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Research Paper

Ectopic Adipose Tissue Storage in the Left and the Right Renal Sinus is Asymmetric and Associated With Serum Kidney Injury Molecule-1 and Fibroblast Growth Factor-21 Levels Increase

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ABSTRACT

Objective: A potential mechanism by which obesity could promote hypertension and kidney diseases is through accumulation of adipose tissue in the renal sinus (RS). The aim of the study was to quantify RS and abdominal adipose tissue volumes and to evaluate serum kidney injury molecule (sKIM)-1 and fibroblast growth factor (FGF)-21 association with different adipose tissue compartments.
Methods: The cross-sectional study included 280 and follow-up study-40 asymptomatic participants; aged 38.30 ± 4.10. For all study participants computed tomography examination was performed, sKIM-1 and FGF-21 levels were measured.
Results: The results indicated asymmetrical deposition of adipose tissue into the RS even after corresponding kidney volume adjustment. The cross-sectional and the follow-up studies showed that sKIM-1 level was positively associated with RS adipose tissue volume increase for both genders. FGF-21 was positively associated with RS and retroperitoneal adipose tissue amount.
Conclusions: Regardless of gender adipose tissue in RS accumulates asymmetrically–the left RS accumulates a significantly higher amount of adipose tissue. Thus, primarily RS adipose tissue effects should be assessed on the left kidney. Accumulation of adipose tissue in the RS is related with the visceral adipose amount, KIM-1 and FGF-21 concentration increase in the blood serum.

1. Introduction

In humans and most animal models, development of obesity also leads to ectopic adipose tissue storage (Bjorndal et al., 2011). Normal renal sinus (RS) contains a small amount of adipose tissue that lines other structures within it. By excess deposition of perirenal adipose tissue in the RS, compression of various renal structures may occur, especially the inner medulla that, unlike the entire kidney, is not protected by the fibrous capsule (Lamacchia et al., 2011). It has been previously shown that RS adipose tissue may have an independent association with renal functions (Chughtai et al., 2010; Foster et al., 2011b). However, RS adipose tissue research is limited to only a couple of recently published studies. Foster et al. (Foster et al., 2011b) showed that RS adipose tissue is associated with an increased risk of hypertension and chronic renal disease. Similarly, Chughtai et al. (Chughtai et al., 2010) indicated that RS adipose tissue volume was associated with the number of prescribed antihypertensive medications and stage II hypertension.

Overall, obesity can lead to renal functional disorders and induce hypertension through a variety of mechanisms: (Hall, 1997; Hall et al., 1999; Hall et al., 2002; Hall et al., 2010; Hall et al., 2015; Hall et al., 2014). Activation of sympathetic nervous system; Physical–mechanical compression; Renin–angiotensin–aldosterone system. It has been hypothesized that RS adipose tissue effect is local and mostly occurs through the physical–mechanical compression (Montani et al., 2004; Hall et al., 2014). However, unfortunately exact mechanisms how RS adipose tissue could influence kidney functions are not described. Additionally, published RS adipose tissue research has some significant disadvantages. Since the object segmentation and 3D reconstruction of organs is labor-intensive and time-consuming, often chosen strategy is computed tomography (CT) or magnetic resonance (MR) single-scan measurement at a specific anatomic level. In this way, the manual data processing is reduced significantly. However, as the RS adipose tissue is a small and diffuse object, this also results in loss of the measurement quality. Since RS adipose tissue compartment is relatively small

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object, then in our study, strategy to segment the entire RS adipose tissue and analyze it's full volumes, was used, thus more accurately characterizing RS adipose tissue and it's role.

In our study we analyze asymptomatic, middle age participants, therefore, it was important to find an earlier diagnostic biomarkers of kidney injury. It is useful to keep in mind that creatinine level may not raise until more than half of the kidney function has been lost due to renal reserve. Kidney injury factor (KIM)-1 serves as an earlier diagnostic biomarker of kidney injury when compared to any of the conventional diagnostic markers, e.g., serum creatinine and cystatin C, increased proteinuria. It has been approved by the US Food and Drug Administration as an acute kidney injury biomarker for preclinical drug development (Dieterle et al., 2010). KIM-1 expression and secretion was observed in the kidney epithelial cells in vitro (Ichimura et al., 2004), in animal models and in patients with various kidney diseases (Lim and Meigs, 2013). Experiments in rodents and studies in humans have shown that kidney ischemia or hypoxia promotes KIM-1 concentrations increase in the urine and blood serum. Chronic KIM-1 expression can promote further tubulointestinal inflammation and hypoxia, further inducing KIM-1 expression that culminate in chronic kidney disease (Humphreys et al., 2013). The ectodomain of KIM-1 is shed into the lumen, and serves as a urinary biomarker of kidney injury (Bonventre, 2009; Kuwata et al., 2015; Jin et al., 2013). Recent study showed that KIM-1 may be released into the circulation and identified KIM-1 as a blood biomarker that specifically reflects injury to the proximal tubule of the kidney, the primary site of injury for ischemia and most nephrotoxicants (Sabbisetti et al., 2014; Bonventre et al., 2010). The proposed mechanisms for the KIM-1 reabsorption are: (1) After kidney proximal tubule injury when tubular cell polarity is lost and KIM-1 may be released directly into the interstitium; (2) Renal microvascular endothelial cells are detached from the basement membrane that facilitate KIM-1 reabsorption into the circulation (Sabbisetti et al., 2014) (Hall et al., 2014).

