Adipose Tissue Inflammation and Fibrosis Contribute to an Adverse Metabolic Phenotype in Patients with Alström Syndrome

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Background

Alström Syndrome is an autosomal recessive ciliopathy caused by mutations in the ALMS1 gene. It is characterised by multi-organ fibrosis and a progressive metabolic phenotype, including obesity, hypertriglyceridemia, hyperinsulinemia, and type 2 diabetes.

The multi-organ fibrosis manifests as cirrhosis, renal glomerulo-fibrosis, fibrotic lung disease and myocardial fibrosis. We hypothesise that patients with Alström syndrome also develop fibrous adipose tissue, and that the resultant adipose dysfunction underpins the metabolic phenotype.

Study

We characterised the metabolic phenotype and degree of hepatic fibrosis in 29 patients with Alström syndrome (20 male and 9 female).

To assess the degree of fibrosis in the adipose tissue we carried out detailed histological and gene expression analysis, comparing subcutaneous abdominal depot biopsies from patients against healthy controls.

Fibrosis

The degree of hepatic fibrosis was determined by standard methods; serum AST and ALT levels, Enhanced Liver Fibrosis (ELF) scoring and hepatic elastography (FibroScan®).

Clinical Characteristics	Alstrom Syndrome (n=29)	
Age (years)	27.3	
Gender (male/female)	20/9	
BMI (kg/m^2)	30.4±0.9	
ALT (mU/L)	66±11	ref. range (7-56)
AST (mU/L)	40±5	ref. range (8-48)
ELF (21/29)		
None to mild	2	
Moderate	12	
Severe	7	
FibroScan® (20/29)		
< 8 kPa	11	
≥ 8 kPa	9	

In the AS cohort, mean AST and ALT were above the local derived reference range.

As judged by the EFL panel, 90% were categorized as having either moderate or severe fibrosis.

31% (9/29) had a liver stiffness index of ≥8 kPa suggestive of hepatic fibrosis.

Adipose Biopsies

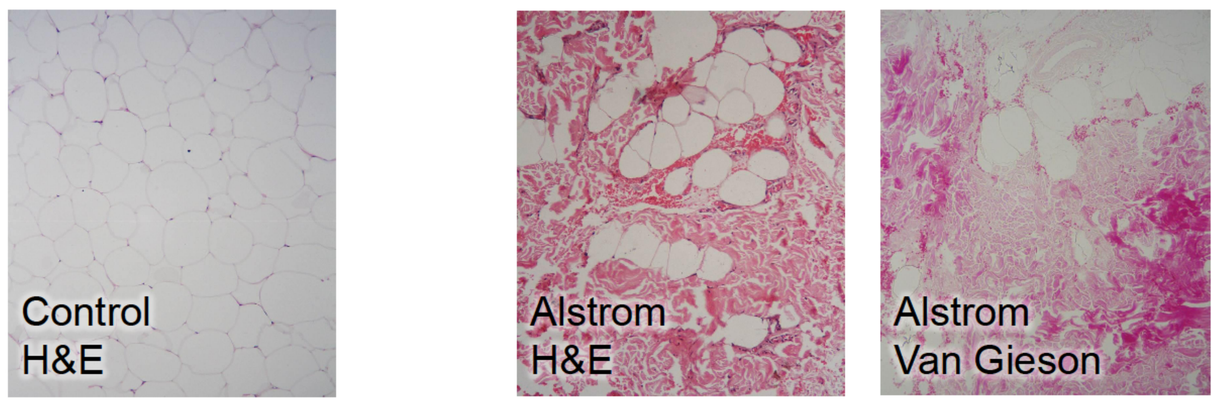
Subcutaneous abdominal adipose tissue biopsies were taken from patients (n=7) and controls (n=9) for comparative histology and gene expression analysis (RT^2 Profiler Fibrosis PCR Array, Qiagen).

Patients and controls were matched for age and BMI. Compared to the control group patients had a significantly increased HbA1c, disproportionately high for their BMI.

