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Diagnostic performance of transthyretin measurement in fat tissue of patients with ATTR amyloidosis

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Abstract: In this article, the diagnostic performance of a transthyretin (TTR) ELISA for detection and characterization of transthyretin-derived (ATTR) amyloid in abdominal subcutaneous fat tissue was studied. Fat tissue specimens were analyzed of 38 patients with ATTR amyloidosis, 70 controls, and 17 carriers of a TTR mutation. Amyloid amount was graded semi-quantitatively in Congo red-stained specimens (0–4+). Amyloid was extracted from tissue in guanidine, and the TTR concentration was measured using a sandwich TTR-ELISA. The TTR concentration of patients with ATTR amyloidosis (mean 0.84 ng/mg fat tissue) was significantly higher than controls ($p < 0.001$). With a TTR concentration of 0.13 ng/mg fat tissue as cut-off value, 32 of the 38 ATTR patients were identified resulting in a sensitivity of 84%. Sixty-seven of the 70 controls had values below the cut-off value resulting in a specificity of 96%. Thus, measuring TTR in fat tissue is useful for detecting ATTR amyloidosis and for characterizing amyloid as ATTR type.

Introduction: Unequivocal characterization of the type of amyloid is essential for assessing prognosis and treatment of patients with systemic amyloidosis. The diagnostic performance was studied of a transthyretin (TTR) ELISA for detection and characterization of transthyretin-derived (ATTR) amyloid in abdominal subcutaneous fat tissue.

Methods: Fat tissue specimens were analyzed of 38 consecutive patients with ATTR amyloidosis, 70 controls (30 disease controls, 20 AA amyloidosis, and 20 AL amyloidosis), and 17 carriers of a TTR mutation. The amount of amyloid was graded semi-quantitatively in Congo red-stained specimens (0, no visible amyloid; 1+, < 1% of surface; 2+, 1–10%; 3+, 10–60%; 4+, > 60%). Amyloid was extracted from tissue in guanidine, and the TTR concentration was measured using a sandwich TTR-ELISA.

Results and discussion: Log transformation was used to obtain normally distributed ranges of TTR values. Mean TTR concentration in all controls was 0.006 ng/mg fat tissue with a 95% interval (mean \pm 2SD) ranging from 0.0001 to 0.33 ng/mg

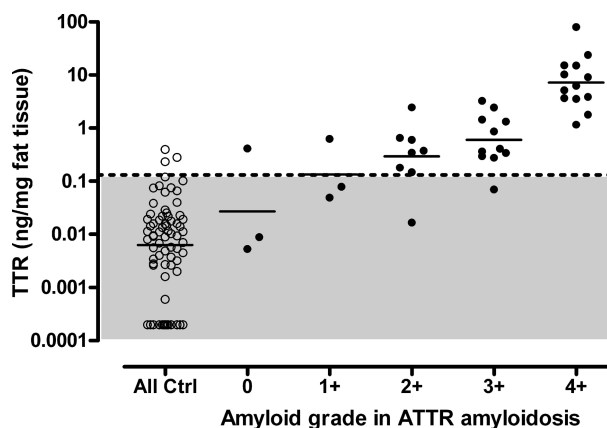


Figure 1. TTR concentration and amyloid grade in fat tissue of patients with ATTR amyloidosis. The dotted line marks the cut-off value (grey area, 0.13 ng/mg fat tissue). Horizontal lines denote the means of the log-transformed values.

fat tissue. The TTR concentration of patients with ATTR amyloidosis (mean 0.84 ng/mg fat tissue; 95% interval 0.012–58.4 ng/mg fat tissue) was significantly higher than controls ($p < 0.001$). When a TTR concentration of 0.13 ng/mg fat tissue was taken as cut-off value, 32 of the 38 ATTR patients were identified resulting in a sensitivity of 84% (95% confidence interval, 68–94%). Sixty-seven of the 70 controls had TTR values below the cut-off value resulting in a specificity of 96% (95% CI, 88–99%). Sixteen of the 17 carriers had values below the cut-off value.

The analysis of variance test showed a linear trend ($p < 0.0001$) of the mean TTR concentrations for higher amyloid grades: mean TTR 0.027, 0.13, 0.29, 0.60, and 7.2 for grade 0, 1+, 2+, 3+, and 4+, respectively (see Figure 1). The percentage of ATTR patients with TTR values above the upper reference limit increased from 33% for grade 0 to 33%, 88%, 91%, and 100% for grade 1+, 2+, 3+, and 4+, respectively.

We conclude that the quantification of TTR concentration of fat tissue is a useful new method for detecting ATTR amyloidosis and for characterizing amyloid as ATTR type. There is good concordance between the TTR concentration and the amount of amyloid in fat tissue of patients with ATTR amyloidosis. Limitations of the study are the relatively small number of ATTR patients, the small number of TTR mutations that have been investigated, and the high variation coefficient (> 30%) of the TTR sandwich ELISA that was used. Current work is directed to further improving accuracy and reproducibility of the TTR ELISA.

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The online version first published on 14 July 2011 showed the incorrect page numbers of this article. They have been now been corrected on this version.