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Pomegranate Fruit Extract Impairs Invasion and Motility in Human Breast Cancer

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ESSENCE OF ARTICLE

“Pomegranate fruit extracts (PFEs) possess polyphenolic and other compounds with antiproliferative, pro-apoptotic and anti-inflammatory effects in prostate, lung, and other cancers. Because nuclear transcription factor- κ B (NF- κ B) is known to regulate cell survival, proliferation, tumorigenesis, and inflammation, it was postulated that PFEs may exert anticancer effects at least in part by modulating NF- κ B activity.”

ARTICLE

Purpose. Pomegranate fruit extracts (PFEs) possess polyphenolic and other compounds with antiproliferative, pro-apoptotic and anti-inflammatory effects in prostate, lung, and other cancers. Because nuclear transcription factor- κ B (NF- κ B) is known to regulate cell survival, proliferation, tumorigenesis, and inflammation, it was postulated that PFEs may exert anticancer effects at least in part by modulating NF- κ B activity. **Experimental design.** The authors investigated the effect of a novel, defined PFE consisting of both fermented juice and seed oil on the NF- κ B pathway, which is constitutively active in aggressive breast cancer cell lines. The effects of the PFE on NF- κ B—regulated cellular processes such as cell survival, proliferation, and invasion were also examined. **Results.** Analytical characterization of the bioactive components of the PFE revealed active constituents, mainly ellagitannins and phenolic acids in the aqueous PFE and conjugated octadecatrienoic acids in the lipid PFE derived from seeds. The aqueous PFE dose-dependently inhibited NF- κ B—dependent reporter gene expression associated with proliferation, invasion, and motility in aggressive breast cancer phenotypes while decreasing RhoC and RhoA protein expression. **Conclusion.** Inhibition of motility and invasion by PFEs, coincident with suppressed RhoC and RhoA protein expression, suggests a role for these defined extracts in lowering the metastatic potential of aggressive breast cancer species.

Key Words: breast cancer • cancer prevention • in vitro studies • *Punica granatum*

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Protective Effects of l- and d-Carnosine on α -Crystallin Amyloid Fibril Formation: Implications for Cataract Disease

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ESSENCE OF ARTICLE

“Moreover, we have found a disassembling effect of carnosine on α -crystallin amyloid fibrils. Finally, we show the ability of carnosine to restore most of the lens transparency in organ-cultured rat lenses exposed to similar denaturing conditions that were used for the in vitro experiments.”

ARTICLE

Abstract

Mildly denaturing conditions induce bovine α -crystallin, the major structural lens protein, to self-assemble into fibrillar structures in vitro. The natural dipeptide l-carnosine has been shown to have potential protective and therapeutic significance in many diseases. Carnosine derivatives have been proposed as potent agents for ophthalmic therapies of senile cataracts and diabetic ocular complications. Here we report the inhibitory effect induced by the peptide (l- and d-enantiomeric form) on α -crystallin fibrillation and the almost complete restoration of the chaperone activity lost after denaturant and/or heat stress. Scanning force microscopy (SFM), thioflavin T, and a turbidimetry assay have been used to determine the morphology of α -crystallin aggregates in the presence and absence of carnosine. DSC and a near-UV CD assay evidenced that the structural precursors of amyloid fibrils are polypeptide chain segments that lack stable structural elements. Moreover, we have found a disassembling effect of carnosine on α -crystallin amyloid fibrils. Finally, we show the ability of carnosine to restore most of the lens transparency in organ-cultured rat lenses exposed to similar denaturing conditions that were used for the in vitro experiments.

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JAMA. 2006;295:655-666.

Low-Fat Dietary Pattern and Risk of Cardiovascular Disease

The Women's Health Initiative Randomized Controlled Dietary Modification Trial

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ESSENCE OF ARTICLE

Conclusions

“Over a mean of 8.1 years, a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women and achieved only modest effects on CVD risk factors, suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk. “

Context Multiple epidemiologic studies and some trials have linked diet with cardiovascular disease (CVD) prevention, but long-term intervention data are needed.

