Elevated Circulating Levels of Hyaluronan in Long-Term Hemodialysis Patients with Dialysis-Associated Arthropathy: What Does It Mean?

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Dear Sir,

We were very interested in the paper of Dr Ozasa [1] relative to plasma levels of hyaluronan (HA) in chronic hemodialysis patients exhibiting characteristic symptoms of dialysis-associated arthropathy (DAA). As it is ubiquitous by nature, HA is not disease specific, but recent studies in joint disorders suggest that it may be a marker of synovial inflammation rather than of the systemic inflammatory reaction [2]. As such, it would be very exciting to look for an association of HA as a potential marker of synovitis with amyloid deposits in joints of long-term hemodialysis patients. Using a highly sensitive radiometric assay ('HA test 50' Pharmacia, Sweden), we found that patients with DAA according to previously published criteria [3] exhibited significantly higher serum HA levels ($524 \pm 499 \mu\text{g/l}$, mean $\pm$ SD; $n = 13$) than control hemodialysis patients ($249 \pm 196 \mu\text{g/l}$; $n = 25$; $p < 0.01$). These preliminary results are in good agreement with those of Ozasa et al. [1] and confirm Honkanen's et al. [4] who reported the highest HA levels in 2 dialysis patients with, respectively, carpal tunnel syndrome and bilateral shoulder pain. In contrast, Turney et al. [5] observed a 'normal' median HA level in DAA ($200 \mu\text{g/l}$), but their criteria for DAA diagnosis were not specified. HA levels appeared increased in DAA, but the question is why?

Age may confound our results since DAA patients were significantly older (69.7 ± 11.3 years) than hemodialysis controls (60.0 ± 17.5 years; $p < 0.05$), much more so that HA levels increase with age in health and uremia [6].

Nevertheless, looking for a correlation between age and serum HA levels in DAA then would be very difficult, since the frequency of DAA increases with age [7] while HA levels are simultaneously influenced by the course of the disease as in joint disorders.

Dialysis duration may also confound our study, since DAA patients underwent hemodialysis for longer time periods than the hemodialysis controls (7.3 ± 5.3 vs. 3.8 ± 3.7 years). In their pioneering study, Hällgren et al [6] reported no correlation between HA levels and duration of

dialysis as do Ozasa et al [1]. Other recent studies suggest a close correlation between circulating HA and the duration of dialysis, confirmed by a relationship with serum β_2 -microglobulin levels [4, 5]. To date, however, no analogous study has been done comparing DAA with dialysis controls matched for dialysis duration.

As serum HA levels are significantly increased in patients with chronic renal failure independent of hemodialysis [4, 6], one may ask whether circulating HA actually reflects renal impairment. The lack of permanent correlation between HA and either serum creatinine, type of dialysis [4-6] or dialysis membranes used [4] and the reduced proportion of small-molecular-weight fragments of HA in serum [5] suggest that diminished renal clearance is probably not the main source of elevated HA levels. In addition, the influence of residual renal function can easily be reduced when studies are done in virtually anuric DAA patients [1] or oligoanuric patients whose urinary output is assessed.

The results of Turney et al. [5] raise the question of the origin of high-molecular-weight HA in the serum of dialysis patients. Based on the molecular-weight-dependent uptake of HA in the liver, a generalized dysfunction of the endothelial system has been evoked through possible endothelial receptor blockade. Further studies are required to investigate if the proportion of high-molecular-weight circulating HA is larger in DAA patients than in hemodialysis controls. Another explanation involves an increased HA outflow to the circulation, as a reflection of an accelerated 'aging' of the connective tissue [6]. As the incidence of DAA increases with age at the beginning of dialysis [7], longitudinal studies are needed to investigate whether DAA strengthens the disturbed connective-tissue metabolism inherent in chronic renal failure. Finally, excessive HA synthesis has to be considered. As numerous studies have reported elevated circulating cytokine levels in chronic hemodialysis patients [8, 9], a cytokine-mediated HA increase has been suggested [1, 5]. However, a 'circulating' mechanism seems unlikely in DAA, since cytokines with major roles in the acute phase response should trigger acute phase reactants (APR) rather than HA synthesis, even with different kinetics. Moreover, studies of C-reactive protein suggest that chronic inflammatory reactions occur in long-term hemodialysis patients, but an inflammatory basis for DAA remains controversial [1, 10]. With this in mind, the contrast between the high HA lev-

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els and the medium APR levels in DAA could simply reflect that these abnormalities are the consequence of separate pathways related to the disease, including an increased HA synthesis in the synovium of the affected joints [1]. This hypothesis requires subsequent demonstration, but recent work [11] using tenosynovial tissues from patients with carpal tunnel syndrome showed a mononuclear cell infiltration with high production of IL-1 and IL-6-like activities. As these cytokines are able to trigger HA synthesis by resident cells and to induce cellular proliferation within the connective tissue [12], a local overload of HA is then plausible.

In conclusion, we confirm the potential use of circulating HA as a biological marker of DAA, although much more work is required to evaluate its pathophysiological relevance in this disease.

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