#FRI-285

Adipose tissue insulin resistance is associated with macrophage activation in non-diabetic patients With Non-Alcoholic Fatty Liver Disease

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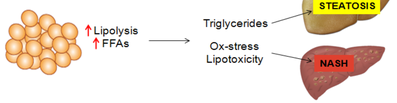
BACKGROUND

The main pathogenetic mechanism for the onset and progression of NAFLD/NASH is insulin resistance (IR).

Particularly, adipose tissue IR (AT-IR) plays a crucial role in the pathogenesis of NASH[1-3].The increased flux of free fatty acids (FFAs) derived from the AT promote liver damage by the activation of several pathways involving lipotoxicity and oxidative stress (**Figure 1**).

Fig. 1



To date, a direct pathway linking AT-IR to the liver damage has not yet been described.

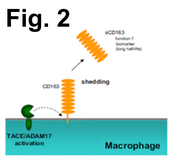
AIM

To examine the association between IR at different sites and macrophages activation in a group of 40 non-diabetic subjects with biopsy-proven NAFLD.

PATIENTS AND METHODS

We measured the soluble fragment CD163 (sCD163) that is a marker of macrophages activation (**Figure 2**).

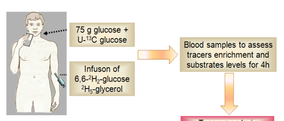
Fig. 2



Adapted from **Moller HJ**. *Scand J Clin Lab Invest* 2015;72:1-13.

IR at different sites was evaluated by in vivo tracer studies (**Figure 3**).

Fig. 3



Hepatic-IR = Endogenous glucose production (EGP) x Fasting Plasma Insulin (FPI)

AT-IR1 = Ra Glycerol x FPI
AT-IR2 = FFAs x FPI

RESULTS

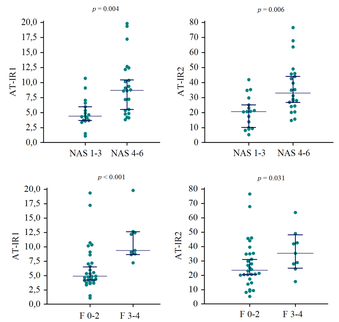
Clinical and biochemical characteristics of NAFLD patients according to the severity of liver damage are reported in **Table 1**.

Table 1

Variable	NAFLD (n = 40)	F < 2 (n=18)	F ≥ 2 (n=22)	*p* value
Age /years	41.9 ± 11.8	41 ± 11	43 ± 12	0.471
Gender M/F	31/9	15/3	16/6	0.675
BMI (kg/m²)	27.6 ± 4.3	25.1 ± 3.5	30.1 ± 3.8	<0.001
ALT (UI/L)	67 (52)	65 (35)	74 (64)	0.089
AST (UI/L)	35 (20)	32 (10)	42 (26)	0.008
Fasting insulin (mU/ml)	12.6 ± 6.6	10.3 ± 4.9	15.5 ± 8.2	0.007
Fasting glucose (mg/dl)	96 ± 11	94 ± 9	98 ± 13	0.403
Fasting triglycerides (mg/dl)	87 (54)	78 (49)	92 (59)	0.723
Total cholesterol (mg/dl)	191 (44)	193 (50)	191 (42)	0.850
HDL-cholesterol (mg/dl)	46 ± 13	46 ± 9	45 ± 15	0.330
FFAs (mmol/l)	0.62 ± 0.21	0.62 ± 0.26	0.64 ± 0.23	0.604
sCD163 (mg/l)	1.96 ± 0.84	1.5 ± 0.5	2.4 ± 1.0	0.001
CK18Asp396 (U/L)	136 (150)	136 (150)	289 (321)	0.034

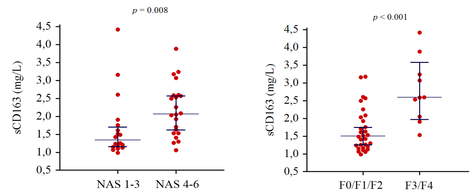
AT-IR is significantly higher in patients with a NAS score ≥ 4 and in those with severe fibrosis (F3/F4), **Figure 8**.

