

## ABSTRACTS

### Oral Health

#### **Periodontal disease and cardiovascular disease: epidemiology and possible mechanisms.**

**BACKGROUND:** Many early epidemiologic studies reported an association between periodontal disease and cardiovascular disease. However, other studies found no association or nonsignificant trends. This report summarizes the evidence from epidemiologic studies and studies that focused on potential contributing mechanisms to provide a more complete picture of the association between periodontal and heart disease. **TYPES OF STUDIES REVIEWED:** The authors summarize the longitudinal studies reported to date, because they represent the highest level of evidence available regarding the connection between periodontal disease and heart disease. The authors also review many of the case-control and cross-sectional studies published, as well as findings from clinical, animal, and basic laboratory studies. **RESULTS:** The evidence suggests a moderate association—but not a causal relationship—between periodontal disease and heart disease. Results of some case-control studies indicate that subgingival periodontal pathogenic infection may be associated with myocardial infarction. Basic laboratory studies point to the biological plausibility of this association, since oral bacteria have been found in carotid atheromas and some oral bacteria may be associated with platelet aggregation, an event important for thrombosis. Animal studies have shown that atheroma formation can be enhanced by exposure to periodontal pathogens. **CONCLUSIONS:** The accumulation of epidemiologic, in vitro, clinical, and animal evidence suggests that periodontal infection may be a contributing risk factor for heart disease. However, legitimate concerns have arisen about the nature of this relationship. These are early investigations. Since even a moderate risk contributed by periodontal disease to heart disease could contribute to significant morbidity and mortality, it is imperative that further studies be conducted to evaluate this relationship. One particularly important study to be carried out is the investigation of a possible clinically meaningful reduction in heart disease resulting from the prevention or treatment of periodontal disease.

*J Am Dent Assoc. 2002 Jun;133 Suppl:14S-22S*

#### **Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients.**

**BACKGROUND:** Periodontitis is a common, often undiagnosed, chronic infection of the supporting tissues of the teeth, epidemiologically associated with cardiovascular diseases. Since C-reactive protein (CRP) and other systemic markers of inflammation have been identified as risk factors for cardiovascular diseases, we investigated whether these factors were elevated in periodontitis. **METHODS:** Consecutive adult patients with periodontitis (localized  $n = 53$ ; generalized  $n = 54$ ), and healthy controls ( $n = 43$ ), all without any other medical disorder, were recruited and peripheral blood samples were taken. **RESULTS:** Patients with generalized periodontitis and localized periodontitis had higher median CRP levels than controls (1.45 and 1.30 versus 0.90 mg/L, respectively,  $P = 0.030$ ); 52% of generalized periodontitis patients and 36% of the localized periodontitis patients were sero-positive for interleukin-6 (IL-6), compared to 26% of controls ( $P = 0.008$ ). Plasma IL-6 levels were higher in periodontitis patients than in controls ( $P = 0.015$ ). Leukocytes were also elevated in generalized periodontitis ( $7.0 \times 10^9/L$ ) compared to localized periodontitis and controls ( $6.0$  and  $5.8 \times 10^9/L$ , respectively,  $P = 0.002$ ); this finding was primarily explained by higher numbers of neutrophils in periodontitis ( $P = 0.001$ ). IL-6 and CRP correlated with each other, and both CRP and IL-6 levels correlated with neutrophils. The current findings for periodontitis were controlled for other known factors associated with cardiovascular diseases, including age, education, body mass index, smoking, hypertension, cholesterol, and sero-positivity for CMV, Chlamydia pneumoniae, and Helicobacter pylori. **CONCLUSIONS:** Periodontitis results in higher systemic levels of CRP, IL-6, and neutrophils. These elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions, potentially increasing the risk for cardiac or cerebrovascular events.

*J Periodontol. 2000 Oct;71(10):1528-34*

#### **Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III.**

**BACKGROUND:** Associations between poor oral health and chronic lung disease have recently been reported. The present study evaluated these potential associations by analyzing data from the National Health and Nutrition Examination Survey III (NHANES III), which documents the general health and nutritional status of randomly selected United States subjects from 1988 to 1994. **METHODS:** This cross-sectional, retrospective study of the NHANES III database included a study population of 13,792 subjects  $> \text{ or } = 20$  years of age with at least 6 natural teeth. A history of bronchitis and/or emphysema was recorded from the medical

