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Acute inflammation plays a limited role in the regulation of adipose tissue COL1A1 protein abundance☆

Venkata J. Adapala[a], Sunday A. Adedokun[a], Robert V. Considine[b], Kolapo M. Ajuwon[a,*]

[a]Department of Animal Sciences, Purdue University, West Lafayette, IN 47907-2054, USA
[b]Department of Medicine, Division of Endocrinology and Metabolism, Indiana University School of Medicine, Indianapolis, IN 46202-5111, USA

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Abstract

Obesity is an inflammatory condition that is also associated with increased extracellular matrix (ECM) gene expression. However, a direct link between adipose tissue inflammation and ECM gene expression has not been established. Therefore, we determined the effect of chronic inflammation induced by obesity and acute inflammation by lipopolysaccharide (LPS) challenge on ECM genes including biglycan (BGN), collagen 1A1 (COL1A1) and COL6A1, major ECM genes in adipose tissue. Male C57BL/6J mice fed either a control diet (10% fat calories) or a high-fat diet (HFD) (60% fat calories) for 6 weeks were treated with LPS or saline 24 h before sacrifice. Expression of ECM genes in the epididymal (EWAT) and subcutaneous adipose tissue (SWAT) was determined by RT-PCR and protein abundance by Western blotting. Human SWAT from lean and obese subjects was also analyzed. Increased messenger RNA (mRNA) expression of ECM genes BGN and COL1A1 was observed in the mouse EWAT after HFD ($P<.05$). However, reduced amount of COL1A1 protein was observed in EWAT of mice on HFD and in SWAT from obese human subjects. Acute inflammation induced BGN mRNA in EWAT, enhanced the gene expression of matrix metalloproteases (MMPs) 3 and 9. Acute inflammation also resulted in higher MMP9 gelatinolytic activity; however, this showed no association with COL1A1 protein abundance. Higher MMP2 expression in mice on HFD suggests its involvement in the reduction of COL1A1 protein abundance with HFD. Elevated MMP9 gelatinolytic activity in SWAT from obese humans indicates a prominent role for MMP9 in SWAT COL1A1 protein turnover in humans.

Keywords: Adipose; Obesity; Extracellular; Matrix; Inflammation; Metalloproteases

1. Introduction

Remodeling of the extracellular matrix (ECM) is a major component of adipogenesis and this involves the breakdown of multiple ECM proteins [1]. The significance of this process in adipogenesis is demonstrated in the severe impairment of adipocyte differentiation or resistance to diet-induced obesity that occurs after pharmacological inhibition of matrix metalloproteases (MMPs), which are proteins that mediate the destruction of ECM proteins [2–4]. Thus, ECM composition and integrity represents a major factor in adipose tissue development [5]. Although obesity is associated with chronic low-grade inflammation [6–10], the role of inflammation on ECM remodeling is poorly investigated. Because of the perpetuation of inflammation in obesity [11–13], a strong possibility exists that inflammatory stimuli play active roles in the remodeling process. Inflammatory cells such as macrophages, which are recruited to adipose tissue in obesity [14,15], induce members of collagen family and fibrin [16,17] and in nonadipose tissues such as the lung, TLR4 activation with lipopolysaccharide (LPS) induces procollagen type 1 expression [18], suggesting that direct activation of TLR4 may play a role in ECM remodeling.

Although ECM protein degradation occurs during adipocyte differentiation, obesity results in elevated messenger RNA (mRNA) abundance of multiple ECM genes [19], and this may reflect the dynamic nature of ECM regulation in adipose tissue. This may also underscore the important role of MMPs in the regulation of adipose tissue development. Because collagen 1A1 (COL1A1) expression often varies by inflammatory state [20] and is a major ECM found in adipose tissue, we tested the possibility that adipose tissue inflammatory milieu plays a major role in the regulation of adipose tissue COL1A1.

