Preventing Brain Inflammation with Dietary and Lifestyle Modifications

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"Maintaining order rather than correcting disorder is the ultimate principle of wisdom. To cure disease after it has appeared is like digging a well when one feels thirsty, or forging weapons after the war has already begun." Nei Jing, 2nd Century BC

I. Inflammation: the cornerstone of many brain disorders, can be initiated when the immune system reacts to a substance in a person's body. When antibodies of the immune system come into contact with a protein or antigen to which a person is allergic, the inflammatory cascade is provoked, releasing a whole host of damaging the chemicals known as cytokines. Gluten Sensitivity in particular is caused by elevated levels of antibodies against the gliadin component of gluten. When the antibody combines with this protein (creating an anti-gliadin antibody), specific genes are turned on in a special type of immune cell in the body. Once the genes are activated, inflammatory cytokine chemicals collect and can attack the brain. Cytokines are highly antagonistic to the brain, damaging tissue and leaving the brain vulnerable to dysfunction and disease.

A. Lancet Neurol. 2010 Mar;9(3):318-30. doi: 10.1016/S1474-4422(09)70290-X.

Gluten sensitivity: from gut to brain.

Hadjivassiliou M[1], Sanders DS, Grünewald RA, Woodroofe N, Boscolo S, Aeschlimann D.

Abstract

Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals. Coeliac disease, or gluten-sensitive enteropathy, is only one aspect of a range of possible manifestations of gluten sensitivity. Although neurological manifestations in patients with established coeliac disease have been reported since 1966, it was not until 30 years later that, in some individuals, gluten sensitivity was shown to manifest solely with neurological dysfunction. Furthermore, the concept of extraintestinal presentations without enteropathy has only recently become accepted. In this Personal View, we review the range of neurological manifestations of gluten sensitivity and discuss recent advances in the diagnosis and understanding of the pathophysiological mechanisms underlying neurological dysfunction related to gluten sensitivity.

B. Arch Neurol. 2006 Oct;63(10):1440-6.

Cognitive impairment and celiac disease.

Hu WT[1], Murray JA, Greenaway MC, Parisi JE, Josephs KA.

Author information
Abstract

OBJECTIVE:
To characterize the clinical, radiological, and electrophysiological laboratory profiles and histological features of patients who developed cognitive impairment temporally associated with celiac disease.

DESIGN:
Case series.

SETTING:
Referral center.

PATIENTS:
Patients with the onset of progressive cognitive decline within 2 years of symptomatic onset or with a severe exacerbation of biopsy-proved adult celiac disease were identified from the Mayo Clinic medical records from January 1, 1970, to December 31, 2005. Patients were excluded if an alternate cause of their cognitive impairment was identified.

RESULTS:
Thirteen patients (5 women) were identified. The median age at cognitive impairment onset was 64 years (range, 45-79 years), which coincided with symptom onset or exacerbation of diarrhea, steatorrhea, and abdominal cramping in 5 patients. Amnesia, acalculia, confusion, and personality changes were the most common presenting features. The average initial Short Test of Mental Status score was 28 of a total of 38 (range, 18-34), which was in the moderately impaired range. The results of neuropsychological testing suggested a trend of a frontosubcortical pattern of impairment. Ten patients had ataxia, and 4 of them also had peripheral neuropathy. Magnetic resonance imaging of the head showed nonspecific T2 hyperintensities, and electroencephalography showed nonspecific diffuse slowing. Deficiencies in folate, vitamin B(12), vitamin E, or a combination were identified in 4 patients, yet supplementation did not improve their neurological symptoms. Three patients improved or stabilized cognitively with gluten withdrawal. A detailed histological analysis revealed nonspecific gliosis.

CONCLUSIONS:
A possible association exists between progressive cognitive impairment and celiac disease, given the temporal relationship and the relatively high frequency of ataxia and peripheral neuropathy, more commonly associated with celiac disease. Given the impact for potential treatment of similar cases, recognition of this possible association and additional studies are warranted.

C. Nutrients. Jan 2014; 6(1): 15–36.Published online Dec 19, 2013. doi: 10.3390/nu6010015 PMCID: PMC3916846

The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities

Aristo Vojdani,[1,*] Datis Kharrazian,[2]

The aim of this study was to look for the presence of IgG, IgM, and IgA antibodies against two widely consumed foods, wheat and milk, in a relatively large number of specimens. As wheat, milk, and their antigens have been found to be involved in neuroimmune disorders, we measured the co-occurrence of their antibodies against various neural antigens. We assessed the reactivity of sera from 400 donors to wheat and milk proteins, GAD-65, cerebellar, MBP, and MOG. Statistical analysis showed significant clustering when certain wheat and milk protein antibodies were cross-referenced with neural antibodies. Approximately half of the sera with antibody elevation against gliadin reacted significantly with GAD-65 and cerebellar peptides; about half of the sera with elevated antibodies against α + β-casein and milk butyrophilin also showed antibody elevation against MBP and MOG. Inhibition studies showed that only two out of four of the samples with elevated cerebellar or MOG antibodies could be inhibited by gliadin or α + β-casein, confirming individual variation in epitope recognition. We conclude that a subgroup of blood donors, due to a breakdown in immunological tolerance, may react and produce significant levels of antibodies (*p*-values less than 0.05) against wheat and milk antigens that cross-react with different neural antigens, which may have broader implications in the induction of neuroimmune reactivities.

