UniversitätsKlinikum Heidelberg

# Amyloid load in fat tissue reflects severity of cardiac involvement and activity of plasma cell dyscrasia and is consecutively prognostic for survival in systemic light chain amyloidosis

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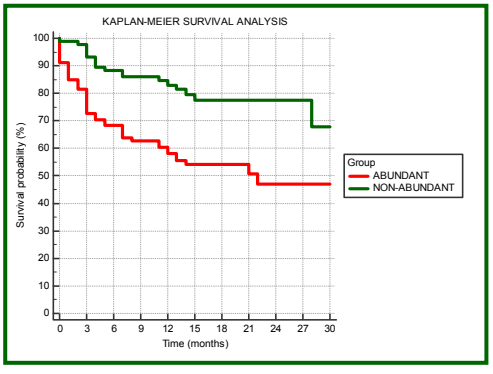
**INTRODUCTION:** Subcutaneous fat aspiration is a simple minimal-invasive technique to detect amyloid with high sensitivity and specificity (1). In addition, an association between amyloid load in fat tissue and its impact on survival was reported (2). We introduced this technique at the University Hospital Heidelberg in May 2013 with the support from the Amyloidosis Centre Groningen.

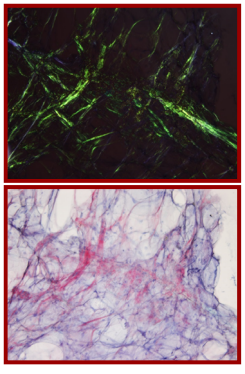
**MATERIALS & METHODS:** We prospectively analysed 183 untreated patients with biopsy-proven systemic light-chain (AL) amyloidosis between September 2013 and June 2015. Fat aspirates were analysed using a 100 watt polarisation microscope (Zeiss Axioplan 2) and graded according to involved surface area as presented (1): negative equals 0, below 1% equals 1+, 1 to 10% equals 2+, 10 to 60% equals 3+ and above 60% equals 4+. For simplification, we performed a split into abundant for 3+ and 4+ and non-abundant for 0, 1+ and 2+. Patients were also assessed clinically, received a broad laboratory analysis, an echocardiography and bone marrow (BM) diagnostics. Furthermore, for the majority of patients regular follow-ups were available (n=178). For organ involvement, we utilised the current consensus criteria (Tours), for cardiac staging, we classified according to (3).

**RESULTS:** Amyloid was detected in 94% (172/183) and was graded as 0+ in 11 (6%), 1+ in 38 (21%), 2+ in 40 (22%), 3+ in 36 (20%) and 4+ in 58 patients (32%). Patients graded as abundant had cardiac involvement significantly more often than patients graded as non-abundant (96% vs. 69%, p<0.001). Cardiac biomarkers and the markers for the underlying plasma cell dyscrasia were significantly higher for patients with abundant deposits compared to patients without these findings (for median values see Table 1). Patients classified as non-abundant had renal involvement significantly more often (63% vs. 40%, p<0.01). No correlation between severity of renal involvement and amyloid load could be detected. Females were classified as abundant significantly more frequently than men (n=47/78, 60% vs. n=47/105, 45%, p<0.05). Six months after fat aspiration 31% (29/93) of patients graded as abundant had died compared to only 12% (10/85) of patients graded as non-abundant (p<0.01).

**DISCUSSION & CONCLUSIONS:** Patients with abundant amyloid deposits in fat aspiration samples nearly always have cardiac involvement with severely increased cardiac biomarkers. Our findings suggest that abundant AL amyloid deposits in fat tissue reflect cardiac injury and the increase in mass. Survival (at six-months) is significantly reduced in patients with abundant amyloid deposits. To the contrary, we show that in renal AL amyloidosis no mass effect can be detected in subcutaneous fat tissue.

**REFERENCES:** 1 van Gameren II et al. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. Arthritis Rheum. 2006 Jun;54(6):2015-21. 2 van Gameren II et al. Amyloid load in fat tissue reflects disease severity and predicts survival in amyloidosis. Arthritis Care Res (Hoboken). 2010 Mar;62(3):296-301. 3 Dispenzieri A et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004 Sep 15;22(18):3751-7.



