

PLASMA SELENOPROTEIN P LEVELS ARE RELATED TO ADIPOSE TISSUE INSULIN RESISTANCE, COMPOSITION OF FREE FATTY ACIDS AND LIVER FIBROSIS IN NON-DIABETIC PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE



Chiara Rosso¹, Ramy Younes¹, Fabrizia Carli², Melania Gaggini², Lavinia Mezzabotta¹, Milena Marietti¹, Federico Salomone³, Roberto Gambino¹, Francesca Saba¹, Emma Buzzigoli², Demetrio Ciociaro², Gian Paolo Cavaglia¹, Elisabetta Morello⁴, Maria Lorena Abate¹, Antonina Smedile¹, Alessia Ciancio¹, Maurizio Cassader¹, Giorgio Maria Saracco¹, Amalia Gastaldelli², Elisabetta Bugianesi¹
1. Department of Medical Sciences, University of Turin, Torino, Italy; 2. Institute of Clinical Physiology, CNR, Pisa, Italy; 3. Division of Gastroenterology, Ospedale di Acireale, Catania, Italy; 4. Department of Clinical and Biological Sciences, University of Turin, Turin, Italy.

Contact information: Dr. Chiara Rosso
E-mail: chiara.rosso@unito.it

INTRODUCTION

Alterations in glucose and lipid metabolism in the setting of insulin resistance (IR) play an important role in the development and progression of Non-alcoholic Fatty Liver Disease (NAFLD) via increased oxidative stress.

Circulating levels of selenoprotein P (Sepp), a selenium carrier protein with antioxidant properties, were found to be higher in obese and diabetic NAFLD subjects compared to controls [1-3]. Moreover, the administration of SeP impaired insulin signaling in hepatocytes while its deficiency in mice leads to an improvement of insulin sensitivity [3].

AIM

The aim of this study were to evaluate the association between plasma Sepp levels and:

- 1) IR at different sites
 - 2) de novo lipogenesis indices
 - 3) liver damage
- in a well characterized group of non-diabetic subjects with biopsy proven NAFLD.

MATERIAL & METHODS

40 subjects with biopsy proven NAFLD underwent tracers studies (6,6D2glucose and D5glycerol) in the basal state (n=40) and after a double tracers 75 g-Oral Glucose Tolerance Test (OGTT)(n=24).

IR components calculation:

- Hepatic IR (Hep-IR) = EGP*insulin
- Adipose tissue (AT)-IR = Glycerol Ra*insulin (AT-IR1) or FFAs* insulin (AT-IR2)
- Peripheral (Per-IR) = EGP/glucose

Gas chromatography mass spectrometry was used to assess FAs composition.

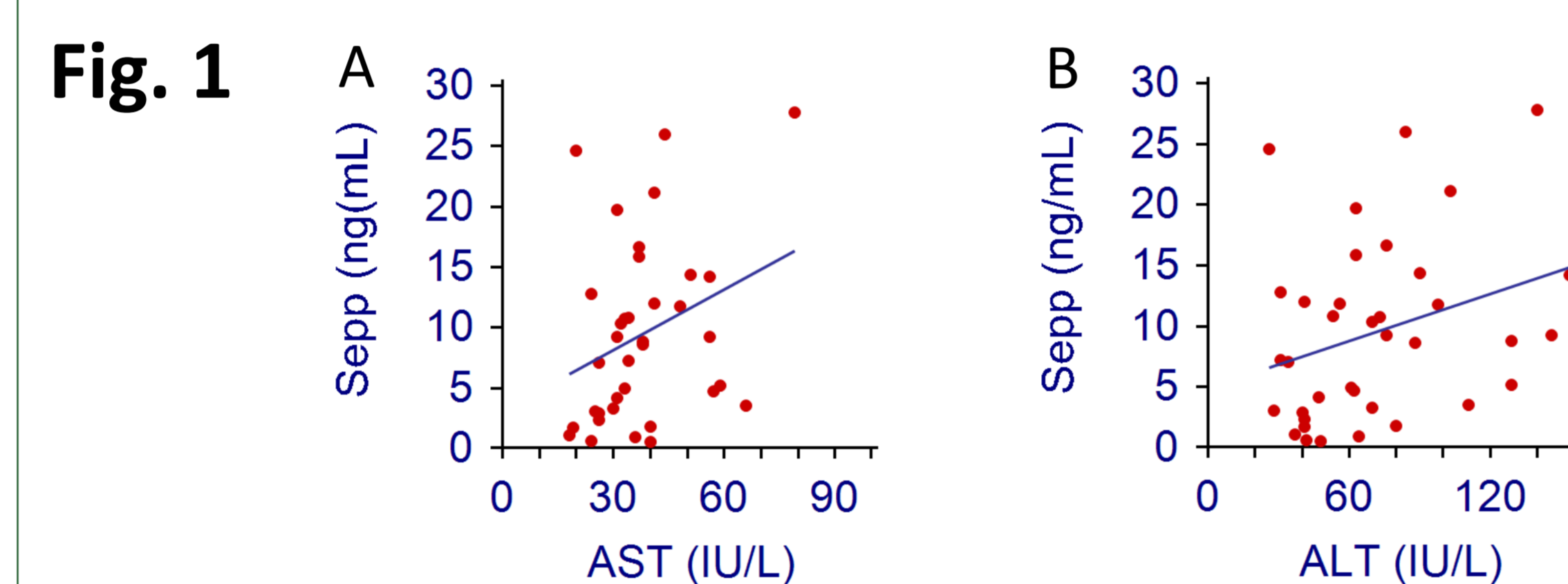
The SCDi and DNLI were derived as the ratio palmitoleic/palmitic acid (16:1/16:0) and palmitic/linoleic (16:0/18:2), respectively.