Keywords: antibodies, wheat proteins, milk proteins, neuroimmune

d. An important conclusion from this information is that celiac disease is not confined to the gut. “I would go so far to say that gluten sensitivity always affects the brain. Neurobiologist Dr. Aristo Vojani, a colleague who has published extensively on the topic of gluten sensitivity, has stated that the incidence of gluten sensitivity in Western populations may be as high as 30 percent. And because most cases of celiac are clinically silent, the prevalence of the disease itself is now recognized to be twenty times higher than it was thought to be two decades ago. Let me share what Dr. Rodney Ford of the Children’s Gastroenterlogy and Allergy Clinic in New Zealand Proposed in his 2009 article titled, “Gluten Syndrome: A neurological Disease”: The fundamental problem with gluten is its “interference with the body’s neural networks……gluten is linked to neurological harm in patients, both with and without evidence celiac disease.” He added, “Evidence points to the nervous system as the prime site of gluten damage,” and he boldly concluded that “the implication of gluten causing neurological network damage is immense. With estimates that at least one in ten

people are affected by gluten, the health impact is enormous. Understanding the gluten syndrome is important for the health of the global community."

Although you may not be sensitive to gluten in the same way an individual with celiac is, I've inundated you with date for good reason: It goes to show that we may all be sensitive to gluten from a neurological standpoint. We just don't know it yet because there are no outward signs or clues to a problem happening deep within the confines of our nervous system and brain. Remember, at the heart of virtually every disorder and disease is inflammation. When we introduce anything to the body that triggers an inflammatory response, we set ourselves up for taking on much greater risk for a medley of health challenges, from chronic daily nuisances like headaches and brain fog to serious ailments such as depression and Alzheimer's. We can even make a case for linking gluten sensitivity with some of the most mysterious brain disorders that have eluded doctors for millennia, such asschizophrenia, epilepsy, depression, bipolar disorder, and, more recently, autism and ADHD." --David Perlmutter M.D. from his book, Grain Brain 2013.

II. Carbohydrates and the Cognitive Performance Association. Sugar is toxic to the brain. Limit Intake of Simple Carbohydrates. Consider the following four items: A candy bar, a slice of whole wheat bread, a spoon of white sugar, and a banana. Which will raise your blood sugar fastest? The glycemic index (GI) is a numerical rating that reflects how quickly blood sugar levels rise after eating a particular type of food. The Glycemic index encompasses a scale of 0 to 100, with higher values given to foods that cause the most rapid rise in blood sugar. The reference point is pure glucose, which has a GI of 100. Sugar has a GI of 68, the candy bar has a GI of 55, the banana has a GI of 54, and the slice of whole wheat bread has a GI of 71. This puts the wheat bread at par with White bread. It has been known for more than 30 years that wheat bread raises blood sugar faster than table sugar.

a. "Relative Intake of Macronutrients Impacts Risk of Mild Cognitive Impairment or dementia"

Rosebud O. Roberts, MD ChB, MS, Lewis A. Roberts, [...], and Ronald C. Petersen, PhD, MD. J Alzheimers Dis. Jan 1, 2012; 32(2): 329–339.

Abstract

High caloric intake has been associated with an increased risk of cognitive impairment. Total caloric intake is determined by the calories derived from macronutrients. The objective of the study was to investigate the association between percent of daily energy (calories) from macronutrients and incident mild cognitive impairment (MCI) or dementia. Participants were a population-based prospective cohort of elderly persons who were followed over a median 3.7 years (interquartile range, 2.5–3.9) of follow-up. At baseline and every 15 months, participants (median age, 79.5 years) were evaluated using the Clinical Dementia

Rating scale, a neurological evaluation, and neuropsychological testing for a diagnosis of MCI, normal cognition, or dementia. Participants also completed a 128-item food-frequency questionnaire at baseline; total daily caloric and macronutrient intakes were calculated using an established database. The percent of total daily energy from protein (% protein), carbohydrate (% carbohydrate), and total fat (% fat) was computed. Among 937 subjects who were cognitively normal at baseline, 200 developed incident MCI or dementia. The risk of MCI or dementia (hazard ratio [HR], [95% confidence interval]) was elevated in subjects with high % carbohydrate (upper quartile: 1.89 [1.17–3.06]; *P* for trend=0.004), but was reduced in subjects with high % fat (upper quartile: 0.56 [0.34–0.91]; *P* for trend=0.03), and high % protein (upper quartile 0.79 [0.52 – 1.20]; *P* for trend=0.03) in the fully adjusted models. A dietary pattern with relatively high caloric intake from carbohydrates and low caloric intake from fat and proteins may increase the risk of MCI or dementia in elderly persons.