questionnaire, and a dichotomized variable combined those with either chronic bronchitis and/or emphysema, together considered as chronic obstructive pulmonary disease (COPD). Subject lung function was estimated by calculating the ratio of forced expiratory volume (FEV) after 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC). Oral health status was assessed from the DMFS/T index (summary of cumulative caries experience), gingival bleeding, gingival recession, gingival probing depth, and periodontal attachment level. Unweighted analyses were used for initial examination of the data, and a weighted analysis was performed in a final logistic regression model adjusting for age, gender, race and ethnicity, education, income, frequency of dental visits, diabetes mellitus, smoking, and alcohol use. RESULTS: The mean age of all subjects was 44.4 +/- 17.8 years (mean +/- SD): COPD = 51.2 +/- 17.9 years and subjects without COPD = 43.9 +/- 17.7 years. Subjects with a history of COPD had more periodontal attachment loss than subjects without COPD (1.48 +/- 1.35 mm versus 1.17 +/- 1.09 mm, P = 0.0001). Subjects with mean attachment loss (MAL) > or = 3.0 mm had a higher risk of COPD than those having MAL < 3.0 mm (odds ratio, 1.45; 95% CI, 1.02 to 2.05). A trend was noted in that lung function appeared to diminish with increasing periodontal attachment loss. CONCLUSIONS: The findings of the present analysis support recently published reports that suggest an association between periodontal disease and COPD.

*J Periodontol. 2001 Jan;72(1):50-6*

### **Inter-relationships between rheumatoid arthritis and periodontal disease. A review.**

This review looks at the considerable similarities between periodontal disease and rheumatoid arthritis (RA). While the etiology of these two diseases may differ, the underlying pathogenic mechanisms are remarkably similar and it is possible that individuals manifesting both periodontitis and RA may suffer from a unifying underlying systemic dysregulation of the inflammatory response. In light of these findings, the implications for the use of disease-modifying medications in the management of these two chronic inflammatory conditions is apparent. Further longitudinal studies and medication-based intervention studies are required to determine just how closely these two conditions are allied.

*J Clin Periodontol. 2003 Sep;30(9):761-72*

### **Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National Health and Nutrition Examination Survey (NHANES III).**

OBJECTIVES: The objective of this study was to investigate the association of body composition (obesity) and periodontal disease using simple, inexpensive nutritional assessment techniques available in the Third National Health and Nutrition Examination Survey (NHANES III). MATERIAL AND METHODS: Caucasian subjects, aged 18 years and above, participating in NHANES III, were used for this study. Weight, height, waist circumference, hip circumference, skinfold thickness (S), and bioelectrical impedance analysis measurements were performed and used in the calculation of body mass index (BMI), waist-to-hip ratio (WHR) (visceral fat), log sum of S (subcutaneous fat), and fat-free mass (FFM). Data were analyzed using SPSS. One-way, factorial ANOVA, multivariate analyses, and regression curve analyses were performed.  $p < 0.05$  was used to reject the null hypothesis. RESULTS: Adjusting for age, gender, history of diabetes, current smoking, and socioeconomic status, statistically significant correlations were found between periodontitis and WHR, BMI, FFM, and in some instances S. CONCLUSION: This study, indicating significant correlations between body composition and periodontal disease (with WHR being the most significant, followed by BMI, FFM, and S), showed similarities to those observed in other obesity-related health problems. This strengthened arguments that periodontal disease and certain obesity-related systemic illnesses are related, with abnormal fat metabolism possibly being an important factor.

*J Clin Periodontol. 2003 Apr;30(4):321-7*

### **Osteoporosis: a possible modifying factor in oral bone loss.**

There has been increasing interest in the interrelationship between systemic osteoporosis, oral bone loss, tooth loss, and risk factors for these conditions. Because the severity of alveolar bone loss increases with age, it has long been hypothesized that it may, in part, be related to systemic conditions that also predispose the patient to osteoporosis/osteopenia. The purpose of this paper is to review the risk factors for osteoporosis and periodontitis, as well as the evidence that loss of oral bone mineral may be related to systemic osteopenia. There is also evidence that therapies designed to influence systemic bone mineral density, such as hormone replacement and bisphosphonate therapy, may be associated with less tooth loss and a slower loss of alveolar bone, respectively.

