

### Serum syndecan-1 in patients with newly diagnosed monoclonal proteinemia

Serum syndecan-1 was investigated in 189 patients with newly diagnosed monoclonal proteinemia [the diagnoses were multiple myeloma (66), monoclonal gammopathies of undetermined significance (MGUS; n=54), provisional MGUS (no bone marrow examination performed; n=69)] and 36 controls. Syndecan-1 levels ranged widely between all diagnostic categories and were of limited discriminatory value (sensitivity 68%, specificity 78%) in patients with newly diagnosed monoclonal proteinemia.

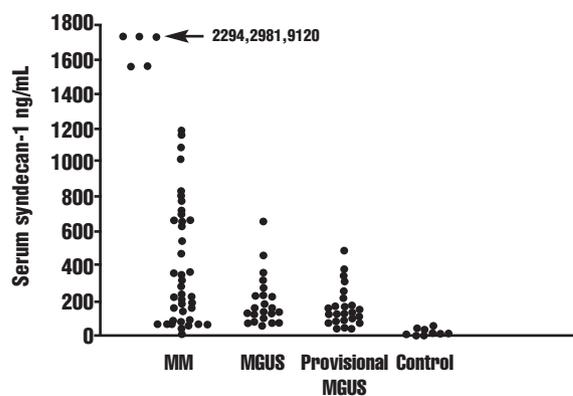
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In the large majority of patients with newly diagnosed monoclonal proteinemia (M-proteinemia) there is no evidence for the presence of multiple myeloma (MM), plasmacytoma, amyloidosis, macroglobulinemia or other hematologic malignancy. The need for an easily obtainable serum discriminatory marker is, therefore, much felt. The best-known serum marker for distinguishing between these categories is the M-protein concentration itself, but there is much overlap.<sup>1</sup> Serum syndecan-1 (CD-138) is an independent prognostic marker in MM and is expressed on pre-B-cells, lost during differentiation and re-expressed on normal and malignant plasma cells.<sup>2,3</sup>

We investigated the discriminatory value of serum syndecan-1 in 189 patients with newly diagnosed M-proteinemia registered prospectively in a population-based registry. During a three-year period 1464 patients with newly diagnosed M-proteinemia or MM were entered in the registry. Information on the patients' characteristics, laboratory tests results, M-protein-related diagnosis, comorbidity, results of bone marrow examination and skeletal X-rays, and therapy were documented annually. A serum sample taken at first diagnosis was frozen at -80°C. The set-up and contents of this registry have been described previously.<sup>4</sup> Of the 867 patients from whom serum was available, 189 were evaluable for the present study. The other 678 sera were excluded for the following reasons: other hematologic malignancy present, insufficient clinical data concerning the stage of disease, the serum was not taken at diagnosis or an insufficient amount was left for the syndecan-1 determination. The diagnoses of MM and MGUS were made according to the criteria described by Durie and Salmon.<sup>5</sup> In the absence of clinical evidence of MM or other hematologic malignancy and a low M-protein concentration (< 20 g/L) the patient is often diagnosed as having MGUS and a bone marrow examination is not considered to be necessary.<sup>6</sup> For precise definition, therefore, MGUS was divided in two categories: *definite* MGUS (confirmed by bone marrow examination) and *provisional* MGUS (no bone marrow examination performed). Control sera were used from patients without M-proteinemia, as confirmed by protein electrophoresis.

Syndecan-1 concentrations were determined using an enzyme-linked immunosorbent assay (Diaclone Research, Besançon, France). The median values of laboratory parameters for different diagnostic categories were compared using Mann-Whitney's test or the Kruskal-Wallis



**Figure 1.** Serum syndecan levels in 226 patients with newly diagnosed M-proteinemia. MM: multiple myeloma; MGUS: definite MGUS; prov MGUS: provisional MGUS. Median serum syndecan-1 levels in ng/mL (range): multiple myeloma 226 (3-9120); MGUS: 128 (50-656); provisional MGUS 91 (22-494), controls 5 (0-52).

**Table 1.** Median serum values (ranges) of syndecan-1 in patients with newly diagnosed M-proteinemia.

Category	N	Syndecan-1 ng/mL
Multiple myeloma (all)	66	226 (3-9120)
MM stage I	24	194 (3-667)
MM stage II	5	290 (160-1019)
MM stage III	37	238 (30-9120)
MGUS	54	128 (50-656)
Provisional MGUS*	69	91 (22-494)
Control patients	36	5 (0-52)

\*MGUS without confirmatory bone marrow examination.

test when appropriate. Survival curves were constructed using the Kaplan Meier method and compared with the log-rank test. Analyses were performed using SPSS 12.0 for Windows.

Serum syndecan-1 levels in all diagnostic categories of newly diagnosed M-proteinemia are shown in Figure 1 and Table 1. The median levels were highest in MM with significant differences between the diagnostic categories ( $p < 0.0001$ ); however, there was a wide overlap. These results are in accordance with two studies on smaller series comparing serum syndecan-1 levels in MGUS and MM.<sup>7,8</sup> In contrast to Seidel but in agreement with Maisnar, we were not able to demonstrate a relation between serum syndecan-1 levels and MM stages (Table 1;  $p = 0.06$ ).<sup>2,7</sup> Using a cut-off value of 166 ng/mL (i.e. the mean level  $\pm 2SD$  of normal human sera; information in kit leaflet) the sensitivity and specificity were 68% and 78%, respectively. Like Seidel *et al.* we confirmed the prognostic significance of high serum syndecan levels at diagnosis in patients with MM.<sup>2</sup> The median time of follow-up for patients with MM still alive was 8.1 (0.9-10.2) years. Patients with MM and high serum syndecan-1 levels ( $\geq 166$  g/L; n=45) had a median survival of 1.3 years compared to 4.7 years in 21 MM-patients with lower serum syndecan-1 levels ( $p = 0.0018$ ). In a Cox regression

analysis corrected for M-protein isotype and Salmon and Durie stage, an elevated concentration of serum syndecan remained of prognostic importance with a hazard ratio of 3.6 (95% CI 1.7-7.6).

During an 8.8 (4.3-10.7) year follow-up of all patients alive with definite MGUS or provisional MGUS (n=123) MM developed in only two patients at 6 and 12 months. One patient had a low level of serum syndecan (83 ng/mL) and the other had a high level (176 ng/mL). In conclusion, serum syndecan-1 is an important prognosticator for patients with MM, but this marker is of no discriminatory value in patients with newly diagnosed M-proteinemia.

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