 268+/-18 microM in the control group and from 273+/-20 to 330+/-15 microM in the wine group ($p<0.03$ vs. control). Ferric reducing antioxidant power increased from 1106+/-60 to 1235+/-42 microM in the control group and from 1219+/-82 to 1450+/-63 microM in the wine group ($p<0.001$ vs. control). **CONCLUSIONS:** The addition of moderate amounts of red wine did not improve endothelial function beyond conventional therapy, whereas it showed benefits in parameters of oxidative stress in these patients.

Int J Cardiol. 2005 Sep 15;104(1):35-8

EFFECT OF MODERATE RED WINE INTAKE ON CARDIAC PROGNOSIS AFTER RECENT ACUTE MYOCARDIAL INFARCTION OF SUBJECTS WITH TYPE 2 DIABETES MELLITUS.

BACKGROUND: Oxidative stress and increased inflammation have been reported to be increased in subjects with diabetes and to be involved in the pathogenesis of cardiovascular complications after myocardial infarction (MI). It is well recognized that red wine has antioxidant and anti-inflammatory activities. We examined the effects of moderate red wine intake on echocardiographic parameters of functional cardiac outcome in addition to inflammatory cytokines and nitrotyrosine (oxidative stress marker), in subjects with diabetes after a first uncomplicated MI. **METHODS:** One hundred and fifteen subjects with diabetes who had sustained a first non-fatal MI were randomized to receive a moderate daily amount of red wine (intervention group) or not (control group). Echocardiographic parameters of ventricular dys-synchrony, circulating levels of nitrotyrosine, tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-18 (IL-18) and C-reactive protein (CRP) were investigated at baseline and 12 months after randomization. **RESULTS:** After 1 year of diet intervention, concentrations of nitrotyrosine ($P < 0.01$), CRP ($P < 0.01$), TNF- α ($P < 0.01$), IL-6 ($P < 0.01$) and IL-18 ($P < 0.01$) were increased in the control group compared with the intervention group. In addition, myocardial performance index ($P < 0.02$) was higher, and transmitral Doppler flow ($P < 0.05$), pulmonary venous flow analysis ($P < 0.02$) and ejection fraction ($P < 0.05$) were lower in the control group, indicating ventricular dys-synchrony. The concentrations of nitrotyrosine, CRP, TNF- α and IL-6 were related to echocardiographic parameters of ventricular dys-synchrony. **CONCLUSIONS:** In subjects with diabetes, red wine consumption, taken with meals, significantly reduces oxidative stress and pro-inflammatory cytokines as well as improving cardiac function after MI. Moderate red wine intake with meals may have a beneficial effect in the prevention of cardiovascular complications after MI in subjects with diabetes.

Diabet Med. 2006 Sep;23(9):974-81

POLYPHENOLIC COMPOUNDS FROM RED GRAPES ACUTELY IMPROVE ENDOTHELIAL FUNCTION IN PATIENTS WITH CORONARY HEART DISEASE.

BACKGROUND: It has been shown that acute intake of red wine improves endothelial-dependent vasodilatation. It is not clear, however, which constituents of red wine are responsible for this effect. We examined whether acute intake of a red grape polyphenol extract has a positive effect on brachial artery flow-mediated dilatation. **METHODS:** We recruited 30 male patients with coronary heart disease. They were randomly assigned either to a red grape polyphenol extract (600 mg) dissolved in 20 ml of water ($n = 15$) or 20 ml of water (placebo) ($n = 15$). The extract of grapes contained 4.32 mg epicatechin, 2.72 mg catechin, 2.07 mg gallic acid, 0.9 mg trans-resveratrol, 0.47 mg rutin, 0.42 mg epsilon-viniferin, 0.28 mg, p-coumaric acid, 0.14 mg ferulic acid and 0.04 mg quercetin per gram. Flow-mediated dilatation of the brachial artery was evaluated after reactive hyperemia induced by cuff obstruction of the forearm, using high-resolution ultrasonography. Particularly, flow-mediated dilatation was measured after fasting and 30, 60 and 120 min after the intake of the grape extract or placebo. **RESULTS:** Intake of the red grape polyphenol extract caused an increase in flow-mediated dilatation, peaking at 60 min, which was significantly higher than the baseline values (4.52 ± 1.34 versus $2.6 \pm 1.5\%$; $P < 0.001$) and the corresponding values at 60 min after the intake of placebo (4.52 ± 1.34 versus $2.64 \pm 1.8\%$, $P < 0.001$). There was no change in FMD values after the intake of placebo throughout the whole duration of the study. **CONCLUSION:** Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. These results could probably, at least partly, explain the favorable effects of red wine on the cardiovascular system.

