Clinica Chimica Acta 479 (2018) 79–83

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Serum CTRP3 level is inversely associated with nonalcoholic fatty liver disease: A 3-y longitudinal study

Wenjing Zhou[1], Yuming Wang[1], Yue Wu, Ji Yang, Liqian Xu, Yunmei Yang*

Department of Geriatrics, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

ARTICLE INFO

Keywords:
C1q Tumor necrosis factor-Related Protein 3 (CTRP3)
Biomarker
Adipokine
Nonalcoholic fatty liver disease (NAFLD)
Longitudinal study

ABSTRACT

Background: CTRP3, a novel adipokine, has been linked with a variety of physiological functions, including adipokines secretion, energy metabolism, through an endocrine mean. This study evaluated the role of serum CTRP3 levels in the development of nonalcoholic fatty liver disease (NAFLD).

Methods: The hospital-based longitudinal study recruited urban residents who took health examination. Serum CTRP3 levels were evaluated by an enzyme-linked immunosorbent assay. The adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the relationship between baseline serum CTRP3 and incidence of NAFLD at follow-up.

Results: Of the 814 participants at baseline, 313 subjects were included at follow-up. At baseline, serum CTRP3 level was lower in subjects with NAFLD (283.3 [159.6–375.0] ng/ml) than it in non-NAFLD subjects (295.0 [184.0–398.0] ng/ml) ($p = 0.006$). Meanwhile, serum CTRP3 level was inversely correlated with body mass index, waist-to-hip ratio, triglycerides and fasting plasma glucose. After a 3-y follow-up, the CTRP3 concentrations decreased from the baseline (206.7 [136.3–322.6] ng/ml) to the follow-up (177.4 [112.1–295.5] ng/ml, $p < 0.001$) in the subjects who developed NAFLD ($n = 55$). Compared with the 1st Quartile of baseline serum CTRP3, the subjects in the 3rd Quartile and 4th Quartile indicated lower risks of NAFLD progression at 3-y (adjusted OR = 0.451, 95% CI [0.270–0.755], $p = 0.002$ and adjusted OR = 0.468, 95% CI [0.310–0.707], $p < 0.001$).

Conclusion: Serum level of CTRP3 was inversely associated with the progress of NAFLD independently at 3-y.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), one of the most prevalent chronic liver diseases, covers a spectrum of diseases ranging from simple hepatic steatosis, to steatohepatitis, fibrosis and finally cirrhosis [1,2]. Current evidence suggests that NAFLD closely associates with obesity and insulin resistance, and now is regarded as hepatic manifestation of the metabolic syndrome [3].

Adipose tissue was conventionally thought to be a reservoir for energy storage, however recent advance supports its role as an endocrine organ [4,5]. The discovery of various adipocyte-derived hormones, i.e. adipokines, revealed their critical roles in metabolic functions [6,7]. The previous studies reported a novel family of adipokines and named Complement C1q Tumor necrosis factor-Related Proteins (CTRPs) [8,9]. Several of these proteins show essential roles in regulating energy metabolism [9,10].

Previous reports revealed that CTRP3, a novel adipokine, has been linked with a variety of physiological functions, including adipokines secretion, energy metabolism, inflammation, cellular differentiation and development, through an endocrine mean [10–14]. Besides, a series of population/hospital-based studies have been conducted [15,16]. A case-control study of Deng et al. [16] found that the serum CTRP3 levels in the subjects with obesity or hypertension were lower than those in the control. It suggested CTRP3 was an independent factor in regulating blood pressure and insulin resistance. Wolf et al. [15] also showed that serum CTRP3 decreased in the subjects with obesity, not in subjects with coronary artery disease, while its level depended on body mass index (BMI). However, Fadaei et al. [17] revealed that decreased serum levels of CTRP3 were associated with increased risk of type 2 diabetes and coronary artery disease. Tan et al. [18] found a decreased concentration of CTRP3 in women with polycystic ovary syndrome, which is an endocrine disorder closely associated with obesity and

Abbreviations: CTRP, Complement C1q Tumor necrosis factor-Related Protein; DBP, Diastolic Blood Pressure; FPG, fasting plasma glucose; HOMA-IR, Homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NAFLD, Non-alcoholic fatty liver disease; SBP, Systolic Blood Pressure; WHR, waist-to-hip ratio

* Corresponding author.
E-mail address: 1194070@zju.edu.cn (Y. Yang).

