specific AOPP prepared in vitro by exposure of human serum albumin (HSA) to HOCl displayed properties similar, yet not identical, to those products isolated from blood of uremic patients. According to the authors, different properties may originate from a heterogeneous nature of the whole AOPP. This indeed may be a very important albeit not sufficiently recognized fact. In 1995, we reported on a macromolecular protein complex (MPC) present in increased quantities in blood of diabetic patients with nephropathy [2], the molecular properties of which are similar, if not identical, to AOPP. Although we have suspected that MPC may contain free radical–modified HSA, no such antigen could be detected by a specific enzyme-linked immunosorbent assay (ELISA) test. However, we have subsequently documented the presence in MPC of both fibrinogen A alpha chain and triglyceride-rich lipoprotein.

Moreover, we were able to prepare a similar complex in vitro by exposure of plasma to a hydroxyl radical generating system [3]. Because the system contained ascorbic acid and a transition metal, it was suggestive that MPC may be formed in vitro by a reductive rather than oxidative conditions.

In conclusion, it appears that both MPC and AOPP represent the same class of free radical–modified proteins circulating in blood of uremic patients. It is, however, not clear whether these products are formed by the action of oxidizing or reducing radical oxygen species [4].

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REFERENCES

1. WITKO-SARSAT V, GAUSSON V, NGUYEN A-H, *et al*: AOPP-induced activation of human neutrophil and monocyte oxidative metabolism: A potential target for N-acetylcysteine treatment in dialysis patients. *Kidney Int* 64:82–91, 2003
2. LIPINSKI B, FEDERMAN SM, KROLEWSKI AS: Plasma macromolecular protein complex: Interaction with fibrin and fibrinolysis. *Thrombos Res* 78:461–465, 1995
3. LIPINSKI B, LIPINSKA I, KATO Y: Is the macromolecular protein complex (MPC) a marker of oxidative stress in diabetes mellitus? *Diabeteologia* 44:1356, 2001
4. LIPINSKI B: Evidence in support of a concept of reductive stress. *Br J Nutrition* 87:93–94, 2002

Reply from the Authors

We wish to thank Dr. Lipinski for his most pertinent remarks. We agree that the species isolated from the blood of diabetic patients, macromolecular complex protein complex (MPC), described in the laboratory of Dr. Lipinski could, most likely, be included in the group of oxidatively-modified proteins including advanced oxidation protein products (AOPP) [1].

We have recently obtained information on the biochemical and molecular characteristics of AOPP. The use of various analytical techniques enabled localizing and identifying the main oxidized proteins in hemodialysis (HD) plasma with human serurm albumin (HAS). To interpret the spectral modifications detected in HD plasma fractions we described in detail some structural modifications that occur as a result of plasma or HSA treatment with HOCl. Our results indicate that HOCl, and not NO_2 generated by myeloperoxidase (MPO), represents a pathway for AOPP production in plasma proteins exposed to activated phagocytes (manuscript submitted for publication). However, this pathway is not exclusive and other oxido-reduction reactions may occur.

The fact that MPC did not react in an enzyme-linked immunosorbent assay (ELISA) specific for the detection of oxidized proteins might be due to restricted epitopes, which might not be apparent on MPC. Therefore, the presence of oxidatively modified protein features in MPC could not be ruled out. Interestingly, MPC contained fibrinogen A alpha chain and triglyceride-rich lipoprotein, the latter also being present in plasma AOPP. In our opinion, the evidence that MPC could be obtained by exposing plasma to hydroxyl radical confirmed that MPC could be generated by oxidants, even if this hydroxyl radical–generating system involved reducing systems such as ascorbic acid and transition metals. Indeed, protein reduction would prevent disulfide bridges and decreased protein cross-linking.

The report of the group of Dr. Lipinski extends the concept of the biologic and pathophysiologic relevance of oxidatively modified proteins. We have recently reported that AOPP could induce interleukin (IL)-8 synthesis by neutrophils and by monocytes, thus corroborating our previous results that demonstrate that AOPP are inflammatory mediators [2]. Therefore, further investigation on the involvement of AOPP and/or MPC should be performed, especially in diabetic or in uremic patients.

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REFERENCES

1. WITKO-SARSAT V, FRIEDLANDER M, NGUYEN KT, *et al*: Advanced oxidation protein products (AOPP) as novel mediators of inflammation and monocyte activation in chronic renal failure. *J Immunol* 161: 2524–2532, 1998
2. WITKO-SARSAT V, GAUSSON V, DESCAMPS-LATSCHA B: Are advanced oxidation protein products potential uremic toxins? *Kidney Int* 63(Suppl):S11–S14, 2003