2. Methods

2.1. Animal studies

Male C57BL/6J mice were obtained from the Jackson Laboratories at 8 weeks of age. Animals were housed in a pathogen-free facility at the Purdue Small Animal Housing facility. All protocols for animal management set by the Purdue Animal Care and Use Committee were followed. Mice had 12 h of daylight and 12 h of darkness. Animals were divided equally (16 mice per group) between a control diet with 10% fat calories (D12450Bi) and a high-fat diet (HFD) with 60% fat calories (D12492i) (Research Diets, New Brunswick, NJ) and were fed these diets *ad libitum* for 6 weeks. Body weights were measured on a weekly basis.

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* Corresponding author. Tel.: +1 765 494 4822; fax: +1 765 494 9346.
E-mail address: kajuwon@purdue.edu (K.M. Ajuwon).

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Table 1
Body composition in mice under control (low-fat diet) *vs.* HFD

Parameters	Diet				Diet	*P*	
	Control		HFD			LPS	Diet×LPS
	Saline (n=8)	LPS (n=8)	Saline (n=8)	LPS (n=8)			
Body weight	28.68±0.80[ab]	26.87±0.80[b]	30.44±0.80[a]	29.31±0.80[a]	0.01	.08	.67
Adipose depot							
Subcutaneous (%)	1.33±0.18[b]	1.33±0.18[b]	2.12±0.18[a]	2.12±0.18[a]	0.0002	1.00	.99
Epididymal (%)	1.95±0.29[b]	2.40±0.29[b]	3.45±0.29[a]	3.94±0.29[a]	0.0001	.12	.95
Retroperitoneal (%)	0.55±0.10[b]	0.67±0.10[b]	0.92±0.10[a]	1.06±0.10[a]	0.0004	.17	.89
Mesenteric (%)	0.61±0.09	0.63±0.09	0.69±0.09	0.73±0.09	0.28	.72	.89
Liver (%)	5.41±0.13[a]	4.82±0.13[a]	4.35±0.13[b]	4.24±0.13[b]	0.0001	.10	.41
Heart (%)	0.69±0.04[a]	0.64±0.04[ab]	0.60±0.04[ab]	0.53±0.04[b]	0.03	.16	.77
Kidney (%)	1.17±0.03	1.18±0.03	1.13±0.03	1.18±0.03	0.53	.24	.49
Muscle (%)[d]	1.76±0.12	1.99±0.12	1.90±0.12	1.88±0.12	0.86	.40	.33

[a–c] Superscripts represent significant differences in mean values (P<.05).
[d] Gastrocnemius muscle.

2.2. Model of acute inflammation

Within each diet group, half of the mice (n=8) were given, via intraperitoneal administration, either saline (0.9%) and/or LPS (Sigma-Aldrich, St. Louis, MO) at a dose of 0.1 mg/kg BW. Twenty-four hours after the LPS injection, mice were killed by CO_2 asphyxiation and tissues were snap-frozen in liquid nitrogen and later preserved at −80°C.

2.3. RNA extraction and quantitative RT-PCR

Total RNA from epididymal and subcutaneous adipose tissues and gastrocnemius muscle was extracted using TRIzol (Invitrogen, Carlsbad, CA) and reverse transcribed with the MMLV reverse transcriptase (Promega, Madison, WI). Real-time PCR was performed using the MyiQ real-time PCR detection system (Bio-Rad, Hercules, CA) with the Faststart SYBR mix (Roche, Indianapolis, IN). Primers were designed with the Invitrogen primer design software and the primer sequences are listed in Supplemental Table 1. Gene specific mRNA abundance was determined from the threshold cycle (Ct) for respective genes and normalized against the Ct for 18S using the ΔΔCt method.

