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Interrelationships Among HDL Metabolism, Aging, and Atherosclerosis

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ESSENCE OF ARTICLE

“Cross-sectionally, by contrast, HDL levels do not change much or even slightly increase with age, suggesting that only people with still high HDL concentrations survive. A selection bias by HDL lowering genetic variation may explain why HDL deficiency is extremely rare among centenarians. Vice versa, HDL may modulate the aging process, not only by its well-known antiatherogenic effects, eg, its

ability to remove cellular lipids and by antiatherogenic pleiotropic effects on cell survival, but possibly also by direct interfering with aging signaling or survival factor KLOTHO”

ARTICLE

Abstract—HDL plasma concentrations decline with age in prospective studies. Decline in HDL concentration and function may occur secondary because of hormonal changes, inflammatory processes, and diabetes mellitus. Beyond these effects specific aging processes may be involved. Replicative aging, the telomere-driven loss of divisional capacity, is a species-specific aging mechanism that may decrease HDL concentration and function. Cross-sectionally, by contrast, HDL levels do not change much or even slightly increase with age, suggesting that only people with still high HDL concentrations survive. A selection bias by HDL lowering genetic variation may explain why HDL deficiency is extremely rare among centenarians. Vice versa, HDL may modulate the aging process, not only by its well-known antiatherogenic effects, eg, its ability to remove cellular lipids and by antiatherogenic pleiotropic effects on cell survival, but possibly also by direct interfering with aging signaling or survival factor KLOTHO. Most of the current findings, however, are based on cell culture and selected animal experiments and await further confirmation by appropriate in vivo models.

Key words: atherosclerosis • aging • high density lipoproteins • KLOTHO 4

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Neuro Endocrinol Lett. 2008 Dec;29(6):902-10.

Normalization of leaky gut in chronic fatigue syndrome (CFS) is accompanied by a clinical improvement: effects of age, duration of illness and the translocation of LPS from gram-negative bacteria.

Maes M, Leunis JC.

MCare4U Outpatient Clinics, Belgium.

ESSENCE OF ARTICLE

“The results show that normalization of the IgA and IgM responses to translocated LPS may predict clinical outcome in CFS. The results support the view that a weakened tight junction barrier with subsequent gut-derived inflammation is a novel pathway in CFS and that it is a new target for drug development in CFS. Meanwhile, CFS patients with leaky gut can be treated with specific NAIOSs and a leaky gut diet.”

ARTICLE

BACKGROUND: There is now evidence that an increased translocation of LPS from gram negative bacteria with subsequent gut-derived inflammation, i.e. induction of systemic inflammation and oxidative & nitrosative stress (IO&NS), is a new pathway in chronic fatigue syndrome (CFS).

METHODS: The present study examines the serum concentrations of IgA and IgM to LPS of gram-negative enterobacteria, i.e. *Hafnia Alvei*; *Pseudomonas Aeruginosa*, *Morganella Morganii*, *Pseudomonas Putida*, *Citrobacter Koseri*, and *Klebsiella Pneumoniae* in CFS patients both before and after intake of natural anti-inflammatory and anti-oxidative substances (NAIOSs), such as glutamine, N-acetyl cysteine and zinc, in conjunction with a leaky gut diet during 10-14 months. We measured the above immune variables as well as the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale in 41 patients with CFS before and 10-14 months after intake of NAIOSs.

RESULTS: Subchronic intake of those NAIOSs significantly attenuates the initially increased IgA and IgM responses to LPS of gram negative bacteria. Up to 24 patients showed a significant clinical improvement or remission 10-14 months after intake of NAIOSs. A good clinical response is significantly predicted by attenuated IgA and IgM responses to LPS, the younger age of the patients, and a shorter duration of illness (< 5 years).

DISCUSSION: The results show that normalization of the IgA and IgM responses to translocated LPS may predict clinical outcome in CFS. The results support the view that a weakened tight junction barrier with subsequent gut-derived inflammation is a novel pathway in CFS and that it is a new target for drug development in CFS. Meanwhile, CFS patients with leaky gut can be treated with specific NAIOSs and a leaky gut diet.

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Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms.

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ESSENCE OF ARTICLE

“Activation of IO&NS pathways is the key phenomenon underpinning chronic fatigue syndrome (CFS): intracellular inflammation, with an increased production of nuclear factor kappa beta (NFkappabeta), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS); and damage caused by O&NS to membrane fatty acids and functional proteins.”

ARTICLE

PURPOSE OF REVIEW: The aim of this paper is to review recent findings on inflammatory and oxidative and nitrosative stress (IO&NS) pathways in chronic fatigue and somatization disorder.

RECENT FINDINGS: Activation of IO&NS pathways is the key phenomenon underpinning chronic fatigue syndrome (CFS): intracellular inflammation, with an increased production of nuclear factor kappa beta (NFkappabeta), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS); and damage caused by O&NS to membrane fatty acids and functional proteins. These IO&NS pathways are induced by a number of trigger factors, for example psychological stress, strenuous exercise, viral infections and an increased translocation of LPS from gram-bacteria (leaky gut). The 'psychosomatic' symptoms experienced by CFS patients are caused by intracellular inflammation (aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection); damage caused by O&NS (aches and pain, muscular tension and fatigue); and gut-derived inflammation (complaints of irritable bowel). Inflammatory pathways (monocytic activation) are also detected in somatizing disorder.

SUMMARY: 'Functional' symptoms, as occurring in CFS and somatization, have a genuine organic cause, that is activation of peripheral and central IO&NS pathways and gut-derived inflammation. The development of new drugs, aimed at treating those disorders, should target these IO&NS pathways.

Publication Types:

- Review

PMID: 19127706 [PubMed - indexed for MEDLINE]

PMID: 18580840 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2008 Jun;29(3):287-91.

The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression.

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ESSENCE OF ARTICLE

“This paper hypothesizes that inflammatory, oxidative and nitrosative (IO&NS) pathways, and an increased translocation of LPS from gram-negative bacteria are causally related to depression following external (psychological) and internal (organic) stressors and that IO&NS pathways are novel targets for antidepressant development.”