[1] W. Zhou and Y. Wang contribute equally.

https://doi.org/10.1016/j.cca.2018.01.003
Received 29 October 2017; Received in revised form 2 January 2018; Accepted 2 January 2018
Available online 03 January 2018
0009-8981/

dyslipidemia. Ban et al. [19] reported that serum CTRP3 decreased in patients with newly diagnosed type 2 diabetes, and furthermore, it positively correlated with serum leptin level, while negatively correlated with glucose and C reactive protein. These data suggested that serum CTRP3 might be a practical biomarker in the clinical management of obesity and its associated diseases.

Recent advance links obesity and metabolic syndrome to NAFLD. It reveals a complex interaction between the liver and adipose tissue via the secretion of adipokines. As a novel adipokine, CTRP3 may play a beneficial role in NAFLD.

2. Methods

2.1. Study design and patients

The hospital-based longitudinal study recruited the subjects who took the annual health examination at the First Affiliated Hospital, College of Medicine, Zhejiang University from January to November 2013. From February to December 2016, the subjects were invited for follow-up assessments. Of the 814 subjects who initially participated in at baseline, 313 were ultimately enrolled in the follow-up study. Subjects with the following medical conditions were excluded: viral/drug-induced/autoimmune liver diseases, pregnancy, excessively alcoholic consumption (> 140 g/w men, > 70 g/w women), malignant tumor, severe cardiopulmonary disorders, renal dysfunction, severe inflammatory and endocrine diseases, and used estrogens or steroids. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University, in accordance with the Helsinki Declaration of 1964. All subjects gave written informed consent before participation.

2.2. Examinations

Fasting blood samples were collected and frozen for the further measurement of serum CTRP3 levels by using enzyme-linked immunosorbent assay. The intra and inter assay CVs of serum CTRP3 measurement were 5.2% and 10.7%, respectively. Besides, routine blood chemistry analyses and anthropometric exam were performed in our hospital, as reported before [20]. NAFLD and its ultrasonographic degrees were diagnosed based on the guidelines for diagnosis and treatment of NAFLD issued by Fatty Liver and Alcoholic Liver Disease Study Group of the Chinese Liver Disease Association [21–23].

2.3. Statistical methods

Normally distributed variables were presented as mean ± standard deviation; variables with a skewed distribution underwent a lg(x) transformation to achieve a normal distribution and were presented as median value (interquartile range). Normality of distribution was tested with the Kolmogorov-Smirnov test. The Student's *t*-test or Mann-Whitney *U* test for continuous variables, and $\chi 2$ test for categorical variables were used to compare the parameters between two groups. Comparisons among three NAFLD groups (mild, moderate and severe) used Kruskal–Wallis test. The $\chi 2$ test was used for testing the difference of NAFLD within the quartiles of serum CTRP3. Wilcoxon matched-pairs signed rank test was used for comparison between baseline and follow-up. To assess the relationship between baseline serum CTRP3 and incidence of NAFLD at follow-up, we calculated the adjusted odds ratio (OR) and 95% confidence interval (CI) with a multivariable binary logistic regression model. Correlation between serum CTRP3 and the anthropometric/biomedical parameters were performed using partial correlation coefficients. All statistical analyses were performed using SPSS (version 21.0). Power of sample size (post hoc) was calculated by G*Power (version 3.1, Heinrich-Heine-Universität Düsseldorf, Germany) [24]. A 2-sided $p < 0.05$ was considered significant.