Plasma Sepp levels was measured using ELISA.

Histology was scored according to Kleiner.

RESULTS

During fasting, plasma Sepp levels were associated with AST and ALT levels ($r=0.35$, $p=0.035$ and $r=0.32$, $p=0.050$) (**Fig. 1A-B**), with AT-IR1 ($r=0.473$, $p=0.004$) and AT-IR2 ($r=0.325$, $p=0.050$) (**Fig.1 C-D**), with lipolysis by tracers ($r=0.352$, $p=0.0329$) and SCDi ($r=0.32$, $p=0.048$) (**Fig.1 E-F**).



Following OGTT:

➤ Sepp levels increased from 11,2 ng/mL at baseline to 17,7 ng/mL at 120' to 23,9 ng/mL at 240' (ANOVA for repeated measures, $p=0.008$) (**Fig.2A**)

➤ SCDi decreased from 0.11 ± 0.03 at baseline to 0.06 ± 0.02 at 240' (ANOVA for repeated measures, $p<0.001$) (**Fig.2B**)

➤ DNLI increased by 35% (1.23 ± 0.4 at baseline vs 1.66 ± 0.4 at 240' (ANOVA for repeated measures, $p=0.016$) (**Fig.2C**), indicating an increase in saturated FAs.

At 120 min OGTT, Sepp levels were directly related to both SCDi and DNLI ($r=0.56$, $p=0.012$ and $r=0.60$, $p=0.008$) (**Fig.3A-B**) suggesting and increased antioxidant response to increased levels of saturated FAs induced by oral glucose ingestion.

Among histological features, Sepp levels showed a stepwise increase from F0 to F1-F2 to F3-F4 (Kruskall-Wallis $p=0.007$), indicating higher scavengers levels in more severe liver damage (**Fig,4**).

