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Effect of *PNPLA3* rs738409 genotype and GDM history on fasting glucagon levels in early NAFLD

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BACKGROUND & AIMS:

The *PNPLA3* rs738409 *G/G* risk genotype is associated to the development and progression of NAFLD.
Fasting glucagon levels are higher in both diabetes mellitus and NAFLD. There is no data available about the effects of rs738409 risk genotype or pGDM history on (fasting) glucagon levels.
We assessed the intraheptic lipid content (IHCL) and the plasma glucagon levels in a diabetes prone young-middle aged female population in context of the *PNPLA3* genotype and GDM history.

Hypothesis

- GDM history and *PNPLA3* rs738409 genotype have an additive effect on NAFLD development
- GDM history and *PNPLA3* rs738409 genotype have an effect on plasma glucagon levels

PATIENTS & METHODS (& STUDY DESIGN):

GDM-genetic association study (2012-2016)*

Follow-up of mothers with information about in the prior pregnancy, incl. routine 75g OGTT (24-28thgw)

Targeted enrollment with known *PNPLA3* rs738409 *C/C* or *G/G* homozygous genotypes

Volunteers: 39 women without using any antidiabetic or lipid lowering drug

- „Routine" clinical laboratory measures (iver enzymes, HbA_{1c}, lipids)
- 75g OGTT: 0'-30'-120', plasma glucose (PG), insulin (using CLIA), 0'-30' glucagon (EURIA Glucagon kit)
- Clinical data and medical history
- Abdominal MR spectroscopy (MRS) & MRI (Multi-echo Dixon methods) measurements for liver&pancreatic proton density fat fraction (PDFF) + routine abdominal MRI (Siemens 3T Prisma MR)
- Patients with elevated liver enzymes were screened for alternative etiology.
- Liver fibrosis scores (NFS, Fib-4) were calculated.
- MW-U, SRO, ANOVA/K-W and post hoc tests were used (Statistica program).

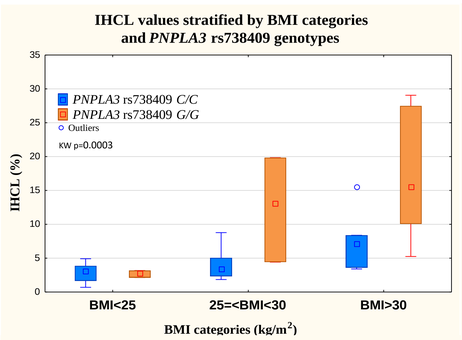
STUDY POPULATION:

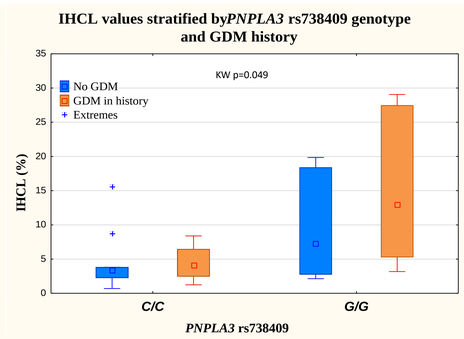
Table 1: Study population's characteristic at enrollment	mean (SD) or n/n
Age (yrs)	37.2 (4.8)
BMI (kg/m^2)	28.2 (6.8)
Time since index pregnancy (yrs) (tot. pop.)	3.5 (1.3)
Time since 1st GDM pregnancy (yrs) (pGDM group only)	6.1 (4.4)
pGDM/total	22/39
rs738409 genotype (*CC*/*GG*)	27/12
DM+prediabetes - at enrollment before follow-up 75g OGTT - (IGT, IFG and/or HbA_{1c} criteria) / total	0/39

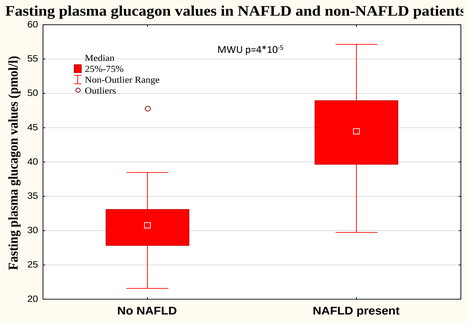
Table 2: Entire study population Clinical data (after study assesment)	n/n or mean (SD)
No of pts with NAFLD (IHCL≥5.5%) / total	14/39
No of pts with HOMA-IR>2.5** /total	19/39
HOMA-B (%)	154 (81.9)
DM+prediabetes (IGT, IFG and/or HbA1c criteria) / total	14/39
FIB4 ≥1.45 / total	0/38
NFS (<-1.455/≤-1.455<0.675/≥0.675)	34/5/0

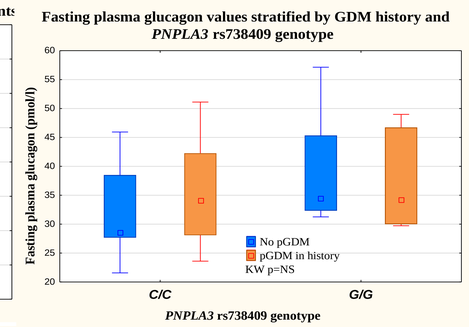
RESULTS:

