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EDITORIAL

A Case for Not Going Global: "Americanization" of Diet Accelerates Hepatic Mitochondrial Injury in a Model of Wilson Disease

Perhaps globalization is not always best, and we should avoid exporting the unhealthy diet responsible for the "American lifestyle induced obesity syndrome" that negatively impacts liver health. Adopt this unhealthy diet and add a sprinkle of copper, and you have a recipe for worsening liver disease. Einer et al[1] gave the equivalent of the American lifestyle high-caloric diet to a rodent model of Wilson disease (WD), and bad things happened. There was increased oxidative stress, promotion of mitochondrial and hepatocellular injury, and earlier-onset liver disease. Proof that copper is the "accelerant" in this model comes from its effects on hepatic mitochondria, where it caused enhanced beta oxidation and breakdown of fatty acids, increased acetyl CoA and cytosolic triglycerides, impaired adenosine triphosphate production, increased hydrogen peroxide production, and elevated synthesis of cholesterol and bile salts.[1]

Copper is an essential element required for neurotransmitter and collagen biosynthesis, angiogenesis, wound healing, and iron utilization.[2] Prosthetic copper in cytochrome c oxidase and in Cu/Zn superoxide dismutase (SOD) is critical for their function. Both cytochrome oxidase and SOD2 are localized to mitochondria, and their enzymatic activity modulates reactive oxygen species within cells.[3] The mitochondria are a target for oxidative injury in copper overloaded states. In WD, excess copper leads to structural changes within hepatocellular mitochondria, including organelle elongations and cristae dilatations.[4] The extent of structural damage to mitochondria directly correlates with the degree of copper overload.[4] Copper accumulation in mitochondria leads to emergence of reactive oxygen species and disintegration of the mitochondrial membrane, signaling cell death.[5] Further supporting the role of mitochondrial damage in the pathogenesis of WD is the successful use of chelation therapy with D-penicillamine in reversing mitochondrial abnormalities.[6] Conversely, in individuals who failed to respond to chelation therapy, their hepatic mitochondria still had significant amounts of copper overload and structural changes.[5] Methanobactin, a post-translational modified peptide from a proteobacterium *Methylosinus trichosporium,* has a high copper binding affinity and therefore was used previously, and again in this study by Einer et al,[1] to chelate mitochondrial copper. It was able to achieve this effect because methanobactin is permeable through the mitochondrial membrane and can remove excess mitochondrial copper better than D-penicillamine or trientene.[7] Lichtmannegger et al[8] showed that treatment of ATP7b−/− rats with methanobactin reduced mitochondrial copper, restored mitochondrial structure and function, and lacked liver damage. Studies have suggested that changes in mitochondrial copper content, structure, and functionality play a pivotal role in early response to chelation treatment and potentially predict response or progression of liver disease.[8] Thus, "happy" mitochondria are a key ingredient in the recipe for successful rescue of copper toxicity, and "unhappy" injured mitochondria portend disease progression or treatment failure.

Hepatic steatosis seen in WD is thought to be directly related to copper overload and copper toxicity, in particular to the mitochondria of hepatocytes.[9] There have been a few studies suggesting an indirect link between copper overload and steatosis, with steatosis occurring with other environmental exposures.[10] One potential influence could be a dysregulation of lipids in patients with WD. Mutations in the apolipoprotein genes APOEε3 and APOEε4 were associated with liver disease, and lower levels of serum cholesterol were seen in some WD patients.[11] In a study by Stattermayer et al,[12] the presence of PNPLA3 G genotype was thought to contribute to steatosis in WD patients. They found that age and PNPLA3 G genotype had a significant impact on the presence of hepatic steatosis, but hepatic copper content did not. However, PNPLA3 G genotype was also associated with mitochondrial dysfunction, again pointing toward the pivotal role of hepatic mitochondria in WD.[13] The plasticity of the mitochondria, compartmentalization of copper in the mitochondria, and other environmental factors could partially explain the wide range of phenotypic differences in WD.

Some of the critical, but yet unanswered, questions raised by these ideas include whether aggressive copper chelation therapy before exposure to a high-calorie diet could mitigate the injury, and whether a combination of a low fat and fructose diet in addition to efforts to reduce hepatic copper could prevent progression of WD. If this were to occur, then we may place an increased emphasis on "decoppering" and intensive dietary counseling to prevent further mitochondrial injury. Perhaps then we can begin to change the "recipe" and start to shift the copper balance in favor of our patients.

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Conflicts of interest
This author discloses the following: Michael L. Schilsky is on the advisory boards of Wilson Therapeutics, Vivet and Kadmon. He is the Chair of the Medical Advisory Committee of the Wilson Disease Association and has received grant support for studies from Wilson Therapeutics (now Alexion) and GMPO. The remaining author discloses no conflicts.


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