Fig. 1

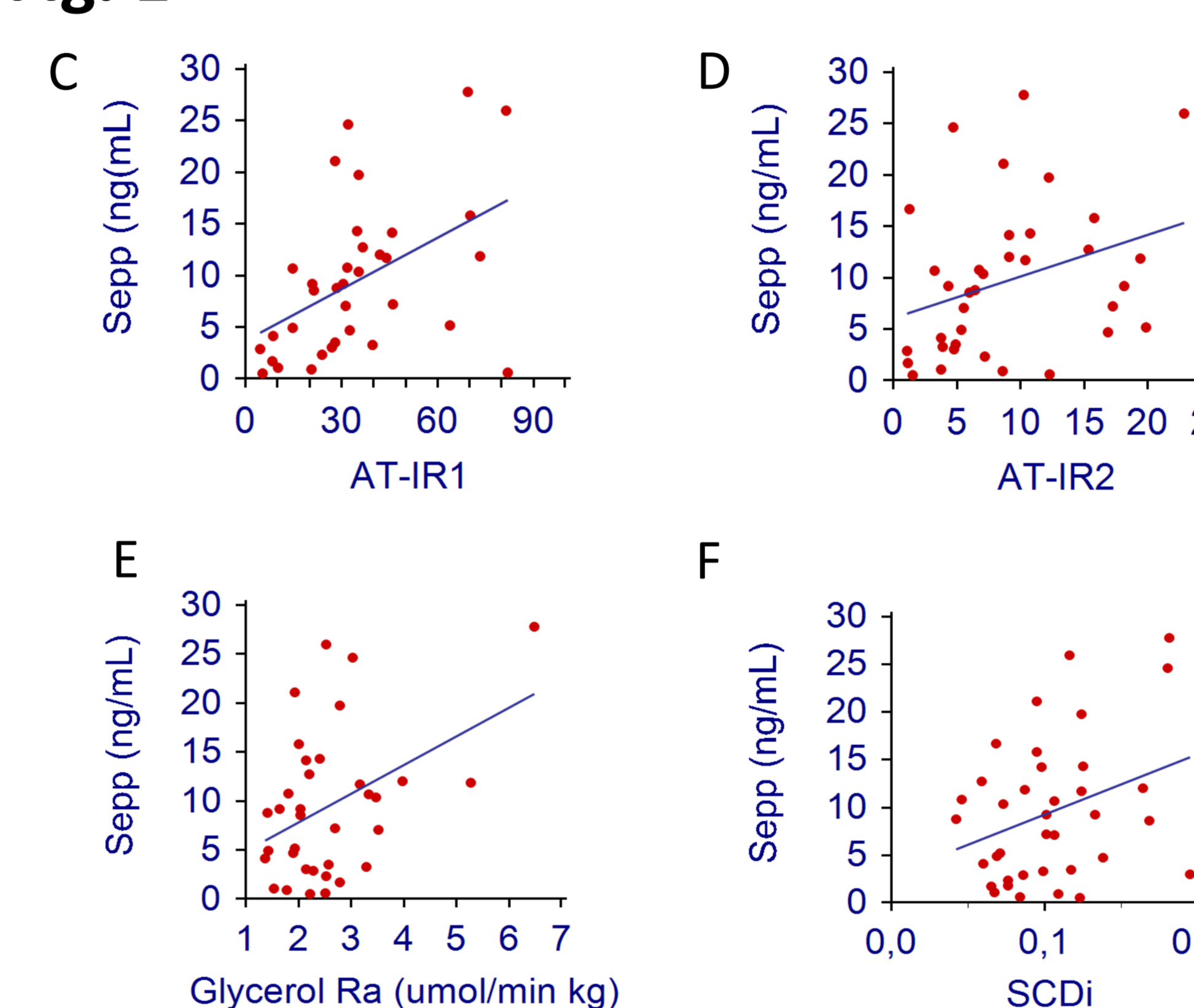


Fig. 2

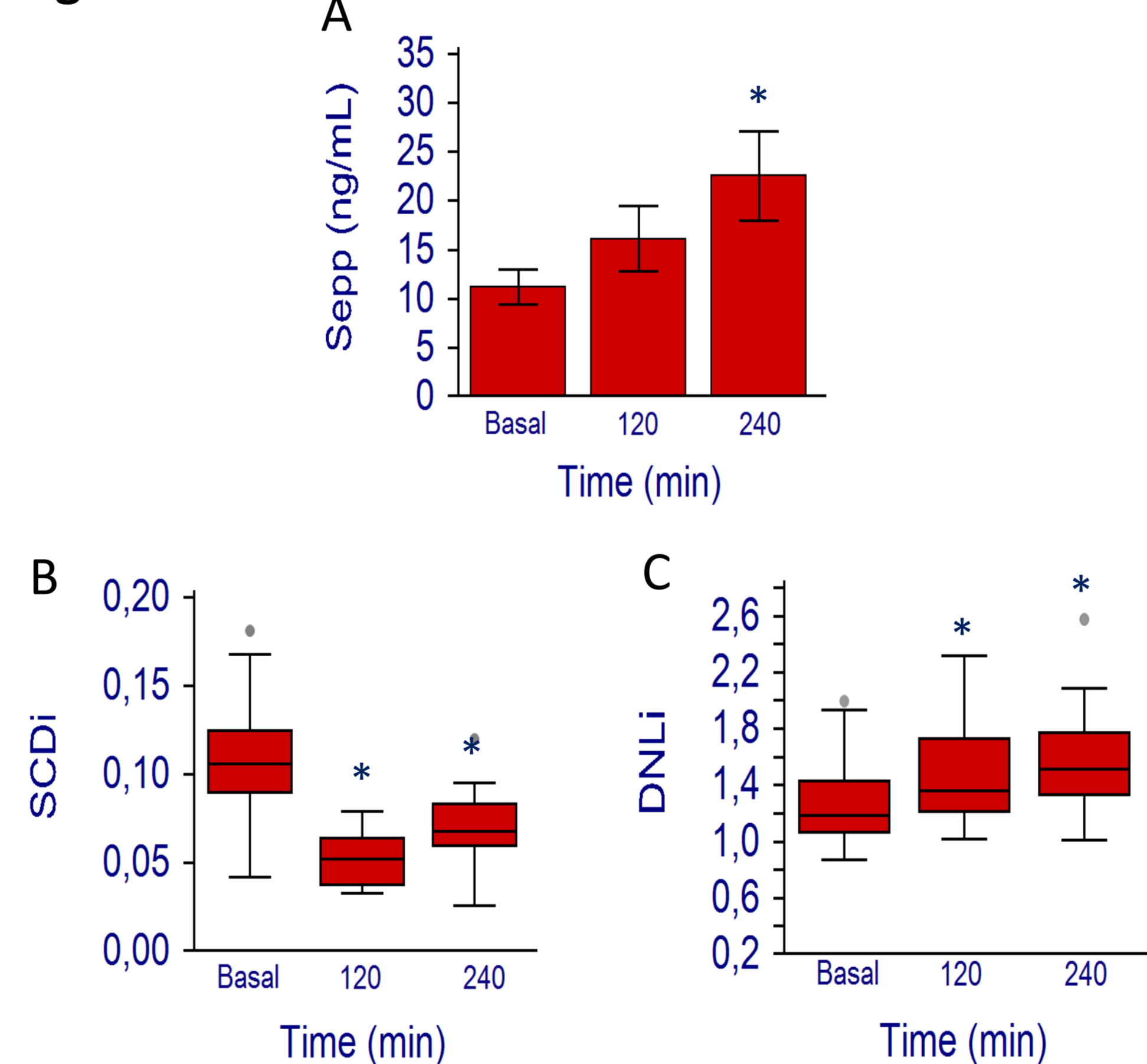


Fig. 3

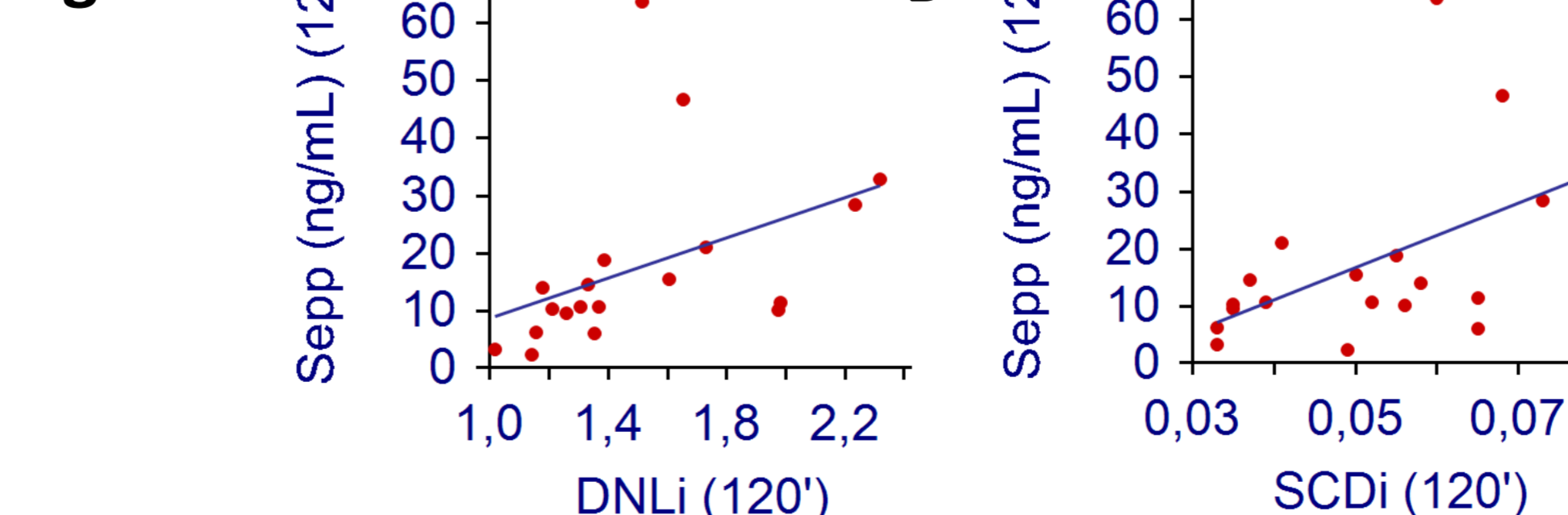
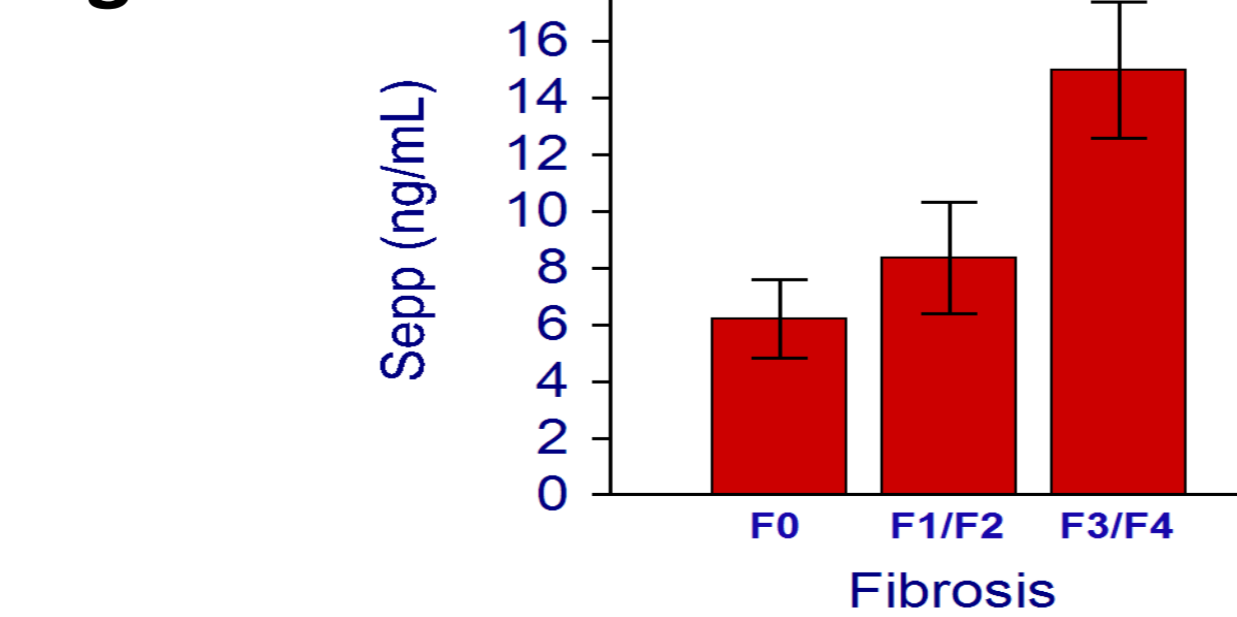


Fig. 4



CONCLUSION

In non-diabetic subjects with NAFLD, basal Sepp levels are related to:

- adipose tissue insulin resistance
- FAs composition
- severe liver damage.

Sepp levels increase in response to unfavorable changes in FAs composition induced by the ingestion of a glucose load suggesting that an altered glucose metabolism play a role in the development and progression of NAFLD.

ACKNOWLEDGEMENTS

Funded by FP7/2007-2013 under grant agreement n HEALTH-F2-2009-241762, project FLIP; Horizon 2020 under grant agreement no. 634413, project EPoS

REFERENCES

- 1) Burk RF and Hill KE. Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis. *Annu Rev Nutr* 2005; 25:215-35.
- 2) Choi HY, Hwang SY, Lee CH, Hong HC, Yang SJ, et al. Increased selenoprotein P levels in subjects with visceral obesity and nonalcoholic fatty liver disease. *Diabetes Metab J* 2013; 37:63-71.
- 3) Misu H, Takamura T, Takayama H, Hayashi H, Matsuzawa-Nagata N, et al. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. *Cell Metabolism* 2010;12:483-95.

DISCLOSURES

Nothing to disclose