2.4. Western blot analysis

Epididymal adipose tissues were homogenized in 1× RIPA buffer [50 mmol/l Trizma-HCl (pH 7.4), 15 mmol/l NaCl, 0.25% deoxycholic acid, 0.1% Triton X, 10 mmol/l

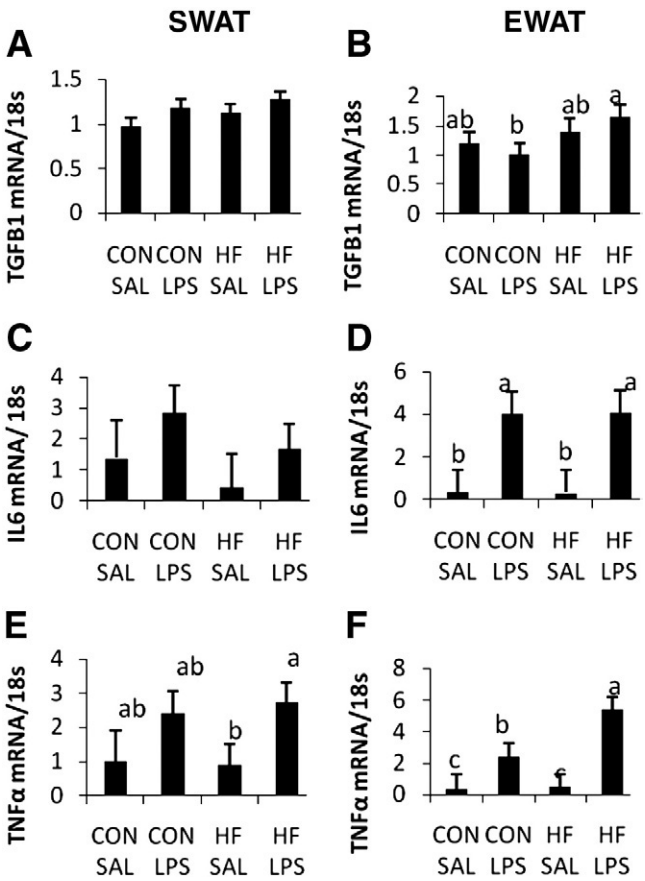

Fig. 1. Expression of selected inflammatory genes in subcutaneous (SWAT) or epididymal (EWAT) adipose tissue of mice under HFD or acute inflammation (LPS). Expression of TGFB1 (A and B), IL6 (C and D) and TNFα (E and F) was determined in both SWAT and EWAT. Bars represent means±S.E. Bars with different superscript letters are different (P<.05).

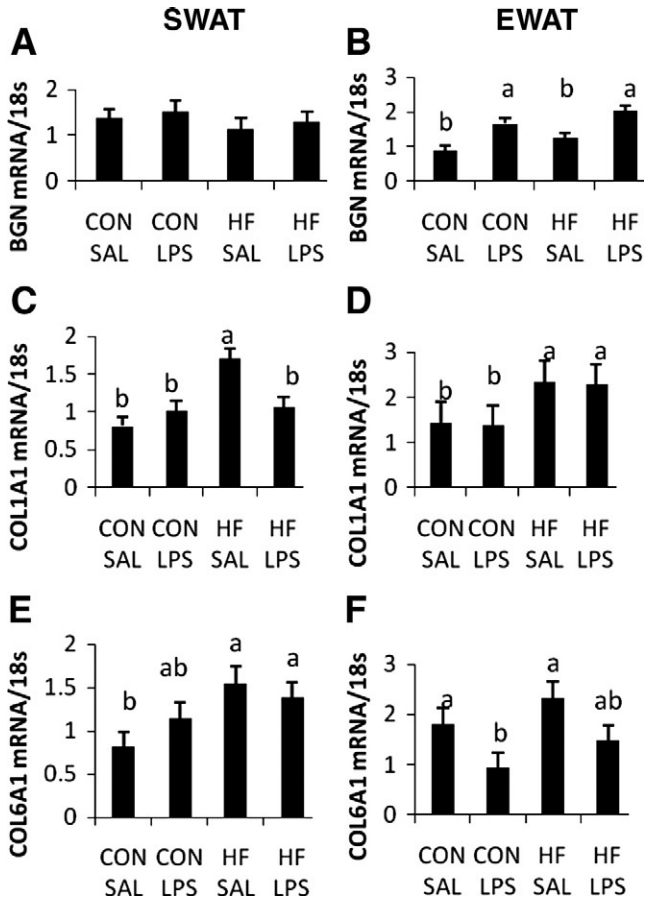

Fig. 2. Gene expression analysis of selected ECM genes in subcutaneous (SWAT) or epididymal (EWAT) adipose tissue of mice under HFD or acute inflammation. Gene expression analysis of BGN (A and B), COL1A1 (C and D) and COL6A1 (E and F) were determined in both SWAT and EWAT. Expression of individual genes was normalized to 18s with the ΔΔCt method. Bars represent means±S.E. Bars with different superscript letters are different (P<.05).

