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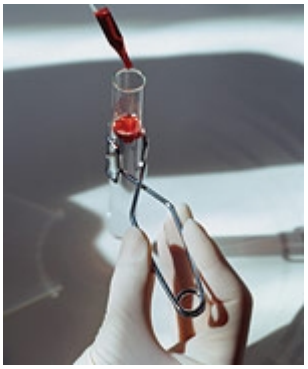
REPORT

Homocysteine as a Risk Factor for Disease

By Laura J. Ninger, ELS



Since 1990, the National Library of Medicine has posted thousands of scientific studies showing that homocysteine is a significant risk factor for disease.[1]

These published reports discuss the lethal illnesses associated with excess homocysteine, how elevations in blood homocysteine levels result in incremental increases in disease risks, the mechanisms by which homocysteine exerts its multiple pathological effects, and methods to reduce toxic homocysteine levels in the body.

Elevated homocysteine levels may be caused by B-vitamin deficiency, genetic factors, increasing age, kidney impairment, or other factors. Homocysteine overload increases the risk of disease in healthy people and magnifies adverse effects in those with pre-existing conditions.

Since 1981, the Life Extension Foundation has published hundreds of pages of text describing the dangers of excess homocysteine in the blood. What follows is a brief chronological review of landmark studies published in major medical journals that describe specific disease risks associated with excess homocysteine.

1990

Cardiovascular Disease: Researchers found that men with premature coronary artery disease (who averaged 50 years of age) had significantly higher homocysteine levels than healthy men. Scientists thus determined that high levels of homocysteine are an independent risk factor for premature coronary atherosclerosis in men.[1]

1991

Early-Onset Vascular Disease: Higher levels of homocysteine raise the risk of premature cardiovascular disease affecting the heart, brain, and peripheral blood vessels. In subjects who developed cardiovascular disease before the age of 55, elevated blood levels of homocysteine were found in 42% of patients with cerebrovascular disease, 30% with coronary vascular disease, and 28% with peripheral vascular disease—but not in any of the healthy control subjects. People with elevated homocysteine had three times the risk of cardiovascular disease compared to healthy individuals.[2]

Cardiovascular Disease Progression: Patients with blocked arteries in the lower body or brain were found to have significantly higher homocysteine levels than healthy individuals. In addition, patients with high homocysteine (versus normal levels) had significantly faster progression of lower-extremity vascular disease and coronary artery disease.[3]

1992

Heart Attack: In a large study, men who had markedly higher homocysteine levels had over three times the risk of heart attack compared to men with lower homocysteine values.[4]

Stroke: Elevated homocysteine levels were independently associated with all types of stroke (ischemic, hemorrhagic, and embolic). Stroke survivors were more likely to demonstrate elevated homocysteine levels (40%) than healthy individuals (6%).[5]

1993

Blood Clotting: High homocysteine levels have been linked with increased blood-clotting tendency. In the laboratory, homocysteine increased the activity of a blood-clotting factor in human cells by 25-100%, and this negative effect increased with rising homocysteine concentrations.[6] In a similar study, homocysteine decreased the production of a substance that helps

prevent blood clots by 65%.[7]

1994

Early-Onset Coronary Artery Disease: Noting that high homocysteine raises the risk of early-onset coronary artery disease, scientists proposed that boosting plasma folate concentration may help reduce homocysteine levels and decrease coronary artery disease risk.[8]

1995

Atherosclerosis: In elderly adults, dangerous narrowing of the arteries that direct blood to the brain was more than twice as common in those with higher homocysteine levels (greater than 14.4 µmol/L) than in those with low levels (less than 9.1 µmol/L).[9] Another study found that individuals with high homocysteine were much more likely to have atherosclerosis (72%) than those with normal homocysteine (44%).10 In patients already at risk for atherosclerosis because of high lipid levels, elevated homocysteine further increased the risk by nearly three times.[10]

Coronary Artery Disease: High homocysteine was found to be an independent risk factor for coronary artery disease among healthy people. Each 4-µmol/L increase in homocysteine level increased risk by 32%.[11]