ARTICLE

This paper hypothesizes that inflammatory, oxidative and nitrosative (IO&NS) pathways, and an increased translocation of LPS from gram-negative bacteria are causally related to depression following external (psychological) and internal (organic) stressors and that IO&NS pathways are novel targets for antidepressant development. We review that depression is accompanied by an inflammatory reaction as indicated by an increased production of pro-inflammatory cytokines, such as interleukin-1beta (IL-1beta), IL-6, tumour necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN)-gamma. These cytokines are

stress-sensitive and may cause depressive behaviors. The latter may be induced by an increased catabolism of tryptophan, the precursor of serotonin, to neurotoxic TRYCATs (tryptophan catabolites along the indoleamine oxidase pathway). Inflammatory biomarkers are detected in animal models of depression. Newly developed animal models of depression are based on induced inflammation. Most if not all antidepressants have specific anti-inflammatory effects. Anti-inflammatory compounds may augment the clinical efficacy of antidepressants. Depression is also accompanied by an IgM-related (auto)immune response directed against disrupted lipid membrane components, such as phosphatidylinositol, by-products of lipid peroxidation, e.g. azelaic acid and malondialdehyde, and NO-modified amino-acids, which are normally not detected by the immune system but due to damage caused by O&NS have become immunogenic. Increased translocation of lipopolysaccharide from gram-negative bacteria, which may be induced by internal and external stressors, may further aggravate the induced IO&NS pathways.

Publication Types:

- Review

PMID: 18580840 [PubMed - indexed for MEDLINE]

PMID: 18283240 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2008 Feb;29(1):117-24.

The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression.

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ESSENCE OF ARTICLE

“It is suggested that the increased LPS translocation may mount an immune response and thus IRS activation in some patients with MDD and may induce specific "sickness behaviour" symptoms. It is suggested that patients with MDD should be checked for leaky gut by means of the IgM and IgA panel used in the present study and accordingly should be treated for leaky gut.”

ARTICLE

There is now evidence that major depression (MDD) is accompanied by an activation of the inflammatory response system (IRS) and that pro-inflammatory cytokines and lipopolysaccharide (LPS) may induce depressive symptoms. The aim of the present study was to examine whether an increased gastrointestinal permeability with an increased translocation of LPS from gram negative bacteria may play a role in the pathophysiology of MDD. Toward this end, the present study examines the serum concentrations of IgM and IgA against LPS of the gram-negative enterobacteria, *Hafnia Alvei*, *Pseudomonas Aeruginosa*, *Morganella Morganii*, *Pseudomonas Putida*, *Citrobacter Koseri*, and *Klebsiella Pneumoniae* in MDD

patients and normal controls. We found that the prevalences and median values for serum IgM and IgA against LPS of enterobacteria are significantly greater in patients with MDD than in normal volunteers. These differences are significant to the extent that a significant diagnostic performance is obtained, i.e. the area under the ROC curve is 90.1%. The symptom profiles of increased IgM and IgA levels are fatigue, autonomic and gastro-intestinal symptoms and a subjective feeling of infection. The results show that intestinal mucosal dysfunction characterized by an increased translocation of gram-negative bacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. It is suggested that the increased LPS translocation may mount an immune response and thus IRS activation in some patients with MDD and may induce specific "sickness behaviour" symptoms. It is suggested that patients with MDD should be checked for leaky gut by means of the IgM and IgA panel used in the present study and accordingly should be treated for leaky gut.

Publication Types:

- Controlled Clinical Trial
- Research Support, Non-U.S. Gov't

PMID: 18283240 [PubMed - indexed for MEDLINE]

PMID: 18063921 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2007 Dec;28(6):875-80.

Why fish oils may not always be adequate treatments for depression or other inflammatory illnesses: docosahexaenoic acid, an omega-3 polyunsaturated fatty acid, induces a Th-1-like immune response.

Maes M, Mihaylova I, Kubera M, Bosmans E.

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ESSENCE OF ARTICLE

“The results of the present study show that treatment with fish oils, containing DHA, should be avoided in the treatment of depression. Toward this end, highly concentrated and pure EPA seems to be indicated.”

ARTICLE

BACKGROUND: We have shown that a depletion of omega3 polysaturated fatty acids (PUFAs) plays a role in the pathophysiology of depression, in part because omega3 PUFAs have anti-inflammatory effects. omega3 PUFAs are frequently employed to treat depression. Most if not all antidepressants have negative immunoregulatory effects by decreasing the production of proinflammatory cytokines, such as interferon-

gamma (IFN γ) and/or increasing that of anti-inflammatory cytokines, such as interleukin10 (IL-10).
AIM: The aim of the present study was to examine the immunoregulatory effects of the omega3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and the omega6 PUFA, arachidonic acid (AA), on the production of interferon-gamma (IFN γ), interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF α).

METHODS: This study examines the ex vivo effects of EPA (4.5 microM, 9 microM, 18 microM and 45 microM), DHA (1.3 microM, 3 microM, 6 microM and 13 microM) and AA (8 microM, 16 microM, 32 microM and 80 microM) on the LPS + PHA-stimulated production of IFN γ , IL-10 and TNF α , and on the IFN γ /IL-10 production ratio. Results: We found that EPA did not have any significant effects on the above cytokines. DHA significantly increased the IFN γ /IL-10 production ratio, caused by a greater reduction in IL-10 than in IFN γ . AA significantly decreased TNF α production.

DISCUSSION: The results show that DHA induces a Th-1-like immune response and that AA has anti-inflammatory effects by decreasing the production of TNF α . Thus, the immune effects of omega3 PUFAs are not compatible with what is expected from antidepressive substances. The results of the present study show that treatment with fish oils, containing DHA, should be avoided in the treatment of depression. Toward this end, highly concentrated and pure EPA seems to be indicated.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 18063921 [PubMed - indexed for MEDLINE]

PMID: 17693979 [PubMed - indexed for MEDLINE]

: Neuro Endocrinol Lett. 2007 Aug;28(4):456-62.

Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta.

Maes M, Mihaylova I, Bosmans E.

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ESSENCE OF ARTICLE

“It is suggested that CFS patients should be treated with antioxidants, which inhibit the production of NF κ beta, such as curcumin, N-Acetyl-Cysteine, quercitin, silimarin, lipoic acid and omega-3 fatty acids.”

