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Irisin in patients with nonalcoholic fatty liver disease

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ARTICLE INFO

Article history:
Received 26 July 2013
Accepted 16 September 2013

Keywords:
Fibronectin type III domain containing 5
Chemerin
Nonalcoholic steatohepatitis
Portal inflammation
Retinol-binding protein-4

ABSTRACT

Objective. Irisin is a recently discovered myokine proposed to increase thermogenesis-related energy expenditure and improve metabolism. We aimed to comparatively evaluate serum irisin levels in patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD) vs. controls and study their association with disease severity.

Methods. Fifteen and 16 consecutively enrolled patients with biopsy-proven nonalcoholic simple steatosis (NAFL) and steatohepatitis (NASH), respectively, and 24 lean and 28 obese controls without NAFLD were recruited. Irisin, established adipokines and biochemical tests were measured.

Results. Serum irisin levels were statistically different in obese controls (33.7 ± 2.7 ng/mL; $p < 0.001$) and patients with NAFL (30.5 ± 1.5 ng/mL; $p < 0.001$) and NASH (35.8 ± 1.9 ng/mL; $p = 0.001$) compared with lean controls (47.7 ± 2.0 ng/mL), but were similar among patients with NAFL, NASH and obese controls. This difference remained significant after adjustment for body mass index (or waist circumference), gender, age, insulin resistance (assessed by HOMA-IR or QUICKI), exercise and time since blood collection. Serum leptin and adiponectin, but not irisin, levels were independently from BMI correlated with insulin resistance and cardiometabolic factors. Serum irisin tended to be higher in patients with (36.7 ± 2.4 ng/mL) than without (30.8 ± 1.2 ng/mL; $p = 0.02$) portal inflammation and independently associated with the latter; these data need to be confirmed by future studies.

Conclusions. Serum irisin levels differ between lean controls and obese controls or NAFLD patients. Despite similar circulating irisin levels between NAFL and NASH groups, irisin may be independently and positively associated with the presence of portal inflammation. Future clinical and mechanistic studies are needed to confirm and extend these data.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; FNDC, fibronectin type III domain containing; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model of assessment insulin resistance; IR, insulin resistance; LETO, Long Evans Tokushima; MetS, metabolic syndrome; NAFL, simple nonalcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; LDL-C, Low density lipoprotein cholesterol; OLETF, Otsuka Long–Evans Tokushima Fatty; QUICKI, quantitative insulin sensitivity check index; RBP, retinol-binding protein; T2DM, type 2 diabetes mellitus; WC, waist circumference.

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0026-0495/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.metabol.2013.09.013

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), a global public health problem of increasing significance, ranges from simple nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), characterized by steatosis, inflammation and fibrosis. NASH, a severe form of NAFLD, may lead to subacute liver failure, liver cirrhosis and/or hepatocellular carcinoma [1]. NAFLD is considered to be the hepatic component of metabolic syndrome, increasing in parallel with the epidemics of obesity and type 2 diabetes mellitus (T2DM) [2]; in this regard, elevated transaminase levels have been associated with the metabolic syndrome [3], even in childhood and adolescence [4]. Therefore, it is important to identify noninvasive indices for NAFLD, thereby grading the severity of the disease at an early stage, early in life. Currently, noninvasive indices for NAFLD represent a field of extensive research worldwide, targeting to replace liver biopsy, which is to-date the gold standard for the diagnosis of NAFLD, but it cannot be performed in all patients, due to its potential complications and to the high disease prevalence [5].

NAFLD is a field of intensive research, but mechanisms underlying its development largely remain to be defined and its treatment is currently an unmet medical need [6]. Weight loss and exercise are regarded as the initial NAFLD management methods by recently published guidelines [7,8]. Given that insulin resistance (IR) and adipokines contribute to the pathogenesis of NAFLD, as reviewed elsewhere [2], the improvement in response to weight loss or exercise may partly occur due to weight loss or exercise-induced improvement in IR or adipokine levels. However, the causative links between exercise and NAFLD improvement are not fully elucidated.

Skeletal muscle has recently emerged as an endocrine organ by secreting myokines, hormones released into the circulation, during or immediately after physical activity [9]. Irisin is a newly discovered exercise-induced myokine [10], implicated in the regulation of energy homeostasis and metabolism and thus proposed to bridge, at least in part, our previous gap of knowledge on interactions between skeletal muscle and other tissues [11,12], although controversy exits [13,14]. Irisin is identical in mice and humans, and its administration results in «browning» or «beigeing» of white adipose tissue, thereby increasing the thermogenesis-related energy expenditure and improving systemic metabolism. Due to its action, irisin is emerging as an appealing therapeutic target for metabolic diseases and other disorders known to improve with exercise, such as NAFLD [15].