Keywords: Mild cognitive impairment, dementia, dietary proteins, dietary fats, dietary carbohydrates, caloric intake, energy intake, prospective studies, community-based

This published research from the Mayo Clinic showed that older people who fill their plates with carbohydrates have nearly four times the risk of developing Mild Cognitive Impairment (MCI) which is generally considered a precursor to Alzheimer's Disease. Those with diets highest in fats were 42% less likely to experience cognitive impairments; people who had the highest intake of protein from healthy sources like chicken, meat, and fish enjoyed a reduced risk of 21%.

b. Consuming Omega-3 rich oils such as olive, flaxseed, and walnut oil were 60 % less likely to develop dementia than those who did not consume such oils.

Dietary patterns and risk of dementia

The Three-City cohort study*

P. Barberger-Gateau, PhD, Raffaitin, MD, . Letenneur, PhD, . Berr, PhD, etal

Neurology November 13, 2007 vol. 69 no. 20 1921-1930

Background: Dietary fatty acids and antioxidants may contribute to decrease dementia risk, but epidemiologic data remain controversial. The aim of our study was to analyze the relationship between dietary patterns and risk of dementia or Alzheimer disease (AD), adjusting for sociodemographic and vascular risk factors, and taking into account the ApoE genotype.

Methods: A total of 8,085 nondemented participants aged 65 and over were included in the Three-City cohort study in Bordeaux, Dijon, and Montpeler (France) in 1999–2000 and had at least one re-examination over 4 years (rate of follow-up 89.1%). An independent committee of neurologists validated 281 incident cases of dementia (including 183 AD).

Results: Daily consumption of fruits and vegetables was associated with a decreased risk of all cause dementia (hazard ratio [HR] 0.72, 95% CI 0.53 to 0.97) in fully adjusted models. Weekly consumption of fish was associated with a reduced risk of AD (HR 0.65, 95% CI 0.43 to 0.994) and all cause dementia but only among ApoE ε4 noncarriers (HR 0.60, 95% CI 0.40 to 0.90). Regular use of omega-3 rich oils was associated with a decreased risk of borderline significance for all cause dementia (HR 0.46, 95% CI 0.19 to 1.11). Regular consumption of omega-6 rich oils not compensated by consumption of omega-3 rich oils or fish was associated with an increased risk of dementia (HR 2.12, 95% CI 1.30 to 3.46) among ApoE ε4 noncarriers.

Conclusion: Frequent consumption of fruits and vegetables, fish, and omega-3 rich oils may decrease the risk of dementia and Alzheimer disease, especially among ApoE ε4 noncarriers.

III. Higher Cholesterol is associated with less dementia and less Parkinson's Disease.

a. "Better memory functioning associated with higher total and LDL cholesterol levels in very elderly subjects without the APOE4 allele". Am J Geriatr Psychiatry. 2008 September ;

Rebecca West, M.A.1, Michal Schnaider Beeri, Ph.D.1, James Schmeidler, Ph.D.1, Christine M. Hannigan, B.S.1, Gary Angelo, M.S.1, Hillel T. Grossman, M.D.1,2, Clive Rosendorff, M.D.,

Abstract

Objective—To examine the association of cholesterol with cognitive functioning in oldest old community dwelling individuals with and without the APOE4 allele.

Method—185 non-demented community dwelling individuals (≥ 85) were assessed with a broad neuropsychological battery. Bloods were drawn to assess total, LDL, and HDL cholesterol, as well as for APOE genotyping.

Results—In contrast to our expectations, high total cholesterol and high LDL cholesterol were associated with higher memory scores for non-carriers of the APOE4 allele. No significant associations between cognitive performance and lipid profile were found for carriers of the APOE4 allele.

Conclusions—In oldest old non-demented non-carriers of the APOE4 allele, high cholesterol is associated with better memory function. Further examination of the role of APOE genotype on the association between cholesterol and cognitive performance, especially in the oldest old, is warranted.

b. "Serum Cholesterol Levels and the Risk of Parkinson's Disease". •

Lonneke M. L. de Lau [1] , [2] , **Peter J. Koudstaal** [2] , **Albert Hofman** American Journal of Epidemiology Volume 164, Issue 10Pp. 998-1002.

Abstract

Several recent findings suggest a role of lipid and cholesterol metabolism in the pathogenesis of Parkinson's disease. Therefore, the authors examined the association between serum levels of cholesterol and the risk of Parkinson's disease in the prospective, population-based Rotterdam Study among 6,465 subjects aged 55 or more years with repeated in-person examination and on average 9.4 years of follow-up (1990–2004). Higher serum levels of total cholesterol were associated with a significantly decreased risk of Parkinson's disease (age- and sex-adjusted hazard ratio per mmol/liter increase in cholesterol = 0.77, 95% confidence interval: 0.64, 0.94), with evidence for a dose-effect relation. The association was restricted to women and remained unchanged after adjustment for multiple potential confounders. These findings may indicate a role of lipids in the pathogenesis of Parkinson's disease. Alternatively, they could reflect the strong correlation—especially in women—between levels of serum cholesterol and the antioxidant coenzyme Q10. If confirmed, this would provide further support for an important role of oxidative stress in the pathogenesis of Parkinson's disease.

