Pigmentation Markers: More Color in the Picture of Uremic Toxicity?

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The retention of solutes during kidney failure gives rise to a complex pattern of accumulation. In 2003, the uremic compounds which until then had been described in the peer-reviewed literature were tabulated by the European Uremic Toxin Work Group and a total number of 90 different compounds were listed [1]. In the meantime, several other compounds have been identified [2], and the results obtained with proteome analysis, describing more than 1,000 peptidic compounds with a molecular weight of >800 Da, in ultrafiltrates from hemodialysis patients [3] infer that what we currently know in fact reveals only the tip of the iceberg.

To enable the identification of toxicity pathways and to develop therapeutic strategies for the removal of relevant toxic solutes or to counteract their metabolic effects, knowledge on uremic retention must be as complete as possible.

In this issue of Blood Purification, pigmentation markers or melanins, previously unknown as retention solutes, are added as a new set of uremic compounds to the existing list of known uremic toxins [1] by Murakami et al. [4]. At the same time the authors offer information related to one of the most intriguing but insufficiently explained epiphenomena of the uremic syndrome: hyperpigmentation from which many patients with chronic kidney disease suffer [5, 6]. Recent nephrological literature pays virtually no attention to this problem.

The results reported by Murakami et al. [4] should be considered with care as they are based on only 16 hemodialysis patients and, therefore, need confirmation; of note, 6 of these patients were diabetics, who are known to suffer from an exponential degree of oxidative stress as compared to non-diabetic chronic kidney failure patients. This is a matter of concern since most of the solutes depicted in their article are the result of oxidative modifications. For this reason, when larger populations are studied for the concentration of these solutes, it would be interesting to compare diabetics with non-diabetics.

Apart from their link to melanoma [7] and skin and hair pigmentation [8, 9], there is only scant information about the clinical and biochemical significance of these pigmentation markers, but a number of features referred to in the article by Murakami et al. [4] are nevertheless striking, especially for those interested in uremic toxicity and the therapeutic options for fighting this condition. Basically, four reflections come to mind.

First, as metabolites of tyrosine, these molecules have family ties with other groups of uremic retention compounds, most of all the phenols, which also originate from tyrosine [10]. In addition, the structural similitude of eumelanin with dihydroxyindole [11] also suggests a tie with another group of important uremic retention solutes, the indoles. Common features of all these categories of molecules are their protein binding and the difficulty of removing them by standard dialysis therapies.
Second, generation of several of the members of this group, e.g. eumelanin, protein-bound 3,4-dihydroxyphenylalanine and 5-S-cysteinyldopa [11–13], is the result of oxidative processes. Since a large fraction of uremic patients, especially those on dialysis, suffer from a protracted micro-inflammatory state [14] resulting in oxidative free radical production [15], the generation of several of the pigmentation markers is thus facilitated by the uremic condition, and this sequence of events might by itself be a suitable explanation for a large proportion of hyperpigmentation observed in chronic kidney disease. Hence, if the held hypothesis is correct, hyperpigmentation could be avoided by eradicating or discouraging any inflammation-generating condition, such as chronic sources of infection like periodontitis, the use of central vein catheters, the application of bio-incompatible dialysis membranes, and/or contact with bacteriologically contaminated dialysis water. With the link to inflammation in mind, it is a bit unfortunate that Murakami et al. [4] did not assess any correlation with inflammatory parameters such as C-reactive protein or cytokine levels.

One might consider the possibility that pigmentation markers could be used as indicators of oxidative stress in uremia. Studies in this context might offer useful information. One should, however, be conscious of the fact that the concentration of these compounds not only depends on oxidation, but also on (lack of) clearance by the uremic condition, and this sequence of events might by itself be a suitable explanation for a large proportion of hyperpigmentation observed in chronic kidney disease. Hence, if the held hypothesis is correct, hyperpigmentation could be avoided by eradicating or discouraging any inflammation-generating condition, such as chronic sources of infection like periodontitis, the use of central vein catheters, the application of bio-incompatible dialysis membranes, and/or contact with bacteriologically contaminated dialysis water. With the link to inflammation in mind, it is a bit unfortunate that Murakami et al. [4] did not assess any correlation with inflammatory parameters such as C-reactive protein or cytokine levels.

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References


