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*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1601116> since 2016-10-12T13:38:31Z

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**Angiopietin like protein 4 (ANGPTL4): a marker of alteration in lipid metabolism, insulin resistance and ectopic fat accumulation**

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**Background and aims:** Alteration in lipid metabolism is a benchmark in the development of insulin resistance, type 2 diabetes and related cardiometabolic diseases. Angiopietin like proteins (ANGPTL) are a family of secreted glycoproteins present in tissues (liver, heart, muscle, adipose tissue), macrophages and blood with pleiotropic effects on vascular cells, stem cell biology, and lipid metabolism. Studies in animals and cell lines have shown that ANGPTL4 is involved in the regulation of lipoprotein lipase (LPL). In plasma, ANGPTL4 inhibits VLDL- and chylomicron- triglyceride (TG) hydrolysis while in adipose tissue stimulates lipolysis. However, the relationship between this secreted glycoprotein and lipid metabolism in vivo in humans has not been studied. Since ANGPTL4 is secreted in plasma, we wanted to explore if circulating ANGPTL4 might be related with lipid dysfunction, ectopic fat accumulation and insulin resistance (IR).

**Materials and methods:** We studied 54 non diabetic subjects (45 with biopsy proven NAFLD and 9 without NAFLD; age and BMI (  $41\pm 1.4$  ;  $27.5\pm 0.6$ ). In all subjects we measured fasting hepatic glucose production (EGP) and lipolysis (Ra glycerol) by stable isotope tracer infusions, abdominal and hepatic fat by MRI, free fatty acid (FFA) concentration and composition (by GCMS), indexes of IR (Adipo-IR FFA x Insulin ; Hep-IR= EGP X Insulin) and of De Novo Lipogenesis index (DNL=16:0/18:2) that we correlated with plasma levels of ANGPTL4. Liver histology was scored according to Kleiner.

**Results:** Circulating ANGPTL4 levels were increased with hepatic fat ( $R=0.41$ ,  $p=0.0064$ ) and upper subcutaneous fat ( $R=0.44$ ,  $p=0.0045$ ) but not visceral fat. Overall, ANGPTL4 correlated positively with plasma concentrations of FFA ( $R=0.49$ ,  $p=0.0003$ ), TG ( $R=0.30$ ,  $p=0.03$ ), DNL index ( $R=0.45$ ,  $p=0.0009$ ), peripheral lipolysis ( $R=0.28$ ,  $p=0.04$ ), Hep-IR ( $R=0.30$ ,  $p=0.03$ ) and Adipo-IR ( $R=0.52$   $p<0.0001$ ). ANGPTL4 was strongly associated with plasma MCP-1 ( $R= 0.52$ ,  $p=0.0001$ ) that is a marker of macrophage related inflammation. Moreover ANGPTL4 was significantly increased with the degree of hepatic fibrosis (in Fib3-4 +24% in vs Fib0-2; +60% vs CT) and hepatic inflammation (by 30% vs CT). Multiple regression analysis showed that ANGPTL4 levels were associated with the degree of fibrosis independently of BMI, AT-IR and MCP-1.

**Conclusion:** Increased plasma levels of ANGPTL4 are markers of alterations of both hepatic and adipose tissue lipid metabolism, whole body and hepatic inflammation and liver damage.

*Supported by: FP7/2007–2013 project FLIP under grant agreement no. HEALTHF2- 2009-241762*

*Disclosure: A. Gastaldelli: None.*