

1 INTRODUCTION

The onset and progression of liver damage in Non-Alcoholic Fatty Liver Disease (NAFLD) is tightly associated with insulin resistance (IR) and secondary hyperinsulinemia.

Typically, NAFLD patients showed higher serum levels of both insulin and C-peptide levels, the cleavage product of pro-insulin.

Despite current national and international guidelines do not advocate the use of C-peptide in the clinical setting,¹ recent insights revealed its potential use in different algorithms aiming to evaluate the degree of IR.^{2,3}

2 AIM

The aim of this study was to compare fasting IR indices based on insulin and C-peptide levels and their ability to predict histological features of NASH in a cohort of non-diabetic subjects with biopsy-proven NAFLD.

3 METHOD

- We studied 119 subjects with histological diagnosis of NAFLD.
- Serum C-peptide was assessed by chemiluminescence assay (Lumipulse®, Fujirebio).
- HOMA-IR was calculated as $[(\text{fasting glucose} \times \text{fasting insulin})/405]$
- HOMA-IR by C-peptide was calculated as $[(\text{fasting glucose} \times \text{fasting C-peptide})/405]$
- C-peptide index (CPI), reflecting β -cell function thus insulin secretion, was calculated as $[(100 \times \text{C-peptide})/\text{fasting glucose}]$
- Histology was scored according to Kleiner.

4 RESULTS

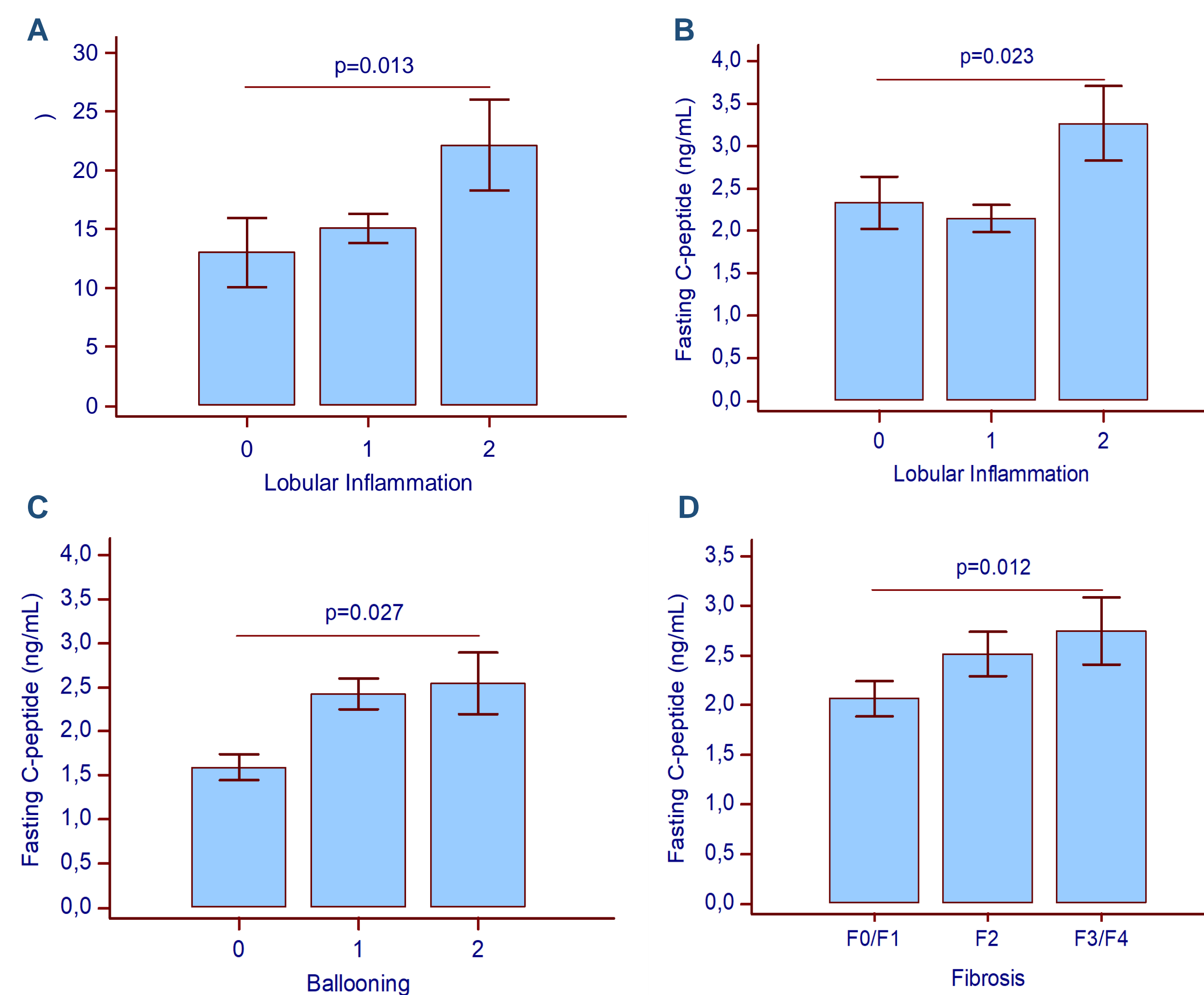
Clinical, biochemical and histological characteristics of the study cohort are reported in Table 1.

