Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Impact of uremia on human adipose tissue phenotype

Karen J. Ho, MD,[a,1] Hui Xue, MD,[b,1] Christine R. Mauro, MD,[a] Binh Nguyen, MD,[a] Peng Yu, MD, PhD,[a] Ming Tao, MD,[a] Michael A. Seidman, MD, PhD,[c] Steven M. Brunelli, MD, MSCE,[b] and Charles Keith Ozaki, MD[a,]*

[a] *Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*
[b] *Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*
[c] *Department of Pathology and Laboratory Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*

ARTICLE INFO

Article history:
Received 21 June 2012
Received in revised form
16 August 2012
Accepted 22 August 2012
Available online 6 September 2012

Keywords:
Uremia
Chronic kidney disease
Adipose tissue
Leptin
Adiponectin
Resistin

ABSTRACT

Background: Recognition of adipose-related signaling in surgery is increasing, although direct interrogation of human adipose has been sparse. Few scenarios rival uremia for health impact. We hypothesized that adipose from uremic patients holds a relatively higher adipose-derived hormone and proinflammatory adipokine signature; we simultaneously evaluated the impact of clinical parameters on adipose phenotype.

Materials and methods: Adipose was harvested from surgical patients. Histology and protein analyses were completed for select mediators.

Results: In the overall cohort of 71 patients, the mean age was 63.4 y; 46.4% of patients had diabetes mellitus, 49.2% had hyperlipidemia, and 53.5% had coronary artery disease. Compared with nonuremic patients, uremic patients had one-tenth of the levels of leptin ($P < 0.001$), one-third of the levels of adiponectin ($P < 0.001$), and threefold higher levels of resistin ($P < 0.001$). Females had sixfold higher levels of leptin, 1.5-fold higher levels of adiponectin, and twofold higher levels of tumor necrosis factor alpha but equivalent resistin. There were differences in mediators when stratified by age. In both the obese and nonobese strata, we observed a concordant pattern of association (magnitude or significance) of uremia and leptin, adiponectin, and resistin. No differentials in other mediators emerged on body mass index stratification. Multiple regression analysis for leptin, adiponectin, and resistin (with age, gender, and uremia as independent variables) showed uremia as the highest independent predictor of all the three mediators.

Conclusions: Advanced chronic kidney disease is associated with perturbations in adipose-derived hormones (leptin, adiponectin, and resistin). Adipose adiponectin and leptin (in contrast to reported plasma levels) were lower in uremic patients; there is an inverse correlation between adipose resistin and renal function. Compared with other clinical parameters including body mass index, uremia dominates overall in determining adipose phenotype, highlighting the complex biological interplay between uremia and adipose biology.

* *Corresponding author*. Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115. Tel.:+1 857 307 1920; fax: +1 857 307 1922.
E-mail address: CKOzaki@partners.org (C.K. Ozaki).
[1] These authors contributed equally to this work.
0022-4804/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jss.2012.08.043

1. Introduction

Adipose tissue is now recognized as a biologically active tissue that participates in signaling through endocrine, paracrine, and autocrine mechanisms [1,2]. Adipocyte-derived secreted proteins such as leptin, adiponectin, resistin, and interleukin (IL) 6 have important roles in homeostasis, inflammation, and glucose metabolism [3]. Although the overall mass of adipose tissue dominates other organs in humans, simple fat volume does not necessarily correlate with clinical phenotypes [4] and surgical outcomes [5]. Substantial knowledge gaps exist regarding the determinants of adipose tissue phenotype and the true role of adipose tissue–related signaling networks in disease. The literature to date largely builds on animal models and human studies considering circulating adipose tissue–derived mediator levels [6–8]. By contrast, direct examination of clinically relevant human adipose tissue phenotype has been sparse [9–13].

Few clinical scenarios rival uremia for overall health impact and implications for surgical care. Patients with chronic kidney disease (CKD) are seen as having a chronic inflammatory state and suffer from markedly increased risks of overall morbidity and mortality, especially cardiovascular complications [14–16]. Single capture evaluations of circulating adiponectin [17], leptin, and resistin [18–21] have suggested that these adipose tissue–derived mediators are affected by uremia, but direct tissue interrogation has largely been lacking [9,10]. In one recent series, abdominal subcutaneous fat in patients with CKD was found to have significantly upregulated gene expression of proinflammatory mediators such as IL-6 and downregulated gene expression of leptin and oxidative stress genes [9] compared with nonuremic controls, suggesting uremia-derived perturbation in local production and action of adipokines.