*Ann Periodontol. 1998 Jul;3(1):312-21*

### **Tooth loss and skeletal bone density in healthy postmenopausal women.**

Associations between dental status and skeletal bone density were investigated in a group of 329 healthy postmenopausal women with normal bone density. Bone mineral density (BMD) of the lumbar spine, femoral neck and distal radius were

measured by dual- or single-photon absorptiometry. Number of teeth remaining were counted and presence of complete dentures noted by a nurse practitioner. Forty-eight women (15%) wore a complete maxillary and/or mandibular denture: 22(7%) were completely edentulous and an additional 26 (8%) had one edentulous ridge. Among women without complete dentures (n = 281), significant positive linear relationships were observed between number of teeth and BMD at the spine ( $p < 0.05$ ) and radius ( $p < 0.01$ ), controlling for years since menopause, pack-years of smoking, education and body mass index. BMD did not differ between the groups with and without dentures. However, women who acquired dentures after the age of 40 years had significantly lower mean spinal and radial BMD than women who acquired dentures at age 40 years or earlier (at the radius,  $0.584 \pm 0.015$  v  $0.630 \pm 0.017$  g/cm<sup>2</sup>,  $p < 0.05$ ; at the spine,  $1.043 \pm 0.031$  v  $1.124 \pm 0.029$  g/cm<sup>2</sup>,  $p = 0.05$ ). In linear regression analysis, significant independent correlations were found among all women (n = 329) between number of teeth and age (partial  $r = -0.19$ ,  $p < 0.001$ ), pack-years of cigarette use (partial  $r = -0.23$ ,  $p < 0.001$ ) and years of education (partial  $r = +0.11$ ,  $p < 0.05$ ). These associations between dental status and BMD support the hypothesis that systemic bone loss may contribute to tooth loss.

*Osteoporos Int. 1994 Mar;4(2):104-9*

### **Periodontal infection and preterm birth: results of a prospective study.**

**BACKGROUND:** Previous studies have suggested that chronic periodontal infection may be associated with preterm births. The authors conducted a prospective study to test for this association. **METHODS:** A total of 1,313 pregnant women were recruited from the Perinatal Emphasis Research Center at the University of Alabama at Birmingham. Complete periodontal, medical, and behavioral assessments were made between 21 and 24 weeks gestation. After delivery, medical records were consulted to determine each infant's gestational age at birth. From these data, the authors calculated relationships between periodontal disease and preterm birth, while adjusting for smoking, parity (the state or fact of having born offspring), race, and maternal age. Results were expressed as odds ratios and 95% confidence intervals, or CIs. **RESULTS:** Patients with severe or generalized periodontal disease had adjusted odds ratios (95% CI) of 4.45 (2.16-9.18) for preterm delivery (that is, before 37 weeks gestational age). The adjusted odds ratio increased with increasing prematurity to 5.28 (2.05-13.60) before 35 weeks' gestational age and to 7.07 (1.70-27.4) before 32 weeks' gestational age. **CONCLUSIONS:** The authors' data show an association between the presence of periodontitis at 21 to 24 weeks' gestation and subsequent preterm birth. Further studies are needed to determine whether periodontitis is the cause. **CLINICAL IMPLICATIONS:** While this large prospective study has shown a significant association between preterm birth and periodontitis at 21 to 24 weeks' gestation, neither it nor other studies to date were designed to determine whether treatment of periodontitis will reduce the risk of preterm birth. Pending an answer to this important question, it remains appropriate to advise expectant mothers about the importance of good oral health.

*J Am Dent Assoc. 2001 Jul;132(7):875-80*

### **Women's health issues and their relationship to periodontitis.**

**BACKGROUND:** The emergence of sex-specific associations between periodontitis and certain systemic disorders has prompted researchers to investigate the possibility of associations between periodontitis and specific women's health issues. The authors review the potential relationships between periodontitis and hormonal changes and their ramifications in regard to pregnancy outcomes, cardiovascular disease, or CVD, and osteoporosis. **METHODS:** Changes in hormone levels, such as those that occur during puberty, pregnancy, menstruation and menopause, as well as those that occur with the use of hormonal supplements, have long been associated with the development of gingivitis. Furthermore, bacterial anaerobes have been found to change during the normal hormonal cycle. In periodontitis, the inflammatory response results in ulceration of the gingivae and the subsequent entry of bacterial cells, bacterial products, peptidoglycan fragments and hydrolytic enzymes into the systemic circulation. The result is a systemic response of increased cytokines and biological mediators, as well as increased levels of serum antibodies. **RESULTS:** Some researchers have found that pregnant women with periodontitis were 7.5 times more likely to have a preterm low-birth-weight infant than were control subjects. Other researchers reported that the risk of preterm birth was directly related to the severity of periodontitis. Similarly, researchers have linked periodontitis to CVD. Many studies have indicated that estrogen exerts a protective effect against CVD development, and much evidence suggests that when hormone replacement therapy is administered to postmenopausal women, this effect continues. A relationship between periodontitis and osteoporosis has been established, such that more clinical attachment loss has been noted in osteoporotic people. **CONCLUSIONS:** The literature suggests that more sex-specific research is essential to determine the strategies needed to prevent and treat adverse pregnancy outcomes, CVD and osteoporosis through hormone modification and periodontitis control. **CLINICAL IMPLICATIONS:** Dentists must assume greater responsibility for the overall health of their patients, and acquire knowledge of relevant systemic conditions to interact meaningfully with medical colleagues.

