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Title: The reduced Co^{2+}-binding ability of ischaemia-modified albumin is unlikely to be due to oxidative modification of the N-terminus

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Abbreviations: FFA, free fatty acid; IMA, ischaemia-modified albumin

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To the Editor,

We read with interest the recent article by Giannone *et al.* where the use of ischaemia-modified albumin (IMA) as a molecular marker of bacterial infection in patients with cirrhosis was assessed [1]. IMA corresponds to a "modified" form of albumin that exhibits reduced ability to bind Co^{2+} (with its presence associated with certain medical conditions, including ischaemia). The study revealed a positive correlation between circulating IMA levels and infection in the examined cohort, suggesting that IMA may be a useful marker for screening and monitoring infection in subjects with cirrhosis. Although these findings are indeed interesting, the authors perpetuate a previously held belief that IMA is a modified form of albumin oxidised at the N-terminus, a known binding site for Cu^{2+} and Ni^{2+} ions.

Recent evidence suggests strongly that the basis of IMA is unlikely to be oxidative modification at the N-terminus. It has been shown that plasma IMA levels and N-terminal albumin modification (as probed using N-terminally-directed antibodies) do not correlate in acute coronary syndrome [2]. Also rapid clearance of IMA, observed within hours of an ischaemic event, is incompatible with serum albumin's 19-day circulating half-life [3]. Moreover, the N-terminus is not a preferred Co^{2+}-binding site on albumin [4]. Such findings, together with the observation that elevated plasma free fatty acid (FFA) levels are associated with disease states where high IMA levels are observed (see [5]), led us to examine whether IMA may be FFA-loaded albumin. The effects of FFAs on Co^{2+} binding to albumin were examined *in vitro*, where it was found that physiologically relevant concentrations of the long-chain FFA myristate reduced the Co^{2+}-binding affinity and capacity of albumin at two sites [5], known as sites A and B, which are preferred binding sites for Co^{2+} [4]. This also resulted in a corresponding increase in measured "IMA" using the standard albumin-cobalt binding assay [5].

These observations have important implications for the study by Giannone *et al.,* as it appears that IMA is strictly speaking neither a marker for oxidative stress nor infection but more likely a proxy measurement of plasma FFA levels. Given that the authors discuss the basis of their results exclusively in the context of covalent albumin modifications (which in light of current evidence are unlikely origins for IMA), a re-evaluation of their data considering potential changes in FFA metabolism within their cohort may provide a more consistent explanation for the reported findings.

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