ARTICLE

There is now some evidence that chronic fatigue syndrome is accompanied by an activation of the inflammatory response system and by increased oxidative and nitrosative stress. Nuclear factor kappa beta (NFkappabeta) is the major upstream, intracellular mechanism which regulates inflammatory and oxidative stress mediators. In order to examine the role of NFkappabeta in the pathophysiology of CFS, this study examines the production of NFkappabeta p50 in unstimulated, 10 ng/mL TNF-alpha (tumor necrosis factor alpha) and 50 ng/mL PMA (phorbolmyristate acetate) stimulated peripheral blood lymphocytes of 18 unmedicated patients with CFS and 18 age-sex matched controls. The unstimulated (F=19.4, df=1/34, p=0.0002), TNF-alpha-(F=14.0, df=1/34, p=0.0009) and PMA-(F=7.9, df=1/34, p=0.008) stimulated production of NFkappabeta were significantly higher in CFS patients than in controls. There were significant and positive correlations between the production of NFkappabeta and the severity of illness as measured with the FibroFatigue scale and with symptoms, such as aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection. The results show that an intracellular inflammatory response in the white blood cells plays an important role in the pathophysiology of CFS and that previous findings on increased oxidative stress and inflammation in CFS may be attributed to an increased production of NFkappabeta. The results suggest that the symptoms of CFS, such as fatigue, muscular tension, depressive symptoms and the feeling of infection reflect a genuine inflammatory response in those patients. It is suggested that CFS patients should be treated with antioxidants, which inhibit the production of NFkappabeta, such as curcumin, N-Acetyl-Cysteine, quercetin, silimarín, lipoic acid and omega-3 fatty acids.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17693979 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2007 Dec;28(6):861-7.

Increased serum IgM antibodies directed against phosphatidyl inositol (Pi) in chronic fatigue syndrome (CFS) and major depression: evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression.

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Major depression and chronic fatigue syndrome (CFS) are accompanied by signs of oxidative and nitrosative stress (O&NS) and an inflammatory response. Phosphatidyl inositol (Pi) is thought to play a role in depression. The aim of the present study is to examine whether depression and CFS are characterized by an IgM-mediated immune response directed against Pi. Toward this end, this study examines the serum IgM antibodies directed against Pi in 14 patients with major depression, 14 patients with CFS, 14 subjects with partial CFS, and in 11 normal controls. We found that the prevalence and mean value for the serum IgM levels directed against Pi were significantly greater in patients with major depression and CFS than in normal controls and patients with partial CFS. There were significant and

positive correlations between serum IgM levels directed against Pi and two symptoms of the FibroFatigue Scale, i.e. fatigue and depression. The results show that an IgM-related immune response directed against Pi may occur in both depression and CFS and may play a role in the pathophysiology of the key symptom of CFS and major depression. It is suggested that the above disorders in Pi result from increased O&NS in both depression and CFS. Autoanti-Pi antibodies may have biological effects, for example, by changing inositol 1,4,5-triphosphate (IP3), phosphatidylinositol-4,5-bisphosphate (PIP2), diacylglycerol and phosphatidylinositol-3,4,5-triphosphate (PIP3) production, thus interfering with intracellular signalling processes. Future research in major depression and CFS should focus on the functional consequences of the immune responses directed against Pi.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18063934 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2007 Dec;28(6):739-44.

Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome.

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MCare4U Outpatient Clinics, Belgium. crc.mh@telenet.be

There is now evidence that chronic fatigue syndrome (CFS) is accompanied by an increased translocation of endotoxins from gram-negative enterobacteria through the gut wall, as demonstrated by increased prevalences and median values for serum IgM and IgA against the endotoxins of gram-negative enterobacteria. This condition can also be described as increased gut permeability or leaky gut and indicates intestinal mucosal dysfunction (IMD). Here we report a case of a 13 year old girl with CFS who showed very high values for serum IgM against the LPS of some enterobacteria and signs of oxidative and nitrosative stress, activation of the inflammatory response system, and IgG3 subclass deficiency. Upon treatment with specific antioxidants and a "leaky gut diet", which both aim to treat increased gut permeability, and immunoglobins intravenously, the increased translocation of the LPS of gram negative enterobacteria normalized and this normalization was accompanied by a complete remission of the CFS symptoms.

Publication Types:

- Case Reports

PMID: 18063928 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2007 Aug;28(4):456-62.

Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta.

Maes M, Mihaylova I, Bosmans E.

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There is now some evidence that chronic fatigue syndrome is accompanied by an activation of the inflammatory response system and by increased oxidative and nitrosative stress. Nuclear factor kappa beta (NFkappabeta) is the major upstream, intracellular mechanism which regulates inflammatory and oxidative stress mediators. In order to examine the role of NFkappabeta in the pathophysiology of CFS, this study examines the production of NFkappabeta p50 in unstimulated, 10 ng/mL TNF-alpha (tumor necrosis factor alpha) and 50 ng/mL PMA (phorbolmyristate acetate) stimulated peripheral blood lymphocytes of 18 unmedicated patients with CFS and 18 age-sex matched controls. The unstimulated ($F=19.4$, $df=1/34$, $p=0.0002$), TNF-alpha ($F=14.0$, $df=1/34$, $p=0.0009$) and PMA ($F=7.9$, $df=1/34$, $p=0.008$) stimulated production of NFkappabeta were significantly higher in CFS patients than in controls. There were significant and positive correlations between the production of NFkappabeta and the severity of illness as measured with the FibroFatigue scale and with symptoms, such as aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection. The results show that an intracellular inflammatory response in the white blood cells plays an important role in the pathophysiology of CFS and that previous findings on increased oxidative stress and inflammation in CFS may be attributed to an increased production of NFkappabeta. The results suggest that the symptoms of CFS, such as fatigue, muscular tension, depressive symptoms and the feeling of infection reflect a genuine inflammatory response in those patients. It is suggested that CFS patients should be treated with antioxidants, which inhibit the production of NFkappabeta, such as curcumin, N-Acetyl-Cysteine, quercetin, silimarin, lipoic acid and omega-3 fatty acids.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17693979 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2006 Oct;27(5):615-21.

Chronic fatigue syndrome is accompanied by an IgM-related immune response directed against neopitopes formed by oxidative or nitrosative damage to lipids and proteins.