Lower serum levels of total cholesterol have been described in patients with Parkinson's disease compared with controls (5, 6). Moreover, serum cholesterol is the most important determinant of serum levels of coenzyme Q10, a powerful antioxidant and mitochondrial electron acceptor, that has shown beneficial effects in animal studies and initial trials on Parkinson's disease (7–9). To evaluate a potential role of cholesterol in Parkinson's disease, we examined the relation between serum levels of total and high density lipoprotein cholesterol and the risk of Parkinson's disease prospectively among 6,465 participants of the population-based Rotterdam Study.

c. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease[1,2,3,4,5]

Patty W Siri-Tarino, Qi Sun, Frank B Hu, and Ronald M Krauss. Am J Clin Nutr **January 2010**ajcn.27725

Abstract

Background: A reduction in dietary saturated fat has generally been thought to improve cardiovascular health.

Objective: The objective of this meta-analysis was to summarize the evidence related to the association of dietary saturated fat with risk of coronary heart disease (CHD), stroke, and cardiovascular disease (CVD; CHD inclusive of stroke) in prospective epidemiologic studies.

Design: Twenty-one studies identified by searching MEDLINE and EMBASE databases and secondary referencing qualified for inclusion in this study. A random-effects model was used to derive composite relative risk estimates for CHD, stroke, and CVD.

Results: During 5–23 y of follow-up of 347,747 subjects, 11,006 developed CHD or stroke. Intake of saturated fat was not associated with an increased risk of CHD, stroke, or CVD. The pooled relative risk estimates that compared extreme quantiles of saturated fat intake were 1.07 (95% CI: 0.96, 1.19; $P = 0.22$) for CHD, 0.81 (95% CI: 0.62, 1.05; $P = 0.11$) for stroke, and 1.00 (95% CI: 0.89, 1.11; $P = 0.95$) for CVD. Consideration of age, sex, and study quality did not change the results.

Conclusions: A meta-analysis of prospective epidemiologic studies showed that there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD. More data are needed to elucidate whether CVD risks are likely to be influenced by the specific nutrients used to replace saturated fat.

d. But what about cholesterol and Heart Disease? Multiple studies have routinely failed to find correlation between cholesterol levels and heart disease. Mounting research like this has prompted Dr. George Mann, a researcher with the Framingham Heart study to go on record stating: "The diet heart hypothesis that suggests that a high intake of fat or cholesterol causes heart disease has been repeatedly shown to be wrong, and yet , for complicated reasons of pride, profit, and prejudice, the hypothesis continues to be exploited by scientists, fund-raising enterprise, food companies, and even governmental agencies. The public is being deceived by the greatest health scam of the century."

e. "Total cholesterol and risk of mortality in the oldest old"

Annelies W E Weverling-Rijnsburger, Gerard J B, etal. The Lancet, vol 350. October 18, 1997.

Abstract

BACKGROUND:

The impact of total serum cholesterol as a risk factor for cardiovascular disease decreases with age, which casts doubt on the necessity for cholesterol-lowering therapy in the elderly. We assessed the influence of total cholesterol concentrations on specific and all-cause mortality in people aged 85 years and over.

The finding that low cholesterol concentrations may be associated with increased mortality risk from cancer, respiratory disease, and trauma, 1 had also caused discussion. Some outcomes of clinical-intervention trials with cholesterol-lowering drugs suggest a similar increased mortality risk among the members of the actively treated group.2,3 To explore further the relation between cholesterol as a risk factor for cardiovascular disease in the elderly, we assessed the effects of total cholesterol concentrations on specific and all-cause mortality in the Leiden 85-plus study.

The issue is that treating with cholesterol drugs is not benign. It contributes to problems with the nervous system and even with exercise. As reported by *The New York Times*[9]:

"The drugs routinely are prescribed for those with high cholesterol and other risk factors for heart disease, and some physicians believe that they should be used prophylactically by virtually everyone over 50.

... [P]eople who should benefit the most from exercise — those who are sedentary, overweight, at risk of heart disease or middle-aged — are also the people most likely to be put on statins, possibly undoing some of the good of their workouts.

... In past studies, researchers have shown that statins reduce the risk of a heart attack in people at high risk by 10 to 20 percent for every 1-millimole-per-liter reduction in blood cholesterol levels (millimoles measure the actual number of cholesterol molecules in the bloodstream), equivalent to about a 40-point drop in LDL levels.

Meanwhile, improving aerobic fitness by even a small percentage through exercise likewise has been found to lessen someone's likelihood of dying prematurely by as much as 50 percent.

... But until the current study, no experiment scrupulously had explored the interactions of statin drugs and workouts in people. And the results, as it turns out, are worrisome."

Statins Can Undo the Benefits of Exercise

The study, published in the *Journal of the American College of Cardiology*[4], discovered that statin use led to dramatically reduced fitness benefits from exercise, in some cases actually making the volunteer LESS fit than before!