Eur J Cardiovasc Prev Rehabil. 2005 Dec;12(6):596-600

RED WINE INDUCED MODULATION OF VASCULAR FUNCTION: SEPARATING THE ROLE OF POLYPHENOLS, ETHANOL, AND URATES.

By using red wine (RW), dealcoholized red wine (DARW), polyphenols-stripped red wine (PSRW), ethanol-water solution (ET), and water (W), the role of wine polyphenols, ethanol, and urate on vascular function was examined in humans ($n = 9$ per beverage) and on isolated rat aortic rings ($n = 9$). Healthy males randomly consumed each beverage in a cross-over design. Plasma ethanol, catechin, and urate concentrations were measured before and 30, 60 and 120 minutes after beverage intake. Endothelial function was assessed before and 60 minutes after beverage consumption by normalized flow-mediated dilation (FMD). RW and DARW induced similar vasodilatation in the isolated vessels whereas PSRW, ET, and W did not. All ethanol-containing beverages induced similar basal vasodilatation of brachial artery. Only intake of RW resulted in enhancement of endothelial response, despite similar plasma catechin concentration after DARW. The borderline effect of RW on FMD ($P = 0.0531$) became significant after FMD normalization ($P = 0.0043$) that neutralized blunting effect of ethanol-induced basal vasodilatation. Effects of PSRW and ET did not differ although plasma urate increased after PSRW and not after ET, indicating lack of urate influence on endothelial response. Acute vascular effects of RW, mediated by polyphenols, cannot be predicted by plasma catechin concentration only.

J Cardiovasc Pharmacol. 2006 May;47(5):695-701

THE EFFECT OF CHRONIC CONSUMPTION OF RED WINE POLYPHENOLS ON VASCULAR FUNCTION IN POSTMENOPAUSAL WOMEN.

OBJECTIVE: To elucidate whether the chronic consumption of dealcoholized red wine (DRW) (polyphenol-rich component) and/or

red wine (RW) improves vascular function in hypercholesterolaemic postmenopausal women. DESIGN, SUBJECTS AND INTERVENTION: A randomised parallel-arm study. Forty-five hypercholesterolaemic postmenopausal women were randomised into either water, DRW or RW group for 6 weeks following a 4 week washout. Fasting measures of central haemodynamic parameters, arterial wave reflection and endothelial nitric oxide were taken at 0 and 6 weeks. SETTING: Clinic in the School of Public Health, Curtin University. RESULTS: There were no significant between group differences in arterial stiffness as measured by augmentation index (AIx) and augmentation pressure (AP). However, a significant within group decrease in AIx (-9%, P=0.02) and AP (-12%, P=0.02) was observed following DRW consumption. No significant changes were observed in central haemodynamic parameters and endothelial nitric oxide levels following DRW and RW consumption, compared to water. CONCLUSIONS: Neither the chronic consumption of DRW nor RW improved markers of arterial stiffness, compared to control. However, the significant within group improvements in these indices following the consumption of DRW cannot be overlooked and warrant further investigation.

Eur J Clin Nutr. 2006 Jun;60(6):740-5

EFFECTS OF ARMAGNAC OR VODKA ON PLATELET AGGREGATION IN HEALTHY VOLUNTEERS: A RANDOMIZED CONTROLLED CLINICAL TRIAL.