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There is now some evidence that chronic fatigue syndrome (CFS) is accompanied by signs of oxidative stress and by a decreased antioxidant status. The aim of the present study was to examine whether CFS is accompanied by an immune response to neopitopes of a variety of modified lipids and proteins

indicating damage caused by oxidative and nitrosative stress. Toward this end we examined serum antibodies to fatty acids (oleic, palmitic and myristic acid), by-products of lipid peroxidation, i.e. azelaic acid and malondialdehyde (MDA), acetylcholine, S-farnesyl-L-cysteine, and N-oxide modified amino-acids in 14 patients with CFS, 14 subjects with partial CFS and 11 normal controls. We found that the prevalences and mean values for the serum IgM levels directed against oleic, palmitic and myristic acid, MDA, azelaic acid, S-farnesyl-L-cysteine, and the N-oxide derivatives, nitro-tyrosine, nitro-phenylalanine, nitro-arginine, nitro-tryptophan, and nitro-cysteinyl were significantly greater in CFS patients than in normal controls, whereas patients with partial CFS took up an intermediate position. There were significant and positive correlations between the serum IgM levels directed against fatty acids, MDA and azelaic acid and the above N-oxide-derivates and the severity of illness (as measured by the FibroFatigue scale) and symptoms, such as aches and pain, muscular tension and fatigue. The results show that CFS is characterized by an IgM-related immune response directed against disrupted lipid membrane components, by-products of lipid peroxidation, S-farnesyl-L-cysteine, and NO-modified amino-acids, which are normally not detected by the immune system but due to oxidative and nitrosative damage have become immunogenic.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 17159817 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2005 Dec;26(6):745-51.

In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation.

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M-Care4U Outpatient Clinics, and the Clinical Research Center for Mental Health, Antwerp, Belgium.

There is now evidence that major depression is accompanied by decreased levels of omega3 poly-unsaturated fatty acids (PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There is a strong comorbidity between major depression and chronic fatigue syndrome (CFS). The present study has been carried out in order to examine PUFA levels in CFS. In twenty-two CFS patients and 12 normal controls we measured serum PUFA levels using gas chromatography and mass spectrometry. We found that CFS was accompanied by increased levels of omega6 PUFAs, i.e. linoleic acid and arachidonic acid (AA), and mono-unsaturated fatty acids (MUFAs), i.e. oleic acid. The EPA/AA and total omega3/omega6 ratios were significantly lower in CFS patients than in normal controls. The omega3/omega6 ratio was significantly and negatively correlated to the severity of illness and some items of the FibroFatigue scale, i.e. aches and pain, fatigue and failing memory. The severity of illness was significantly and positively correlated to linoleic and arachidonic acid, oleic acid, omega9 fatty acids and

one of the saturated fatty acids, i.e. palmitic acid. In CFS subjects, we found significant positive correlations between the omega3/omega6 ratio and lowered serum zinc levels and the lowered mitogen-stimulated CD69 expression on CD3+, CD3+ CD4+, and CD3+ CD8+ T cells, which indicate defects in early T cell activation. The results of this study show that a decreased availability of omega3 PUFAs plays a role in the pathophysiology of CFS and is related to the immune pathophysiology of CFS. The results suggest that patients with CFS should respond favourably to treatment with--amongst other things--omega3 PUFAs, such as EPA and DHA.

Publication Types:

- Controlled Clinical Trial
- Research Support, Non-U.S. Gov't

PMID: 16380690 [PubMed - indexed for MEDLINE]

Neuro Endocrinol Lett. 2005 Oct;26(5):487-92.

Decreased dehydroepiandrosterone sulfate but normal insulin-like growth factor in chronic fatigue syndrome (CFS): relevance for the inflammatory response in CFS.

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There are a few reports that chronic fatigue syndrome (CFS) may be accompanied by changes in hormones, such as dehydroepiandrosterone (DHEA) and insulin-like growth factor (IGF1). This study examines the serum concentrations of DHEA-sulfate (DHEAS), IGF1 and IGF1 binding protein-3 (IGFBP3) in 20 patients with CFS and in 12 normal controls. The IGFBP3/IGF1 ratio was computed as an index for IGF1 availability. We found significantly lower serum DHEAS concentrations in CFS, but no significant differences either in IGF1 or the IGFBP3/IGF1 ratio between CFS patients and normal controls. The decrease in serum DHEAS was highly sensitive and specific for CFS. There were significant and positive correlations between serum DHEAS and serum zinc and the mitogen-induced expression of the CD69 molecule on CD3+CD8+ T cells (an indicator of early T cell activation). There was a significant and negative correlation between serum DHEAS and the increase in the serum alpha-2 protein fraction (an inflammatory marker). Serum IGF1, but not DHEAS, was significantly and inversely correlated to age. The results show that CFS is accompanied by lowered levels of DHEAS and that the latter may play a role in the immune (defect in the early activation of T cells) and the inflammatory pathophysiology of CFS.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16264414 [PubMed - indexed for MEDLINE]

Am J Cardiol. 2002 Dec 15;90(12):1368-70.

Comment in:

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Relation of levels of serum lipoproteins to depression after acute myocardial infarction.

Strik JJ, Lousberg R, Crijs HJ, Maes M, Honig A.

Department of Psychiatry, Academic Hospital Maastricht/University of Maastricht, Maastricht, The Netherlands.