Clinical Characteristics	Alstrom Syndrome	Control
Age (years)	26.3±5	31.2
Gender (male/female)	4/2	0/9
BMI (kg/m^2)	30.1±2.3	29.4±2.59
HbA1c (mmol/mol)	49.7±4.8	35.5±0.56
Total cholesterol (mmol/L)	4.7±0.6	5.08±0.31
HDL cholesterol (mmol/L)	0.7±0.06	1.6±0.26

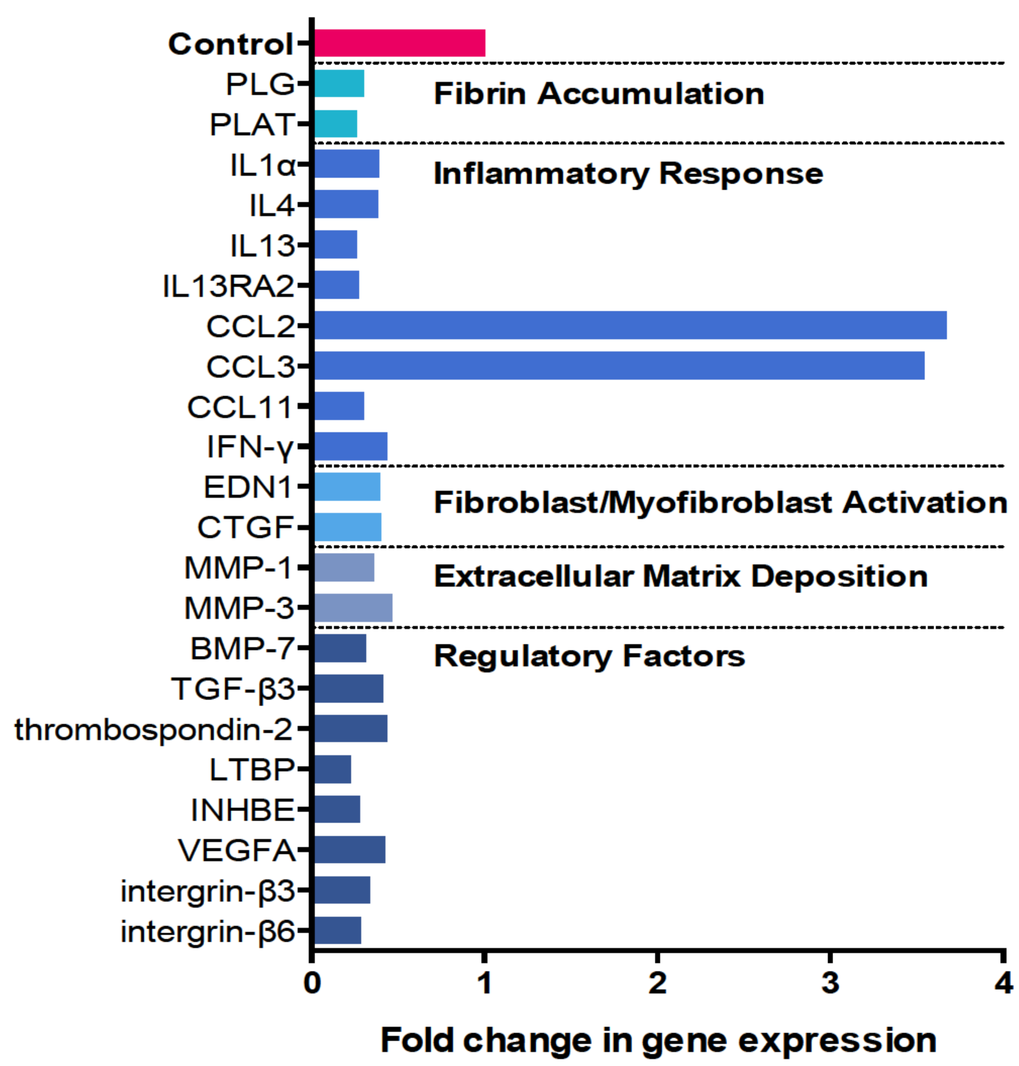
Adipose Phenotype

A) Histology



Histology demonstrates pronounced fibrosis in the abdominal adipose depot Representative sections; control H&E staining, Alström syndrome H&E staining, Alström syndrome Van Gieson's staining (collagen).

B) Fibrotic Gene Expression



Abdominal subcutaneous adipose tissue gene expression is dysregulated in patients with Alström syndrome (AS n=6, Ctrl n=9).

Conclusion

This data clearly demonstrates that the systemic fibrosis observed in Alström Syndrome extends to adipose tissue. Adipose tissue dysfunction may well contribute to the pronounced metabolic phenotype seen in these patients.

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