Lean Subjects With Fatty Liver Show decreased GLP-1 And GIP Response During OGTT

A. Gastaldelli, J. Garduno-Garcia, R. A. DeFronzo, J. J. Holst, N. Musi

University of Texas Health Science Center at San Antonio USA; Institute of Clinical Physiology CNR Pisa Italy; University of Copenhagen, Denmark

Background and aims

Subjects with non alcoholic fatty liver disease (NAFLD) are at high risk of type 2 diabetes even if they are not obese. Recent studies have indicated that liver fat (LF)>2.5% was already associated with alteration in glucose and insulin metabolism (Bril, Hepatology 2017). Our aim was to investigate if having LF as low as 2.5% was associated to impairment in insulin sensitivity, secretion (ISR) and/or incretin hormones glucagon-like peptide (GLP) 1 and glucose-dependent insulinotropic peptide (GIP) released during an oral glucose tolerance test (OGTT).

Materials and Methods

We studied 49 non diabetic non obese subjects (age 52±4; BMI 24.2±0.4 kg/m2). All subjects underwent a 2 h OGTT with plasma insulin, C-peptide, GLP-1, and GIP concentrations measured every 15-30 min. Insulin secretion rates (ISR) were quantitated by C-peptide deconvolution. Insulin sensitivity was quantified by HOMA and Matsuda index. Liver fat (LF) accumulation was quantified by magnetic resonance spectroscopy (MRS).

Results

In this group of non obese subjects the great majority were non NAFLD (31 had LF<2.5%), while 18 had LF>2.5% (9 had LF 2.5-5% and 9 had LF>5%), Table 1. Age, BMI, HOMA, fasting glucose, insulin, ALT, AST and TG were similar in NAFLD and non-NAFLD.

Table 1: subject characteristics

	LF<2.5%	LF 2.5-5.5%	LF>5.5%
n	31	9	9
Gender (M/F)	14/17	6/3	3/6
Age (y)	55.2 ± 4.4	43.7 ± 7.3	50.8 ± 9.0
BMI (kg/m2)	24.2 ± 0.5	23.8 ± 0.9	25.0 ± 0.9
Liver (%)	1.2 ± 0.1	3.4 ± 0.2*	14.2 ± 3.8*
AST (mU/l)	23.7 ± 1.1	25.0 ± 1.0	25.3 ± 1.8
ALT (mU/l)	18.9 ± 1.5	17.5 ± 2.5	21.3 ± 1.6
TG (mg/dl)	87.6 ± 6.4	81.5 ± 16.1	111.0 ± 43.0
total CHOL (mg/dl)	163.5 ± 5.7	183.0 ± 23.6	148.8 ± 12.6
HDL (mg/dl)	60.5 ± 3.0	62.0 ± 8.9	48.2 ± 3.2
LDL (mg/dl)	87.1 ± 5.6	104.7 ± 21.0	78.5 ± 8.5
Matsuda index	10.2 ± 1.3	8.2 ± 0.9	5.8 ± 0.9*

Table 2: correlations among liver fat and metabolic parameters

Liver fat vs.	Rho	P value
GLP-1 (0-120 min)	-0.35	<0.02
GIP (0-120 min)	-0.11	ns
INS (0-120 min)	-0.01	ns
ISR (0-120 min)	-0.29	0.04
Ins Clearance (0-120 min)	-0.40	0.006
Glucose (0-120 min)	-0.27	0.06
HOMA-IR	0.23	ns
Matsuda index	-0.13	ns

Figure 3: GLP-1 and GIP AUC (0-120min) in subjects with different degrees of LF

Results

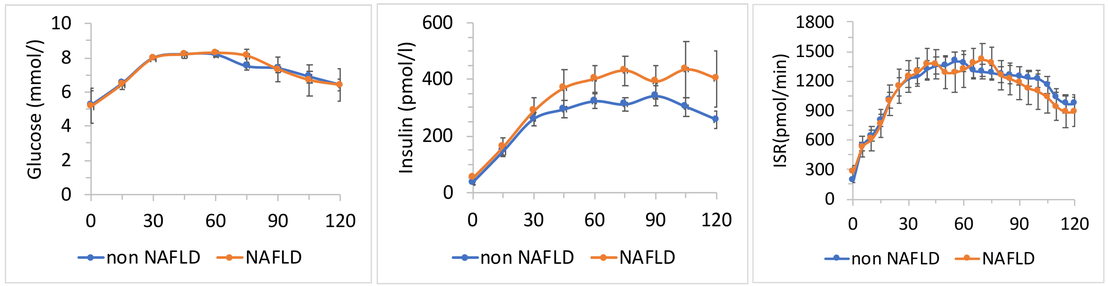

Figure 1: Glucose and hormone curves after OGTT (NAFLD if LF>5.5% otherwise non NAFLD)

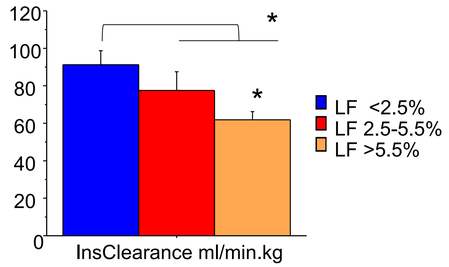

Figure 2: Insulin clearance (MCRI) is decreased proportionally to LF

Subjects with/without NAFLD (LF>5.5%) had similar glucose and ISR curves but higher insulin concentrations indicating lower insulin clearance (Figure 1). Subjects with LF as low as 2.5% had lower GLP-1, GIP (Figure 3) and insulin clearance (Figure 2) compared to LF<2.5%. Insulin secretion ISR_AUC$_{0\text{-}120}$ [142±8 vs 127±9 nmol, p=ns], glucose [Glu$_{0\text{-}120}$ 820±40 vs 901±34 mmol/l] and insulin [Ins$_{0\text{-}120}$ 35.0±3.1 vs 32.8±2.9 nmol/l] concentrations during OGTT were similar. Liver fat accumulations correlated with lower GLP-1, ISR and MCRI (Table 2).

Conclusions

Liver fat accumulation (as low as LF>2.5%) is associated with reduced ISR, incretin and MCRI; this can help to explain the increased risk of T2D of subjects with NAFLD.

References

1. Bril F, Barb D, Portillo-Sanchez P, Biernacki D, Lomonaco R, Suman A, Weber MH, Budd JT, Lupi ME, Cusi K. Metabolic and histological implications of intrahepatic triglyceride content in nonalcoholic fatty liver disease. Hepatology. 2017 Apr;65(4):1132-1144

Acknowledgements

This work was supported by grants from the NIH (R01-DK80157 and R01-DK089229), and the American Diabetes Association to N.M. This work also was supported grants UL1TR000149 (CTSA), AG044271 (San Antonio Claude D. Pepper Older Americans Independence Center) and AG013319 (San Antonio Nathan Shock Center) and grants from the NovoNordisk Foundation (JJH). AG has received research funds from H2020-2014 EPOS (GA #193284); H2020-MSCA RISE 2015 MAST4HEALTH (GA #691042); H2020-MSCA RISE-2016 mitoFOIE GRAS (GA #734719); H2020-MSCA ITN-2016 FOIE GRAS (GA # 722619).