PMID: 12480046 [PubMed - indexed for MEDLINE]

<http://cancerres.aacrjournals.org/cgi/content/abstract/66/24/12026>

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This Article

Epidemiology and Prevention

Anti-Aromatase Activity of Phytochemicals in White Button Mushrooms (*Agaricus bisporus*)

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ESSENCE OF ARTICLE

”Because only conjugated linoleic acid was found to inhibit the testosterone-dependent proliferation of MCF-7aro cells, the physiologically relevant aromatase inhibitors in mushrooms are most likely conjugated linoleic acid and its derivatives. The in vivo action of mushroom chemicals was shown using nude mice injected with MCF-7aro cells. The studies showed that mushroom extract decreased both tumor cell proliferation and tumor weight with no effect on rate of apoptosis. Therefore, our studies illustrate the anticancer activity in vitro and in vivo of mushroom extract and its major fatty acid constituents. (Cancer Res 2006; 66(24): 12026-34)”

ARTICLE

White button mushrooms (*Agaricus bisporus*) are a potential breast cancer chemopreventive agent, as they suppress aromatase activity and estrogen biosynthesis. Therefore, we evaluated the activity of mushroom extracts in the estrogen receptor–positive/aromatase-positive MCF-7aro cell line in vitro and in vivo. Mushroom extract decreased testosterone-induced cell proliferation in MCF-7aro cells but had no effect on MCF-10A, a nontumorigenic cell line. Most potent mushroom chemicals are soluble in ethyl acetate. The major active compounds found in the ethyl acetate fraction are unsaturated fatty acids such as linoleic acid, linolenic acid, and conjugated linoleic acid. The interaction of linoleic acid and conjugated linoleic acid with aromatase mutants expressed in Chinese hamster ovary cells showed that these fatty acids inhibit aromatase with similar potency and that mutations at the active site regions affect its interaction with these two fatty acids. Whereas these results suggest that these two compounds bind to the active site of aromatase, the inhibition kinetic analysis indicates that they are noncompetitive inhibitors with respect to androstenedione. Because only conjugated linoleic acid was found to inhibit the testosterone-dependent proliferation of MCF-7aro cells, the physiologically relevant aromatase inhibitors in mushrooms are most likely conjugated linoleic acid and its derivatives. The in vivo action of mushroom chemicals was shown using nude mice injected with MCF-7aro cells. The studies showed that mushroom extract decreased both tumor cell proliferation and tumor weight with no effect on rate of apoptosis. Therefore, our studies illustrate the anticancer activity in vitro and in vivo of mushroom extract and its major fatty acid constituents. (*Cancer Res* 2006; 66(24): 12026-34)

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1: *Nutr Cancer*. 2008;60(6):744-56. Links

White button mushroom (*Agaricus bisporus*) exhibits antiproliferative and proapoptotic properties and inhibits prostate tumor growth in athymic mice.

Adams LS, Phung S, Wu X, Ki L, Chen S.

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ESSENCE OF ARTICLE

” The data provided by this study illustrate the anticancer potential of phytochemicals in mushroom extract both in vitro and in vivo and supports the recommendation of white button mushroom as a dietary component that may aid in the prevention of prostate cancer in men.”

White button mushrooms are a widely consumed food containing phytochemicals beneficial to cancer prevention. The purpose of this research was to evaluate the effects of white button mushroom extract and its major component, conjugated linoleic acid (CLA) on prostate cancer cell lines in vitro and mushroom extract in vivo. In all cell lines tested, mushroom inhibited cell proliferation in a dose-dependent manner and induced apoptosis within 72 h of treatment. CLA inhibited proliferation in the prostate cancer cell lines in vitro. DU145 and PC3 prostate tumor size and tumor cell proliferation were decreased in nude mice treated with mushroom extract, whereas tumor cell apoptosis was increased compared to pair-fed controls. Microarray analysis of tumors identified significant changes in gene expression in the

mushroom-fed mice as compared to controls. Gene network analysis identified alterations in networks involved in cell death, growth and proliferation, lipid metabolism, the TCA cycle and immune response. The data provided by this study illustrate the anticancer potential of phytochemicals in mushroom extract both in vitro and in vivo and supports the recommendation of white button mushroom as a dietary component that may aid in the prevention of prostate cancer in men.

PMID: 19005974 [PubMed - indexed for MEDLINE]

Related articles

- Anti-aromatase activity of phytochemicals in white button mushrooms (*Agaricus bisporus*).

Cancer Res. 2006 Dec 15; 66(24):12026-34.

[Cancer Res. 2006]

- Anti-prostate cancer activity of a beta-carboline alkaloid enriched extract from *Rauwolfia vomitoria*.

Int J Oncol. 2006 Nov; 29(5):1065-73.

[Int J Oncol. 2006]

- Prostate-specific antigen modulates the expression of genes involved in prostate tumor growth.

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[Neoplasia. 2005]

- Monomethylated selenium inhibits growth of LNCaP human prostate cancer xenograft accompanied by a decrease in the expression of androgen receptor and prostate-specific antigen (PSA).

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- Suppression of advanced human prostate tumor growth in athymic mice by silibinin feeding is associated with reduced cell proliferation, increased apoptosis, and inhibition of angiogenesis.

Cancer Epidemiol Biomarkers Prev. 2003 Sep; 12(9):933-9.

[Cancer Epidemiol Biomarkers Prev. 2003]

<http://www.sciencedaily.com/releases/2009/10/091020162237.htm>

Low-Carb Diet Speeds Recovery From Spinal Cord Injury

ScienceDaily (Oct. 22, 2009) — A diet high in fat and low in carbohydrates, known as the "ketogenic" diet, quickens recovery in paralyzed rats after spinal cord injury, according to new research.

The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. More than 10,000 North Americans suffer a new spinal cord injury each year and more than one million people live with such damage.

Patients recovering from spinal cord injuries are typically given high-calorie solutions containing large amounts of sugar intravenously as they heal, even though this nutritional plan has never been validated. Previous studies have shown that fasting is beneficial after partial cervical spinal cord injury in rats, but this strategy is unpopular with patients and clinicians.

In this study, researchers investigated the ketogenic diet as a fasting alternative. As is the case with fasting, a lack of carbohydrates forces the body to use fat as fuel. To test the diet, rats were put on either a standard or ketogenic diet immediately after undergoing a cervical spinal cord contusion. The rats on the ketogenic diet recovered faster: after 14 weeks, 54 percent used their injured paws 15 times more frequently than the rats on a standard diet.

"Our results suggest that a ketogenic diet might be an appropriate initial treatment to improve outcomes in human spinal cord injuries," said Wolfram Tetzlaff, MD, PhD, at International Collaboration on Repair Discoveries, and the study's senior author. "Although there are still many unanswered questions and more research is needed, the early results from these animal experiments support the rationale for human trials."

A ketogenic diet is already used as a therapy for epilepsy. Furthermore, animal studies during the past decade have shown that this diet may also be helpful for neurodegenerative diseases such as brain injury, Alzheimer's and Parkinson's diseases, and amyotrophic lateral sclerosis.