Birth Defects: Abnormal homocysteine metabolism may be associated with birth defects that affect the coverings of the nervous system (neural tube defects).[12] Elevated homocysteine levels have been found in the amniotic fluid of fetuses with neural tube defects and in blood samples of women carrying fetuses with these birth defects.[12,13] Folic acid supplements may help prevent such birth defects by correcting high homocysteine levels.[12,13]

1996

Pediatric Atherosclerosis: In boys and girls aged 10-19, elevated homocysteine levels were significantly associated with atherosclerosis in the carotid arteries, which supply the brain with blood. This suggests that homocysteine levels correlate with atherosclerosis, even as early as in the second decade of life.[14]

Cardiovascular Disease: In another pediatric study, homocysteine levels were significantly higher among children who had a male relative who died prematurely (under 55 years of age) of heart attack. Nutritional modifications may help reduce cardiovascular risk in children with a family history of heart disease.[15]

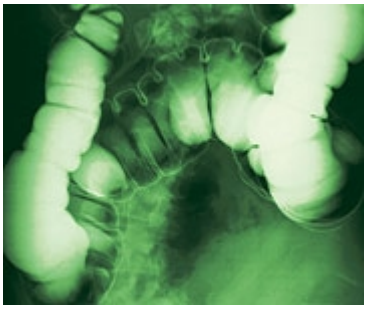
Coronary Artery Disease: Scientists discovered that one of the causes of elevated homocysteine levels is a particular genetic mutation, and that people with this mutation had a significantly higher risk of premature coronary heart disease.[16]

Birth Defects: Scientists again noted that homocysteine levels are significantly higher in women with fetuses that have neural tube birth defects than in those with healthy fetuses, further supporting the theory that folic acid supplementation may help prevent birth defects by improving homocysteine metabolism.[17]

1997

Atherosclerosis: Scientists found that elevated homocysteine was just as serious a risk factor for atherosclerosis as smoking or high lipid levels, and that it dramatically aggravated the risk associated with smoking or high blood pressure.[18] In one study, every 5-µmol/L increase in homocysteine level led to a 30% increased risk of severe atherosclerosis.[19] In addition, researchers found that people with higher levels of homocysteine had more blocked arteries than people with lower homocysteine levels.[19]

Death from Coronary Artery Disease: Higher homocysteine levels strongly predict mortality risk in people with coronary heart disease. People with homocysteine levels above 15 µmol/L had a 25% mortality rate over four years, compared to only 4% for those who had homocysteine levels below 9 µmol/L. Death rates rose dramatically as homocysteine levels rose from 9 to 20 µmol/L.[20]



1998

Cardiovascular Disease and Stroke: High levels of homocysteine increase the risk of diseased arteries of the extremities, heart, and brain.[21,22] One study suggested that every 5-µmol/L increase in homocysteine level increases the risk of peripheral vascular disease by 44%, coronary artery disease by 25%, cerebrovascular disease by 24%, and any cardiovascular disease by 39%.[21] In people who have type II diabetes or impaired glucose tolerance, elevated homocysteine poses even greater dangers to the cardiovascular system.[21] In one study, elderly men with high homocysteine had almost twice the risk of heart attack and more than four times the risk of stroke, as well as six times the risk of fatal stroke.[23]

Ischemic Heart Disease: Men with higher homocysteine levels were up to three times more likely to die of ischemic heart disease—caused by a diminished supply of blood and oxygen to the heart muscle—than those who had lower levels. This correlation was so strong that scientists proposed that elevated homocysteine might actually cause heart disease, rather than simply be a risk factor for it.[24]

1999

Cardiovascular Disease: Homocysteine damages endothelial cells, promotes blood clots, and supports free radical damage.[25] Homocysteine is associated with risks in both adults and children. In fact, healthy children with higher homocysteine levels were more likely to have increased blood pressure compared to their peers with normal homocysteine. These children have a higher risk for future cardiovascular disease.[26] Testing blood homocysteine levels in children may help to identify those with a high level of heart disease risk, so that preventive strategies can be started as soon as possible.[26]

Colon Cancer: Women with higher homocysteine had a higher risk of colorectal cancer than women with lower levels. Those with the highest homocysteine levels had a more than 70% higher colorectal cancer risk than those with the lowest values. This led scientists to suggest that vitamin supplementation strategies to lower homocysteine levels might also decrease colorectal cancer risk.[27]