The participants in the study included 37 overweight, sedentary men and women, all of whom had symptoms of metabolic problems, such as high blood pressure or excess abdominal fat. None of them had exercised regularly within the past 12 months, and most had slightly but not excessively elevated cholesterol levels.

Before the trial, muscle biopsies were taken from each participant to evaluate mitochondrial content, and their aerobic fitness was determined using treadmill testing. All participants were instructed to maintain their regular diet. The participants were then divided into two groups. One group was given a daily 40 mg dose of simvastatin (Zocor). The other group did not receive any medication. Both groups then began a supervised 12-week exercise program, walking or jogging on a treadmill for 45 minutes, five days a week. At the end of the three-month long trial, their aerobic fitness and muscles were retested. The results were astounding:

- On average, unmedicated volunteers improved their aerobic fitness by more than 10 percent. Mitochondrial content activity increased by 13 percent
- Volunteers taking 40mg of simvastatin improved their fitness by a mere 1.5 percent on average, and some had *reduced* their aerobic capacity at the end of the 12-week fitness program. Mitochondrial content activity *decreased* by an average of 4.5 percent

According to senior study author John P. Thyfault, a professor of nutrition and exercise physiology at the University of Missouri[5]:

"Low aerobic fitness is one of the best predictors of premature death. And if statins prevent people from raising their fitness through exercise, then that is a concern."

How Statins Might Undo Fitness Benefits and Make Your Heart Health Worse

The key to understanding why statins prevent your body from reaping the normal benefits from exercise lies in understanding what these drugs do to your mitochondria—the energy chamber of your cells, responsible for the utilization of energy for all metabolic functions.

The primary fuel for your mitochondria is Coenzyme Q10 (CoQ10), and one of the primary mechanisms of harm from statins in general appears to be related to CoQ10 depletion. This also explains why certain statin users in the featured trial ended up with *worse* aerobic fitness after a steady fitness regimen.

It's been known for many decades that exercise helps to build and strengthen your muscles, but more recent research has revealed that this is just the tip of the iceberg when it comes to the potential role exercise can play in your health. A 2011 review published in *Applied Physiology, Nutrition and Metabolism*[8] pointed out that exercise induces changes in mitochondrial enzyme content and activity (which is what they tested in the featured study), which can increase your cellular energy production and in so doing decrease your risk of chronic disease.

The researchers stated:

"Increasing evidence now suggests that exercise can induce mitochondrial biogenesis in a wide range of tissues not normally associated with the metabolic demands of exercise. Perturbations [changes] in mitochondrial content and (or) function have been linked to a wide variety of diseases, in multiple tissues, and exercise may serve as a potent approach by which to prevent and (or) treat these pathologies."

Increasing mitochondrial activity is incredibly important because free radicals, which are toxic byproducts of metabolism as well as exposures to chemicals, pollutants and other toxins, can overwhelm your body's defenses, leading to oxidative damage to cells and tissues that can destroy cellular proteins, lipids and DNA, as well as lead to the loss of mitochondrial function. In the long-term, irreversible damage in the mitochondria can occur, leading to:

- Lower threshold for physical exercise
- Impaired ability to utilize carbohydrates and fat for energy
- Insulin resistance
- Excessive weight gain
  - Reference:

- J Am Coll Cardiol. 2013 Apr 10. pii: S0735-1097(13)01403-4. doi: 10.1016/j.jacc.2013.02.074. [Epub ahead of print]

- **Simvastatin impairs exercise training adaptations.**
- Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, Fletcher J, Meers GM, Ruebel M, Laughlin MH, Dellsperger KC, Fadel PJ, Thyfault JP.

- **Source**
- Division of Cardiology at Duke University Medical Center, Durham, NC.

- **Abstract**
- ***OBJECTIVES:***
- Determine if simvastatin impairs exercise training adaptations.

- ***BACKGROUND:***
- Statins are commonly prescribed in combination with therapeutic lifestyle changes, including exercise, to reduce cardiovascular disease risk in patients with the metabolic syndrome. Statin use has been linked to skeletal muscle myopathy and impaired mitochondrial function, but it is unclear whether statin use alters adaptations to exercise training.

IV. People with diabetes are twice as likely to develop Alzheimer's Disease! They are also 1.75 times more likely to develop dementia of any kind.

Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population

The Hisayama Study

1. **T. Yoshitake, MD, Y. Kiyohara, MD, I. Kato, MD, T. Ohmura, M, etal** 1Neurology June 1995 vol. 45 no. 6 1161-1168

Article abstract—We followed 828 nondemented residents of Hisayama Town, Kyushu, Japan, aged 65 years or older (88.3% of the elderly population) for 7 years starting in 1985 in order to determine the type-specific incidence of dementia and its risk factors in the general Japanese population. Only two subjects were lost to the follow-up, during which period 103 subjects developed dementia. Morphologic examination of the brains of 89 subjects (86.4%) was made by autopsy or CT. We made the initial diagnosis of dementia based on the DSM-111-R criteria, with the diagnoses of vascular dementia (VD) being based on the NINDS-AIREN criteria and Alzheimer's disease (AD) on the NINCDS-ADRDA criteria. The incidence of VD and AD increased with age for both sexes. The age-adjusted total incidence (per 1,000 person-years) of dementia was 19.3 for men and 20.9 for women. The corresponding rates for VD were 12.2 for men and 9.0 for women, and for AD, 5.1 for men and 10.9 for women. Among the VD subjects whose brain morphology we examined, the most frequent type of stroke was multiple lacunar infarcts (42%), but half these subjects lacked a stroke episode in their histories. Multivariate analysis showed that age, prior stroke episodes, systolic blood pressure, and alcohol consumption were significant independent risk factors for the occurrence of VD. In contrast, age and a low score on Hasegawa's dementia scale were significant risk factors for AD, and physical activity was a significant preventive factor for AD. Our findings suggest that asymptomatic stroke is an important factor in the development of VD, with age, prior stroke episodes, systolic blood pressure, and alcohol consumption being independent risk factors for its occurrence. Age and a low scare on Hasegawa's dementia scale are significant risk factors for AD, with moderate physical activity having a statistically significant preventive effect.

v. Statin drugs are associated with causing diabetes in Post menopausal women.

Arch Intern Med. 2012 Jan 23;172(2):144-52. doi: 10.1001/archinternmed.2011.625. Epub 2012 Jan 9.

"Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative."

Culver AL[1], Ockene IS, Balasubramanian R, Olendzki BC

Abstract

BACKGROUND:
This study investigates whether the incidence of new-onset diabetes mellitus (DM) is associated with statin use among postmenopausal women participating in the Women's Health Initiative (WHI).

METHODS:
The WHI recruited 161,808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the United States from 1993 to 1998 with ongoing follow-up. The current analysis includes data through 2005. Statin use was captured at enrollment and year 3. Incident DM status was determined annually from enrollment. Cox proportional hazards models were used to estimate the risk of DM by statin use, with adjustments for propensity score and other potential confounding factors. Subgroup analyses by race/ethnicity, obesity status, and age group were conducted to uncover effect modification.

RESULTS:
This investigation included 153,840 women without DM and no missing data at baseline. At baseline, 7.04% reported taking statin medication. There were 10,242 incident cases of self-reported DM over 1,004,466 person-years of follow-up. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83). This association remained after adjusting for other potential confounders (multivariate-adjusted HR, 1.48; 95% CI, 1.38-1.59) and was observed for all types of statin medications. Subset analyses evaluating the association of self-reported DM with longitudinal measures of statin use in 125,575 women confirmed these findings.

CONCLUSIONS:
Statin medication use in postmenopausal women is associated with an increased risk for DM. This may be a medication class effect. Further study by statin type and dose may reveal varying risk levels for new-onset DM in this population.

Special note: There is a 48% increase in diabetes with statin drug use. One of the world's most widely used drugs, statins have been hailed by the medical community for their ability to prevent heart disease.
Still, the researchers, who have published their findings in the journal *Diabetes*, were confused as to why diabetes was linked to statin use.

"Recently, an increased risk of diabetes has been added to the warning label for statin use," says lead author Jonathan Schertzer, assistant professor of Biochemistry and Biomedical Sciences, and Canadian Diabetes Association Scholar.

v. Association of diabetes and cognitive impairment.

Journal of Neurology
April 2006, Volume 253, Issue 4, pp 477-482
Date: 14 Nov 2005

Diabetes and cognitive impairment

Dr. G. J. Biessels, Dr. A. Koffeman, Dr. Ph. Scheltens

Abstract

Background

Diabetes is a risk factor for dementia,but the issue whether this concerns only vascular dementia or also Alzheimer's disease is debated. We compared the clinical diagnoses and abnormalities on brain MRI in patients with or without diabetes who received standardised, detailed diagnostic studies at a memory clinic, in order to establish whether one specific type of dementia or specific MRI abnormalities were more common in diabetes.

Patients and methods

Patients who visited our memory clinic between January 2002 and June 2004 were divided into a group with (n = 42) or without diabetes (n = 389).The diagnoses were recorded, and MRI scans were rated for (sub)cortical atrophy, medial temporal lobe atrophy, infarctions, and white matter changes.

Results

The proportion of Alzheimer's disease (36% versus 28%; OR 1.1 (95% CI 0.5–2.2), adjusted for age and sex), vascular dementia (5% versus 2%; OR 2.4 (0.5–12.1)), and so called "cognitive impairment no dementia" (24% versus 17%; 1.3 (0.6–2.9)) was similar in patients with or without diabetes. On MRI lacunar and cortical infarctions were more common and cortical atrophy more pronounced among diabetic patients. By contrast, the severity of white matter changes was similar in the two groups.

Conclusion

The relative frequency of different diagnoses among diabetic and non–diabetic patients attending a memory clinic was similar, indicating that diabetes does not predispose to one particular subtype of dementia.The imaging findings support the notion that the increased risk of cognitive decline and dementia in elderly subjects with diabetes is due to dual pathology, involving both cerebrovascular disease and cortical atrophy.