BACKGROUND: Cardiovascular mortality is especially low in southwest France (the French Paradox). In previous experimental studies, we found that alcohol-free extracts of armagnac could inhibit human platelet function in vitro and experimental thrombosis in vivo. To test the possible relevance of these findings, we tested the effects of daily use of small quantities of armagnac against same alcohol strength, polyphenol-free vodka in healthy volunteers. METHOD: Randomized controlled trial comparing 5-year-old armagnac (30 ml/day for 2 weeks) to same alcoholic strength vodka, in 20 healthy volunteers, on platelet aggregation induced by ADP, collagen, and thrombin, as well as bleeding time, partial thromboplastin time (pTT), and plasma lipids during and after consumption. Platelet testing was done blind. RESULTS: After 14 days, ADP-induced platelet aggregation was inhibited more in armagnac (-31+/-3.2% compared to pretreatment values, p<.01) than in vodka (-11.0+/-6.8%, NS) users (p<.05, armagnac vs. vodka). A rebound increase of aggregation was found 2 weeks later in vodka but not in armagnac users. The same pattern was found for thrombin-induced aggregation, including post-treatment rebound. No effect was found on collagen-induced aggregation, bleeding time, pTT, or plasma lipids. CONCLUSION: The chronic ingestion of moderate quantities of armagnac modified platelet aggregation to ADP in healthy volunteers. The difference with the effects of same alcohol degree vodka is in favour of an effect of the nonalcoholic fraction in the effects of armagnac, rather than just alcohol. All spirits may not be equal for cardioprotection.

Thromb Res. 2005;115(1-2):31-7

LOW MOLECULAR PROANTHOCYANIDIN DIETARY BIOFACTOR OLIGONOL: ITS MODULATION OF OXIDATIVE STRESS, BIOEFFICACY, NEUROPROTECTION, FOOD APPLICATION, AND CHEMOPREVENTION POTENTIALS.

Interdisciplinary research endeavors are directed at understanding the molecular mechanisms of neurodegenerative and chronic diseases that affect human lifestyle. Hence the potential for developing medicinal herb-derived and food plant-derived prophylactic agents directed at neurological, metabolic, cardiovascular and psychiatric disorders abounds. Oligonol is a novel technology product emanating from the oligomerization of polyphenols, typically proanthocyanidin from a variety of fruits (grapes, apples, persimmons etc.) that has optimized bioavailability. It is an optimized phenolic product containing catechin-type monomers and oligomeric proanthocyanidins, the easily absorbed forms. Typically the constituents of Oligonol are 15-20% monomers, 8-12% dimers and 5-10% trimers. Supplementation of mice with Oligonol prior to the administration of ferric-nitrosyltriacetic complex (a Fenton chemistry model) significantly reduced the extent of lipid peroxidation in the kidney, brain and liver. Oligonol triggers apoptosis in the MCF-7 and MDA-MB-231 breast cancer cells through modulation of the pro-apoptotic Bcl-2 family of proteins and the MEK/ERK signaling pathway, an observation suggesting its important chemopreventive effects. The senescence-accelerated strain of mice (SAM) are models of senescence acceleration and geriatric disorders which exhibit learning and memory deficits and enhanced production or defective control of oxidative stress leading.

Biofactors. 2006;27(1-4):245-65

GRAPE POWDER POLYPHENOLS ATTENUATE ATHEROSCLEROSIS DEVELOPMENT IN APOLIPOPROTEIN E DEFICIENT (E0) MICE AND REDUCE MACROPHAGE ATHEROGENICITY.

The beneficial health effects of red wine have been attributed to the antioxidant activity of its polyphenols. The present study investigated the effects of a standardized freeze-dried powder made from fresh grapes, rich in grape-specific polyphenols and free of alcohol, on oxidative stress, atherogenicity of macrophages, and the development of atherosclerotic lesions in apolipoprotein E deficient (E0) mice. Thirty E(0) mice were assigned to 3 groups. Mice consumed water alone (control), 150 mug total polyphenols/d in the form of grape powder (grape powder), or the equivalent amount of glucose and fructose (placebo) in drinking water for 10 wk. Consumption of grape powder reduced the atherosclerotic lesion area by 41% (P < 0.0002) compared to the control or placebo mice. The antiatherosclerotic effect was at least partly due to a significant 8% reduction in serum oxidative

stress, an up to 22% increase in serum antioxidant capacity, a significant 33% reduction in macrophage uptake of oxidized LDL, and a 25% decrease in macrophage-mediated oxidation of LDL relative to controls. Grape powder directly protected both plasma LDL and macrophages from oxidative stress in vitro. We conclude that polyphenols from fresh grape powder directly affect macrophage atherogenicity by reducing macrophage-mediated oxidation of LDL and cellular uptake of oxidized LDL. Both of these processes can eventually reduce macrophage cholesterol accumulation and foam cell formation and hence attenuate atherosclerosis development.