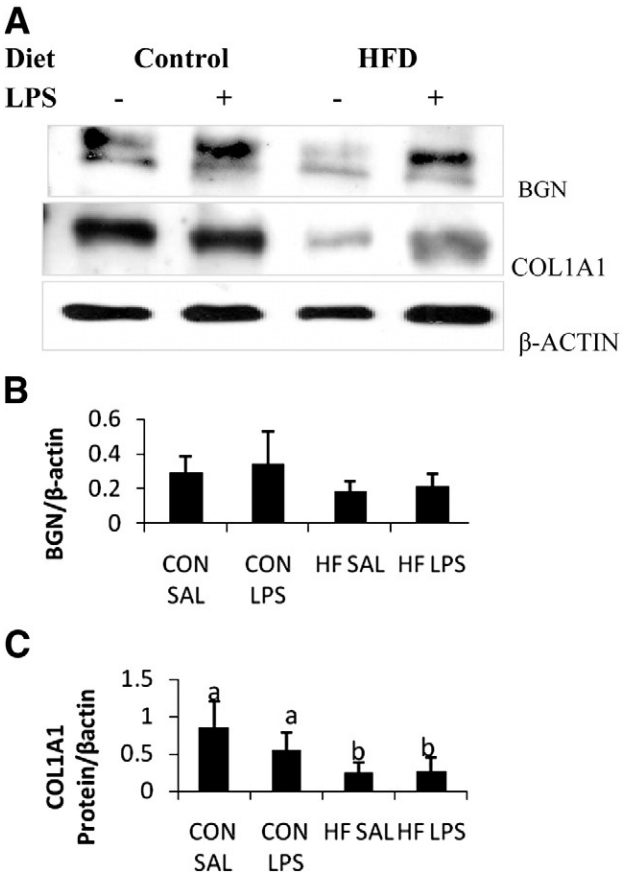

Fig. 3. Effect of HFD and acute inflammation on protein abundance of BGN and COL1A1 in epididymal tissue. Densitometric data were obtained for the abundance of BGN and COL1A1 and normalized to β-actin. (Fig. 3B and C). Bars represent means±S.E.M. Bars with different superscript letters are different (P<.05).

EDTA, 1 mmol/l Na_2VO_3 and protease inhibitor cocktail] (Sigma-Aldrich). Tissue homogenates were centrifuged at 10,000*g* for 10 min at 4°C, and the fat debris was removed. Protein concentration in clear homogenates was determined with the bicinchoninic acid (BCA) protein assay kit (Sigma-Aldrich). Enzymatic removal of glycosaminoglycan side-chains from ECM proteoglycans was performed by treating 50-μg protein samples with chondroitinase ABC (0.05 U; Sigma-Aldrich) in a digestion buffer [50 mmol/l Tris, 60 mmol/l sodium acetate, pH 8, 0.02% bovine serum albumin (BSA)] for 4 h at 37°C. Thereafter, protein samples were resolved by SDS-PAGE on a 10% acrylamide gel. Proteins were transferred to a 0.2-μmol/l nitrocellulose membrane by the semidry method (Bio-Rad, Hercules, CA). Membranes were blocked in 5% BSA in TTBS (50 mmol/l Tris–HCl, pH 7.4, 150 mmol/l NaCl, 0.1% Tween 20). Immunoblotting was performed using a polyclonal antibody against mouse biglycan (BGN; kindly provided by Larry W. Fisher, National Institute of Dental and Craniofacial Research, Bethesda, MD) at a dilution of 1:500. The antibody against COL1A1 was a goat polyclonal antibody (Santa Cruz Biotechnology, Santa Cruz, CA) and was used at dilution of 1:200. Membranes were stripped and reblotted with rabbit anti-β-actin antibody (Cell Signaling Technology, Beverly, MA) at a dilution of 1:1000. Blots were then incubated with the appropriate secondary antibodies [goat anti-rabbit horseradish peroxidase-linked IgG (Cell Signaling Technology) at a dilution of 1:2000 for BGN and β-actin and donkey anti-goat horseradish peroxidase-linked IgG (Millipore, Billerica, MA) for COL1A1. Signal was detected by autoradiography by chemiluminescence with the Super Signal West Pico reagent (Pierce, Rockford, IL). Densitometric analyses of Western blots were performed using Kodak EDAS290 imaging system (Kodak, New Haven, CT).

