Opinion

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Laboratory role in measuring transthyretin and homocysteine

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It has been a half-century since Ingenbleek and Carpentier reported that low transthyretin (TTR) is a hallmark of kwashiorkor, severe protein-energy malnutrition in African Children. This protein is a 55-KDa protein that is the third transport protein (beside albumin and thyroxin-binding globulin) that carries thyroxin in the circulation synthesized by the liver.[1,2] It had long been known that serum albumin declines with protein under nutrition or the systemic inflammatory response, such as burn injury or trauma. However, the serum albumin has a half-life in the circulation of 20days, while TTR has a very short half-life. Moreover, the serum concentration of transthyretin is directly correlated with lean body mass.[1–3]

Transthyretin circulates with thyroxin and retinol-binding protein in a complex. Under the activity of systemic inflammatory response TTR, TBG and CBG are suppressed. TTR is an essential protein in the visceral compartment. Its hepatic synthesis is regulated consistent with the adequacy and levels of protein and energy intakes. The measurement of this protein has been challenged with respect to urinary dialysis, and with respect to acute injury, but these issues have been addressed.[4,5] TTR plasma levels are proportionate to the severity of insult and reflects the magnitude and adequacy of the stress response, which depend on the preceding nutritional status. The level of TTR is directly related to the dietary intake of methionine (MET). The source of MET from a vegan diet provides roughly half the MET per gram than an animal source. This has been a subject of considerable discussion, mainly because of the effect of animal sourced food on serum lipids and the relief of obesity and of cardiovascular disease. The fact remains that MET sulfur (S) is a essential amino acid (AA) that is only obtained by dietary intake, and it is used to synthesize other AAs.[6]

Inhibition of cystathionine-β-synthase activity causes increased homocysteine (HCY) and decreased cysteine and glutathione. Sulfur (S)-deficiency is a causal factor in hyper homocysteinemic patients. Elevation of homocysteine plasma levels is correlated with LBM reduction and declining TTR plasma levels. Cystathionine-β-synthase activity suppression promotes the upstream accumulation and remethylation of homocysteine molecules.[3]

McCully and Wilson described arteriosclerotic plaques in the aorta and arteries of rabbits given homocysteine thiolactone, methionine or homocysteic acid.[7] This followed the discovery of arteriosclerotic plaques in children with homocystinuria caused by inherited enzymatic deficiencies of cystathionine synthase, methionine synthase, or methylene-tetrahydrofolate reductase.[8] Arterial plaques were not only found, but also in normal and hypophysectomized animals, and by discovery of a pathway for conversion of homocysteine thiolactone to sulfate in cell cultures from children with homocystinuria. Two molecules of thioretinamide combine with cobalamin to form thioretinaco, and based on its structure, it was proposed that the active site of adenosine triphosphate synthesis in mitochondria is attributed to oxidation to a disulfonium derivative by ozone, binding of oxygen, nicotinamide adenine dinucleotide and phosphate. A study be McCulln et al.[8,9] showed strong correlation (r=−0.71) between transthyretin and homocysteine which implicated lean body mass as a critical determinant of hyper homocysteinemia.

They concluded that low dietary intake of protein and sulfur amino acids by a plant-eating population leads to subclinical protein malnutrition. Thus, hyper homocysteinemia indicates increased vulnerability of these vegetarian subjects to cardiovascular diseases.[9] These works provide a challenge to the practice of laboratory medicine. Insurance payers are and have been indifferent to the laboratory in a diagnostic facilitating role. Physicians are stressed with patient evaluation and treatment loads. This could be where both the laboratory and dietitians engage in collaboration with respect to the elderly and high risk patients.

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Conflict of interest

The author declares no conflict of interest.

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