Birth Defects: Because high homocysteine levels are associated with both neural tube birth defects and heart disease, scientists proposed that disturbances in homocysteine breakdown might underlie both conditions. By supporting homocysteine breakdown, folic acid supplements might help prevent birth defects as well as heart disease.[28]

2000

Atherosclerosis: Elevated homocysteine is associated with an increased risk of atherosclerosis, heart attack, and heart disease mortality.[29] Elevated homocysteine levels are strongly associated with severe atherosclerosis in one of the body's main blood vessels, the aorta.[30]

Kidney and Heart Disease: In patients with early- or end-stage kidney disease, elevated homocysteine is an independent predictor of cardiovascular disease.[31]

Cervical Cancer: Elevated homocysteine levels may increase the risk of cervical cancer. One study found that women who had a precursor to cervical cancer had higher homocysteine levels than healthy subjects. High homocysteine also increased the cervical cancer risk associated with smoking, having several previous births, and infection with a virus associated with cervical cancer. Elevated homocysteine increases the risk of cervical tissue changes that can lead to cancer, and enhances the effects of other risk factors.[32]

Depression: Scientists noted that 52% of patients with severe depression had elevated homocysteine levels, as well as decreased levels of folate and impaired metabolism of certain neurotransmitters. A significant correlation between elevated homocysteine and decreased folate concentrations was noted in depressed people. Scientists thus proposed that measuring homocysteine levels may help identify people with depression, and that homocysteine-lowering therapies might elevate mood.[33]

Pregnancy Complications: Elevated homocysteine levels may increase the risk of several complications of pregnancy. In a large study, scientists found that pregnant women with the highest homocysteine levels had an increased risk of premature births, low-birth-weight infants, and stillbirths.[34]

2001

Alzheimer's Disease: Elevated homocysteine levels may contribute to cognitive decline and Alzheimer's disease.[35,36] In healthy older adults, high homocysteine was associated with poorer cognitive function and faster cognitive decline over the course of five years.[36] Although scientists do not know whether homocysteine causes cognitive decline or Alzheimer's, they have noted that high homocysteine correlates with the progression and severity of these conditions.[35]

Invasive Cervical Cancer: Homocysteine may increase the risk for cervical cancer. Researchers found that women with elevated homocysteine levels were two to three times more likely to have invasive cervical cancer.[37]

Coronary Artery Disease: Since 1998, grain products in the United States have been fortified with folic acid to promote good health. By lowering homocysteine levels, grain fortification could reduce heart attacks and heart disease deaths by 8% in women and 13% in men. This strategy may save several hundred thousand lives and several billion dollars in health care costs over the course of 10 years, according to one analysis.[38]

Blood Clots: One study found that when homocysteine levels are high, the risk of dangerous blood clots (deep vein thrombosis) more than doubled. Blood clots are potentially lethal, since they can lead to heart attack or stroke.[39]

Overall Mortality: Elevated homocysteine increases the risk of death due to cancer and other causes. A 2001 study showed that each 5-µmol/L increase in homocysteine was associated with a 26% increase in cancer deaths, a 49% increase in all-cause mortality, a 50% increase in cardiovascular deaths, and a 104% increase in deaths not due to cancer or cardiovascular disease. Managing homocysteine levels may thus be crucial to prolonging life and preventing death from numerous health conditions.[40]

REPORT

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2002

Alzheimer's Disease: Rising levels of homocysteine could be an early warning signal of impending dementia and Alzheimer's in elderly men and women. High homocysteine (greater than 14 µmol/L) almost doubled the risk of Alzheimer's disease, suggesting a possible cause-and-effect relationship between homocysteine and Alzhiemer's.[41]

Cardiovascular Disease: High homocysteine levels make the cardiovascular risks of smoking even more dangerous. In one study, smokers with high homocysteine levels had 12 times the risk of cardiovascular disease compared to nonsmokers with normal homocysteine.[42]

Ischemic Heart Disease and Stroke: Lowering homocysteine levels may decrease the risk of heart disease and stroke.[43-45] Studies have suggested that lowering one's homocysteine level by 3 µmol/L could decrease the risk of ischemic heart disease by 11-16%, while decreasing the risk of stroke by 19-24%.[43,44]