Objective To test the hypothesis that a dietary intervention, intended to be low in fat and high in vegetables, fruits, and grains to reduce cancer, would reduce CVD risk.

Design, Setting, and Participants Randomized controlled trial of 48 835 postmenopausal women aged 50 to 79 years, of diverse backgrounds and ethnicities, who participated in the Women's Health Initiative Dietary Modification Trial. Women were randomly assigned to an intervention (19 541 [40%]) or comparison group (29 294 [60%]) in a free-living setting. Study enrollment occurred between 1993 and 1998 in 40 US clinical centers; mean follow-up in this analysis was 8.1 years.

Intervention Intensive behavior modification in group and individual sessions designed to reduce total fat intake to 20% of calories and increase intakes of vegetables/fruits to 5 servings/d and grains to at least 6 servings/d. The comparison group received diet-related education materials.

Main Outcome Measures Fatal and nonfatal coronary heart disease (CHD), fatal and nonfatal stroke, and CVD (composite of CHD and stroke).

Results By year 6, mean fat intake decreased by 8.2% of energy intake in the intervention vs the comparison group, with small decreases in saturated (2.9%), monounsaturated (3.3%), and

polyunsaturated (1.5%) fat; increases occurred in intakes of vegetables/fruits (1.1 servings/d) and grains (0.5 serving/d). Low-density lipoprotein cholesterol levels, diastolic blood pressure, and factor VIIc levels were significantly reduced by 3.55 mg/dL, 0.31 mm Hg, and 4.29%, respectively; levels of high-density lipoprotein cholesterol, triglycerides, glucose, and insulin did not significantly differ in the intervention vs comparison groups. The numbers who developed CHD, stroke, and CVD (annualized incidence rates) were 1000 (0.63%), 434 (0.28%), and 1357 (0.86%) in the intervention and 1549 (0.65%), 642 (0.27%), and 2088 (0.88%) in the comparison group. The diet had no significant effects on incidence of CHD (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.90-1.06), stroke (HR, 1.02; 95% CI, 0.90-1.15), or CVD (HR, 0.98; 95% CI, 0.92-1.05). Excluding participants with baseline CVD (3.4%), the HRs (95% CIs) for CHD and stroke were 0.94 (0.86-1.02) and 1.02 (0.90-1.17), respectively. Trends toward greater reductions in CHD risk were observed in those with lower intakes of saturated fat or trans fat or higher intakes of vegetables/fruits.

Conclusions Over a mean of 8.1 years, a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women and achieved only modest effects on CVD risk factors, suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk.

Clinical Trials Registration [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT00000611

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JAMA. 2006;295:629-642.

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Low-Fat Dietary Pattern and Risk of Colorectal Cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial

Shirley A. A. Beresford, Karen C. Johnson, Cheryl Ritenbaugh, Norman L. Lasser, Linda G. Snetselaar, Henry R. Black, Garnet L. Anderson, Annlouise R. Assaf, Tamsen Bassford, Deborah Bowen, Robert L. Brunner, Robert G. Brzyski, Bette Caan, Rowan T. Chlebowski, Margery Gass, Rosanne C. Harrigan, Jennifer Hays, David Heber, Gerardo Heiss, Susan L. Hendrix, Barbara V. Howard, Judith Hsia, F. Allan Hubbell, Rebecca D. Jackson, Jane Morley Kotchen, Lewis H. Kuller, Andrea Z. LaCroix, Dorothy S. Lane, Robert D. Langer, Cora E. Lewis, JoAnn E. Manson, Karen L. Margolis, Yasmin Mossavar-Rahmani, Judith K. Ockene, Linda M. Parker, Michael G. Perri, Lawrence Phillips, Ross L. Prentice, John Robbins, Jacques E. Rossouw, Gloria E. Sarto, Marcia L. Stefanick, Linda Van Horn, Mara Z. Vitolins, Jean Wactawski-Wende, Robert B. Wallace, and Evelyn Whitlock

JAMA. 2006;295:643-654.

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Cheryl A. M. Anderson and Lawrence J. Appel

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JAMA. 2006;295:643-654.