*J Am Dent Assoc. 2002 Mar;133(3):323-9*

### **Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study.**

Periodontitis has been linked to clinical cardiovascular disease but not to subclinical atherosclerosis. The purpose of this study

was to determine whether periodontitis is associated with carotid artery intima-media wall thickness (IMT). Cross-sectional data on 6,017 persons aged 52 to 75 years were obtained from the Atherosclerosis Risk in Communities Study 1996 to 1998 examination. The dependent variable was carotid IMT  $\geq 1$  mm. Periodontitis was defined by extent of attachment loss  $\geq 3$  mm: none/mild ( $< 10\%$ ), moderate ( $10\%$  to  $< 30\%$ ), or severe ( $\geq 30\%$ ). Covariates included age, sex, diabetes, LDL cholesterol, HDL cholesterol, triglycerides, hypertension, smoking, waist-hip ratio, education, and race/study center. Odds of IMT  $\geq 1$  mm were higher for severe periodontitis (OR 2.09, 95% CI 1.73 to 2.53) and moderate periodontitis (OR 1.40, CI 1.17 to 1.67) compared with no periodontitis. In a multivariable logistic regression model, severe periodontitis (OR 1.31, CI 1.03 to 1.66) was associated with IMT  $\geq 1$  mm, while adjusting for the other factors in the model. These results provide the first indication that periodontitis may play a role in the pathogenesis of atheroma formation, as well as in cardiovascular events.

*Arterioscler Thromb Vasc Biol.* 2001 Nov;21(11):1816-22

## ABSTRACTS

### Sytrinol

#### **Treatment of dyslipidemia in high-risk patients: too little, too late.**

Evidence that lowering low-density cholesterol (LDL-C) reduces coronary events and mortality is now overwhelming and is reflected in treatment guidelines from around the world. The Joint European Guidelines recommend an LDL-C goal of <3.0 mmol/l in high-risk subjects. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP)-III guidelines suggest an even more aggressive approach in high-risk individuals, with a recommended LDL-C goal of <2.6 mmol/l. Large numbers of high-risk patients are still not achieving the more conservative goals recommended in the Joint European Guidelines, let alone the more aggressive LDL-C target recommended in the new NCEPATP-III guidelines. The recognition in the NCEP ATP-III guidelines that a high-density lipoprotein cholesterol (HDL-C) level <1.0 mmol/l represents an important risk factor highlights the emergence of HDL-C as a key player in the genesis of coronary heart disease (CHD) and as a potential target for therapy. This may be especially important in people with insulin resistance with or without type 2 diabetes. There is evidence from the Helsinki Heart Study and the more recent Veterans Affairs HDL Intervention Trial (VA-HIT), both of which used gemfibrozil as the active agent, that the observed reduction in coronary events was correlated with the magnitude of the increase in HDL-C. The challenge for future management of high-risk individuals will be not only to reduce the level of LDL-C to below 2.6 mmol/l but also to increase HDL-C to levels above 1.0 mmol/l.

*Int J Clin Pract Suppl. 2002 Jul;(130):15-9*

#### **Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults: findings from the National Health and Nutrition Examination Survey, 1999 to 2000.**

**BACKGROUND:** Serum cholesterol concentrations have decreased in the US population. Whether the decline continued during the 1990s is unknown. **METHODS AND RESULTS:** We used data from 4,148 men and women aged > or =20 years who had a total cholesterol determination or reported using cholesterol-lowering medications and who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2000 (this is a cross-sectional health examination survey of the US population), and we compared the results with data from 15,719 participants in NHANES III (1988 to 1994). For all adults, the age-adjusted mean total cholesterol concentration decreased from 5.31 mmol/L (205 mg/dL) in NHANES III to 5.27 mmol/L (203 mg/dL) in NHANES 1999 to 2000 (P=0.159). The age-adjusted mean total cholesterol concentration decreased by 0.02 mmol/L (0.7 mg/dL) among men (P=0.605) and 0.06 mmol/L (2.3 mg/dL) among women (P=0.130). Significant decreases were observed among men aged > or =75 years, black men, and Mexican-American women. Among participants who had a total cholesterol concentration > or =5.2 mmol/L (200 mg/dL) or who reported using cholesterol-lowering medications, 69.5% reported having had their cholesterol checked, 35.0% were aware that they had hypercholesterolemia, 12.0% were on treatment, and 5.4% had a total cholesterol concentration <5.2 mmol/L (200 mg/dL) after age adjustment. **CONCLUSIONS:** The mean serum total cholesterol concentration of the adult US population in 1999 to 2000 has changed little since 1988 to 1994. The low percentage of adults with controlled blood cholesterol concentration suggests the need for a renewed commitment to the prevention, treatment, and control of hypercholesterolemia.