2.5. Analysis of human adipose tissue

Subcutaneous adipose tissue was obtained after informed consent from obese (BMI>30; n=5, age 20–56 years) and lean (BMI<25; n=5; age 39–56) women undergoing bariatric surgery or outpatient needle biopsy. Protocols were approved by the IUPUI Institutional Review Board and the Purdue Human Research Protection Board. Tissues were frozen in liquid nitrogen and preserved in −80°C freezer before analysis. Extraction of RNA, RT-PCR and Western blotting assays were as described for mouse samples.

2.6. Adipose tissue zymography

Zymography was conducted with SDS-polyacrylamide gel containing gelatin (0.8 mg/ml). The samples were mixed with SDS-PAGE sample buffer without reducing agent and were subjected to electrophoretic analysis at room temperature. Gels were stained with Coomassie Brilliant Blue R-250 for the visualization of enzymatic activity. Densitometric analysis of gelatinolytic bands was as described for Western blotting.

2.7. Statistical analyses

Data were examined for normality and analyzed using the mixed-model analysis (SAS Institute, Cary, NC). Mean separation was accomplished using the least-squares mean separation (pdiff) procedure. Differences were considered significant at P<.05. Values in the text are means±S.E.M.

3. Results

3.1. Obesity and inflammatory effects of HFD

As expected higher body weights were obtained in mice on HFD relative to those on the control diet (Table 1). Additionally, the subcutaneous, epididymal and retroperitoneal fat pad weights of HFD group were significantly larger (P<.05) than the control group. However, similar mesenteric adipose tissue weights were observed in both dietary groups. There was no effect of acute inflammation with LPS on tissue weights or overall animal weights. To determine the effects of acute inflammation on inflammatory genes, we quantified the expression of TGFB1, IL6 and TNFα. Although no differences were found in the SWAT on the expression of TGFB1 (Fig. 1A), acute inflammation plus HFD induced the expression of TGFβ1 in EWAT of mice on HFD (Fig. 1B) (P<.05). There was also a strong effect of acute inflammation on the expression of IL6 and TNFα in the EWAT (P<.05). Although acute inflammation did not affect the expression of IL6 in SWAT it up-regulated TNFα expression (Fig. 1C–F). Thus, acute inflammation was achieved by the administration of endotoxin,

