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Circulating levels of adipocytokine omentin-1 in patients with renal cell cancer

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ABSTRACT

Renal cell carcinoma (RCC) is the fifth most common cancer worldwide, and becomes one of the leading causes of genitourinary cancer-related death in both males and females. Genetic alternations, alcohol consumption, occupationally harmful exposure and even obesity are well-established risk factors of RCC. Omentin-1 is a plasma adipokine synthesized in visceral adipose tissue, and its circulating serum concentration alters not only in conditions associated with insulin resistance such as Polycystic Ovary Syndrome (PCOS), but also in colorectal cancer and prostate cancer. To our best knowledge, the relationship between omentin-1 and RCC has not been clarified previously. Thus, we evaluated serum omentin-1 levels in RCC patients in the current matched case-control study. Forty-one patients newly diagnosed with RCC and forty-two healthy controls confirmed by the comprehensive medical examination were assessed. The omentin-1 concentrations were determined via utilizing enzyme-linked immunosorbent assays (ELISA) in the paired groups, in which the patients and healthy controls had no statistically significant differences in gender, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist-hip ratio (WHR), estimate glomerular filtration rate (eGFR), body-mass index (BMI) and biochemical parameters. The omentin-1 levels in healthy people were 9.86 ± 1.44 ng/mL and the circulating omentin-1 levels were dramatically decreased to 3.62 ± 0.76 ng/mL in RCC patients ($p < 0.001$). Besides, we revealed a negative correlation between omentin-1 with WHR ($r = -0.261$, $p = 0.017$) and BMI ($r = -0.310$, $p = 0.004$), further indicating BMI was the main influential factor on omentin-1 levels ($p = 0.0091$). Follow-up studies would be conducted to establish the concrete mechanisms underlying the altered circulating levels of omentin-1 and elucidate the interaction between "RCC complex system" and adipose tissues, which may together provide promising and novel pharmacological insights for RCC theragnosis in the near future.

1. Introduction

Renal cell carcinoma (RCC) is the fifth most common cancer of all human cancers around the world, and the most majority of RCC are clear cell renal cell carcinoma (ccRCC) [1]. According to the most recent estimation data of cancer incidence and mortality conducted by the American Cancer Society for 2014, RCC will account for about 3.8% of all newly diagnosed cancers and nearly 3% of all newly cancer-related cell death in America, respectively [2]. Accumulating evidences have suggested the genetic alternations in RCC and also demonstrated the interactions between genetic effects and several etiologic factors including alcohol consumption, occupationally harmful exposure and even nonoptimal

Abbreviations: RCC, renal cell cancer; BMI, body mass index; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triacylglycerol; TC, total cholesterol; FBG, fasting blood glucose; CRE, creatinine; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; PCA, Pearson correlation analysis; CSS, cancer-specific survival; RFS, recurrence free survival; VHL, von Hippel-Lindau; eNOS, endothelial nitric oxide synthase; AMPK, adenosine monophosphate-activated protein kinase; PI3K, phosphoinositide 3-kinase; Sirt1, silent mating type information regulation 2 homolog 1 deacetylase; OR, odds ratio; CI, confidence interval; SE, standard error; Asymp. Sig., asymptotic significance.

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physical qualities, whose interactions are believed to increase the risk of developing RCC in a combinational manner [3]. Among the various established risk factors, obesity is regarded as an increasingly prevalent factor in contributing to the high incidence of RCC [4]. Several case-control studies have reported a strong association between body-mass index (BMI) and RCC risk after adjusting age, gender, tumor size, epidermal growth factor receptor (EGFR), diabetes mellitus, hypertension, smoking and other confounding factors [5–8]. For instance, a systematic review and meta-analysis conducted by Renehan et al. have provided convincing evidences for a statistically significant association between BMI and RCC incidence with summary risk estimates (per 5 kg/m^2 increase in BMI) of risk ratio 1.24 in males and 1.34 in females (p value < 0.0001), respectively [8]. Although the biological mechanisms underlying the association between BMI and cancer occurrence or progression are not well-clarified and conclusive, several molecular components and related biological processes such as insulin resistance, aberrant insulin growth factor (IGF) expression, sex hormones disorder, obesity-induced hypoxia, oxidative stress and shared genetic susceptibility have been revealed to be the risk factors contributing to the obesity-cancer association and determining the patient's risk [9]. In addition, various novel mechanisms have been proposed to elucidate obesity may initiate or promote carcinogenesis, including chronic inflammation responses caused by abnormal production of adipokines from adipose tissue, which was presently recognized as an active endocrine organ [10]. Adipokines, such as adiponectin, leptin, resistin, apelin and omentin are biologically active polypeptides produced by adipocytes and have been regarded as potential modulators involved in obesity's associations with RCC. Controversially, some studies advocated that both high adiponectin and leptin levels were significantly correlated with reduced RCC risk [11,12], while another study has demonstrated that enhanced adiponectin and leptin concentrations were positively associated with increased risk of RCC [10].