2003

Dementia: Because elevated homocysteine plays a role in stroke and Alzheimer's disease—two major causes of dementia—researchers proposed that dietary supplementation to normalize homocysteine levels could reduce rates of dementia.[46]

Cognitive Impairment: Healthy people who wish to maintain their cognitive function should monitor their homocysteine levels. Over the course of six years, healthy individuals with high homocysteine levels at the study's onset had much poorer scores on word-learning tests than their counterparts with low homocysteine levels.[47]

Inflammatory Bowel Disease: High levels of homocysteine in the colon and blood may predispose individuals to two inflammatory bowel diseases: ulcerative colitis and Crohn's disease. Homocysteine levels were significantly elevated in the colons of patients with inflammatory bowel diseases compared to healthy subjects.[48]

Ischemic Heart Disease and Stroke: People with high homocysteine levels have a much greater risk of ischemic heart disease and stroke.[49] In patients with coronary heart disease, those with the highest homocysteine levels had an almost fivefold greater risk of stroke.[50] Some research suggests that lowering homocysteine by 25% may lead to an 11% decrease in ischemic heart disease risk and a 20% decrease in stroke risk.[49]

2004

Aneurysm: One of the most dangerous manifestations of cardiovascular disease is aortic aneurysm, a bulging of the body's largest artery that can lead to rupture, a potentially fatal surgical emergency. Researchers found that 68% of adults with abdominal aortic aneurysm had elevated homocysteine levels, compared to only 6% of unaffected individuals. Patients with aneurysm had an average homocysteine level of 19.4 µmol/L, compared to 10.9 µmol/L among unaffected adults.[51]

Cardiovascular Disease: About half of all deaths occur because of cardiovascular disease, and elevated homocysteine may contribute to 10% of cardiovascular disease cases and deaths.[52] Cardiovascular disease risk grows as homocysteine increases, and the risk is especially high in people with high blood pressure, diabetes, or high lipid levels.[52] Homocysteine damages blood vessels, promotes blood clotting, and generates oxidative stress.[52] Some experts estimate that lowering homocysteine could prevent 25% of cardiovascular events,[52] and some recommend that all individuals at risk for heart disease should be treated regardless of their baseline homocysteine values.[53] Homocysteine poses risks to men, women, and children, and particularly to people with underlying illnesses.[54-56]

Cognitive Impairment: High levels of homocysteine are associated with detrimental changes in the nervous system that can be detected using radiological imaging[57] or clinical assessments.[58] In one study, people with the highest homocysteine levels had lower scores on cognitive function tests. High homocysteine levels were also associated with a 4.3 times higher risk of dementia and a 3.7 times greater risk of Alzheimer's disease.[58]

Osteoporosis: Elevated homocysteine levels may increase the risk of osteoporotic fractures in older men and women.[59,60] In one

report, the risk of hip fracture increased with rising levels of homocysteine in both sexes.[59] Men with the highest levels had about four times the risk of fracture as men with the lowest levels, and women with the highest values had twice the risk as those with the lowest levels.[59] Lowering homocysteine levels using nutritional strategies may thus help protect bone health.[59]

2005

Alzheimer's Disease: Rising levels of homocysteine may predict impending cognitive decline and Alzheimer's disease.[61,62] In one study, high levels of homocysteine were associated with worse cognitive function, and elevated homocysteine predicted more severe cognitive decline during seven years of follow-up.[61] Moreover, elevated homocysteine was associated with a three times higher risk of Alzheimer's disease and a 2.6 times higher risk of mild cognitive impairment, which typically precedes more severe dementia.[62]

Aneurysm: People who have high homocysteine levels may have an eightfold greater risk of abdominal aortic aneurysm. When an aneurysm ruptures, fatal bleeding can occur unless the patient receives prompt surgical care.[63]

Atherosclerosis: Elevated homocysteine may speed the progression of atherosclerosis. One study showed that atherosclerosis progressed by 35% annually for patients with high homocysteine levels (greater than or equal to 12 µmol/L), but by only 17% per year in people with lower levels (less than 12 µmol/L).[64]