The primary aim of this study was the evaluation of serum irisin levels in patients with biopsy-proven NAFLD, as well as their association with the disease severity. Secondary aims were: 1) the association of irisin levels with IR, cardiometabolic risk factors, liver function tests and other adipokines and

Table 1 – Baseline characteristics of subjects per study group.

	Lean controls	Obese controls	NAFL	NASH	p-value for trend [a]	Reference range
Total number of Patients/Women (N)	24/20	28/20	15/10	16/13	0.58	–
Age (years)	54.2 ± 1.6	52.6 ± 1.6	53.9 ± 2.6	53.9 ± 2.9	0.95	–
BMI (kg/m^2)	25.3 ± 0.3	30.9 ± 0.6 *	31.9 ± 1.3 *	34.1 ± 1.4 *	<0.001	20–25
WC (cm)	85 ± 2	100 ± 2 *	105 ± 3 *	107 ± 3 *	<0.001	Male < 94 Female < 80
Crude Exercise Index (min/week)	336 ± 150	166 ± 46	108 ± 34	77 ± 27 *	0.046	na
AST (U/L)	21 ± 1	19 ± 1	27 ± 2	49 ± 9 *,**,***	<0.001	10–31
ALT (U/L)	21 ± 1	20 ± 2	42 ± 6	71 ± 15 *,**,***	<0.001	10–34
AST/ALT ratio	1.14 ± 0.12	1.11 ± 0.08	0.76 ± 0.07	0.81 ± 0.06	<0.001	–
GGT (U/L)	17 ± 1	21 ± 3	46 ± 12 *	64 ± 12 *,**	<0.001	0–38
Total cholesterol (mg/dL)	215 ± 9	231 ± 7	202 ± 10	222 ± 10	0.15	<200 [b]
HDL-C (mg/dL)	57 ± 3	57 ± 3	51 ± 3	47 ± 1	0.03	Male > 40 Female > 50
LDL-C (mg/dL)	131 ± 6	147 ± 6	119 ± 10 **	135 ± 9	0.049	<160 [b]
Triglycerides (mg/dL)	95 ± 6	119 ± 10	162 ± 22 *	199 ± 27 *,**	<0.001	<150
Uric acid (mg/dL)	4.5 ± 0.2	4.9 ± 0.2	5.5 ± 0.2	5.3 ± 0.3	0.045	2.6–6.6
Glucose (mg/dL)	86 ± 2	91 ± 4	92 ± 8	95 ± 4	0.20	60–100
Insulin (μU/mL)	6.0 ± 0.6	9.5 ± 1.1	19.3 ± 5.8 *	24.3 ± 5.0 *,**	<0.001	6–27
HOMA-IR	1.27 ± 0.13	2.15 ± 0.25	5.34 ± 2.52	5.78 ± 1.14 *	<0.001	na
QUICKI	0.38 ± 0.01	0.35 ± 0.01	0.33 ± 0.01 *	0.31 ± 0.01 *,**	<0.001	na
Leptin (ng/mL)	10.2 ± 1.5	17.0 ± 2.5	20.1 ± 4.0	32.2 ± 5.7 *,**	0.002	na
Adiponectin (μg/mL)	15.7 ± 1.1	11.1 ± 0.8 *	8.1 ± 1.3 *	4.6 ± 0.7 *,**	<0.001	na
RBP-4 (μg/mL)	0.59 ± 0.06	0.85 ± 0.10	0.61 ± 0.10	0.64 ± 0.13	0.14	na
Chemerin (ng/mL)	11.8 ± 0.6	13.3 ± 0.1	12.9 ± 0.7	11.3 ± 0.7	0.31	na
Irisin (ng/mL)	49.7 ± 2.0	33.7 ± 2.7 *	30.5 ± 1.5 *	35.8 ± 1.9 *	<0.001	na

Data are presented as mean ± standard error of the mean (SEM) or absolute numbers.
[a] Between groups comparison.
[b] For patients without other cardiovascular risk factors.
* $p < 0.05$ compared to the lean control group.
** $p < 0.05$ compared to the obese control group.
*** $p < 0.05$ compared to NAFL group (Bonferroni *post hoc* adjustment).