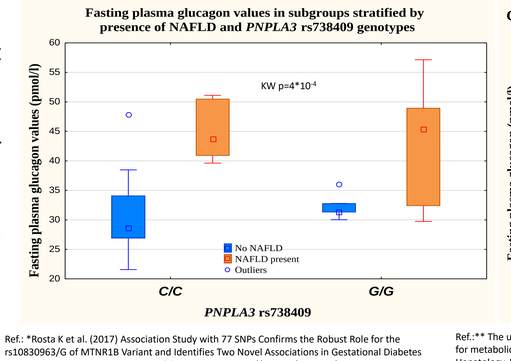
BMI (pGDM vs. non pGDM, median, MWU)= 28.3 vs 25.6kg/m^2 (p=0.25)

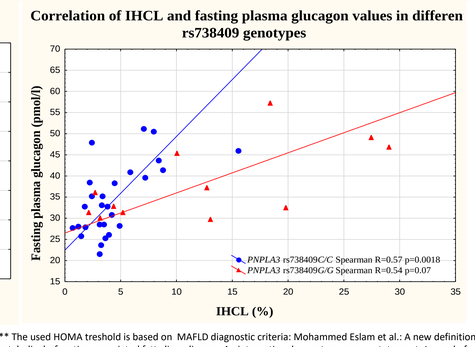


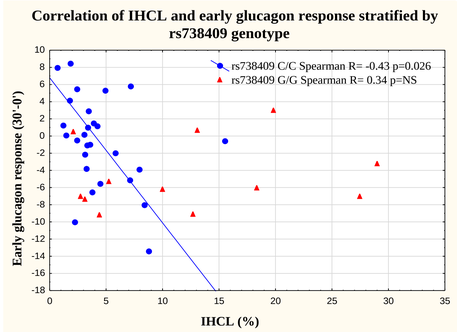


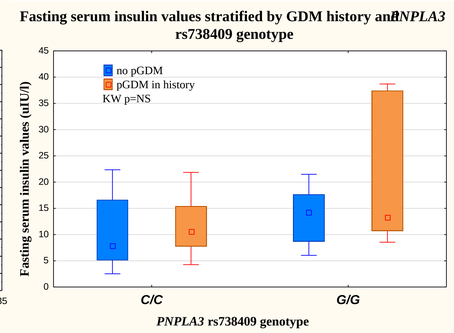


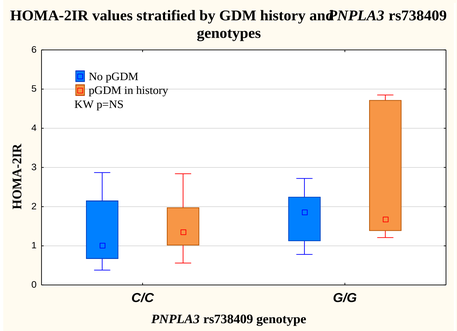


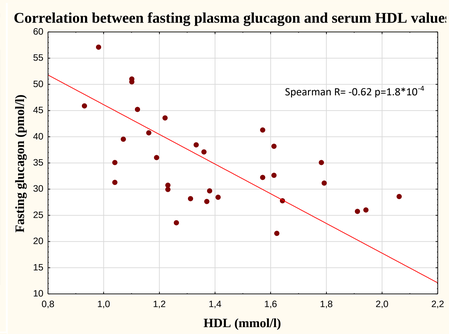


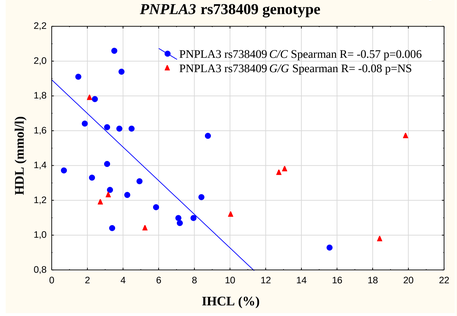


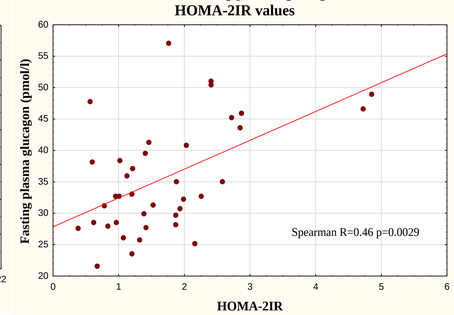












CONCLUSION:

- We confirmed the hypothesis that the GDM history and the *PNPLA3* rs738409 gene variant have an additive effect on NAFLD development
- The fasting plasma glucagon levels were increased both in the risk and non risk genotype groups, however
- the track of the correlation between the fasting glucagon levels and the IHCL was modified by the rs738409 genotype
- We could not detect significant effect of prior GDM on the fasting glucagon levels with this limited sample size.
- To our knowledge we first report a significant negative correlation between the fasting plasma glucagon and serum HDL levels and
- HDL levels were also inversely correlated with the IHCL values only in patients with rs738409 C/C genotype

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Ref.: *Rosta K et al. (2017) Association Study with 77 SNPs Confirms the Robust Role for the rs10830963/G of MTNR1B Variant and Identifies Two Novel Associations in Gestational Diabetes Mellitus Development. PLOS ONE 12(1): e0169781. https://doi.org/10.1371/journal.pone.0169781

Ref.:** The used HOMA treshold is based on MAFLD diagnostic criteria: Mohammed Eslam et al.: A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement, Journal of Hepatology, Volume 73, Issue 1, 2020, Pages 202-209, ISSN 0168-8278, https://doi.org/10.1016/j.jhep.2020.03.039.