*Circulation. 2003 May 6;107(17):2185-9*

#### **Contemporary awareness and understanding of cholesterol as a risk factor: results of an American Heart Association national survey.**

**BACKGROUND:** Public awareness and understanding of risk factors for atherosclerotic vascular disease are essential for successful primary and secondary prevention. The American Heart Association is committed to reducing cardiovascular disease. **METHODS:** A professional market survey company conducted a structured national telephone survey of English-speaking adults 40 years and older on behalf of the American Heart Association. Regional and sex quotas were imposed on the sample, and responses were weighted to match the 1999 census projections for region of the country, age, sex, and race. **RESULTS:** Interviews were completed with 1,163 adults 40 years and older. A national probability sample of 1,114 was created. Of the final sample, 28.5% were 65 years or older, 56.1% were women, and 86.5% were white. Although 91.2% of respondents stated that it was "important to them personally to have a healthy cholesterol level" (77.6% extremely or very important), 51% did not know their own level. Only 40.2% were aware of national guidelines for cholesterol management, and 53.1% either did not know or overestimated the correct desirable total cholesterol level for a healthy adult. When asked what sources of information they rely on the most, 66.8% identified physicians, while only 3.7% rely primarily on the Internet. **CONCLUSIONS:** Public understanding of cholesterol management is suboptimal. Physicians have a unique opportunity, on the basis of public attitudes and access, to improve cholesterol education.

*Arch Intern Med. 2003 Jul 14;163(13):1597-600*

## **Use of nutritional supplements for the prevention and treatment of hypercholesterolemia.**

**OBJECTIVE:** Hypercholesterolemia is a major risk factor for the development of coronary artery disease. Studies have shown that several vitamins and nutritional supplements may contribute to a reduction in total and low-density lipoprotein cholesterol. This goal of this study was to document the use of vitamins and nutritional supplements that may treat or prevent hypercholesterolemia. **METHODS:** Secondary analysis of the National Health and Nutrition Examination Survey III responses from 13,990 patients were available to use for making population estimates. **RESULTS:** Of those individuals with a known diagnosis of hypercholesterolemia, 3.6% were taking at least one vitamin or nutritional supplement to decrease cholesterol levels. For individuals trying to prevent hypercholesterolemia, 1.2% were using one of these vitamin or nutritional supplements. Only 0.7% of individuals without or trying to prevent hypercholesterolemia used one of these specific supplements. We used multivariate analysis to control for several factors, and individuals with a diagnosis of hypercholesterolemia had an adjusted odds ratio of 2.10 (95% confidence interval, 1.38-3.21) for vitamin use compared with those without or trying to prevent high cholesterol. Those trying to prevent hypercholesterolemia had an adjusted odds ratio of 0.69 (95% confidence interval, 0.48-1.00) for vitamin use compared with those without or trying to prevent high cholesterol. **CONCLUSIONS:** The use of vitamins and nutritional supplements that may reduce total and low-density lipoprotein cholesterol levels is low in the United States. Future research is needed to confirm the effectiveness of these products, examine the quality and purity of currently available products, and explore whether using these supplements are an adequate low-cost alternative to pharmaceuticals now available.