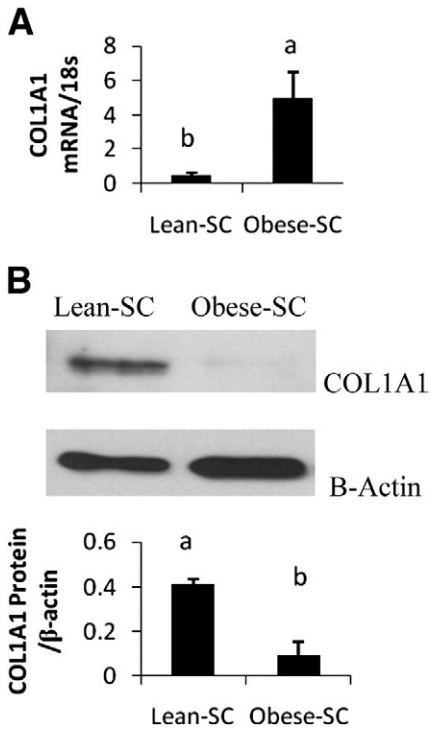

Fig. 4. Effect of obesity on COL1A1 expression in human subcutaneous adipose tissue. Subcutaneous adipose tissue was obtained from lean (Lean-Sc) or obese (Obese-Sc) human subjects. COL1A1 mRNA abundance was determined by RT-PCR (Fig. 4A). Protein abundance is normalized to β-actin (B and C).

whereas consumption of HFD for 6 weeks resulted in a modest proinflammatory outcome.

3.2. Regulation of ECM genes and metalloproteases

Inflammation induced an up-regulation of expression of BGN in EWAT but not SWAT (Fig. 2A, B). In the EWAT, HFD up-regulates COL1A1 without any additional effect of acute inflammation (Fig. 2D) ($P<.05$). COL6A1 was equally induced by HFD in the SWAT without additional effect of acute inflammation (Fig. 2E) ($P<.05$). Because BGN mRNA was induced by acute inflammation in the EWAT, we conducted Western blot analyses to determine its protein abundance. Mice on HFD showed a trend ($P<.08$) for a reduced abundance of BGN protein (Fig. 3A). Additionally, lower amount of COL1A1 ($P<.05$) was present in EWAT of mice on HFD irrespective of whether they were under acute inflammation or not (Fig. 3A, C). Due to the discordance between protein and mRNA abundance of COL1A1 in lean and HFD mice, we further analyzed its protein and mRNA abundance in SWAT from lean and obese human subjects. Higher mRNA expression of COL1A1 was obtained in obese subjects (Fig. 4A). However, its protein abundance was much lower in obese subjects (Fig. 4B, C). Because MMPs degrade collagens we hypothesized that the lower COL1A1 protein abundance in HFD fed mice and obese human subjects resulted from a higher MMP expression and activity. Therefore, we determined the abundance of key MMPs (1, 2, 3, 9, 13 and 14) in the EWAT of HFD-fed mice (Fig. 5). Although acute inflammation induced the expression of MMPs 3 and 9, it led to a down-regulation of MMP13 and up-regulation of MMP14 in HFD-fed mice (Fig. 5C–F). Although there was no effect of acute inflammation on MMP1 and 2, HFD led to an increase in the mRNA expression of MMP2 ($P<.05$). Additionally, we analyzed for MMP gelatinolytic activity with zymography. We found an increase in MMP9 activity due to acute inflammation; however, the activity of MMP2 was undetectable (Fig. 6A). Further analysis of human adipose tissue with zymography also showed a higher MMP9 activity in obese *vs.* lean subjects ($P<.05$), and a detectable MMP2 activity in a subset of obese subjects whereas none apparent in lean subjects.

4. Discussion

Remodeling of the ECM is a major event in adipose tissue development [1–3]. Although the existence of regional differences between subcutaneous and visceral adipose depots are well recognized [20–25], potential differences in the regulation of ECM gene expression between the two depots are poorly characterized. We have used diet-induced obesity, which induces chronic inflammation in adipose tissue and LPS administration, a model that mimics acute inflammation, to investigate the possibility that changes in ECM gene expression in the different adipose depots are connected to the inflammatory state of the adipose depots. At the mRNA level, BGN is

