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Circulating adipocyte fatty acid binding protein is increased in chronic and acute renal dysfunction

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Abstract *Background and aims:* The adipokine adipocyte fatty acid binding protein (AFABP) is positively associated with the development of the metabolic syndrome, diabetes mellitus, and cardiovascular disease. We hypothesized that AFABP also increases with deteriorating renal function.

Methods and results: Serum AFABP levels were quantified by enzyme linked immunosorbent assay in 532 patients with chronic kidney disease (CKD) covering the whole spectrum of estimated glomerular filtration rate (eGFR) categories from G1 to G5 (study population 1). Furthermore, AFABP was measured in 32 patients before and within 30 h after elective unilateral nephrectomy, a model of acute kidney dysfunction (AKD) (study population 2). Moreover, circulating AFABP was investigated in rats undergoing bilateral nephrectomy (BNE) as compared to sham-operated animals.

Median serum AFABP levels adjusted for age, gender, and body mass index significantly increased with increasing eGFR category (G1: 22.0 μg/l; G2: 34.6 μg/l; G3: 56.7 μg/l; G4: 95.2 μg/l; and G5: 173.9 μg/l). Furthermore, renal dysfunction remained positively associated with AFABP in multivariate analysis in this cohort. In patients undergoing unilateral nephrectomy, AFABP increased significantly after surgery (42.1 μg/l) as compared to pre-surgical values (29.3 μg/l). Furthermore, relative changes of post-to-pre-surgical AFABP levels were independently associated with relative changes of post-to-pre-surgical creatinine concentrations. After BNE in rats, AFABP increased significantly as compared to sham-operated animals.

Conclusions: We show that AFABP is significantly elevated in CKD and AKD patients. Furthermore, measures of renal function are associated with circulating AFABP. Moreover, animal experiments indicate that AFABP levels strongly depend on renal function.

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Introduction

Accumulating evidence suggests that altered adipokine secretion contributes to obesity-related complications, e.g. type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension, indicating the major role of adipose tissue as an endocrine organ. Among these adipokines, adiponectin has anti-diabetic and anti-atherogenic properties [1]. In contrast, the appetite-suppressive adipokine leptin is associated with an increased risk for cardiovascular disease [2].

Recently, adipocyte fatty acid binding protein (AFABP) has been introduced as a circulating adipokine which might induce metabolic and vascular disease [3]. Thus, Furuhashi and co-workers convincingly demonstrated that pharmacological inhibition of AFABP improves insulin sensitivity and decreases atherosclerotic lesion formation in susceptible animal models [4]. In agreement with these findings, AFABP knockout mice are more insulin-sensitive [5] and less atherosclerosis-prone as compared to wild-type littermates [6]. Furthermore, two recent back-to-back studies demonstrated that AFABP is in fact secreted via unconventional mechanisms and by adipocyte-derived microvesicles despite the lack of a secretion-directed signal [7,8]. Circulating AFABP is positively associated with facets of the metabolic syndrome and risk factors of cardiovascular disease in human subjects [9]. Even more interestingly, elegant prospective studies convincingly demonstrated that elevated AFABP serum levels are associated with an increased risk to develop metabolic disease [10,11], as well as cardiovascular complications [12–14]. Most recently, Cao and co-workers convincingly demonstrated that mice receiving recombinant AFABP have increased basal and clamp hepatic glucose production and a mild glucose intolerance [15]. These studies indicate that AFABP might be a major adipocyte-secreted protein linking obesity with metabolic, as well as cardiovascular, disease states [3].

In contrast to these extensive results on AFABP in metabolic and cardiovascular disease, data on AFABP elimination are limited so far. Some studies suggest that AFABP might be eliminated by the kidney. Thus, increased AFABP serum levels have been described in patients with hemodialysis [16,17], mild chronic kidney disease (CKD) [18], and diabetic albuminuria [19]. However, several limitations concerning these previous studies need to be emphasized: No study so far 1) covered the whole spectrum of renal dysfunction ranging from estimated glomerular filtration rate (eGFR) categories G1 to G5, 2) included >250 patients, and 3) elucidated the effect of acute renal dysfunction on circulating AFABP.

To address these issues and to elucidate AFABP regulation by kidney function more comprehensively, two renal disease populations were investigated in the current study: 1) In study population 1 (CKD), circulating AFABP concentrations were quantified in 532 patients with eGFR categories G1 to G5. 2) In study population 2 (acute kidney dysfunction, AKD), AFABP levels were assessed in patients before and after partial or total nephrectomy. Furthermore, we correlated AFABP concentrations to clinical and biochemical markers of renal function, glucose and lipid metabolism, as well as inflammation in both studies. Moreover, the impact of renal function on AFABP levels was determined in rats undergoing bilateral nephrectomy (BNE) as compared to sham-operated animals. If AFABP was – in fact – eliminated by the kidneys, we hypothesized that circulating AFABP should increase 1) with increasing eGFR category; 2) after nephrectomy; and 3) after BNE in rats as compared to sham-operated animals.

Methods

Human studies

Study population 1 (CKD)

The design of this cross-sectional study has recently been described [20]. In brief, 532 patients (men: $n = 305$; women: $n = 227$) were recruited by the Department of Endocrinology and Nephrology, University of Leipzig, as well as from three outpatient Nephrology Care Units (Hospital St. Georg, Division of Nephrology, KfH Renal Unit, 04129 Leipzig; outpatient Nephrology Care Units, 04107 and 04178 Leipzig). The following inclusion and exclusion criteria were applied: inclusion criteria, age >18 years, nonpregnant, and provided written informed consent; exclusion criteria, end-stage malignant diseases, acute generalized inflammation, acute infectious disease, and history of drug abuse. In all patients, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as described elsewhere [21]. Patients were classified into eGFR categories G1 to G5 according to the Kidney Disease Improving Global Outcomes guidelines [22]. Of the 181 patients in eGFR category G5 in our study, 162 were on chronic hemodialysis. Body mass index (BMI) was determined as weight divided by squared height. Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were calculated after waist and hip circumferences, as well as height were assessed. Age of the study population ranged from 19 to 92 years and BMI from 14.3 to 49.0 kg/m^2. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as previously described [23]. All blood samples were taken after an overnight fast. In all hemodialysis patients, blood was obtained just before hemodialysis started.

Study population 2 (AKD)

The study design has recently been described [24]. Briefly, 32 patients (men: $n = 26$; women: $n = 6$) were consecutively recruited before elective partial or total unilateral nephrectomy by the Department of Urology, University of Leipzig. Indications for surgery included renal carcinoma, renal shrinkage, and renal cysts. The following inclusion and exclusion criteria were applied: inclusion criteria, age between 18 and 80 years and provided written informed consent; exclusion criteria, hemodialysis, hereditary renal cysts, glomerulonephritis, and generalized inflammation. In all patients, eGFR was calculated using the CKD-EPI equation as described in Ref. [21]. Age of the study population ranged from 22 to 78 years and BMI from 18.2 to 37.0 kg/m^2.