Research was supported by the Christopher and Dana Reeve Foundation, the Craig H. Neilsen Foundation, and the Canadian Institutes of Health Research.

Adapted from materials provided by Society for Neuroscience, via EurekAlert!, a service of AAAS.

Email or share this story:

<http://www.raysahelian.com/pomegranate.html>

Pomegranate supplement, juice, fruit benefit and extract information

by Ray Sahelian, M.D.

Breast cancer chemopreventive properties of pomegranate (*Punica granatum*) fruit extracts in a mouse mammary organ culture.

Eur J Cancer Prev. 2004 Aug;13(4):345-8.

Mehta R, Lansky EP. University of Illinois at Chicago, Chicago

We previously reported anticancer effects of pomegranate extracts in human breast cancer cells in vitro and also chemopreventive activity of pomegranate fermented juice polyphenols (W) in a mouse mammary organ culture. In the present study we decided to expand the investigations to also include an

evaluation of the potential chemopreventive efficacy of a purified chromatographic peak of W (Peak B), and also of whole pomegranate seed oil. The results highlight enhanced breast cancer preventive potential both for the purified compound peak B and for pomegranate seed oil, both greater than that previously reported for pomegranate fermented juice polyphenols.

Pomegranate fruit extract can block skin tumor formation in mice exposed to a cancer-causing agent, according to a report in the *International Journal of Cancer*. Dr. Hasan Mukhtar and colleagues from the University of Wisconsin at Madison conducted a variety of experiments to test the anti-cancer effects of pomegranate, a chemical with strong anti-inflammatory and antioxidant properties. In mice, putting pomegranate on the skin before exposure to the cancer-causing substance TPA inhibited the skin swelling and excessive cell growth that typically occurs. Moreover, mice treated with pomegranate developed fewer skin tumors than untreated mice.

Punica granatum (Pomegranate) juice provides an HIV-1 entry inhibitor and candidate topical microbicide.

BMC Infect Dis. 2004 Oct 14;4(1):41.

HIV-1 entry inhibitors from pomegranate juice adsorb onto corn starch. The resulting complex blocks virus binding to CD4 and CXCR4/CCR5 and inhibits infection by primary virus clades A to G and group O. These results suggest the possibility of producing an anti-HIV-1 microbicide from inexpensive, widely available sources, whose safety has been established throughout centuries, provided that its quality is adequately standardized and monitored.

Concentrated pomegranate juice improves lipid profiles in diabetic patients with hyperlipidemia.

J Med Food. 2004 Fall;7(3):305-8.

This study assessed the effect of concentrated pomegranate juice consumption on lipid profiles of type II diabetic patients with hyperlipidemia. In this quasi-experimental study 22 otherwise healthy diabetic patients, 14 women and eight men were recruited from among patients referred to the Iranian Diabetes Society. The patients were followed for 8 weeks to establish a baseline for normal dietary intake before beginning the concentrated pomegranate juice intervention. During the pre-study period a 24-hour food recall and food records (recording flavonoid-rich foods) were completed every 10 days. At the end of the eighth week, anthropometric and biochemical assessments were done. Thereafter the patients consumed 40 g/day of concentrated pomegranate juice for 8 weeks, during which time dietary assessment was continued. After completing the study, anthropometric and blood indices were again evaluated. After consumption of concentrated pomegranate juice, significant reductions were seen in total cholesterol, low-density lipoprotein (LDL)-cholesterol, LDL-cholesterol / high-density lipoprotein (HDL)-cholesterol, and total cholesterol/HDL-cholesterol. But, there were no significant changes in serum triacylglycerol and HDL-cholesterol concentrations. Anthropometric indices, physical activity, kind and doses of oral hypoglycemic agents, and the intakes of nutrients and flavonoid-rich foods showed no change during the concentrated pomegranate juice consumption period. It is concluded that concentrated pomegranate juice consumption may modify heart disease risk factors in hyperlipidemic patients, and its inclusion therefore in their diets may be beneficial.

Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells.

J Med Food. 2004 Fall;7(3):274-83.

We completed a multicenter study of the effects of pomegranate cold-pressed (Oil) or supercritical CO₂-extracted (S) seed oil, fermented juice polyphenols (W), and pericarp polyphenols (P) on human prostate cancer cell xenograft growth in vivo, and/or proliferation, cell cycle distribution, apoptosis, gene expression, and invasion across Matrigel, in vitro. Oil, W, and P each acutely inhibited in vitro proliferation of LNCaP, PC-3, and DU 145 human cancer cell lines. The dose of P required to inhibit cell proliferation of the prostate cancer cell line LNCaP by 50% (ED₅₀) was 70 microg/mL, whereas normal prostate epithelial cells (hPrEC) were significantly less affected (ED₅₀ = 250 g/mL). Overall, this study demonstrates significant antitumor activity of pomegranate-derived materials against human prostate cancer.

Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation.

Clin Nutr. 2004 Jun;23(3):423-33.

Dietary supplementation with polyphenolic antioxidants to animals was shown to be associated with inhibition of LDL oxidation and macrophage foam cell formation, and attenuation of atherosclerosis development. We investigated the effects of pomegranate juice (PJ, which contains potent tannins and anthocyanins) consumption by atherosclerotic patients with carotid artery stenosis (CAS) on the progression of carotid lesions and changes in oxidative stress and blood pressure. Ten patients were supplemented with pomegranate juice for 1 year and five of them continued for up to 3 years. Blood samples were collected before treatment and during pomegranate juice consumption. In the control group that did not consume pomegranate juice, common carotid intima-media thickness (IMT) increased by 9% during 1 year, whereas, pomegranate juice consumption resulted in a significant IMT reduction, by up to 30%, after 1 year. The results of the present study thus suggest that pomegranate juice consumption by patients with CAS decreases carotid IMT and systolic blood pressure and these effects could be related to the potent antioxidant characteristics of pomegranate juice polyphenols.

Differentiation-promoting activity of pomegranate (*Punica granatum*) fruit extracts in HL-60 human promyelocytic leukemia cells.

J Med Food. 2004 Spring;7(1):13-8.