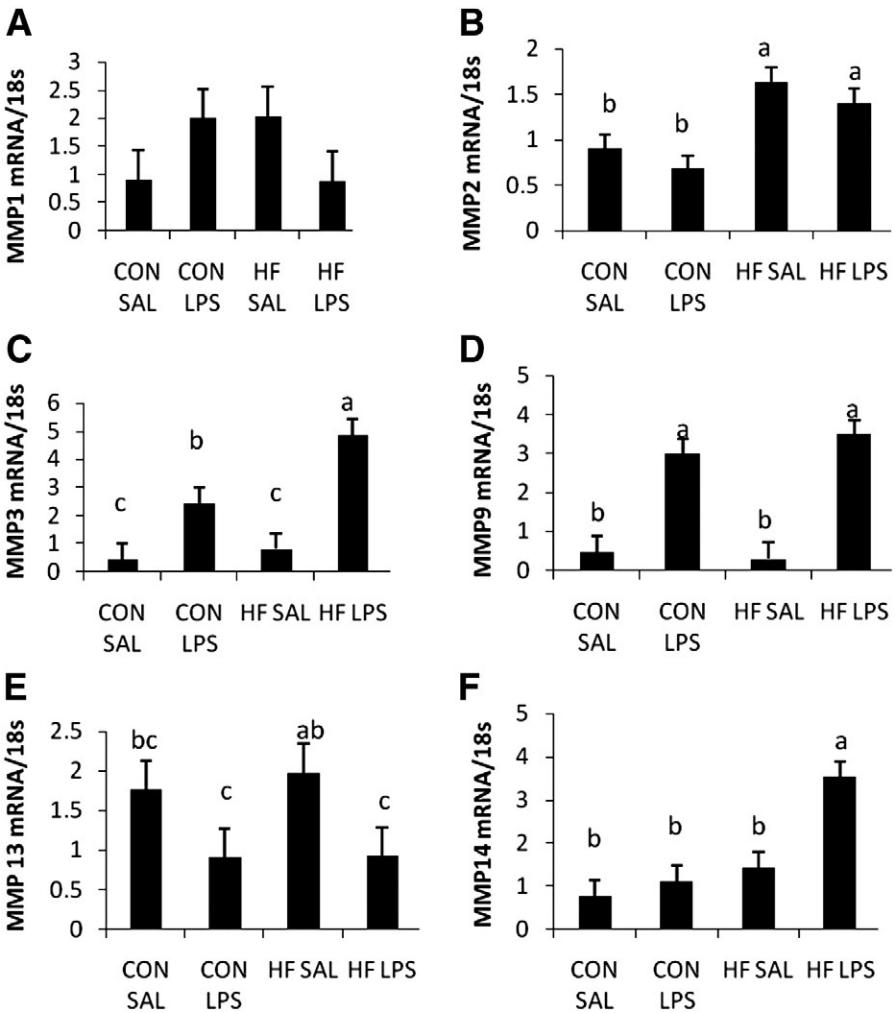

Fig. 5. Effect of high-fat (HF) diet and acute inflammation with LPS on MMP expression. Expression of MMPs was determined by RT-PCR and normalized to 18s. Bars with different superscript letters are different ($P<.05$).