Table 1.

Variables	N = 119
Age, y	44 (20-70)
BMI, kg/m ²	27.7 ± 4.2
AST, U/l	32 (15-229)
ALT, U/l	58 (13-323)
Platelets, 10 ⁹ /l	216 (111-686)
Albumin, mg/dl	4.5 ± 0.4
Fasting insulin, mIU/ml	12 (2-76)
Fasting C-peptide, ng/ml	2 (0.01-10.5)
Fasting glucose, mg/dl	88 (70-116)
Histology	
Fibrosis 0/1/2/3/4, n (%)	45/29/22/18/5 (38/24/19/15/4)
Steatosis 1/2/3, n (%)	68/36/15 (57/30/13)
Lobular Inflammation 0/1/2, n (%)	25/84/10 (21/71/8)
Ballooning 0/1/2, n (%)	25/62/32 (21/52/27)
NASH, n(%)	76 (64)

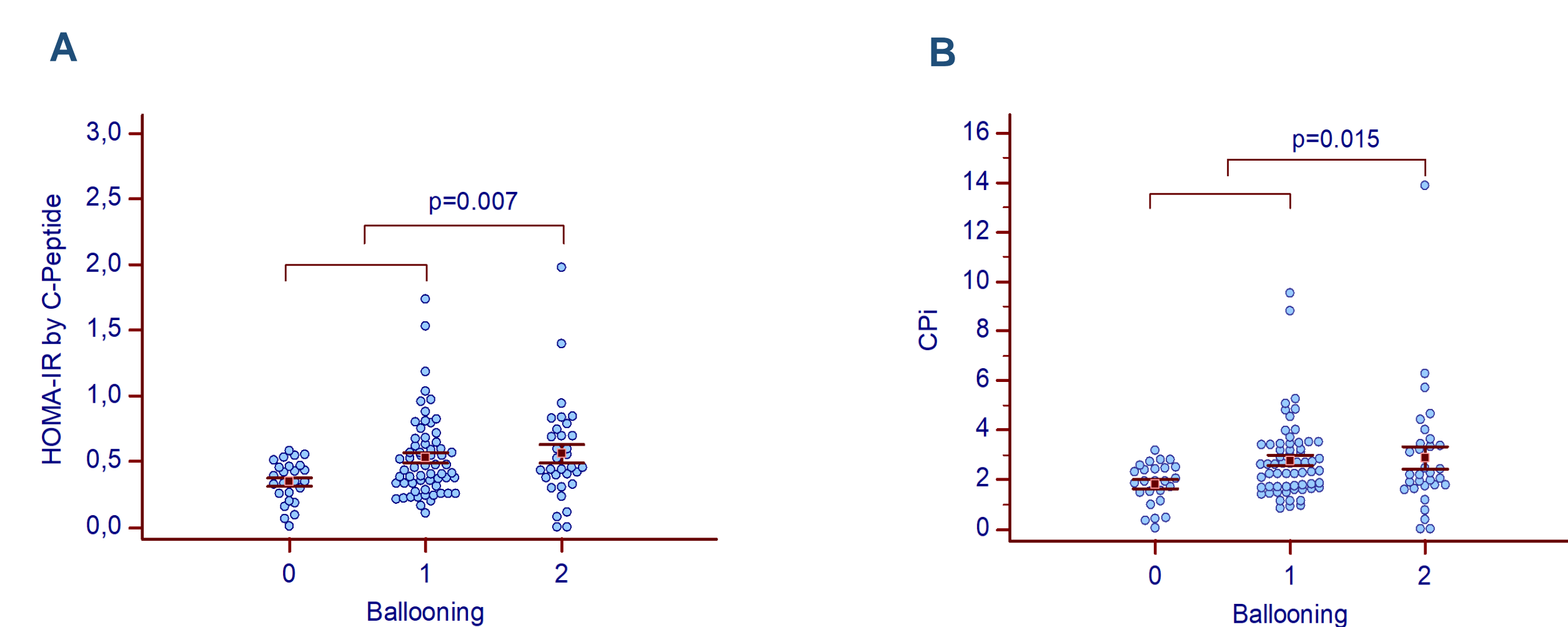
Insulin and C-peptide levels significantly increased according to lobular inflammation (Fig. 1A-B), but only C-peptide showed a stepwise increase according to ballooning (Fig. 1C) and fibrosis (Fig. 1D).

