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, Häggren 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 ß2-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-