Fig. 8



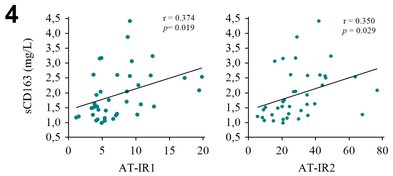
sCD163 levels are significantly higher in patient with a NAS score ≥ 4 and in those with severe fibrosis (F3/F4), **Figure 9**.

Fig. 9



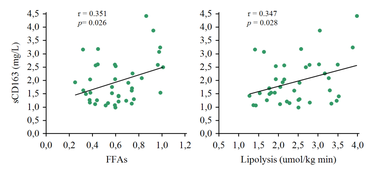
sCD163 levels shows a significant association with AT-IR (**Figure 4**).

Fig. 4



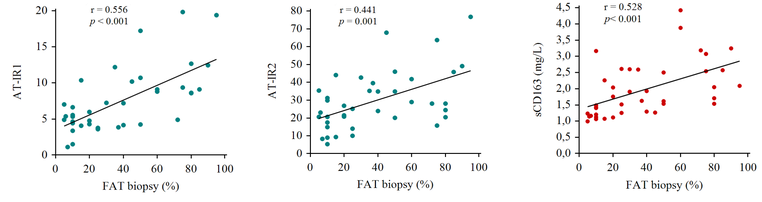
sCD163 levels correlate with either plasma levels of FFAs and lipolysis (RaGlycerol) in the adipose tissue (**Figure 5**)

Fig. 5



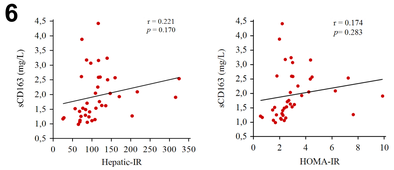
Both AT-IR and sCD163 significantly correlate with hepatic fat (**Figure 10**).

Fig. 10



sCD163 levels do not correlate with Hep-IR (**Figure 6**).

Fig. 6



sCD163 levels do not correlate with insulin and EGP by the liver (**Figure 7**).

Fig. 7

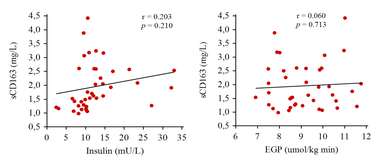
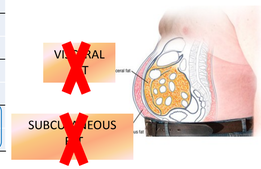


Table 2

		VF	SC
AT-IR1	*r*	0.225	0.477
	p	0.223	**0.008**
AT-IR2	*r*	0.218	0.428
	p	0.240	**0.018**
sCD163 (mg/L)	*r*	0.154	0.171
	p	0.407	0.365



Interestingly, sCD163 do not correlate with visceral and subcutaneous fat (**Table 2**).

At multiple and logistic regression analysis, sCD163 levels are significantly associated to fibrosis, particularly with advanced fibrosis (F ≥ 2) independently of BMI, AT-IR and CK18 Asp396 levels (**Table 3A-B**).

Table 3A

Variables	r	t	p
Gender, M	-0.166	0.1	0.947
BMI	0.567	3.4	**0.002**
AT-IR2	0.337	0.2	0.857
CK18 Asp396 (U/L)	0.356	1.1	0.266
sCD163 (mg/L)	0.589	3.7	**<0.001**

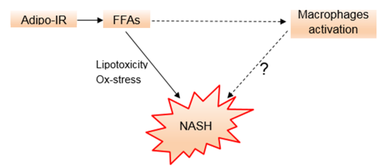
Table 3B

Variables	OR	95% CI	p
Gender, M	0.8	0.1-10.9	0.885
BMI	1.5	1.1-1.9	**0.009**
AT-IR2	0.9	0.9-1.1	0.283
CK18 Asp396 (U/L)	1	0.9-1	0.866
sCD163 (mg/L)	4.2	1.1-15.7	**0.031**

CONCLUSIONS

- In NAFLD patients, macrophages activity is significantly associated with AT-IR
- Both AT-IR and sCD163 levels are significantly associated with fibrosis
- sCD163 levels are significantly associated with hepatic fat but not with VF and SF

We hypothesize that in NAFLD, AT-IR can stimulate hepatic macrophage activation via an increased flux of FFAs thus concurring to liver damage.



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1)Bugianesi E, *Diabetologia* 2005
2) Musso G, *Hepatology* 2008
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