Omentin-1, also known as intelectin-1, intestinal lactoferrin receptor, endothelial lectin HL-1 or galactofuranose-binding lectin, has been intensively studied during the past decades [14]. It is a novel 34 kDa plasma adipocytokine which is selectively and abundantly expressed in visceral adipose tissue compared with subcutaneous adipose tissue, and the circulating omentin levels are positively correlated with adiponectin, high-density lipoprotein cholesterol (HDL-C) and endothelial functions, while negatively correlated with BMI, insulin resistance and fasting plasma insulin. Notably, several most recent studies demonstrated significantly altered expression of serum omentin-1 in chronic kidney disease patients [15,16] and deregulated circulating levels in either colorectal cancer [17] or prostate cancer patients [18], compared to the healthy controls, respectively. However, to our best knowledge, circulating serum omentin levels associated with the metabolic risk factors in RCC patients has not yet been revealed. Therefore, this matched case-control study that determined the serum omentin concentrations in patients with RCC and paired control cases, will undoubtedly help to provide potential diagnostic perspectives for RCC in clinical trial, especially in consideration of the fact that approximately one-third of patients with RCC have tumor metastasis at the time of diagnosis.

2. Methods

2.1. Patients and controls

Written informed consent was obtained from all patients and the study was approved by the Institutional Review Board of the first affiliated hospital of Anhui Medical University, Hefei, Anhui, People's Republic of China (Approval No. PJ20140907). Forty-one patients who had undergone radical nephrectomy at the first affiliated hospital of Anhui Medical University and histopathologically diagnosed with RCC by hospital pathologists were enrolled in the study in July 2013 to July 2014. All patients met the following criteria: no curative medication for RCC; no previous history of malignancy or renal operations; no diagnosis of nephritis, diabetes and any other heart, liver or renal damages. At the same time, we selected a matched healthy control group from people who confirmed their fitness at the comprehensive medical examination center at the first affiliated hospital of Anhui Medical University. Venous blood was obtained from all patients and healthy controls in a fasting state. After centrifuging the blood at 4 °C with 3000g for 10 min and harvesting the supernatant, all the serums were kept in polypropylene tubes and stored at −80 °C until detection.

2.2. Physical and biochemical measurements

Anthropometric measurements obtained in this study included height, weight, SBP, DBP and waist circumference. BMI was calculated as body weight divided by height squared (kg/m^2) and the abdominal circumference was measured at the umbilicus level. Biochemical parameters were measured in the stored serum samples. The serum levels of triacylglycerol (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) levels, fasting blood glucose (FBG) and creatinine (CRE) were detected using the standard methods at the Kingmed Diagnostics Center at Hefei, Anhui. The estimated glomerular filtration rates (eGFR) were assessed by using the optimized equation: $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [If female]. [Note: Scr is serum creatinine in μmol/L, κ is 61.9 for females and 79.6 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1] [19].

2.3. Omentin-1 measurements

Omentin-1 concentrations were determined in stored serum samples using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol (Aviscera Bioscience, CA 95051, USA). The linear range of the assay was 0.50–32.0 μg/L. The inter- and intra-assay coefficients of variation were 8–10% and 4–6%, respectively.

2.4. Statistical analysis

Measurement data were expressed as mean ± standard error. Kolmogorov–smirnov test was used to validate whether the data were normally-distributed. If they were normally-distributed variables, the t-test was introduced for comparison within the group and between groups; if not, we selected the nonparametric Wilcoxon Mann–Whitney test to assess the significant differences between different groups [20,21]. Subsequently, Spearman's rank correlation coefficient analyses were conducted to test for associations between omentin-1 levels and general clinical characteristics and biochemical parameters [22]. Finally, the influential factors of omentin-1 levels were identified by using multiple-factor binary logistic regression analysis [23,24] for meaningful clinical characteristics, biochemical parameters and nonparametric Kruskal–Wallis test for RCC status [25]. SPSS software version 18.0 (SPSS, Chicago, IL, USA) was used and $p < 0.05$ was considered to be statistically significant.

3. Results

In Table 1, the general characteristics, including anthropometric measurements, blood pressure and various biochemical