Arch Neurol. Aug 2008; 65(8): 1066–1073.

b. Duration and Severity of Diabetes Are Associated with Mild Cognitive Impairment

Rosebud O. Roberts, MB ChB, MS, Yonas E. Geda, MD, David S. Knopman, MD, J.H. Teresa, BS Christianson, V. Shane Pankratz, PhD, Bradley F. Boeve, MD, Adrian Vella, MD, Walter A. Rocca, MD, MPH, and Ronald C. Petersen, MD

Results

We compared 329 patients with MCI to 1640 subjects free of MCI and of dementia. The frequency of diabetes was similar in subjects with MCI (20.1%) and in subjects without MCI (17.7%; odds ratio [OR], 1.16; 95% confidence interval [CI], 0.85-1.57). However, MCI was associated with onset of diabetes before age 65 years (OR, 2.20; 95% CI, 1.29-3.73), diabetes duration ≥10 years (OR, 1.76; 95% CI, 1.16-2.68), treatment with insulin (OR, 2.01; 95% CI, 1.22-3.31), and presence of complications (OR, 1.80; 95% CI, 1.13-2.89) after adjustment for age, sex, and education. Analyses using alternative definitions of diabetes yielded consistent findings.

Conclusions

These findings suggest an association between earlier onset, longer duration, and greater severity of diabetes and MCI.

Special Note: If diabetes began before age sixty-five years old, the risk of mild cognitive impairment was increased by a whopping 220%. And the risk of mild cognitive impairment in individuals who had diabetes for ten years or longer was increased by 176%. If people were taking insulin, their risk was increased by 200%. The authors described a proposed mechanism for the connection with persistent high blood sugar and Alzheimer's disease: "increased production of advanced glycation end products".

VII. Free Radical damage plays a role in cellular damage in brain injury.

Arch Neurol. 2007 Jul;64(7):954-6.

Damage to lipids, proteins, DNA, and RNA in mild cognitive impairment.

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Author information

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Abstract

Free radical-mediated oxidative damage is thought to play a role in the pathogenesis of Alzheimer disease. Previous studies have shown oxidative damage to lipids, proteins, DNA, and RNA in multiple brain regions in late-stage Alzheimer disease. Recent studies on patients with amnestic mild cognitive impairment who have undergone autopsy have shown increased lipid peroxidation as well as protein, DNA, and RNA oxidation in multiple brain regions. These studies establish oxidative damage as an early event in the pathogenesis of Alzheimer disease that can serve as a therapeutic target to slow the progression or perhaps the onset of the disease.

VIII. Activate the Nrf2 Pathway for health. Humans and other mammals have developed our own biochemsitry to create more protective antioxidants during time of high oxidative stress. Far from being entirely dependent on extenal food sources of antioxidants, our cells have their own innate ability to generate antioxidant enzymes on demand. High levels of free radicals turn on a specific protein in the nucleus called Nrf2, which essentially prepares the cell to produce a vast array of not only important antioxidants such as: Super oxide Dismutase (SOD), Glutathione Peroxidase, and Catalase, but also detoxification enzymes. So if excessive free radicals induce better antiooxidant production through this pathway, then the next obvious question is what else activates this pathway for NRF2?

a. J Biol Chem. 2007 Jan 26;282(4):2529-37. Epub 2006 Nov 25.

- **Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3.**
- Gao L[1], Wang J, Sekhar KR, Yin H, Yared NF, Schneider SN, Sasi S, Dalton TP, Anderson ME, Chan JY, Morrow JD, Freeman ML.
- **Author information**
- **Abstract**
- Consumption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can mitigate the progression of diseases in which oxidative stress represents a common underlying biochemical process. Nrf2-regulated gene expression regulates detoxification of reactive oxygen species. EPA and DHA were subjected to an in vitro free radical oxidation process that models in vivo conditions. Oxidized n-3 fatty acids reacted directly with the negative regulator of Nrf2, Keap1, initiating Keap1 dissociation with Cullin3, thereby inducing Nrf2-directed gene expression. Liquid chromatography-tandem mass spectrometry analyses of oxidized EPA demonstrated the presence of novel cyclopentenone-containing molecules termed J3-isoprostanes in vitro and in vivo and were shown to induce Nrf2-directed gene expression. These experiments provide a biochemical basis for the hypothesis that formation of J-ring compounds generated from oxidation of EPA and DHA in vivo can reach concentrations high enough to induce Nrf2-based cellular defense systems.

b. J Nutr Biochem. 2005 Mar;16(3):129-37.

Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems.

