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

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 ± 499 µg/l, mean ± SD; n = 13) than control hemodialysis patients (249 ± 196 µg/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 µg/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

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**Letter to the Editor**

Nephron 1993;64:498-499

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*aURA CNRS 1288, Faculté de Médecine; bServices de Néphrologie et de Rhumatologie, Hôpital de Nancy-Brabois, Vandœuvre, France

Dr. Patrick Netter, URA CNRS 1288, Faculté de Médecine, BP 184, F-54505 Vandœuvre Cedex (France)
dialysis as do Ozasa et al. Other recent studies suggest a close correlation between circulating 
HA and the duration of dialysis, confirmed by a relationship with serum β2-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 cre-atinine, 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 cyto-kine-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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0028-2766/93/
0643-0498 $2.75/0

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 tenosyno-vial 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 works are required to evaluate its physiopathological relevance in this 
disease. 

References