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ESSENCE OF ARTICLE

“Conclusion In this study, a low-fat dietary pattern intervention did not reduce the risk of colorectal cancer in postmenopausal women during 8.1 years of follow-up. “

ARTICLE

Context

Observational studies and polyp recurrence trials are not conclusive regarding the effects of a low-fat dietary pattern on risk of colorectal cancer, necessitating a primary prevention trial.

Objective

To evaluate the effects of a low-fat eating pattern on risk of colorectal cancer in postmenopausal women.

Design, Setting, and Participants

The Women’s Health Initiative Dietary Modification Trial, a randomized controlled trial conducted in 48 835 postmenopausal women aged 50 to 79 years recruited between 1993 and 1998 from 40 clinical centers throughout the United States.

Interventions

Participants were randomly assigned to the dietary modification intervention (n = 19 541; 40%) or the comparison group (n = 29 294; 60%).The intensive behavioral modification program aimed to motivate and support reductions in dietary fat, to increase consumption of vegetables and fruits, and to increase grain servings by using group sessions, self-monitoring techniques, and other tailored and targeted strategies. Women in the comparison group continued their usual eating pattern.

Main Outcome Measure

Invasive colorectal cancer incidence.

Results

A total of 480 incident cases of invasive colorectal cancer occurred during a mean follow-up of 8.1 (SD, 1.7) years. Intervention group participants significantly reduced their percentage of energy from fat by 10.7% more than did the comparison group at 1 year, and this difference between groups was mostly maintained (8.1% at year 6). Statistically significant increases in vegetable, fruit, and grain servings were also made. Despite these dietary changes, there was no evidence that the intervention reduced the risk of invasive colorectal cancer during the follow-up period. There were 201 women with invasive colorectal cancer (0.13% per year) in the intervention group and 279 (0.12% per year) in the comparison group (hazard ratio, 1.08; 95% confidence interval, 0.90-1.29). Secondary analyses suggested potential interactions with baseline aspirin use and combined estrogen-progestin use status (P = .01 for each). Colorectal examination rates, although not protocol defined, were comparable between the intervention and comparison groups. Similar results were seen in analyses adjusting for adherence to the intervention.

Conclusion

In this study, a low-fat dietary pattern intervention did not reduce the risk of colorectal cancer in postmenopausal women during 8.1 years of follow-up.

Clinical Trials Registration ClinicalTrials.gov Identifier: NCT00000611

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Low-Fat Dietary Pattern and Risk of Cardiovascular Disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial

Howard et al.

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ESSENCE OF ARTICLE

"Comment: These results demonstrate a continuum of risk for developing type 2 diabetes, even for patients whose fasting plasma glucose levels fall within the so-called normal range. The findings could serve as an incentive for patients with fasting glucose levels in the 90s to lose weight and increase exercise."

ARTICLE

High-Normal Fasting Glucose and Diabetes Risk

Patients with fasting plasma glucose levels of 100 to 125 mg/dL are considered to have "impaired fasting glucose" because they are at increased risk for eventually developing type 2 diabetes. In this study, Israeli researchers sought to determine whether a gradient of risk exists even among people with normal fasting glucose levels.

The study included 13,163 male military personnel (age, 26-45 years) with baseline fasting plasma glucose levels in the normal range (<100 mg/dL). During an average follow-up of 5.7 years, 208 men developed type 2 diabetes. The risk for diabetes increased progressively across quintiles of baseline fasting glucose: For example, the risk ranged from 0.8% among men whose baseline fasting glucose was in the lowest quintile (50–81 mg/dL) to 2.8% among those whose baseline fasting glucose was in the highest quintile (95–99 mg/dL). Even in a multivariate analysis that adjusted for potentially confounding variables such as body-mass index and family history, fasting glucose in the upper end of the normal range was associated independently with an increased risk for diabetes. Nevertheless, obesity did augment the risk.

Comment: These results demonstrate a continuum of risk for developing type 2 diabetes, even for patients whose fasting plasma glucose levels fall within the so-called normal range. The findings could serve as an incentive for patients with fasting glucose levels in the 90s to lose weight and increase exercise.