Mattson MP[1], Wan R.
Author information
Abstract

Intermittent fasting (IF; reduced meal frequency) and caloric restriction (CR) extend lifespan and increase resistance to age-related diseases in rodents and monkeys and improve the health of overweight humans. Both IF and CR enhance cardiovascular and brain functions and improve several risk factors for coronary artery disease and stroke including a reduction in blood pressure and increased insulin sensitivity. Cardiovascular stress adaptation is improved and heart rate variability is increased in rodents maintained on an IF or a CR diet. Moreover, rodents maintained on an IF regimen exhibit increased resistance of heart and brain cells to ischemic injury in experimental models of myocardial infarction and stroke. The beneficial effects of IF and CR result from at least two mechanisms--reduced oxidative damage and increased cellular stress resistance. Recent findings suggest that some of the beneficial effects of IF on both the cardiovascular system and the brain are mediated by brain-derived neurotrophic factor signaling in the brain. Interestingly, cellular and molecular effects of IF and CR on the cardiovascular system and the brain are similar to those of regular physical exercise, suggesting shared mechanisms. A better understanding of the cellular and molecular mechanisms by which IF and CR affect the blood vessels and heart and brain cells will likely lead to novel preventative and therapeutic strategies for extending health span.

c. Neurology. 2012 Apr 24;78(17):1323-9. doi: 10.1212/WNL.0b013e3182535d35. Epub 2012 Apr 18.

Total daily physical activity and the risk of AD and cognitive decline in older adults.

Buchman AS[1], Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA.

Author information

Abstract

OBJECTIVE:

Studies examining the link between objective measures of total daily physical activity and incident Alzheimer disease (AD) are lacking. We tested the hypothesis that an objective measure of total daily physical activity predicts incident AD and cognitive decline.

METHODS:

Total daily exercise and nonexercise physical activity was measured continuously for up to 10 days with actigraphy (Actical®; Philips Healthcare, Bend, OR) from 716 older individuals without dementia participating in the Rush Memory and Aging Project, a prospective, observationalcohort study. All participants underwent structured annual clinical examination including a battery of 19 cognitive tests.

RESULTS:

During an average follow-up of about 4 years, 71 subjects developed clinical AD. In a Cox proportional hazards model adjusting for age, sex, and education, total daily physical activity was associated with incident AD (hazard ratio = 0.477; 95% confidence interval 0.273-0.832). The association remained after adjusting for self-report physical, social, and cognitive activities, as well as current level of motor function, depressive symptoms, chronic health conditions, and APOE allele status. In a linear mixed-effect model, the level of total daily physical activity was associated with the rate of global cognitive decline (estimate 0.033, SE 0.012, p = 0.007).

CONCLUSIONS:

A higher level of total daily physical activity is associated with a reduced risk of AD.

d. Mol Aspects Med. 2011 Aug;32(4-6):234-46. doi: 10.1016/j.mam.2011.10.006. Epub 2011 Oct 15.

Oxidative stress in health and disease: the therapeutic potential of Nrf2 activation.

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Abstract

For the past 40 years or so, oxidative stress has been increasingly recognized as a contributing factor in aging and in various forms of pathophysiology generally associated with aging. Our view of oxidative stress has been largely "superoxide-centric", as we focused on the pathological sources of this oxygen-derived free radical and the types of molecular havoc it can wreak, as well as on the protection provided by the antioxidant enzymes, especially the superoxide dismutases, catalases, and glutathione peroxidases. In the last decade our view of oxidative stress has broadened considerably, and it is now often seen as an imbalance that has its origins in our genes, and the ways in which gene expression is regulated. At the center of this new focus is the transcription factor called nuclear factor (erythroid-derived 2)-like 2, or Nrf2. Nrf2 is referred to as the "master regulator" of the antioxidant response, modulating the expression of hundreds of genes, including not only the familiar antioxidant enzymes, but large numbers of genes that control seemingly disparate processes such as immune and inflammatory responses, tissue remodeling and fibrosis, carcinogenesis and metastasis, and even cognitive dysfunction and addictive behavior. Thus, the dysregulation of Nrf2-regulated genes provides a logical explanation for the connections, both direct and indirect, between observable oxidative stress and perhaps 200 human diseases involving these various physiological processes, each reflecting a network involving many gene products. The evolutionary self-association of these many genes under the common control of Nrf2 suggests that the immune and inflammatory systems may present the largest demand for increased antioxidant protection, apart from constitutive oxidative stress resulting from mitochondrial oxygen consumption for metabolic purposes. Gene expression microarray data on human primary vascular endothelial cells and on the SK-N-MC human neuroblastoma-derived cell line have been obtained in response to the dietary supplement Protandim, a potent composition of highly synergistic phytochemical Nrf2 activators. Pathway analysis of results shows significant modulation by Protandim of pathways involving not only antioxidant enzymes, but of those related to colon cancer, cardiovascular disease, and Alzheimer disease.

Conclusion: Cholesterol is important for brain health. Sugar is the problem as it damages the body through diabetes which is associated with glycation products that damage cells and interfere with protein functions. Statins increase diabetes risk which further impairs cognitive performance. Solutions include consuming more fat in the diet to decrease the sugar loads and the oxidative stress associated with sugar metabolism. Activate the Nrf2 pathway to reduce oxidative stress through exercise, Fasting, supplements: Fish oil and Protandim.