Figure 1



HOMA-IR by insulin did not significantly increase according to the histological features of NASH while both HOMA-IR by C-peptide and CPI were significantly higher in patients with hepatic ballooning compared to those without (0.35 vs 0.54, p=0.006; 1.82 vs 2.81, p=0.01, respectively) (Fig. 2A-B).

Figure 2



At univariate logistic regression analysis, BMI and HOMA-IR by C-peptide were significantly associated with significant fibrosis (F_≥2), but at multivariable logistic regression analysis adjusted for age and BMI, no index among HOMA-IR by insulin, HOMA-IR by C-peptide and CPI, was significantly associated with F_≥2, (Table 2).

Table 2. Regression analysis for the identification of the best index associated with significant fibrosis (F_≥2)

Variable	Univariate Analysis		Multivariable Analysis					
	OR (95%CI)	P value	OR (95%CI)*	P value*	OR (95%CI)#	P value#	OR (95%CI)§	P value§
Age	1 (0.9-1)	0.602	1 (0.9-1)	0.376	1 (0.9-1)	0.456	1 (0.9-1)	0.397
BMI	1.1 (1.1-1.2)	0.012	1.2 (1-1.3)	0.005	1.1 (1-1.2)	0.034	1.1 (1-1.2)	0.021
HOMA-IR by insulin	1 (0.9-1)	0.978	0.9 (0.8-1)	0.235	-	-	-	-
HOMA-IR by C-peptide	4.1 (1.1-14.4)	0.031	-	-	2.8 (0.8-10)	0.105	-	-
CPI	1.2 (0.9-1.5)	0.112	-	-	-	-	1.1 (0.9-1.4)	0.226

Table 3. Regression analysis for the identification of the best index associated with the presence of hepatic ballooning.

Variable	Univariate Analysis		Multivariable Analysis					
	OR (95%CI)	P value	OR (95%CI)*	P value*	OR (95%CI)#	P value#	OR (95%CI)§	P value§
Age	1 (0.9-1)	0.933	1 (0.9-1)	0.876	0.9 (0.9-1)	0.927	1 (0.9-1)	0.870
BMI	1 (0.9-1.2)	0.119	1.1 (0.9-1.2)	0.262	1 (0.9-1.2)	0.529	1 (0.9-1.2)	0.479
HOMA-IR by insulin	1.1 (0.9-1.4)	0.199	1.1 (0.9-1.4)	0.449	-	-	-	-
HOMA-IR by C-peptide	25 (2-244)	0.006	-	-	19 (2-224)	0.018	-	-
CPI	1.9 (1.2-3)	0.008	-	-	-	-	1.8 (1.1-2.8)	0.021

At univariate logistic regression analysis, HOMA-IR by C-peptide and CPI were significantly associated with the presence of ballooning; at multivariable logistic regression analysis adjusted for age and BMI, both HOMA-IR by C-peptide and CPI, were independently associated with ballooning (OR=25, 95% CI=2-244, p=0.006 and OR=1.9, 95%CI=1.2-3, p=0.008, respectively (Table 3).

5 CONCLUSIONS

In non-diabetic patients with NAFLD, fasting IR indices derived from C-peptide levels were closely related to hepatic ballooning suggesting the importance of insulin secretion in the onset and progression of liver disease.

7 REFERENCES

- WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. *World Health Organization 2013.*
- Loopstra-Masters RC, et al. Proinsulin-to-C-peptide ratio versus proinsulin-to-insulin ratio in the prediction of incident diabetes: the insulin resistance atherosclerosis study (IRAS). *Diabetologia 2011;54:3047-54.*
- Kim JD, et al. C-peptide-based index is more related to incident type 2 diabetes in non-diabetic subjects than insulin-based index. *Endocrinol Metab 2016;31:320-7.*

8 CONTACT

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