— Allan S. Brett, MD

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Normal Fasting Plasma Glucose Levels and Type 2 Diabetes in Young Men

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Editorial

by Arky, R. A.

ESSENCE OF ARTICLE

"A multivariate model, adjusted for age, family history of diabetes, body-mass index, physical-activity level, smoking status, and serum triglyceride levels, revealed a progressively increased risk of type 2 diabetes in men with fasting plasma glucose levels of 87 mg per deciliter (4.83 mmol per liter) or more, as compared with those whose levels were in the bottom quintile (less than 81 mg per deciliter [4.5 mmol per liter], P for trend <0.001)."

ARTICLE

ABSTRACT

Background The normal fasting plasma glucose level was recently defined as less than 100 mg per deciliter (5.55 mmol per liter). Whether higher fasting plasma glucose levels within this range independently predict type 2 diabetes in young adults is unclear.

Methods We obtained blood measurements, data from physical examinations, and medical and lifestyle information from men in the Israel Defense Forces who were 26 to 45 years of age.

Results A total of 208 incident cases of type 2 diabetes occurred during 74,309 person-years of follow-up (from 1992 through 2004) among 13,163 subjects who had baseline fasting plasma glucose levels of less than 100 mg per deciliter. A multivariate model, adjusted for age, family history of diabetes, body-mass index, physical-activity level, smoking status, and serum triglyceride levels, revealed a progressively increased risk of type 2 diabetes in men with fasting plasma glucose levels of 87 mg per deciliter (4.83 mmol per liter) or more, as compared with those whose levels were in the bottom quintile (less than 81 mg per deciliter [4.5 mmol per liter], P for trend <0.001). In multivariate models, men with serum triglyceride levels of 150 mg per deciliter (1.69 mmol per liter) or more, combined with fasting plasma glucose levels of 91 to 99 mg per deciliter (5.05 to 5.50 mmol per liter), had a hazard ratio of 8.23 (95 percent confidence interval, 3.6 to 19.0) for diabetes, as compared with men with a combined triglyceride level of less than 150 mg per deciliter and fasting glucose levels of less than 86 mg per deciliter (4.77 mmol per liter). The joint effect of a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more and a fasting plasma glucose level of 91 to 99 mg per deciliter resulted in a hazard ratio of 8.29 (95 percent confidence interval, 3.8 to 17.8), as compared with a body-mass index of less than 25 and a fasting plasma glucose level of less than 86 mg per deciliter.

Conclusions Higher fasting plasma glucose levels within the normoglycemic range constitute an independent risk factor for type 2 diabetes among young men, and such levels may help, along with body-mass index and triglyceride levels, to identify apparently healthy men at increased risk for diabetes.

Source Information

From the Medical Corps Headquarters (A.T., E.I., T.S., I.K.) and the Center for Medical Services (D.T.-M.), Israel Defense Forces Medical Corps; the Department of Internal Medicine A, Sheba Medical Center, Tel-Hashomer (A.T.); the S. Daniel Abraham International Center for Health and Nutrition (I.S.,

A.R.), the Department of Epidemiology (I.S.), and the Department of Clinical Biochemistry (A.R.), Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva; and the Department of Internal Medicine A, Meir Hospital, Sapir Medical Center, Kfar-Sava (D.P.) — all in Israel.

Drs. Tirosh and Shai contributed equally to the study.

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PMID: 7572907 [PubMed - indexed for MEDLINE]

Am J Gastroenterol. 1995 Oct;90(10):1847-52. [Related Articles](#), [Links](#)

Serum cryoglobulin and chronic hepatitis C virus disease among Japanese patients.

Tanaka K, Aiyama T, Imai J, Morishita Y, Fukatsu T, Kakumu S.

Department of Internal Medicine, Nagoya University School of Medicine, Japan.

ESSENCE OF ARTICLE

“These findings suggest that HCV is a major cause of cryoglobulins and advanced liver damage.”

