#FRI-286

Angiopoietin-like4 is associated with lipid metabolism and severe fibrosis in non-diabetic patients with Non-Alcoholic Fatty Liver Disease

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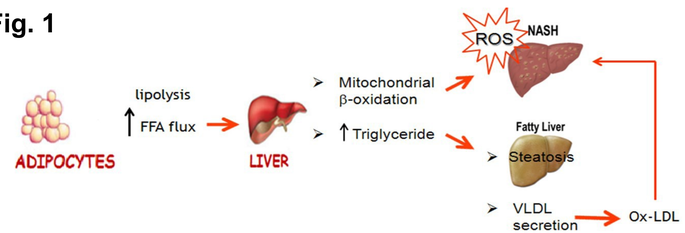
BACKGROUND

Non-Alcoholic Fatty Liver Disease (NAFLD) results from an imbalance between lipid deposition and removal, driven by increased lipid flow and de novo lipogenesis in insulin resistance (IR) state.
Accumulation of Free Fatty Acids (FFAs) in the hepatocytes promotes inflammation and oxidative stress (**Figure 1**) leading to the release of hypoxia-inducible factors, such as angiopoietin-like proteins (ANGPTLs).

Fig. 1



Particularly, ANGPTL4 is involved in the regulation of lipid metabolism through the inhibition of lipoprotein lipase, leading to systemic hypertriglyceridemia and hepatic steatosis.

AIM

To explore the association between ANGPTL4, lipid metabolism, monocyte chemoattractant protein-1 (MCP-1) and liver damage in a group of non-diabetic NAFLD patients.

PATIENTS AND METHODS

Fifty-four non-frankly obese, non-diabetic patients with biopsy-proven NAFLD and 9 healthy controls (CT) were enrolled for clinical studies.
Adipose-tissue IR (AT-IR) indices in fasting condition were derived from FFAs levels and tracer studies (D2 glycerol):
AT-IR1: FFAs x fasting plasma insulin (FPI);
AT-IR2: Ra glycerol x FPI
ANGPTL4 and MCP-1 plasma levels were measured by Multiplex Assay based on the Luminex technology.
Liver histology was scored according to Kleiner.

RESULTS

Clinical, biochemical and histological characteristics of NASH patients and CT are reported in Table 1.

Table 1

Variables	CT (n=9)	NAFLD (n=45)	*P* value
Age (year)	27 ± 1.8	41 ± 11.3	<0.001
Sex, n (M/F)	5/4	35/10	0.169
BMI (kg/m^2)	21.3 ± 1.8	27.9 ± 4.2	<0.001
Waist (cm)	70 ± 2.7	95 ± 9.6	<0.001
AST (IU/L)	19 (5)	36 (26)	<0.001
ALT (IU/L)	15 (6)	70 (49)	<0.001
FFAs (mmol/L)	0.62 ± 0.19	0.63 ± 0.24	0.479
Triglycerides (mg/dL)	54 (39)	87 (54)	0.001
Total cholesterol (mg/dL)	169 (21)	193 (43)	0.095
Glucose (mg/dL)	90 ± 6.0	96 ± 11.3	0.290
Insulin (mU/mL)	5.7 (2.4)	10.7 (4.9)	<0.001
HOMA-IR	1.23 ± 0.37	3.19 ± 2.1	<0.001
ANGPTL4 (ng/mL)	132 (48)	123 (78)	0.972
MCP-1 (pg/mL)	65 (50)	118 (51)	0.019
Histological features			
Steatosis (%)	-	39 ± 28	-
Fibrosis, n (%)			
F0/F1	-	21 (47)	-
F2	-	11 (24)	-
F3/F4	-	13 (29)	-
NAS score, n (%)			
1-2	-	6 (13)	-
3-4	-	23 (51)	-
5-6	-	16 (36)	-
Lobular inflammation, n (%)			
0	-	10 (22)	-
≥ 1	-	35 (78)	-

Overall, ANGPTL4 resulted positively associated with lipolysis, plasma levels of FFAs and with hepatic fat (**Figure 3 A-C**)