J Nutr. 2005 Apr;135(4):722-8

ATHEROSCLEROSIS—EPIDEMIOLOGICAL STUDIES ON THE HEALTH EFFECTS OF A MEDITERRANEAN DIET.

Mediterranean diets are characterized by olive oil, as the dominant fat source and a high to moderate consumption of fruit and vegetables, cereal products, fish, legumes, in combination with little meat and wine with meals. The “reference” Mediterranean diet seems to differ according to country, but is associated with good health and a long life expectancy. From the Seven Countries Studies, it has been shown that especially the traditional Cretan diet was associated with very low 25-year mortality rates for coronary heart disease, cancer and all-causes. In terms of nutrients and bioactive compounds the “reference” Mediterranean diet is low in saturated fat and high in monounsaturated fatty acids, high in antioxidants especially vitamin C and E, and high in fiber and folic acid. Several epidemiological studies have investigated these dietary components either separately or in combination in other than Mediterranean populations. In general, also in other populations beneficial effects on the coronary risk profile have been observed, which gives further support to the positive health effects of the Mediterranean diet. Intervention studies in East Finland and Southern Italy have convincingly shown that the coronary risk profile (lower LDL cholesterol and blood pressure levels) is improved by a Mediterranean diet. Moreover, the Cretan diet was tested in cardiac patients and showed a 70% lower cardiac and all-causes mortality compared to the control diet. In conclusion, epidemiological studies and intervention trials suggest that the Cretan Mediterranean diet lowers the risk of coronary heart disease.

Eur J Nutr. 2004 Mar;43 Suppl 1:1/2-5

OLIVE OIL AND MODULATION OF CELL SIGNALING IN DISEASE PREVENTION.

Epidemiological studies show that populations consuming a predominantly plant-based Mediterranean-style diet exhibit lower incidences of chronic diseases than those eating a northern European or North American diet. This observation has been attributed to the greater consumption of fruits and vegetables and the lower consumption of animal products, particularly fat. Although total fat intake in Mediterranean populations can be higher than in other regions (ca. 40% of calories), the greater proportion is derived from olive oil and not animals. Increased olive oil consumption is implicated in a reduction in cardiovascular disease, rheumatoid arthritis, and, to a lesser extent, a variety of cancers. Olive oil intake also has been shown to modulate immune function, particularly the inflammatory processes associated with the immune system. Olive oil is a nonoxidative dietary component, and the attenuation of the inflammatory process it elicits could explain its beneficial effects on disease risk since oxidative and inflammatory stresses appear to be underlying factors in the etiology of these diseases in man. The antioxidant effects of olive oil are probably due to a combination of its high oleic acid content (low oxidation potential compared with linoleic acid) and its content of a variety of plant antioxidants, particularly oleuropein, hydroxytyrosol, and tyrosol. It is also possible that the high oleic acid content and a proportionate reduction in linoleic acid intake would allow a greater conversion of alpha-linolenic acid (18:3n-3) to longer-chain n-3 PUFA, which have characteristic health benefits. Adoption of a Mediterranean diet could confer health benefits in high-risk populations.

Lipids. 2004 Dec;39(12):1223-31

THE EFFECT OF POLYPHENOLS IN OLIVE OIL ON HEART DISEASE RISK FACTORS: A RANDOMIZED TRIAL.