| | GRADING | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NON-ABUNDANT | | | ABUNDANT | | SUM | | SUM | | |
| | 0 | 1+ | 2+ | 3+ | 4+ | 0 | 1+ 2+ | 3+ | 4+ | p-Value |
| **SEPTAL WALL THICKNESS in mm** | | | | | | | | | | |
| Median | 12 | 12 | 13 | 17 | 16 | 13 | | 16 | | |
| ≤12mm | 6 | 20 | 13 | 5 | 8 | 39 (44%) | | 13 (14%) | | p<0.001 |
| >12mm | 5 | 18 | 26 | 30 | 50 | 49 (56%) | | 80 (86%) | | |
| **NT-PROBNP in ng/l** | | | | | | | | | | |
| Median | 505 | 1047 | 542 | 6911 | 6057 | 607 | | 6297 | | p<0.001 |
| <332ng/l | 5 | 12 | 14 | 3 | 1 | 31 (35%) | | 4 (4%) | | |
| 332-1799ng/l | 3 | 9 | 13 | 6 | 10 | 25 (28%) | | 16 (18%) | | not tested |
| 1800-8500ng/l | 3 | 15 | 10 | 13 | 24 | 28 (31%) | | 37 (41%) | | |
| >8500ng/l | | 2 | 3 | 14 | 20 | 5 (6%) | | 34 (37%) | | |
| **TROPONIN T in µg/l** | | | | | | | | | | |
| Median | 10 | 24 | 24 | 54 | 58 | 23 | | 55 | | |
| <25µg/l | 7 | 18 | 20 | 6 | 6 | 45 (53%) | | 12 (13%) | | p<0.001 |
| ≥25µg/l | 4 | 18 | 18 | 27 | 50 | 40 (47%) | | 77 (87%) | | |
| **TROPONIN I in µg/l** | | | | | | | | | | |
| Median | <0.04 | <0.04 | <0.04 | 0.10 | 0.12 | <0,04 | | 0,1 | | |
| <0.1µg/l | 10 | 34 | 27 | 16 | 24 | 71 (86%) | | 40 (49%) | | p<0.001 |
| ≥0.1µg/l | 1 | 3 | 8 | 17 | 24 | 12 (14%) | | 41 (51%) | | |
| **dFLC in mg/l** | | | | | | | | | | |
| Median | 73 | 114,5 | 94 | 219,5 | 366,5 | 96 | | 305 | | |
| <180mg/l | 7 | 24 | 25 | 16 | 15 | 56 (63%) | | 31 (33%) | | p<0.001 |
| ≥180mg/l | 4 | 14 | 15 | 20 | 43 | 33 (37%) | | 63 (67%) | | |
| **RENAL INVOLVEMENT (Consensus Criteria)** | | | | | | | | | | |
| No renal disease | 5 | 13 | 15 | 14 | 42 | 33 (37%) | | 56 (60%) | | p<0.003 |
| Renal disease | 6 | 25 | 25 | 22 | 16 | 56 (63%) | | 38 (40% | | |
| **RENAL STAGING (Palladini et al., Blood, 2014)** | | | | | | | | | | |
| Stage I | 3 | 5 | 7 | 7 | 4 | 15 | | 11 | | not |
| Stage II | 1 | 9 | 12 | 8 | 8 | 22 | | 16 | | significant |
| Stage III | 2 | 10 | 5 | 5 | 2 | 17 | | 7 | | (n.s.) |
| **eGFR in ml/min** | | | | | | | | | | |
| Median | 61 | 71 | 69 | 55 | 69 | 69 | | 63 | | n.s. |
| **PROTEINURIA in mg/day** | | | | | | | | | | |
| Median | 848 | 3477 | 2389 | 1932 | 253 | 2389 | | 446 | | |
| <5g/day | 9 | 19 | 26 | 26 | 40 | 54 (61%) | | 66 (80%) | | p<0.01 |
| ≥5g/day | 2 | 18 | 13 | 8 | 8 | 33 (39%) | | 16 (20%) | | |
| **AGE in years** | | | | | | | | | | |
| Median | 62 | 66 | 61,5 | 64 | 63 | 66 | | 64 | | n.s. |
| **SEX** | | | | | | | | | | |
| male | 7 | 27 | 24 | 24 | 23 | 58 (65%) | | 47 (50%) | | p<0.04 |
| female | 4 | 11 | 16 | 12 | 35 | 31 (35%) | | 47 (50%) | | |
| **SUBTYPE** | | | | | | | | | | |
| lambda | 6 | 28 | 31 | 27 | 46 | 65 (76%) | | 73 (78%) | | n.s. |
| kappa | 5 | 8 | 7 | 9 | 12 | 20 (24%) | | 21 (22%) | | |
| **BONE MARROW PLASMA CELL PERCENTAGE** | | | | | | | | | | |
| Median | 7,5 | 10 | 7,5 | 11 | 12,5 | 8 | | 12 | | |
| ≤10% | 7 | 26 | 28 | 17 | 25 | 61 (74%) | | 42 (46%) | | p<0.001 |
| >10% | 3 | 9 | 9 | 17 | 33 | 21 (26%) | | 50 (54%) | | |
| **PROGNOSTIC SCORE (Dispenzieri et al., JCO, 2004)** | | | | | | | | | | |
| Median | II | II | II | III | III | II | | III | | |
| Stage I | 5 | 12 | 14 | 3 | 1 | 31 (35%) | | 4 (4%) | | |
| Stage II | 5 | 22 | 17 | 13 | 25 | 44 (49%) | | 38 (40%) | | p<0.001 |
| Stage III | 1 | 4 | 9 | 19 | 29 | 14 (16%) | | 48 (51%) | | |
| not available | | | | 1 | 3 | | | 4 (4%) | | |
| **REVISED PROGNOSTIC SCORE (Kumar et al., JCO, 2012)** | | | | | | | | | | |
| Median | II | II | II | III | IV | II | | IV | | |
| Stage I | 5 | 12 | 12 | 4 | 4 | 29 (33%) | | 8 (9%) | | |
| Stage II | 3 | 7 | 12 | 3 | 3 | 22 (25%) | | 6 (6%) | | |
| Stage III | 1 | 11 | 9 | 13 | 14 | 21 (24%) | | 27 (29%) | | p<0.001 |
| Stage IV | 2 | 6 | 5 | 13 | 34 | 13 (15%) | | 47 (50%) | | |
| not available | | 2 | 2 | 3 | 3 | 4 (4%) | | 6 (6%) | | |