Fig. 3A

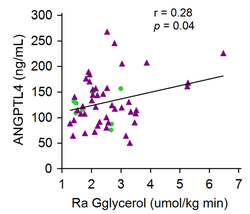


Fig. 3B

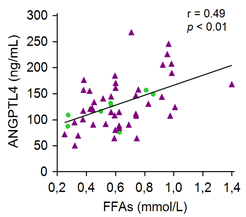
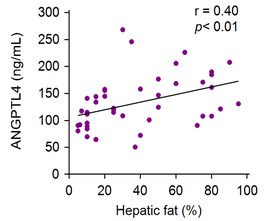


Fig. 3C



Compared to CT, NAFLD patients had increased AT-IR (**Figure 4A**) which in turn was significantly related to ANGPTL4 levels (**Figure 4B**).

Fig. 4A

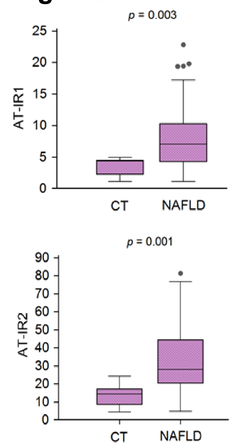
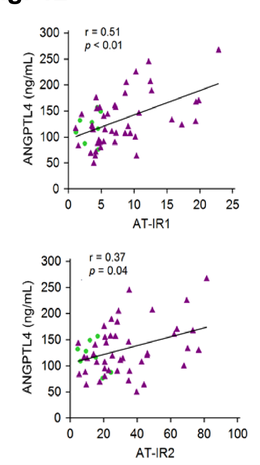
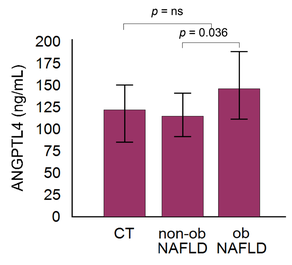


Fig. 4B



Plasma levels of ANGPTL4 were similar to CT when NAFLD were analyzed as a whole group, but was 22% higher in obese *vs* non-obese NAFLD (**Figure 2**).

Fig. 2



MCP-1 levels were increased by 40% in NAFLD subjects vs CT and was directly related to ANGPTL4 levels (**Figure 5A-B**).

Fig. 5A

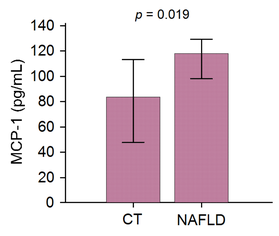
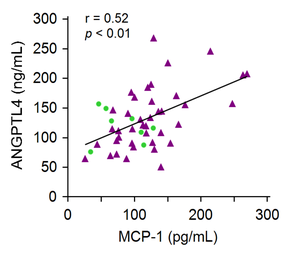


Fig. 5B



Among histological features, ANGPTL4 levels were increased by 30% in the presence of inflammation and by 60% in severe fibrosis (**Figure 6A-B**).

Fig. 6A

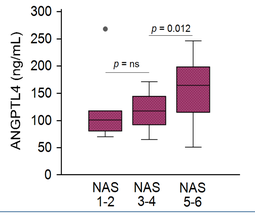
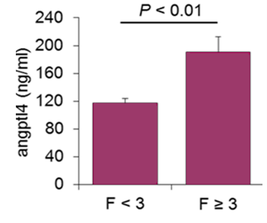


Fig. 6B



At logistic regression analysis, ANGPTL4 levels were significantly associated with the degree of fibrosis independent of BMI, AT-IR and MCP-1 (OR=1.03; 95%CI=1.01-1.05; p=0.003).

CONCLUSIONS

Ox-stress-inducible factors are important mediators of necro-inflammation and fibrosis in patients with NAFLD. Particularly, we found that ANGPTL4 levels were significantly associated with alterations in lipid metabolism, AT-IR and severe hepatic fibrosis in non-diabetic subjects with NAFLD.

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