Differentiation refers to the ability of cancer cells to revert to their normal counterparts, and its induction represents an important noncytotoxic therapy for leukemia, and also breast, prostate, and other solid malignancies. Flavonoids are a group of differentiation-inducing chemicals with a potentially lower toxicology profile than retinoids. Flavonoid-rich polyphenol fractions from the pomegranate (*Punica granatum*) fruit exert anti-proliferative, anti-invasive, anti-eicosanoid, and pro-apoptotic actions in breast and prostate cancer cells and anti-angiogenic activities in vitro and in vivo. Here we tested flavonoid-rich fractions from fresh (J) and fermented (W) pomegranate juice and from an aqueous extraction of pomegranate pericarps (P) as potential differentiation-promoting agents of human HL-60 promyelocytic leukemia cells. Four assays were used to assess differentiation: nitro blue tetrazolium reducing activity,

nonspecific esterase activity, specific esterase activity, and phagocytic activity. In addition, the effect of these extracts on HL-60 proliferation was evaluated. Extracts W and P were strong promoters of differentiation in all settings, with extract J showing only a relatively mild differentiation-promoting effect. The extracts had proportional inhibitory effects on HL-60 cell proliferation. The results highlight an important, previously unknown, mechanism of the cancer preventive and suppressive potential of pomegranate fermented juice and pericarp extracts.

Pomegranate extract improves a depressive state and bone properties in menopausal syndrome model ovariectomized mice.

J Ethnopharmacol. 2004 May;92(1):93-101.

Pomegranate is known to contain estrogens (estradiol, estrone, and estriol) and show estrogenic activities in mice. In this study, we investigated whether pomegranate extract is effective on experimental menopausal syndrome in ovariectomized mice. Prolongation of the immobility time in forced swimming test, an index of depression, was measured 14 days after ovariectomy. The bone mineral density (BMD) of the tibia was measured by X-ray absorptiometry and the structure and metabolism of bone were also analyzed by bone histomorphometry. Administration of pomegranate extract (juice and seed extract) for 2 weeks to ovariectomized mice prevented the loss of uterus weight and shortened the immobility time compared with 5% glucose-dosed mice (control). In addition, ovariectomy-induced decrease of BMD was normalized by administration of the pomegranate extract. The bone volume and the trabecular number were significantly increased and the trabecular separation was decreased in the pomegranate-dosed group compared with the control group. Some histological bone formation/resorption parameters were significantly increased by ovariectomy but were normalized by administration of the pomegranate extract. These changes suggest that the pomegranate extract inhibits ovariectomy-stimulated bone turnover. It is thus conceivable that pomegranate is clinically effective on a depressive state and bone loss in menopausal syndrome in women.

Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo.

Angiogenesis. 2003;6(2):121-8.

We previously showed pomegranate seed oil and fermented juice polyphenols to retard oxidation and prostaglandin synthesis, to inhibit breast cancer cell proliferation and invasion, and to promote breast cancer cell apoptosis. Here we evaluated the anti-angiogenic potential of these materials in several ways. We checked a possible effect on angiogenic regulation by measuring vascular endothelial growth factor (VEGF), interleukin-4 (IL-4) and migration inhibitory factor (MIF) in the conditioned media of estrogen sensitive (MCF-7) or estrogen resistant (MDA-MB-231) human breast cancer cells, or immortalized normal human breast epithelial cells (MCF-10A), grown in the presence or absence of pomegranate seed oil (SESCO) or fermented juice polyphenols (W). VEGF was strongly downregulated in MCF-10A and MCF-7, and MIF upregulated in MDA-MB-231, overall showing significant potential for downregulation of angiogenesis by pomegranate fractions. An anti-proliferative effect on angiogenic cells was shown in human umbilical vein endothelial cell (HUVEC) and in myometrial and amniotic fluid fibroblasts, and inhibition of HUVEC tubule formation demonstrated in an in vitro model employing glass carrier beads. Finally, we showed a significant decrease in new blood vessel formation using the chicken chorioallantoic membrane (CAM) model in vivo. In sum, these varied studies employing different models in different

laboratories overall demonstrate for the first time an anti-angiogenic potential of pomegranate fractions, suggesting further in vivo and clinical investigations

Chemopreventive effects of pomegranate seed oil on skin tumor development in CD1 mice.

J Med Food. 2003 Fall;6(3):157-61.

Hora JJ, Maydew ER, Lansky EP, Dwivedi C.

Department of Pharmaceutical Sciences, College of Pharmacy, South Dakota State University, Brookings, SD

Pomegranate seed oil was investigated for possible skin cancer chemopreventive efficacy in mice. In the main experiment, two groups consisting each of 30, 4-5-week-old, female CD(1) mice were used. Both groups had skin cancer initiated with an initial topical exposure of 7,12-dimethylbenzanthracene and with biweekly promotion using 12-O-tetradecanoylphorbol 13-acetate (TPA). The experimental group was pretreated with 5% pomegranate seed oil prior to each TPA application. Conclusions: Pomegranate seed oil (5%) significantly decreased tumor incidence, multiplicity, and TPA-induced ODC activity. Overall, the results highlight the potential of pomegranate seed oil as a safe and effective chemopreventive agent against skin cancer.

Repeated oral administration of high doses of the pomegranate ellagitannin punicalagin to rats for 37 days is not toxic.

J Agric Food Chem. 2003 May 21;51(11):3493-501.

The water-soluble ellagitannin punicalagin has been reported to be toxic to cattle. Taking into account that this antioxidant polyphenol is very abundant in pomegranate juice (> or =2 g/L), the present study evaluated the possible toxic effect of punicalagin in Sprague-Dawley rats upon repeated oral administration of a 6% punicalagin-containing diet for 37 days. Punicalagin and related metabolites were identified by HPLC-DAD-MS-MS in plasma, liver, and kidney. Five punicalagin-related metabolites were detected in liver and kidney, that is, two ellagic acid derivatives, gallagic acid, 3,8-dihydroxy-6H-dibenzo[b,d]pyran-6-one glucuronide, and 3,8,10-trihydroxy-6H-dibenzo[b,d]pyran-6-one. Feedstuff intake, food utility index, and growth rate were lower in treated rats during the first 15 days without significant adverse effects, which could be due to the lower nutritional value of the punicalagin-enriched diet together with a decrease in its palatability (lower food intake). No significant differences were found in treated rats in any blood parameter analyzed (including the antioxidant enzymes glutathione peroxidase and superoxide dismutase) with the exception of urea and triglycerides, which remained at low values throughout the experiment. Although the reason for the decrease is unclear, it could be due to the lower nutritional value of the punicalagin-enriched diet with respect to the standard rat food. Histopathological analysis of liver and kidney corroborated the absence of toxicity. In principle, the results reported here, together with the large safety margin considered, indicate the lack of toxic effect of punicalagin in rats during the 37 day period investigated. However, taking into account the high punicalagin content of pomegranate-derived foodstuffs, safety evaluation should be also carried out in humans with a lower dose and during a longer period of intake.