*Nutrition. 2003 May;19(5):415-8*

## **Treating hyperlipidemia for the primary prevention of coronary disease. Are higher dosages of lovastatin cost-effective?**

**OBJECTIVE:** To compare the average and marginal life-time cost-effectiveness of increasing dosages of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, such as lovastatin, for the primary prevention of coronary heart disease (CHD). **METHODS:** We estimated the lifelong costs and benefits of the modification of lipid levels achieved with lovastatin based on published studies and a validated CHD prevention computer model. Patients were middle-aged men and women without CHD, with mean total serum cholesterol levels of 6.67, 7.84, and 9.90 mmol/L (258, 303, and 383 mg/dL), and high-density lipoprotein cholesterol levels of 1.19 mmol/L (46 mg/dL), as described in clinical trials. We estimated the cost per year of life saved for dosages of lovastatin ranging from 20 to 80 mg/d that reduced the total cholesterol level between 17% and 34%, and increased high-density lipoprotein cholesterol level between 4% and 13%. **RESULTS:** After discounting benefits and costs by 5% annually, the average cost-effectiveness of lovastatin, 20 mg/d, ranged from \$11,040 to \$52,463 for men and women. The marginal cost-effectiveness of 40 mg/d vs 20 mg/d remained in this range (\$25,711 to \$60,778) only for persons with baseline total cholesterol levels of 7.84 mmol/L (303 mg/dL) or higher. However, the marginal cost-effectiveness of lovastatin, 80 mg/d vs 40 mg/d, was prohibitively expensive (\$99,233 to \$716,433 per year of life saved) for men and women, irrespective of the baseline total cholesterol level. **CONCLUSIONS:** Assuming that \$50,000 per year of life saved is an acceptable cost-effectiveness ratio, treatment with lovastatin at a dosage of 20 mg/d is cost-effective for middle-aged men and women with baseline total cholesterol levels of 6.67 mmol/L (258 mg/dL) or higher. At current drug prices, treatment with 40 mg/d is also cost-effective for total cholesterol levels of 7.84 mmol/L (303 mg/dL) or higher. However, treatment with 80 mg/d is not cost-effective for primary prevention of CHD.

*Arch Intern Med. 1998 Feb 23;158(4):375-81*

## **Serum cholesterol levels and in-hospital mortality in the elderly.**

**PURPOSE:** Although total cholesterol levels among middle-aged persons correlate with long-term mortality from all causes, this association remains controversial in older persons. We explored whether total cholesterol levels were independently associated with in-hospital mortality among elderly patients. **METHODS:** We analyzed data from a large collaborative observational study, the Italian Group of Pharmacoepidemiology in the Elderly (GIFA), which collected data on hospitalized patients. A total of 6,984 patients aged 65 years or older who had been admitted to 81 participating medical centers during four survey periods (from 1993 to 1998) were enrolled. Patients were divided into four groups based on total cholesterol levels at hospital admission: <160 mg/dL (n = 2115), 160 to 199 mg/dL (n = 2210), 200 to 239 mg/dL (n = 1719), and  $\geq$ 240 mg/dL (n = 940). **RESULTS:** Patients (mean  $\pm$  SD age, 78  $\pm$  7 years) were hospitalized for an average of 15  $\pm$  10 days. The mean total cholesterol level was 186  $\pm$  49 mg/dL. A total of 202 patients died during hospitalization. Mortality was inversely related to cholesterol levels (<160 mg/dL: 5.2% [110/2115]; 160-199 mg/dL: 2.2% [49/2210]; 200-239 mg/dL: 1.6% [27/1719]; and  $\geq$ 240 mg/dL: 1.7% [16/940]; P for linear trend <0.001). After adjustment for potential confounders (demographic characteristics, smoking, alcohol use, indicators of nutritional status, markers of frailty, and comorbid conditions), low cholesterol levels continued to be associated with in-hospital mortality. Compared with patients who had cholesterol levels <160 mg/dL, the odds ratios for in-hospital mortality were 0.49 (95% confidence interval [CI]: 0.34 to 0.70) for participants with cholesterol levels of 160 to 199 mg/dL, 0.41 (95% CI: 0.26 to 0.65) for those with cholesterol levels of 200 to 239 mg/dL, and 0.56 (95% CI: 0.32 to 0.98) for those with cholesterol levels  $\geq$ 240 mg/dL. These estimates were similar after further adjustment for inflammatory markers and after excluding patients with liver disease. **CONCLUSIONS:** Among older hospitalized adults, low serum cholesterol levels appear to be an independent

predictor of short-term mortality.

