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## Authors' response

We thank Leslie M. Klevay[1] for comments on our article and also for providing an interesting review on the association between copper deficiency and age related eye lesions.

Klevay suggests, based on literary evidence that copper supplementation might help people with ARMD and in general, neuropathies. We endorse that copper deficiency is associated with hyper-homocystemia and oxidative stress[2]. However, it has been seen in patients with ARMD and other retinopathies that circulating copper level is low but their corresponding tissue levels are higher than in normal individuals which indicates that the copper transport and homeostasis may be affected[2,3]. Copper is proangiogeneic and stimulates vascular endothelial growth factor (VEGF) expression, while use of agents to reduce copper uptake in endothelial cells reverses the condition[4]. Therefore, before advocating copper supplementation, one must know the biochemical mechanism. Why and how does homocysteine (Hcy) influence the intracellular and plasma levels of copper in an individual? In reverse, homocysteine induces cardiac hypertrophy by upregulating expression of ATP7a, a protein, which is responsible for copper efflux[5]. The direct effect of Hcy on copper homeostasis in cardiac cells is that it induces the expression of ATP7a - the efflux chaperone which drains out the copper from the cell and the delivery of copper to superoxide dismutase (SOD) enzyme and cytochrome c oxidase (COX) activity is thus hindered.

They have also reported increased serum copper levels in these conditions[5].

The homeostasis mechanism of copper and the effect of Hcy need to be studied with respect to ocular cells and tissues, for example, in retinal pigment epithelial cells (RPE), choroid and retina. We observed a decrease copper levels in plasma of idiopathic retinal vascular diseases[3]. The choroid and retinal tissues showed increased copper accumulation in the ARMD tissues[6] indicating intracellular copper accumulation in ARMD. A study needs to be conducted to understand the effect of varying concentrations of homocysteine on copper uptake and efflux in RPE cells.

The increased Hcy was associated with low levels of copper resulting in decreased (amine oxidase) lysyl oxidase activity in vascular diseases[7]. It is known that increased levels of Hcy chelate copper and impair copper dependent enzymes and further, copper supplementation improves the cardiac function in pressure overload heart failure[7]. Copper chelating peptides are antiangiogenic by restricting copper accumulation inside endothelium[8].

Dong *et al*[9] showed that homocysteine disturbed copper homeostasis leading to mitochondrial dysfunction and endothelial cell injury.

In short, we need to study more to understand the relationship between copper and Hcy, at the levels of the protein involvement in Hcy pathways, copper transport and homeostasis.

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