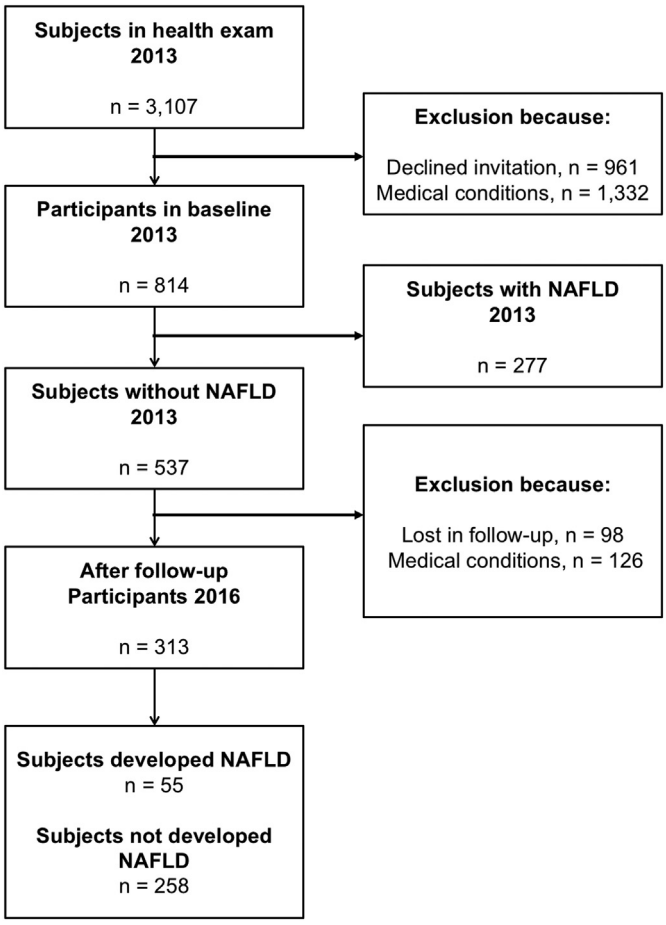

Fig. 1. Flow chart of the study population.

Table 1
Baseline characteristics of subjects by NAFLD.

Parameter	Non-NAFLD	NAFLD	*p*
No. of subjects	537	277	
Age (y)	53.9 ± 12.8	54.3 ± 13.5	NS
Male, n (%)	185, 34.5%	101, 36.5%	NS
IFG&IGT, n (%)	138, 25.7%	79, 28.5%	NS
Hypertension, n (%)	117, 21.8%	99, 35.7%	< **0.001**
SBP (mm Hg)	111.8 ± 22.3	121.0 ± 23.0	< **0.001**
DBP (mm Hg)	73.8 ± 16.2	79.3 ± 16.6	< **0.001**
BMI (kg/m^2)	22.7 ± 3.3	23.4 ± 3.5	**0.003**
WHR	0.82 ± 0.09	0.87 ± 0.09	< **0.001**
CTRP3 (ng/ml)	295.0 [184.0–398.0]	283.3 [159.6–375.0]	**0.006**
ALT (U/l)	20.0 [13.0–32.0]	22.0 [15.0–34.0]	**0.017**
AST (U/l)	18.0 [15.0–25.0]	22.0 [17.0–29.0]	< **0.001**
GGT (U/l)	33.0 [23.0–49.0]	32.0 [23.0–52.0]	NS
TG (mmol/l)	1.10 [0.82–1.77]	1.39 [1.02–2.04]	< **0.001**
HDL-C (mmol/l)	1.15 ± 0.36	1.17 ± 0.36	NS
LDL-C (mmol/l)	2.29 ± 0.90	2.52 ± 0.89	**0.001**
FPG (mmol/l)	3.91 [3.05–5.70]	4.40 [3.71–5.88]	< **0.001**
Insulin (mU/l)	12.5 [8.4–18.3]	12.5 [9.2–18.4]	NS
HbA1c (%)	6.28 [5.20–8.96]	6.20 [5.20–9.00]	NS
HOMA-IR	2.30 [1.40–3.56]	2.59 [1.71–3.98]	**0.007**
C peptide (ng/ml)	1.13 ± 0.68	1.12 ± 0.69	NS
UA (μmol/l)	322.6 ± 86.7	313.0 ± 85.4	NS

Data are mean ± SD or median (interquartile range). *p* values indicated the comparisons between non-NAFLD (n = 537) and NAFLD (n = 277) at baseline. HOMA-IR, Homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; SBP, Systolic Blood Pressure; WHR, waist-to-hip ratio. Status of bold applies when *p* value lesses than .05.