BACKGROUND: Virgin olive oils are richer in phenolic content than refined olive oil. Small, randomized, crossover, controlled trials on the antioxidant effect of phenolic compounds from real-life daily doses of olive oil in humans have yielded conflicting results. Little information is available on the effect of the phenolic compounds of olive oil on plasma lipid levels. No international study with a large sample size has been done. **OBJECTIVE:** To evaluate whether the phenolic content of olive oil further benefits plasma lipid levels and lipid oxidative damage compared with monounsaturated acid content. **DESIGN:** Randomized, crossover, controlled trial. **SETTING:** 6 research centers from 5 European countries. **PARTICIPANTS:** 200 healthy male volunteers. **MEASUREMENTS:** Glucose levels, plasma lipid levels, oxidative damage to lipid levels, and endogenous and exogenous antioxidants at baseline and before and after each intervention. **INTERVENTION:** In a crossover study, participants were randomly assigned to 3 sequences of daily administration of 25 mL of 3 olive oils. Olive oils had low (2.7 mg/kg of olive oil), medium (164 mg/kg), or high (366 mg/kg) phenolic content but were otherwise similar. Intervention periods were 3 weeks preceded by 2-week washout periods. **RESULTS:** A linear increase in high-density lipoprotein (HDL) cholesterol levels was observed for low-, medium-, and high-polyphenol olive oil: mean change, 0.025 mmol/L (95% CI, 0.003 to 0.05 mmol/L), 0.032 mmol/L (CI, 0.005 to 0.05 mmol/L), and 0.045 mmol/L (CI, 0.02 to 0.06 mmol/L), respectively. Total cholesterol-HDL cholesterol ratio decreased linearly with the phenolic content of the olive oil. Triglyceride levels decreased by an average of 0.05 mmol/L for all olive oils. Oxidative

stress markers decreased linearly with increasing phenolic content. Mean changes for oxidized low-density lipoprotein levels were 1.21 U/L (CI, -0.8 to 3.6 U/L), -1.48 U/L (-3.6 to 0.6 U/L), and -3.21 U/L (-5.1 to -0.8 U/L) for the low-, medium-, and high-polyphenol olive oil, respectively. LIMITATIONS: The olive oil may have interacted with other dietary components, participants' dietary intake was self-reported, and the intervention periods were short. CONCLUSIONS: Olive oil is more than a monounsaturated fat. Its phenolic content can also provide benefits for plasma lipid levels and oxidative damage.

Ann Intern Med. 2006 Sep 5;145(5):333-41

ANTI-INFLAMMATORY EFFECT OF VIRGIN OLIVE OIL IN STABLE CORONARY DISEASE PATIENTS: A RANDOMIZED, CROSSOVER, CONTROLLED TRIAL.

Objectives: To assess the effect of two similar olive oils, but with differences in their phenolic compounds (powerful antioxidant compounds), on inflammatory markers in stable coronary heart disease patients. **Design:** Placebo-controlled, crossover, randomized trial. **Setting:** Cardiology Department of Hospital del Mar and Institut Municipal d'Investigació Mèdica (Barcelona). **Subjects:** Twenty-eight stable coronary heart disease patients. **Interventions:** A raw daily dose of 50 ml of virgin and refined olive oil (ROO) was sequentially administered over two periods of 3-weeks, preceded by 2-week washout periods in which ROO was used. **Results:** Interleukin-6 ($P < 0.002$) and C-reactive protein ($P = 0.024$) decreased after virgin olive oil intervention. No changes were observed in soluble intercellular and vascular adhesion molecules, glucose and lipid profile. **Conclusions:** Consumption of virgin olive oil, could provide beneficial effects in stable coronary heart disease patients as an additional intervention to the pharmacological treatment.

Eur J Clin Nutr. 2007 Mar 21

OLIVES AND OLIVE OIL IN CANCER PREVENTION.