Cardiovascular Disease: When researchers followed healthy men for 10 years, they noticed that the men with the highest homocysteine levels had nearly twice the risk of cardiovascular disease death.[65] Homocysteine was even more dangerous in smokers and in men with high cholesterol.[65] In healthy women, increased homocysteine levels were associated with decreased oxygen uptake, indicating poorer cardiovascular fitness.[66]

Cognitive Impairment: Homocysteine may interfere with healthy mental function.[67-69] In one report, healthy elderly people with high homocysteine levels experienced more dramatic cognitive decline over six years than did their counterparts with lower homocysteine levels.[68] One study suggested that homocysteine may prematurely age the brain. A rise in homocysteine was equivalent to an extra 4.2 years of age on cognitive performance tests. Homocysteine might thus be a modifiable cause of cognitive decline.[69]

Depression: Depression and high homocysteine appear to be closely related. In people aged 60-64, a higher homocysteine level was associated with a higher prevalence of depression.[70]

Macular Degeneration: Homocysteine may damage eye health and threaten visual function. In fact, scientists found that patients with age-related macular degeneration had significantly higher homocysteine levels than healthy subjects.[71,72]

Bipolar Disorder: Homocysteine may be associated with bipolar (manic depressive) disorder. One study showed that young men with bipolar disorder had much higher homocysteine levels than healthy subjects, and homocysteine levels were highest in those with progression of the disease.[73]

Osteoporosis: Elevated homocysteine may adversely affect bone health and fracture risk.[74] In healthy adults, high homocysteine was associated with 3.8 times the risk of fracture in men and 2.8 times the risk in women.[75] Scientists believe that elevated homocysteine could be a clinical sign of osteoporosis related to nutritional deficiencies.[74] High homocysteine may especially increase the risk of fractures in people suffering from underlying illnesses, such as Parkinson's disease or a history of stroke.[76,77]

Schizophrenia: Some scientists believe that schizophrenia begins even before birth. Pregnant women with high levels of homocysteine were found to be more likely to have children who later developed schizophrenia. Researchers believe this may be one more reason why pregnant women should take steps to correct elevated homocysteine levels.[78]

Stroke: Over the course of 10 years, men with high homocysteine levels had nearly three times the risk of stroke as men with low levels of homocysteine. High serum folate levels, however, were associated with protection against stroke.[79]

2006

Coronary Artery Disease: People with elevated levels of homocysteine were found to have more calcification of the coronary arteries than people with lower homocysteine values. Coronary artery calcification is a measure of the severity of coronary artery disease.[80]

Kidney Disease: Patients with chronic kidney disease were found to have significantly higher levels of homocysteine than healthy people. In fact, 89% of these patients had homocysteine levels greater than 14 µmol/L, which may increase their risk of developing many other diseases.[81]

Macular Degeneration: Patients with age-related macular degeneration, a common cause of visual loss, were found to have higher homocysteine levels than healthy subjects. Levels above 12 µmol/L particularly increased the risk of macular degeneration. High homocysteine level may thus be an independent risk factor for age-related macular degeneration.[82]

Osteoporosis: Women with high homocysteine levels were found to have significantly lower bone mineral density in the hip than control subjects. In fact, the risk of low bone density was 96% higher among women with high homocysteine (greater than 15 µmol/L) compared to women with lower homocysteine (less than 9 µmol/L). Homocysteine may be a modifiable risk factor for osteoporosis in women.[83]

Schizophrenia: Homocysteine levels are extremely high in many patients with schizophrenia. When these individuals used vitamins to decrease homocysteine, their symptoms of schizophrenia lessened.[84]

CONCLUSION

Elevated homocysteine levels have now been correlated with a wide array of illnesses, including heart disease, stroke, osteoporosis, depression, schizophrenia, macular degeneration, cervical cancer, and birth defects.

Fortunately, those seeking to safeguard their health and longevity can readily modulate elevated homocysteine levels using nutritional therapies such as vitamins B6 and B12, folic acid, and trimethylglycine.[85] These important nutritional strategies may help you avert the wide array of diseases that have been found to accompany excessive levels of homocysteine.

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