‘Accelerated aging’ in DMARD and treatment naïve early rheumatoid arthritis patients measured by a stem cell assay is associated with increased LDL and is linked to impaired cardiopulmonary function.

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Objectives

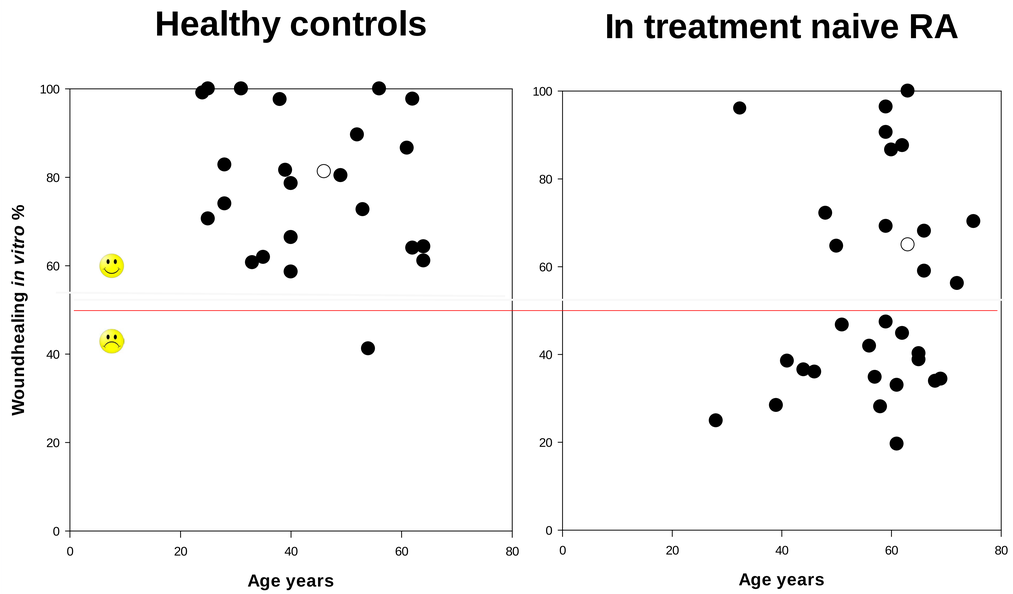
We investigated cell migration and proliferation of human cells *in vitro* in a so-called wound healing assay, using telomerase-immortalized mesenchymal stem cells (hTERT-MSC)[1]. Confluent monolayers of hTERT-MSC were mechanically “wounded” creating a fixed size scratch and then allowed to “heal” in the presence of culture medium containing 5% serum from RA-patients (n=30) or healthy subjects (n=25) for 3 days. Since it is known that various biological activities of human serum decline with age, our hypothesis is that serum from RA-patients is significantly less effective in supporting wound healing as compared with healthy controls.

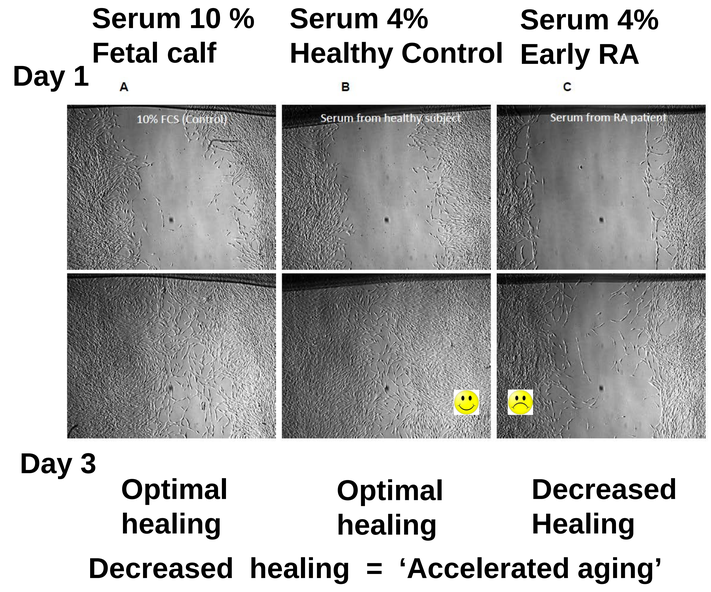
Our current focus is to examine the effect of serum from RA-patients and controls on hTERT-M and to correlate these in vitro measures to standardized measures of cardiopulmonary parameters assessing global longitudinal systolic strain (GLS) by speckle tracking echocardiography[2], coronary calcium score (Agaston score) by coronary computer tomography (CT COR), diffusing capacity of the lungs for carbon monoxide (DLCO), LDL, C-reactive protein (CRP), fasting Insulin (fIns) levels and whole body fat procent by whole body DXA-scan.

´´Wound healing *in vitro* `` were performed on serum from thirty treatment naive RA patients (mean age 56 range 27-73) and 24 healthy controls (age 44 (24-64)).RA patients and controls were free of medication at the time of serum sampling (the RA patients received methotrexate treatment at year one). Disease activity was scored by the use of the Danish national DANBIO registry using standard assessments, IgM rheumafactor (IgM-RF), anti-CCP titers, and LDL were evaluated by standardized techniques before treatment was initiated. Serum was obtained at baseline before methotrexate treatment and after one year.

[1] Demirovic, D. and Rattan, S.I.S. Curcumin induces stress response and hormetically modulates wound healing ability of human skin fibroblasts undergoing ageing in vitro. *Biogerontology, 12: 437-444, 2011*

[2] Løgstrup BB, Deibjerg LK, Hedemann-Andersen A, Ellingsen T: Left ventricular function in treatment-naive early rheumatoid arthritis. In Press. American Journal of Cardiovascular Disease.





In vitro* wound healing: Cell migration and proliferation of human cells *in vitro in a so called wound healing assay, using **telomerase-immortalized mesenchymal stem cells** (hTERT-MSC). **Confluent monolayers** of hTERT-MSC are mechanically “wounded” creating a fixed size scratch and then allowed to “heal” in the presence of culture medium containing **4% serum from RA-patients or healthy subjects for 3 days**

Results

We found ‘accelerated aging’ measured as ‘decreased wound healing’ *in vitro* by mean 53% (range 20-100%) in RA patients compared to healthy controls (p<0.0001). One year of national guideline DMARD treatment improved the *in vitro* decreased wound healing to mean 60% although not significant (p=0.068). We found decreased wound healing *in vitro* to be associated with increased LDL levels (p=0.02; r=0.43) in univariate analysis (no association to GLS, Agaston calcium score, DLCO (mmol/min/kPa/L), total fat %, fIns and CRP (p-values in the range 0.31-0.79). We also found a significant difference in GLS in patients with high values of anti-CCP (titers ≥ 340) compared to patients with normal titers and anti-CCP titers <340 (p=0.04).

Similarly DLCO was found decreased in patients with increased anti-CCP titers. Anti-CCP larger than 7 and below 340 p=0.02 (DLCO mean 88%) and if anti>340 p=0.004 (DLCO mean 82%) in anti-CCP negative patients mean DLCO% 102%).

Conclusion

IIn treatment-naive early RA compared to controls we observed a significant decreased ´´wound healing *in vitro* `` using hTERT-MSC assay. The ´´decreased *in vitro* wound healing`` in the RA patient was significantly associated with increased LDL, a well known risk factor in RA for developing acute myocardial infarction. Further we found a significant association between increased anti-CCP titers and initial increased cardiac function and decreased pulmonary function.