ARTICLE

OBJECTIVES: Hepatitis C virus (HCV)-associated mixed cryoglobulins appear to be detected often in hepatitis C-related chronic liver disease. The association of the two phenomenon among Japanese patients is the subject of the present study. **METHODS:** Serum levels of total hemolytic complement (CH50) and anti-C3d-binding immune complex, as well as the prevalence of cryoglobulins, were studied in 213 patients with chronic liver disease (hepatitis C, 155; hepatitis B, 58). Cryoprecipitates were tested for anti-HCV Ab and HCV RNA. **RESULTS:** CH50 activity was significantly lower in patients with hepatitis C than in those with hepatitis B except in responders to interferon who showed a sustained loss of HCV RNA. Cryoglobulins were detected in 24 (37%) of 65 patients with hepatitis C; they generally consisted of polyclonal immunoglobulins but one case. Cryoglobulins were more frequently observed in cirrhotic patients and in those with a longer duration of disease. Cryoglobulinemia-related clinical signs such as vasculitis occurred in only three cases. Patients with cryoglobulins had lower CH50 activity and higher immune complex values than those without cryoglobulins. Anti-HCV Ab and HCV RNA were detected in all cryoprecipitates tested. **CONCLUSIONS:** These findings suggest that HCV is a major cause of

cryoglobulins and advanced liver damage. However, serum cryoglobulins with polyclonal immunoglobulins appear to be less frequent among Japanese patients than among those studied in Western countries.

MeSH Terms:

- Adult
- Aged
- Carrier State/blood
- Chronic Disease
- Complement Hemolytic Activity Assay
- Cryoglobulins/analysis*
- Female
- Hepacivirus/genetics
- Hepacivirus/isolation & purification
- Hepatitis B/blood
- Hepatitis C/blood*
- Hepatitis C/immunology
- Hepatitis C/therapy
- Hepatitis C/virology
- Hepatitis C Antibodies/analysis
- Humans
- Interferon-alpha/therapeutic use
- Japan
- Male
- Middle Aged
- Prospective Studies
- RNA, Viral/analysis
- Research Support, Non-U.S. Gov't

Substances:

- Cryoglobulins
- Hepatitis C Antibodies
- Interferon-alpha
- RNA, Viral

PMID: 7572907 [PubMed - indexed for MEDLINE]

PMID: 8380394 [PubMed - indexed for MEDLINE]

Gastroenterology. 1993 Jan;104(1):272-7.

- Gastroenterology. 1993 Jan;104(1):320-3.

Cryoglobulinemia with vasculitis associated with hepatitis C virus infection.

Marcellin P, Descamps V, Martinot-Peignoux M, Larzul D, Xu L, Boyer N, Pham BN, Crickx B, Guillemin L, Belaich S, et al.

Service d'Hepatology and INSERM U 24, Hopital Beaujon, Clichy, France.

ESSENCE OF ARTICLE

“HCV infection is responsible for the production of cryoglobulinemia and vasculitis. It is proposed that HCV infection is a cause of cryoglobulinemia associated with chronic hepatitis.”

ARTICLE

Essential mixed cryoglobulinemia is frequently associated with chronic hepatitis. This report presents four cases of cryoglobulinemia with vasculitis associated with chronic hepatitis related to hepatitis C virus infection. Hepatitis C virus infection was ascertained in the four patients by both the presence in the serum of anti-HCV antibodies detected by the four-antigen recombinant immunoblot assay and of HCV RNA detected by polymerase chain reaction. In two patients tested, anti-HCV antibodies were not detected after centrifugation in the purified cryoglobulin but were detected in the supernatant. HCV RNA was detected in the purified cryoglobulin in all four patients and was detected in the supernatant in three patients. In one patient receiving recombinant interferon alfa, serum aminotransferases normalized and cryoglobulin disappeared; in another patient receiving recombinant interferon alfa, serum aminotransferases remained high and the cryoglobulin persisted. The presence of HCV RNA in the cryoglobulin and the parallelism of the changes of the cryoglobulinemia and of the serum aminotransferases during recombinant interferon alfa administration suggest that HCV infection is

responsible for the production of cryoglobulinemia and vasculitis. It is proposed that HCV infection is a cause of cryoglobulinemia associated with chronic hepatitis.