Epidemiologic studies conducted in the latter part of the twentieth century demonstrate fairly conclusively that the people of the Mediterranean basin enjoy a healthy lifestyle with decreased incidence of degenerative diseases. The data show that populations within Europe that consume the so-called 'Mediterranean diet' have lower incidences of major illnesses such as cancer and cardiovascular disease. Studies have suggested that the health-conferring benefits of the Mediterranean diet are due mainly to a high consumption of fibre, fish, fruits and vegetables. More recent research has focused on other important factors such as olives and olive oil. Obviously fibre (especially wholegrain-derived products), fruits and vegetables supply an important source of dietary antioxidants. What is the contribution from olives and olive oil? Apparently the potential is extremely high but epidemiologic studies rarely investigate consumption of these very important products in-depth, perhaps due to a lack of exact information on the types and amounts of antioxidants present. Recent studies have shown that olives and olive oil contain antioxidants in abundance. Olives (especially those that have not been subjected to the Spanish brining process) contain up to 16 g/kg typified by acteosides, hydroxytyrosol, tyrosol and phenyl propionic acids. Olive oil, especially extra virgin, contains smaller amounts of hydroxytyrosol and tyrosol, but also contains secoiridoids and lignans in abundance. Both olives and olive oil contain substantial amounts of other compounds deemed to be anticancer agents (e.g. squalene and terpenoids) as well as the peroxidation-resistant lipid oleic acid. It seems probable that olive and olive oil consumption in southern Europe represents an important contribution to the beneficial effects on health of the Mediterranean diet.

Eur J Cancer Prev. 2004 Aug;13(4):319-26

MEDITERRANEAN DIETARY TRADITIONS FOR THE MOLECULAR TREATMENT OF HUMAN CANCER: ANTI-ONCOGENIC ACTIONS OF THE MAIN OLIVE OIL'S MONOUNSATURATED FATTY ACID OLEIC ACID (18:1N-9).

The final proof about the specific mechanisms by which the different components of olive oil, the principal source of fat in a typical "Mediterranean diet," exert their potential protective effects on the promotion and progression of several human cancers requires further investigations. A recent discovery that dietary fatty acids can interact with the human genome by regulating the amount and/or activity of transcription factors has opened a whole new line of research aimed to molecularly corroborate the anticancer benefits of the olive oil-based Mediterranean diet and the underlying mechanisms. Our most recent findings reveal that oleic acid (OA; 18:1n-9), the main olive oil's monounsaturated fatty acid, can suppress the overexpression of HER2 (erbB-2), a well-characterized oncogene playing a key role in the etiology, invasive progression and metastasis in several human cancers. First, exogenous supplementation with physiological concentrations of OA significantly down-regulates HER2-coded p185(Her-2/neu) oncoprotein in human cancer cells naturally harboring amplification of the HER gene. Second, OA exposure specifically represses the transcriptional activity of the human HER2 gene promoter in tumor-derived cell lines naturally exhibiting HER2 gene amplification and p185(Her-2/neu) protein overexpression but not in cancer cells expressing physiological levels of HER2. Third, OA treatment induces the up-regulation of the Ets protein PEA3 (a transcriptional repressor of the HER2 gene promoter) solely in cancer cells naturally displaying HER2 gene amplification. Fourth, HER2 gene promoter bearing a PEA3 site-mutated sequence cannot be negatively regulated by OA, while treatment with OA fails to repress the expression of a human full-length HER2 cDNA controlled by a SV40 viral promoter. Fifth, OA-induced inhibition of HER2 promoter activity does not occur if HER2 gene-amplified cancer cells do not concomitantly exhibit high levels of Fatty Acid Synthase (FASN; Oncogenic antigen-519) as specific depletion

of FASN, which itself similarly suppresses HER2 overexpression by inducing PEA3-dependent repression of HER2 gene promoter, strongly antagonizes the inhibitory effects of OA on HER2 gene promoter activity. Considering that OA treatment efficiently blocks FASN activity and down-regulates FASN protein expression, it is reasonable to suggest that an accumulation of supra-physiological concentrations of the FASN substrate malonyl-CoA, due to its reduced utilization by FASN in the presence of exogenous OA, appears to act as an indicator of "cell fuel" availability capable to suppress HER2 expression via formation of inhibitory "PEA3 protein-PEA3 DNA binding site" complexes on the endogenous HER2 promoter. Indeed, malonyl-CoA on its own dramatically decreases HER2 promoter activity, while OA or malonyl-CoA similarly up-regulates PEA3 gene promoter activity. This previously unrecognized ability of OA to directly affect the expression of a cluster of interrelated human cancer genes (i.e., HER2, FASN and PEA3) should open a new line of research aimed to explore the anti-cancer effects of OA. Certainly, an appropriate dietary intervention reproducing this prominent anti-oncogenic feature of the "Mediterranean diet" must be carried out in animal models and human pilot studies in the future. Only then we will know whether the old "Mediterranean dietary traditions" will become a new molecular approach in the management of cancer disease.