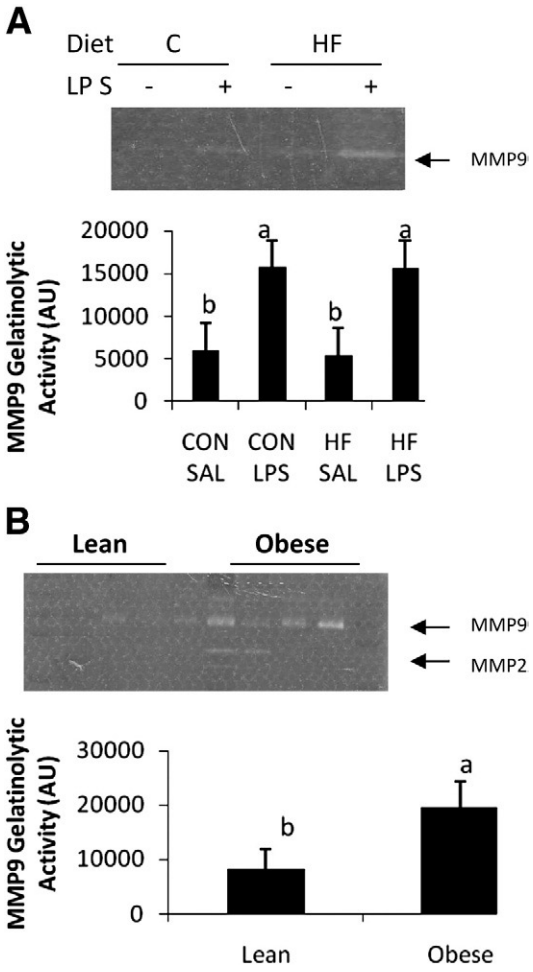

Fig. 6. Effect of HFD and obesity on MMP activity. Matrix metalloprotease activity was determined with gelatin zymography. Zymography was performed on epididymal adipose tissue from control (CON) and HFD-fed mice given either saline (CON-SAL, CON-LPS, HF-SAL and HF-LPS) (A) and subcutaneous human subcutaneous adipose tissue from lean (Lean-Sc) or obese (Obese-Sc) human subjects (B). Increased MMP9 activities were found in A and B. Bars with different superscript letters are different ($P<.05$).

the only ECM gene that is up-regulated by acute inflammation in EWAT (Fig. 2B). Biglycan is related to induction of inflammation [26–28], and its up-regulation in adipose tissue during inflammation may implicate it in the perpetuation of inflammatory milieu in adipose tissue. Indeed, we have found reduced expression of TNFα in the adipose tissue of BGN knockout mice *vs.* wild-type mice (unpublished). Recently, Khan et al. [29] reported an increase in expression of COL1A1 and COL6A1 mRNA in the epididymal adipose tissue of *db*/*db* mice. Our analysis of human adipose tissue also confirms the increase in COL1A1 mRNA in obesity. However, acute inflammation did not alter the expression of COL1A1 in EWAT but instead down-regulated it in SWAT of mice on HFD. These data underscore the complexity of ECM gene regulation in adipose tissue and reflect the dynamic nature of ECM gene regulation in adipose tissue. Interestingly, analysis of ECM gene expression of gastrocnemius muscle of the same experimental animals revealed no change in the expression of these genes (data not shown), confirming the specificity of these ECM changes to adipose tissue. The lack of effect of acute inflammation on COL1A1 expression suggests that inflammatory factors may not mediate its expression during HFD-induced obesity.

The discordance between protein and mRNA abundance of COL1A1 highlights the significant role that MMPs play in adipose tissue expansion. Thus, a scenario exists in adipose tissue during HFD and obesity in which accelerated degradation of ECM proteins by MMPs results in increased mRNA expression of ECM genes to replace lost matrix proteins. Adipose tissue expresses multiple MMPs [2] that cleave ECM fragments. Although deletion of MMPs such as MMP10 does not affect adipose tissue development [30], global inhibition of MMPs prevents diet-induced obesity [2,3]. In mice under HFD, although MMPs 3 and 9 were induced by acute inflammation, this induction did not correlate to the observed levels of COL1A1 protein, a strong indication that these MMPs may not be critical for HFD-induced obesity. Recent work [31] confirms that genetic deletion of MMP9 does not affect adipose tissue development in mice. However, obese humans have an elevated MMP9 activity and therefore MMP9 could play a significant role in human adipose tissue development. Increased expression of MMP2 in HFD-fed mice points to its possible involvement and that of other collagenases in the reduced COL1A1 expression in adipose tissue during HFD. In support of a major role for MMP2 in murine adipose tissue expansion, deletion of MMP2 leads to resistance to diet induced obesity [32]. Additionally, higher MMP2 activity in a subset of obese humans supports a possibility that it is also involved in the development of human obesity. Therefore, although MMP2 appears to play a dominant role in murine adipose tissue development, obesity in humans is associated with elevated activities of both MMPs 2 and 9. The lack of induction of MMP2 by acute inflammation shows that inflammation plays a limited role in regulating its expression in obesity. Determining the mechanisms that regulate MMP2 and MMP9 activities may be important in reducing obesity in humans.

Supplementary materials related to this article can be found online at doi:10.1016/j.jnutbio.2011.02.013.

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