Publication Types:

- Case Reports

MeSH Terms:

- Adult
- Aged
- Alanine Transaminase/blood
- Aspartate Aminotransferases/blood
- Cryoglobulinemia/complications*
- Enzyme-Linked Immunosorbent Assay
- Female
- Hepacivirus/genetics
- Hepacivirus/immunology
- Hepatitis Antibodies/analysis
- Hepatitis C/complications*
- Hepatitis C/immunology
- Hepatitis C/therapy
- Humans
- Immunoblotting
- Interferon-alpha/therapeutic use
- Male
- Middle Aged
- Polymerase Chain Reaction
- RNA, Viral/analysis
- Recombinant Proteins

- Vasculitis/complications*

Substances:

- Hepatitis Antibodies
- Interferon-alpha
- RNA, Viral
- Recombinant Proteins
- Aspartate Aminotransferases
- Alanine Transaminase

PMID: 8380394 [PubMed - indexed for MEDLINE]

PMID: 4009970 [PubMed - indexed for MEDLINE]

Jpn Heart J. 1985 Mar;26(2):289-96. Related Articles, Links

Effects of pantethine on action potential of canine papillary muscle during hypoxic perfusion.

Hayashi H, Kobayashi A, Terada H, Nagao B, Nishiyama T, Kamikawa T, Yamazaki N.

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ESSENCE OF ARTICLE

“Pantethine, which is known to be converted to coenzyme A, has been reported to have antiarrhythmic action on experimental cardiac arrhythmias.”

ARTICLE

Pantethine, which is known to be converted to coenzyme A, has been reported to have antiarrhythmic action on experimental cardiac arrhythmias. Using standard microelectrode techniques, the electrophysiological effects of pantethine under hypoxic (95% N₂ + 5% CO₂) perfusion were studied. Hypoxia decreased resting membrane potential, action potential amplitude and maximum velocity of phase 0 and shortened action potential duration and effective refractory period. Application of pantethine 5 X 10⁽⁻³⁾ Gm/ml under hypoxic perfusion prolonged action potential duration and effective refractory period significantly. Prolongation of action potential duration by pantethine might be caused by an

increase in intracellular ATP. The findings in this study could be an explanation of the possible antiarrhythmic effects of pantethine.

PMID: 4009970 [PubMed - indexed for MEDLINE]

Journal of American Physicians and Surgeons

<http://www.jpands.org/vol11no3/colpo.pdf>

Colpo A.

LDL Cholesterol: "Bad" Cholesterol, or Bad Science?

Fall 2005; 10 (3): 83-89.

ESSENCE OF ARTICLE

ABSTRACT

“The belief that low-density lipoprotein (LDL) cholesterol causes atherosclerosis and subsequent heart disease is a fundamental precept of modern medicine. Therapies aimed at reducing serum LDL cholesterol are currently considered to be an essential element of any attempt to prevent coronary heart disease (CHD).

While it currently enjoys widespread acceptance among health authorities and medical practitioners, numerous lines of evidence raise questions about the LDL hypothesis. Native LDL cholesterol is a vitally important substance and is not in any way atherogenic.

Statin drugs, the only LDL-lowering agents shown to have clinical benefit in reducing the incidence of heart disease, have been shown to exert their benefits via mechanisms totally unrelated to LDL cholesterol reduction.

A potential causative role in atherosclerosis and heart disease has indeed been detected for oxidized LDL, but this form of LDL shows no correlation with serum levels of native LDL. Rather, individual antioxidant status appears to be a key factor influencing serum concentrations of oxidized LDL.”

“The change in CRP levels associated with pravastatin treatment was not correlated with the reduction in LDL cholesterol levels. In the Effects of Atorvastatin vs Simvastatin on Atherosclerosis Progression (ASAP) study, baseline CRP values were similar among patients given either simvastatin (40 mg/d) or atorvastatin (80 mg/d), but declined over the next 2 years to a greater extent in the latter group. A significant correlation was found between the decrease of CRP and reduction in intima media thickness (IMT) of carotid artery segments. No correlation was observed between change in CRP and change in lipids”

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report/2004/financial/financial2004.pdf. Accessed Jun 19, 2005.

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