Pomegranate juice flavonoids inhibit low-density lipoprotein oxidation and cardiovascular diseases: studies in atherosclerotic mice and in humans.

Drugs Exp Clin Res. 2002;28(2-3):49-62.

The beneficial health effects attributed to the consumption of fruit and vegetables are related, at least in part, to their antioxidant activity. Of special interest is the inverse relationship between the intake of dietary nutrients rich in polyphenols and cardiovascular diseases. This effect is attributed to polyphenols' ability to inhibit low-density lipoprotein (LDL) oxidation, macrophage foam cell formation and atherosclerosis. Pomegranate polyphenols can protect LDL against cell-mediated oxidation via two pathways, including either direct interaction of the polyphenols with the lipoprotein and/or an indirect effect through accumulation of polyphenols in arterial macrophages. Pomegranate polyphenols were shown to reduce the capacity of macrophages to oxidatively modify LDL, due to their interaction with LDL to inhibit its oxidation by scavenging reactive oxygen species and reactive nitrogen species and also due to accumulation of polyphenols in arterial macrophages; hence, the inhibition of macrophage lipid peroxidation and the formation of lipid peroxide-rich macrophages. Furthermore, pomegranate polyphenols increase serum paraoxonase activity, resulting in the hydrolysis of lipid peroxides in oxidized lipoproteins and in atherosclerotic lesions. These antioxidative and antiatherogenic effects of pomegranate polyphenols were demonstrated *in vitro*, as well as *in vivo* in humans and in atherosclerotic apolipoprotein E deficient mice. Dietary supplementation of polyphenol-rich pomegranate juice to atherosclerotic mice significantly inhibited the development of atherosclerotic lesions and this may be attributed to the protection of LDL against oxidation.

Studies on antioxidant activity of pomegranate (*Punica granatum*) peel extract using *in vivo* models.

J Agric Food Chem. 2002 Aug 14;50(17):4791-5.

Pomegranate (*Punica granatum*) peel extracts from the pomegranate tree fruit have been shown to possess significant antioxidant activity in various *in vitro* models. Dried pomegranate peels were powdered and extracted with methanol for 4 h. The dried methanolic extract was fed to albino rats of the Wistar strain, followed by carbon tetrachloride (CCl₄), and the levels of various enzymes, such as catalase, peroxidase, and superoxide dismutase (SOD), and lipid peroxidation were studied. Treatment of rats with a single dose of CCl₄ at 2.0 g/kg of body weight decreases the levels of catalase, SOD, and peroxidase by 81, 49, and 89% respectively, whereas the lipid peroxidation value increased nearly 3-fold. Pretreatment of the rats with a methanolic extract of pomegranate peel at 50 mg/kg (in terms of catechin equivalents) followed by CCl₄ treatment causes preservation of catalase, peroxidase, and SOD to values comparable with control values, whereas lipid peroxidation was brought back by 54% as compared to control. Histopathological studies of the liver were also carried out to determine the hepatoprotection effect exhibited by the pomegranate peel extract against the toxic effects of CCl₄. Histopathological studies of the liver of different groups also support the protective effects exhibited by the MeOH extract of pomegranate peel by restoring the normal hepatic architecture. Pomegranate juice.

Anti-oxidative effects of pomegranate juice consumption by diabetic patients on serum and on macrophages.

Atherosclerosis. 2006 Aug;187(2):363-71. The Lipid Research Laboratory, Technion Faculty of Medicine, The Rappaport Family Institute for Research in the Medical Sciences, Rambam Medical Center, 31096 Haifa, Israel.

In the present study, we investigated the effects of pomegranate juice; which contains sugars and potent anti-oxidants) consumption by diabetic patients on blood diabetic parameters, and on oxidative stress in their serum and macrophages. Ten healthy subjects (controls) and 10 non-insulin dependent diabetes mellitus (NIDDM) patients who consumed pomegranate juice (50ml per day for 3 months) participated in the study. In the patients versus controls serum levels of lipid peroxides and thiobarbituric acid reactive substances (TBARS) were both increased, by 350% and 51%, respectively. Pomegranate juice consumption did not affect serum glucose, cholesterol and triglyceride levels, but it resulted in a significant reduction in serum lipid peroxides and TBARS levels by 56% and 28%. Pomegranate juice consumption significantly reduced cellular peroxides (by 71%), and increased glutathione levels (by 141%). We thus conclude that pomegranate juice consumption by diabetic patients did not worsen the diabetic parameters, but rather resulted in anti-oxidative effects on serum and macrophages, which could contribute to attenuation of atherosclerosis development in these patients.

Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease.

Am J Cardiol. 2005 Sep 15;96(6):810-4. Sumner MD, Elliott-Eller M, Weidner G, Daubenmier JJ, Chew MH, Marlin R, Raisin CJ, Ornish D. The Preventive Medicine Research Institute, Sausalito, California, USA.

We investigated whether daily consumption of pomegranate juice for 3 months would affect myocardial perfusion in 45 patients who had CHD and myocardial ischemia in a randomized, placebo-controlled, double-blind study. Patients were randomly assigned into 1 of 2 groups: a pomegranate juice group (240 ml/day) or a placebo group that drank a beverage of similar caloric content, amount, flavor, and color. After 3 months, the extent of stress-induced ischemia decreased in the pomegranate group but increased in the control group. This benefit was observed without changes in cardiac medications, blood sugar, hemoglobin A1c, weight, or blood pressure in either group. In conclusion, daily consumption of pomegranate juice may improve stress-induced myocardial ischemia .