*Am J Med. 2003 Sep;115(4):265-71.*

### **Low total cholesterol and increased risk of dying: are low levels clinical warning signs in the elderly? Results from the Italian Longitudinal Study on Aging.**

**OBJECTIVES:** To analyze the relationship between serum total cholesterol (TC) and all-cause mortality, taking into account various potential confounders. **DESIGN:** Population-based prospective cohort study. **SETTING:** Older Italians residing in the general community. **PARTICIPANTS:** Four thousand five hundred twenty-one men and women aged 65-84. **MEASUREMENTS:** Vital status data were available for 1992-95. The hazard ratios of dying for subjects in the second, third, and fourth quartiles compared with the first quartile of TC were computed using Cox proportional hazards, adjusting for lifestyle factors, anthropomorphic and biochemical measures, preexisting medical conditions, and frailty indicators. **RESULTS:** Blood samples were obtained from 3,295 (73%) of the participants, of whom 399 died during almost 3 years of follow-up. Low TC was associated with a higher risk of death. Those with TC in the second, third, and fourth quartiles (TC > 189 mg/dL or 4.90 mmol/L) had lower hazard ratios (HRs) of death than subjects in the first quartile (0.57, 95% confidence interval (CI) = 0.38-0.87; 0.56, 95% CI = 0.36-0.88; and 0.53, 95% CI = 0.33-0.84, respectively). Few subjects taking lipid-lowering drugs (LLDs) were in the lowest quartile of cholesterol, suggesting that these individuals have low TC values for reasons other than LLD use. **CONCLUSION:** Subjects with low TC levels (< 189 mg/dL) are at higher risk of dying even when many related factors have been taken into account. Although more data are needed to clarify the association between TC and all-cause mortality in older individuals, physicians may want to regard very low levels of cholesterol as potential warning signs of occult disease or as signals of rapidly declining health.

*J Am Geriatr Soc. 2003 Jul;51(7):991-6*

## ABSTRACTS

### DMAE

#### **Acetylcholine in mind: a neurotransmitter correlate of consciousness?**

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain and controls activities that depend on selective attention, which are an essential component of conscious awareness. Psychopharmacological and pathological evidence supports the concept of a 'cholinergic component' of conscious awareness. Drugs that antagonize muscarinic receptors induce hallucinations and reduce the level of consciousness, while the nicotinic receptor is implicated as being involved in the mechanism of action of general (inhalational) anaesthetics. In degenerative diseases of the brain, alterations in consciousness are associated with regional deficits in the cholinergic system. In Alzheimer's disease (AD), there is a loss of explicit (more than implicit) memory and hypoactivity of cholinergic projections to the hippocampus and cortex, while the visual hallucinations experienced by subjects with Dementia with Lewy bodies (DLB) are associated with reductions in neocortical ACh-related activity. In Parkinson's disease, the additional loss of pedunculopontine cholinergic neurones, which control REM (rapid eye movement) sleep or dreaming, is likely to contribute to REM abnormalities, which also occur in DLB. Widespread basal-forebrain and rostral brainstem cholinergic pathways, which include converging projections to the thalamus, appear to be located strategically for generating and integrating conscious awareness. Alleviation of a range of cognitive and non-cognitive symptoms by drugs that modulate the cholinergic system, which are being developed for the treatment of AD and related disorders, could be caused by changes in consciousness.

*Trends Neurosci.* 1999 Jun;22(6):273-80

#### **Dimethylaminoethanol (deanol) metabolism in rat brain and its effect on acetylcholine synthesis.**

Specific methods utilizing combined gas chromatography mass spectrometry were used to measure the metabolism of [2H6]deanol and its effects on acetylcholine concentration in vitro and in vivo. In vitro [2H6]deanol was rapidly taken up by rat brain synaptosomes, but was neither methylated nor acetylated. [2H6]Deanol was a weak competitive inhibitor of the high affinity transport of [2H4]choline, thus reducing the synthesis of [2H4]acetylcholine. In vivo [2H6]deanol was present in the brain after i.p. or p.o. administration, but was not methylated or acetylated. Treatment of rats with [2H6]deanol significantly increased the concentration of choline in the plasma and brain but did not alter the concentration of acetylcholine in the brain. Treatment of rats with atropine (to stimulate acetylcholine turnover) or with hemicholinium-3 (to inhibit the high affinity transport of choline) did not reveal any effect of [2H6]deanol on acetylcholine synthesis in vivo. However, since [2H6]deanol did increase brain choline, it may prove therapeutically useful when the production of choline is reduced or when the utilization of choline for the synthesis of acetylcholine is impaired.

