

The Role of Homocysteine and B Vitamins In Erectile Dysfunction

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How B Vitamins Can Be Transformative for Erection Quality in Individuals Poorly Responsive to Phosphodiesterase Type-5 Inhibitors.

Numerous studies have shown a relationship between homocysteine (HCY) elevation and erectile dysfunction (ED). Elevated levels of HCY are associated with endothelial dysfunction and uncoupling of the nitric oxide synthase enzyme;[1],[2] thus, we also see a relationship between hyper-HCY and conditions with vascular underpinnings, including cardiovascular disease,[3] cognitive decline and Alzheimer's disease,[4],[5] and chronic kidney disease.[6] High levels of HCY also create oxidative stress by a variety of mechanisms,[7],[8],[9] hence its broad relationship with many chronic conditions including depression and metabolic disease.[10],[11],[12],[13]

A 2018 systemic review and meta-analysis of nine studies including 1,320 men found that the men with ED were approximately twice as likely to have elevated levels of HCY.[14] Elevated homocysteine has even been shown to be an independent risk factor for ED, particularly when it exceeds 12.65 $\mu\text{mol/L}$. [15] It has been reported that HCY levels above 14.3 $\mu\text{mol/L}$ increases the risk of ED nearly fivefold in men with diabetes.[16]

Proper metabolism of HCY requires numerous B vitamins and depends on the functionality of several enzymes. Depletion of vitamin B12 or folate can have a major impact on HCY,

increasing serum HCY by a factor of three to 20 times the upper normal limit.[17],[18] Low levels of folic acid have been shown in men with ED in multiple clinical studies.[19],[20] In addition to assessing B12 and folate levels, evaluation of serum methylmalonic acid (MMA) is important to distinguish between B12 and folate deficiencies. When MMA is *not* elevated but HCY is, a deficiency of folate is indicated, while if both are elevated, B12 is deficient.[21] However, if both are elevated, folate deficiency cannot be ruled out.

Of these two B vitamins, folate stands out as an intervention for specifically addressing ED, with multiple clinical studies supporting its use. In men ages 30 to 60 diagnosed with idiopathic vasculogenic ED, supplementation of 500 µg of folic acid daily for three months significantly improved median International Index of Erectile Function (IIEF-5) scores from 6 to 14.[22] Parameters related to penile blood velocity also had highly significant improvements with the intervention. Although it was not a criteria for study inclusion, HCY levels were significantly higher at baseline in individuals diagnosed with ED (median of 2.84 µmol/L) compared to the control population, and were significantly reduced with the intervention to a median value of 0.19 µmol/L.

Folic acid has been shown in a randomized, double-blind, placebo-controlled trial to improve ED scores in men with type 2 diabetes (T2D) when taken as an adjunctive treatment to a phosphodiesterase type 5 inhibitor (PDE5I). After being given folic acid at a dose of 5 mg a day for three months, an improvement in mean IIEF-5 scores from 11.65 to 16.80 was seen in those receiving both interventions, with final scores also being significantly better than those in the placebo group who received only the PDE5I medication.[23]

Folic acid also has been investigated in combination with inositol in patients with T2D. Inositol has been described as being functionally similar to B vitamins, but, because the body produces it, it is not an essential dietary substance.[24] In the individuals with T2D, those receiving 400 µg of folic acid in combination with 4 g of myoinositol daily for 12 weeks had significantly improved IIEF-5 scores from 12 to 20, while there were no significant improvements in the placebo group.[25]

One reason why supplemental folate is a key factor for homocysteine metabolism relates to the enzyme methylenetetrahydrofolate reductase (MTHFR). MTHFR converts methylenetetrahydrofolate to its more biologically active form, 5-methyltetrahydrofolate. A variant of the MTHFR enzyme, known as the 677TT polymorphism, has been shown to be more common in males with vasculogenic ED, particularly those who experience the problem at a young age.[26] With this genetic variant, homocysteine metabolism is compromised as the “gears” that must “rotate” to convert it to methionine in essence get stuck because there are inadequate amounts of 5-MTHF. One can push the system to cycle again by adding additional folate, ideally in the form of 5-MTHF to bypass the poorly functioning MTHFR enzyme.[27]

One study specifically considered the impact of folate and vitamin B6 supplementation on erectile function in individuals with the MTHFR 677TT and heterozygous 677CT variants who were nonresponsive to PDE5I treatment.^[28] After an initial intervention of treatment with the PDE5I for two months, a group of 18 individuals who were PDE5I nonresponders were selected for the nutritional intervention, which consisted of 15 mg of folic acid/day and 600 mg of

pyridoxine hydrochloride (vitamin B6) twice weekly. At the re-evaluation point six weeks later, the combination of folic acid and vitamin B6 was found to improve IIEF-5 scores in 88.9% of this population.

Given their essentiality for all aspects of physical function, B vitamins should come high at the list of nutritional considerations for any man dealing with erectile dysfunction, particularly if it comes at a young age. Beyond this, there are numerous other nutrients that enhance nitric oxide production, as well as French Maritime pine bark extract, which both offer additional benefits for cardiovascular health.

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