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Comparative Assessment of Serum Adipokines Zinc-α2-glycoprotein and Adipose Triglyceride Lipase and Cardiovascular Risk Factors Between Normal Weight and Obese Patients with Hemodialysis

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Background. Little is known about the potential relationship of obesity, adipose tissue and novel adipokines with cardiometabolic risk factors in end-stage renal disease. Zinc-α2-glycoprotein (ZAG) and adipose triglyceride lipase (ATGL) are novel adipokines with proposed desirable effects on inflammation, and lipid and glucose metabolism. The aim of this study was to investigate serum concentrations of ZAG and ATGL, and the relationship of these adipokines with cardiovascular risk factors in normal weight (NW) and obese (OB) patients undergoing hemodialysis.

Methods. Patients with regular hemodialysis including 44 normal weight ($18.5 < BMI < 25$ kg/m^2) and 44 obese (BMI$\geq$30 kg/m^2) were enrolled. Serum lipid profile, high-sensitivity C-reactive protein (hsCRP) and nitric oxide metabolites along with ZAG and ATGL concentrations were assessed.

Results. ZAG concentrations were significantly lower in OB compared to NW group (100 ± 34 vs. 106 ± 31 ng/mL; $p = 0.007$). No significant difference was observed in ATGL between the two groups. A significant inverse correlation between ZAG and HDL ($r = -0.236$, $p = 0.048$) and a marginal inverse correlation between ATGL and HDL ($r = -0.211$, $p = 0.078$) were observed in all patients. ZAG had positive correlations with triglyceride/HDL ($r = 0.279$, $p = 0.019$), cholesterol/HDL ($r = 0.319$, $p = 0.007$), and LDL/HDL ($r = 0.26$, $p = 0.029$) ratios. Among cardiovascular risk factors, only LDL/HDL ratio and hsCRP were significantly higher in OB patients ($p = 0.009$ and $p = 0.038$, respectively).

Conclusions. Serum concentrations of ZAG, but not ATGL, were significantly lower in the OB group. It appears that obesity overrides the role of hemodialysis in determining ZAG concentration. In contrast, uremic condition might overshadow the role of obesity in determining levels of traditional cardiovascular risk factors. © 2017 IMSS. Published by Elsevier Inc.

Key Words: Adipokine, Zinc-α2-glycoprotein, Adipose triglyceride lipase, Obesity, Hemodialysis.

Introduction

End stage renal disease (ESRD) could lead to various metabolic and endocrine disorders due to uremia (1). Cardiovascular diseases (CVD) are the main cause of disability and death in all stages of chronic kidney disease (CKD) (2). The conventional risk factors could not entirely account

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for accelerated CVD incidence and outcomes in CKD. Thus, the probable roles of novel parameters and mechanisms including oxidative stress, inflammation, endothelial dysfunction, and obesity-induced metabolic disorders have been taken into account.

Obesity was traditionally considered as an independent risk factor in the initiation, progression and poor outcomes of advanced kidney insufficiency (3). Along with dramatic advances in recognizing obesity pathophysiology and adipose tissue as an endocrine organ that secretes a wide range of peptides, there has been much interest to understand the potential relationship of obesity, adipose tissue and adipokines with metabolic disorders in ESRD. Apart from the role of adipokines in the pathophysiology of renal diseases, the concentrations of these peptides change with the progression of kidney failure (4,5). These changes might induce remarkable metabolic, pathophysiologic and clinical effects (5,6), which are not well studied or understood.

Zinc-α_2-glycoprotein (ZAG) was recognized as an adipokine in 2004 (7). The gene expression and protein levels of ZAG decrease in obese people (8−10); and a negative association has been reported between ZAG, body mass index (BMI) and total body fat mass (9−11). ZAG could induce lipolysis and affect body composition dose-dependently (12,13). Moreover, experimental and clinical studies have demonstrated the role of ZAG in lipid and glucose metabolism (10,14). It has been shown that ZAG gene expression and its serum concentrations will increase in uremic condition (15−18). Adipose Triglyceride Lipase (ATGL) is one of the three recognized triglyceride (TG) hydrolyzing enzymes (19), which is highly expressed by adipose tissue (20). ZAG and ATGL have a functional relationship. ZAG could induce the visceral and subcutaneous adipose tissue expression of ATGL and its products (10,21). There is evidence of decreased levels of ATGL in overweight and obese individuals compared to normal weight people. ATGL was also associated with metabolic profile (22). The precise role of ZAG and ATGL in modulating metabolic disorders in uremia has not been well studied. To date, few studies are available on the contribution of adipose tissue on determining the concentration of adipokines including ZAG and ATGL, and also the relationship of these peptides with adiposity and cardiometabolic risk factors in hemodialysis. No hemodialysis studies have investigated ZAG and ATGL in obese patients. The current study was conducted with the aim of investigating serum levels of ZAG and ATGL in two groups of normal weight (NW) and obese (OB) patients undergoing hemodialysis and the correlations of these adipokines with other cardiovascular risk factors.

Material and Methods

Patients

ZAG was the main variable to determine sample size. Based on the formula for cross-sectional studies, the sample size of 38 patients in each group would be sufficient. To account for possible dropouts, 44 patients in the NW ($18.5 < BMI < 25$ kg/m^2) and 44 patients in the OB group (BMI$\geq$30 kg/m^2) were recruited from five different dialysis centers affiliated to Tehran and Shahid Beheshti medical universities. All patients were on regular hemodialysis three times a week for at least six months prior to the study. Patients had no clinical or laboratory signs of inflammatory or infectious diseases, no other organ failure, no critical condition over the last three months, and no history of cancer and thyroid diseases. Patients with history of glucocorticoid therapy, smoking and drug abuse, deliberate weight changes, and receiving fish oil, omega-3 fatty acids or eicosapentaenoic acid in the past three months were not enrolled. The bioethics committee of Tehran University of Medical Sciences approved this study in accordance with the Declaration of Helsinki. All patients completed a written informed consent.

The malnutrition inflammation score (MIS) was used to evaluate wasting status and inflammation. This valid method in dialysis patients has 10 components; the first seven questions have been adapted from the conventional subjective global assessment (SGA) and there are three additional questions including BMI status, and the concentrations of albumin and total iron binding capacity (TIBC). Each question was scored from 0−3 (normal to very severe). The total score of each patient was between 0 and 30 (23). Anthropometric indexes including dry weight, height, waist circumference (WC) and BMI were evaluated immediately after dialysis for minimizing the probable effect of fluid retention. The percentage of body fat mass was calculated based on the validated formula by Deurenberg et al (24):

$$\text{Adult body fat percentage (\%)} = (1.2 \times \text{BMI}) + (0.23 \times \text{Age}) - (10.8 \times \text{gender}) - 5.4;\ \text{if male gender} = 1 \text{ and if female gender} = 0.$$

Biochemical Assays

Serum samples were obtained between 7−9 AM following an overnight fasting and before dialysis. Following centrifugation of samples at 4°C, the sera were instantly frozen at −80°C. Total cholesterol (TC), TG, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and fasting blood sugar (FBS) were investigated through enzymatic techniques using standard laboratory kits (Pars Azmoon, Tehran, Iran). Lipid profile was evaluated compared with the recommended cut offs of the National Cholesterol Education Program (NCEP) 2002 to assess the probable abnormalities. Insulin concentrations were assessed using the radioimmunoassay kit (DiaSource, Louvain-la-Neuve, Belgium). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated based on the