*J Pharmacol Exp Ther.* 1979 Dec;211(3):472-9

#### **Deanol acetamidobenzoate inhibits the blood-brain barrier transport of choline.**

Competition by deanol (dimethylaminoethanol) with choline for uptake from the bloodstream into the brain was demonstrated by simultaneous intracarotid administration of carbon 14-labeled choline with deanol (plus tritiated water and indium 113m, to calculate a brain uptake index) and by measuring the brain uptake of 14C-labeled choline mixed with sera from rats pretreated with deanol (300 or 500 mg/kg 8 or 30 minutes earlier). The inhibition constant for inhibition of choline uptake by deanol (159 micrograms) was actually lower than the Michaelis constant for choline itself (442 micrograms); hence, the affinity of the carrier mechanism for deanol is at least as great as it is for choline. Deanol administration also elevated blood choline levels; thus, the effect of the drug on brain choline (and acetylcholine) levels is the result of the increase it produces in blood choline and the suppression it causes in choline uptake. These findings may explain discrepant results from laboratories seeking increases in brain acetylcholine or clinical improvement in patients with tardive dyskinesia after deanol treatment.

*Ann Neurol.* 1978 Oct;4(4):302-6

#### **Phosphatidylethanolamine and sarcolemmal damage during ischemia or metabolic inhibition of heart myocytes.**

Phosphatidylethanolamine (PE) is a nonbilayer-preferring and fusogenic phospholipid. It is kept in the bilayer configuration by interaction with other phospholipids in biologic membranes. However, reorganization of the membrane phospholipids could lead to expression of the nonbilayer nature of PE and induce bilayer instability. During ischemia a transbilayer reorganization of sarcolemmal PE is observed, and results have been published that suggest a lateral phase separation in the inner sarcolemmal leaflet phospholipids. These reorganizations and the subsequent expression of the nonbilayer behavior of PE are proposed to

form the basis for sarcolemma destabilization and destruction. Lowering the PE content of myocytes, especially of the sarcolemma, is then expected to attenuate myocyte damage after simulated ischemia or metabolic inhibition. Culturing neonatal rat heart myocytes in the presence of N,N-dimethylethanolamine resulted in the synthesis of the bilayer-preferring N,N-dimethyl-PE and a lowering of the ratio between nonbilayer- and bilayer-preferring phospholipids from 0.58 to 0.30. This change in phospholipid composition did not impair cell functioning but did result in a strong attenuation of cell damage on ischemia or metabolic inhibition. A good correlation between the nonbilayer-preferring phospholipid content and the degree of cell damage was obtained ( $r = 0.98$ ). These results provide further evidence that physicochemical properties of the sarcolemmal phospholipids play a crucial role in the sarcolemmal disruption during prolonged ischemia and/or reperfusion.

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### **Pharmacological interventions against aging through the cell plasma membrane: a review of the experimental results obtained in animals and humans.**

As was shown in a recent review by this author (*Ann NY Acad Sci.*, 928: 187-199, 2001), oxyradicals cannot be considered only as harmful by-products of the oxidative metabolism, but living cells and organisms implicitly require their production. This idea is supported by numerous facts and arguments, the most important of which is that the complete inhibition of the oxyradical production by KCN (or by any block of respiration) kills the living organisms long before the energy reserves would be exhausted. This new theoretical approach not only helps our understanding of the normal functions of the living organisms, such as the basic memory mechanisms in the brain cells, but also helps in identifying the site-specific, radical-induced damaging mechanisms that represent the undesirable side effects of oxygen free radicals. First of all, these effects make the cell plasma membrane vulnerable and cause a series of intracellular functional disorders, as described by the membrane hypothesis of aging (MHA). The logical way for any antiaging intervention therefore should be to increase the available number of loosely bound electrons inside the plasma membrane that are easily accessible for OH(\*) free radical scavenging. The present review summarizes the available knowledge regarding the theory of the use of membrane-related antiaging pharmaca, like centrophenoxine (CPH), tested in both animal experiments and human clinical trials. A modified, developed version of CPH coded as BCE-001 is also reported.

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### **Split face study on the cutaneous tensile effect of 2-dimethylaminoethanol (deanol) gel.**

**BACKGROUND/AIMS:** Beyond subjective assessments, the effect of skin tensors is difficult to assess. The present 2-phase randomized double-blind split face study was designed to compare the effect of a gel containing 3% 2-dimethylaminoethanol (deanol, DMAE) with the same formulation without DMAE. **METHODS:** In a first pilot study, sensorial assessments and measures of the skin distension under suction were performed in eight volunteers. In a second study conducted in 30 volunteers, shear wave propagation was measured. **RESULTS:** Large interindividual variations precluded any significant finding in the first study. The DMAE formulation showed, however, a significant effect characterized by increased shear wave velocity in the direction where the mechanical anisotropy of skin showed looseness. **CONCLUSION:** The DMAE formulation under investigation increased skin firmness.

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