To advance the understanding of the spectrum and determinants of human adipose tissue biology, we compared protein levels of key mediators isolated from subcutaneous adipose tissue from patients with and without uremia. The use of fresh human clinical specimens from select anatomic locations offers insights into the variability and clinical determinants of human adipose tissue phenotypes. We hypothesized that there would be more variation between uremic and nonuremic patients than within these groups and that patients with uremia would display a relatively higher proinflammatory adipokine signature. Finally, beyond comparisons between uremic and nonuremic patients, we also evaluated the impact of standard clinical parameters on adipose tissue phenotype.

2. Materials and methods

This prospective study consisted of a series of patients undergoing lower extremity major amputation (below or above knee), elective open orthopedic procedures, arteriovenous fistula creation for permanent hemodialysis access, or open plastic surgery procedures at Brigham and Women's Hospital (Boston, MA, USA). Protocol approvals were obtained from the Partners Healthcare Institutional Review Board, and participating subjects all provided informed consent.

Table 1 – Demographic and clinical characteristics.

Characteristics	Total cohort ($n = 71$)	Uremia ($n = 17$)	No uremia ($n = 54$)	P value
Age (y)	63.4 ± 15.9	63.8 ± 12.3	63.3 ± 17.0	0.89
Male gender, *n* (%)	32 (54.9)	5 (29.6)	27 (50)	0.22
Caucasian, *n* (%)	42 (59.2)	5 (29.4)	37 (68.5)	**0.01**
Diabetes, *n* (%)	33 (46.4)	12 (70.5)	21 (38.9)	**0.04**
Hypertension, *n* (%)	52 (73.2)	12 (70.5)	40 (74.1)	0.76
CAD, *n* (%)	38 (53.5)	12 (70.5)	16 (29.6)	**0.01**
Hyperlipidemia, *n* (%)	35 (49.2)	10 (58.8)	25 (46.3)	0.53
Current or former smoker, *n* (%)	34 (47.9)	9 (52.9)	25 (46.2)	0.84
Total cholesterol (mg/dL)	158.0 ± 44.5	134.5 (128.8–164.8)	163.4 ± 43.8	0.14
HDL (mg/dL)	47.3 ± 14.0	45.7 ± 12.1	48.1 ± 15.0	0.47
LDL (mg/dL)	85.4 ± 40.0	75.9 ± 46.3	90.3 ± 36.4	0.11
Triglycerides (mg/dL)	125.2 ± 57.7	126.0 ± 48.1	124.8 ± 62.7	0.60
HgbA1c (%)	6.4 (5.7–7.7)	6.4 ± 1.6	6.9 (6.2–8.4)	**0.04**
HgbA1c (%) in diabetics only	6.9 (5.9–9.1)	8.0 ± 1.9	5.9 (5.3–7.2)	**0.03**
BMI (kg/m^2)	29.6 ± 7.6	26.9 ± 5.9	29.1 ± 8.2	0.25
BMI ≥30, *n* (%)	27 (38.0)	6 (35.2)	21 (38.9)	0.79
ASA, *n* (%)	43 (60.6)	11 (64.7)	32 (59.3)	0.91
Beta-blocker, *n* (%)	38 (53.5)	15 (88.2)	23 (42.6)	**0.01**
Statin, *n* (%)	40 (56.3)	11 (64.7)	29 (53.7)	0.93
Metformin, *n* (%)	7 (9.9)	0	7 (13.0)	0.18
Glitazone, *n* (%)	0	0	0	**0**
ACE inhibitor and/or ARB, *n* (%)	30 (42.2)	6 (35.3)	24 (44.4)	0.58

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASA = aspirin; HDL = high-density lipoprotein; HgbA1c = hemoglobin A1c; LDL = low-density lipoprotein.
Bold values indicate P value < .05.