Curr Pharm Biotechnol. 2006 Dec;7(6):495-502

SUPPLEMENTATION OF FISH OIL AND OLIVE OIL IN PATIENTS WITH RHEUMATOID ARTHRITIS.

OBJECTIVE: This study evaluated whether supplementation with olive oil could improve clinical and laboratory parameters of disease activity in patients who had rheumatoid arthritis and were using fish oil supplements. **METHODS:** Forty-three patients (34 female, 9 male; mean age = 49 +/- 19y) were investigated in a parallel randomized design. Patients were assigned to one of three groups. In addition to their usual medication, the first group (G1) received placebo (soy oil), the second group (G2) received fish oil omega-3 fatty acids (3 g/d), and the third group (G3) received fish oil omega-3 fatty acids (3 g/d) and 9.6 mL of olive oil. Disease activity was measured by clinical and laboratory indicators at the beginning of the study and after 12 and 24 wk. Patients' satisfaction in activities of daily living was also measured. **RESULTS:** There was a statistically significant improvement ($P < 0.05$) in G2 and G3 in relation to G1 with respect to joint pain intensity, right and left handgrip strength after 12 and 24 wk, duration of morning stiffness, onset of fatigue, Ritchie's articular index for pain joints after 24 wk, ability to bend down to pick up clothing from the floor, and getting in and out of a car after 24 wk. G3, but not G2, in relation to G1 showed additional improvements with respect to duration of morning stiffness after 12 wk, patient global assessment after 12 and 24 wk, ability to turn faucets on and off after 24 wk, and rheumatoid factor after 24 wk. In addition, G3 showed a significant improvement in patient global assessment in relation to G2 after 12 wk. **CONCLUSIONS:** Ingestion of fish oil omega-3 fatty acids relieved several clinical parameters used in the present study. However, patients showed a more precocious and accentuated improvement when fish oil supplements were used in combination with olive oil.

Nutrition. 2005 Feb;21(2):131-6

PHYTOCHEMISTRY: IBUPROFEN-LIKE ACTIVITY IN EXTRA-VIRGIN OLIVE OIL.

Newly pressed extra-virgin olive oil contains oleocanthal--a compound whose pungency induces a strong stinging sensation in the throat, not unlike that caused by solutions of the non-steroidal anti-inflammatory drug ibuprofen. We show here that this similar perception seems to be an indicator of a shared pharmacological activity, with oleocanthal acting as a natural anti-inflammatory compound that has a potency and profile strikingly similar to that of ibuprofen. Although structurally dissimilar, both these molecules inhibit the same cyclooxygenase enzymes in the prostaglandin-biosynthesis pathway.

Nature. 2005 Sep 1;437(7055):45-6

IN VITRO ACTIVITY OF OLIVE OIL POLYPHENOLS AGAINST HELICOBACTER PYLORI.

Helicobacter pylori is linked to a majority of peptic ulcers and to some types of gastric cancer, and resistance of the microorganism to antibiotic treatment is now found worldwide. Virgin olive oil is an unrefined vegetable oil that contains a significant amount of phenolic compounds. Under simulated conditions, we have demonstrated that these substances can diffuse from the oil into the gastric juice and be stable for hours in this acidic environment. In vitro, they exerted a strong bactericidal activity against eight strains of *H. pylori*, three of them resistant to some antibiotics. Among the phenolic compounds, the dialdehydic form of decarboxymethyl ligstroside aglycon showed the strongest bactericidal effect at a concentration as low as 1.3 microg/mL. Although the experimental conditions are different from other reported works, this bactericidal concentration is much lower than those found for phenolic compounds from tea, wine, and plant extracts. These results open the possibility of considering virgin olive oil a chemopreventive agent for peptic ulcer or gastric cancer, but this bioactivity should be confirmed in vivo in the future.

J Agric Food Chem. 2007 Feb 7;55(3):680-6

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