Recently, fibroblast growth factor (FGF)-21 was introduced as a renal function marker. FGF-21 levels were higher in the patients with both chronic and acute renal dysfunctions. Additionally, FGF-21 levels gradually increased with the development or renal diseases from the early to late stage (Zhang et al., 2015). FGF-21 serve as renal function marker because renal elimination is a major route by which physiological FGF-21 serum levels are maintained (Stein et al., 2009). Respectively, if renal function is impaired, serum FGF-21 level rise.

In general, there is limited information about the mechanism how RS adipose tissue induce renal disease and hypertension. There is no information about RS adipose tissue and early diagnostic biomarkers of kidney injury. Additionally, all previously conducted researches were based on RS adipose tissue single slice measurements. Thereby, the aim of the study was to quantify RS and abdominal adipose tissue volumes and to evaluate sKIM-1 (as primary kidneys damage marker) and FGF-21 association with different adipose tissue compartments in the observational study with a cross-sectional design and a prospective one-year naturalistic follow-up study. We hypothesized that RS adipose tissue would be independently associated with sKIM-1 and FGF-21 levels after accounting for abdominal adipose tissue segments (retroperitoneal (RP), intraperitoneal (IP) and subcutaneous (SC)) as a measure of abdominal obesity.

2. Methods

2.1. Participants and Study Design

An observational study with a cross-sectional design and a prospective one-year naturalistic follow-up study. The period of recruitment was from January 2011 till January 2014. The sample size was calculated according to proportions ($n = 1.96^2 \times 4\,p(1-p)/d^2$; where: p – expected population proportion; d - the desired width of the confidence interval (CI)). In our case: an estimate of the prevalence of adipose tissue accumulation in the RS is 0.99 (99%). The width of the 95% CI is 0.1. Estimated minimal sample size was 153 subjects.

The cross-sectional study participants were selected from family physician's practices of a Health care center in Riga. The exclusion criteria for the participants selection were a recorded diagnosis of chronic kidney diseases (nephrolithiasis; renal cysts; nephroptosis; an extra kidney; renal lipomatosis), cardiovascular diseases, thyroid diseases, diabetes or malignancy; use of tobacco and alcohol (male >140 g ethanol per week; female >70 g ethanol per week); anamnesis of arterial hypertension, pregnancy and lactation, taking any regular medications; body mass index (BMI) < 18 kg/m^2 and BMI > 35 kg/m^2. The inclusion criteria were BMI = 18–35 kg/m^2, age 30–45 years. In the cross-sectional study 280 participants were recruited (144/136, F/M) aged 37.30 ± 4.10 years, ethnicity – Caucasians.

Participants ($n = 40$; 20/20, F/M) for the prospective one-year naturalistic follow-up study were recruited from the cross-sectional study group. The inclusion criteria for this study were left RS ratio > 0.025 (see Section 2.3). The participants were randomized into two groups: participants (10/10, F/M) randomized for the intervention received daily text messages for one year. Text messages included practical recommendations on how to balance caloric intake and physical activity to achieve and maintain a healthy body weight. The recommendations were prepared by the general practitioner according to the diet and lifestyle recommendations (Eckel et al., 2014). Other randomized 10 males and 10 females did not receive any intervention for one year. The study design is shown in the Fig. 1.

Experimental procedures were approved by the Ethical Committee of the Institute of Experimental and Clinical Medicine, University of Latvia. All procedures performed in this study were in accordance with the ethical standards of the institutional and international research committee and with the 1964 Helsinki declaration. Informed consent was obtained from all study participants.

2.2. Anthropometric Parameters

BMI was calculated as the ratio of weight to height squared. Normal weight was defined as BMI 18.0–24.9 kg/m^2; overweight – as BMI 25.0–29.9 kg/m^2 and obesity – as BMI ≥ 30 kg/m^2. Waist circumference (WC) was measured using a tape rule, and the point of measurement was the anterior superior iliac spine (Kovesdy et al., 2010). Blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)) measurements were performed by professional medical assistant.

2.3. Abdominal and RS Adipose Tissue Quantification

Native abdominal (~Th10 to ~L4) CT scans were captured using spiral (128-slice configuration) CT SOMATOM Definition AS/AS (Siemens AG, Forchheim, Germany) with automated tube current modulation (CareDose4D, Siemens) during inspiratory breath-hold (slice thickness

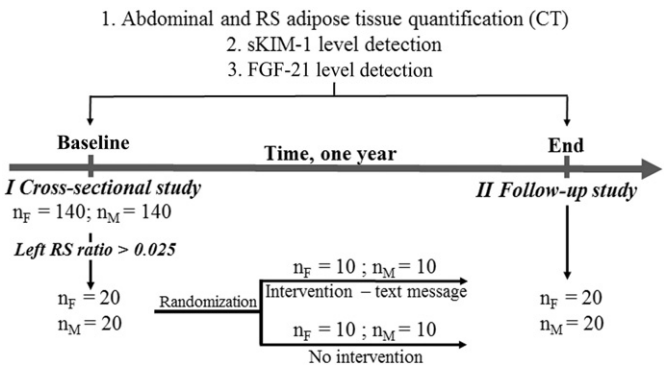

Fig. 1. Design of the cross-sectional and the prospective one-year naturalistic follow-up study.