EASD 2020
56th Annual Meeting
European Association for the Study of Diabetes
21 - 25 September 2020 Vienna, Austria

Control/Tracking Number: A-20-2781-EASD
Activity: Abstract
Current Date/Time: 4/17/2020 4:32:42 AM

Effect of PNPLA3 rs738409 genotype and gestational diabetes history on fasting glucagon levels in early NAFLD

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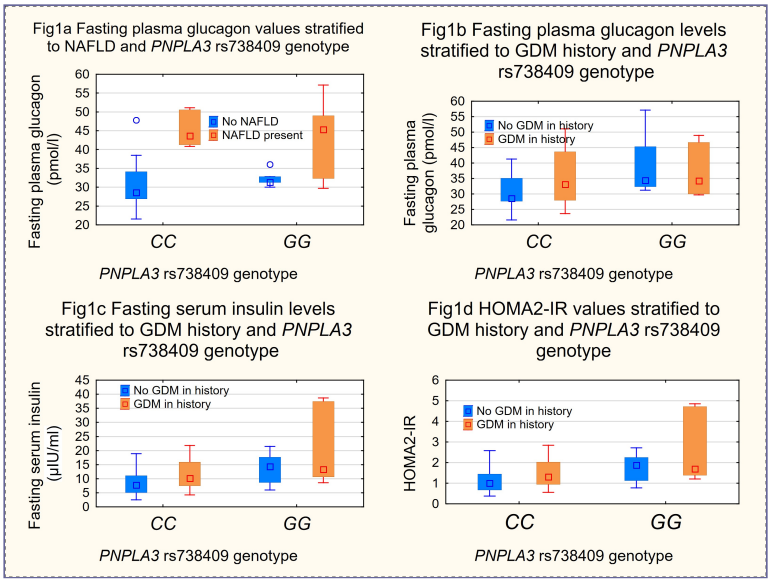
Abstract:
Background and aims: The *PNPLA3* rs738409 *G/G* risk genotype is implicated in the development and progression of NAFLD. The fasting glucagon levels were reported to be higher in patients with NAFLD, however there was no data available on the effect of *PNPLA3* rs738409 risk genotype on plasma glucagon levels. We assessed the intraheptic lipid content (IHCL) and the plasma glucagon levels in context of *PNPLA3* genotypes and GDM history in middle aged women.
Materials and methods: We targetedly enrolled 39 women (mean age: 37.2±4.8yrs) based on the *PNPLA3* rs738409 genotype (*C/C* n=27 vs. *G/G* n=12) from our prior GDM genetic association study (non-GDM n=18, pGDM n=21, 6.1 yrs after 1st GDM pregnancy). Proton density fat fractions (PDFF) were measured using MRS and Multi-echo Dixon methods (Siemens 3T Prisma MR) in the liver and pancreas. Routine abdominal MRI was also performed to exclude focal liver lesions. Liver fibrosis scores (NFS, Fib-4) were calculated. Liver enzymes, HbA1c, lipids, 75g OGTT: PG, serum insulin (CLIA): 0'-30'-120', plasma glucagon 0', 30' (RIA) were measured. Patients with elevated liver enzymes were screened for alternative etiology. MW-U, SRO, ANOVA/K-W and post hoc tests were used (Statistica program).
Results: Fourteen patients were identified with NAFLD out of the 39. We have observed a significant (KW: $p=7x10^{-4}$) step-wise increase in IHCL after adjusting the PDFF results to BMI categories (BMI<25, 25≤BMI<30, ≥30kg/m^2) and *PNPLA3* genotype (*CC* vs *GG*). We identified 13 patients with prediabetes and 1 with type 2 diabetes mellitus. The increase of fasting plasma glucagon levels was confirmed in our NAFLD patients in both genotype groups (Fig1a). When the fasting glucagon levels were stratified to *PNPLA3* genotypes and GDM history we obsereved an increasing trend in the rs738409 *G/G* genotype group vs. *CC*, and the difference is near-significant in the non-GDM subgroup (Fig1b), that were interestingly completely abolished after the adjustment to the fasting serum insulin levels. A step-wise trend for increase was found both in the fasting insulin and HOMA-IR levels (nGDM<GDM, rs738409 *CC*<*GG*). (Fig 1c,d)
Conclusion: We concluded that the *PNPLA3* genotype effect in combination with the GDM history have a role on the fasting plasma glucagon levels via early NAFLD development. The result confirms that additional regulatory elements to insulin should be present in the liver-alpha cell axis which explains the parallel increase in fasting glucagon, insulin and HOMA-IR levels in patients with a *PNPLA3* risk genotype for NAFLD development.



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Keyword (Complete): 67 Non-alcoholic fatty liver disease (NAFLD)
Study information (Complete):
***Human studies**: Yes
***Animal Studies**: No

Grant Acknowledgement (Complete):
Please select Yes or No: Yes
Support: : EFSD-NH grant, Wörwag Pharma award for PhD students

Clinical Trial Registration Number (Complete):
: No
: N/A

Status: Complete

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