Role of ASGR1 on obesity and metabolic syndrome

🅾 **Monika Svecla[1], Annalisa Moregola[1], Lorenzo Da Dalt[1], Jasmine Nour[1], Andrea Baragetti[1], Patrizia Uboldi[1], Fabrizia Bonacina[1], Giuseppe Danilo Norata[1,2]**

[1]*Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy*
[2]*SISA Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo, Milan, Italy*
https://doi.org/10.56095/eaj.v2i1.39
Monika Svecla: monika.svecla@unimi.it

Background: Obesity-related fat accumulation is linked to the metabolic syndrome and increases the risk of CVD by involving FFA, insulin resistance, and inflammation. Taking into account the findings from the third chapter, our goal was to assess the potential role of ASGR1 in metabolic reprogramming and immunoinflammatory state during obesity.

Methods: After 20 weeks of high fat diet, flow cytometry, proteomics, lipid profile, glucose tolerance, and insulin tolerance were assessed in WT and ASGR1-/- mice (HFD). Additionally, metabolic parameters such as oxygen consumption, CO_2 production, and food intake were measured during the diet.

Results: After 20 weeks of HFD, the ASGR1−/− mice displayed a significant reduction in the circulating monocytes compared to WT. The body weight and food intake were comparable in between two groups. The adipose tissue VAT was significantly increased in ASGR1-/- compared to WT mice (WT 3.2%±0.8%, ASGR1-/- 4.7%±1.2%, P-value<0.001). The proteomics revealed, n=3412 proteins were aligned from which 624 proteins were significantly differentially expressed on the liver of ASGR1-/- and WT mice under HFD. From prediction analysis the significant proteins that were increase in the liver of ASGR1-/- mice were necrosis, apoptosis, and inflammation compared to the WT. Additionally, a significant downregulation in proteins protein expression involved in fatty acid synthesis and fatty acid uptake, except the increased expression of fatty acid coenzyme A ligase (FATP5), which belongs to very long chain acyl-CoA synthetases, capable mediation the transport of long chain fatty acids.

Conclusion: Our findings indicate that ASGR1 deficiency causes increased inflammation and changes in metabolic pathways when subjected to HFD. This can also have an impact on the synthesis of apolipoproteins secreted in plasma.

Thrombocytopenia and Kidney disease, two possible hallmark of FCS phenotype: preliminary evidence from a cohort study

🅾 **Daniele Tramontano, Simone Bini, Alessia Di Costanzo, Ilenia Minicocci, Stella Covino, Marcello Arca, Laura D'Erasmo**

Department of Translational and Precision Medicine, Sapienza University of Rome, Italy
https://doi.org/10.56095/eaj.v2i1.42
Daniele Tramontano: daniele.tramontano@uniroma1.it

Background and Aim: Familial Chylomicronemia Syndrome (FCS) is a rare monogenic autosomal recessive disorder of lipid metabolism determining severe hypertriglyceridemia (HTG). As the use of Volanesorsen, a novel FCS treating drug, has been associated with thrombocytopenia, the relationship between FCS and low platelets counts should be firmly established. It has been reported also kidney complication in FCS, but the data are sparse. To this aim, we have retrospectively evaluated the spontaneous variation of platelet counts and Kidney impairment in a cohort of patients with FCS.

Methods: Single-center retrospective cohort study on 20 FCS patients included in the LIPIGEN. Medical charts have been revised to collect retrospectively information on kidney function in a cohort of patients with FCS.

Results: Across the study population, the median PLT count was 187,225 platelet/mcL. The median on treatment TG levels in the whole cohort was 1309 mg/dl. During follow-up, 8 (44.4%) patients experienced at least one episode of mild and 1 (5%) of moderate thrombocytopenia. None had severe thrombocytopenia. Mean triglycerides do not significantly predict mean platelet values. However, when considering a multivariate model including mean triglycerides, sex, the presence of hepatic steatosis and age we found that male sex and the presence of ultrasound estimated hepatic steatosis were associated with significantly lower platelet (respectively β-0,473, P=0,044 and β-0,469, P=0,048). Age was of borderline statistical significance (β-0,388, P=0,087). Across the study population, the median GFR values was 99.5 ml/min. Median eGFR was significantly associated with history of hypertension (β-0,508, P=0,031). Overall, proteinuria occurred in 5 (25%) patients, and it did not associate with hypertension, diabetes, age, sex nor triglyceride levels. Four (20.0%) patients meet the criteria of hyperfiltration whereas 3 (15.0%) were exhibiting an eGFR below 90 ml/min. Among hyperfiltrating, two had also proteinuria in at least one occasion during life. One patient with eGFR below 90 ml/min and proteinuria had a biopsy-proven diagnosis of glomerulonephritis. Overall, the impairment in kidney function was independent from age, diabetes, hypertension, median TGs, AP, sex.

Conclusions: The present analysis confirmed that thrombocytopenia and kidney impairment might be a clinical characteristics of FCS phenotype. Further studies in larger cohort are needed to better clarify if kidney disease and thrombocytopenia might be a hallmark of FCS in broader population and understand the potential patho-physiological mechanism.