Increased Xanthine Oxidase in the Skin of Preeclamptic Women

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Xanthine oxioreductase is the holoenzyme responsible for terminal purine catabolism. Under conditions of metabolic stress or heightened proinflammatory cytokine production, this enzyme is preferentially in its oxidized form, xanthine oxidase, with catalytic action that generates uric acid and the free radical superoxide. As preeclampsia is characterized by heightened inflammation, oxidative stress, and hyperuricemia, it has been proposed that xanthine oxidase plays a pivotal role in this hypertensive disorder of pregnancy. We sought to determine whether xanthine oxidase protein content was higher in maternal tissue of preeclamptic mothers, compared to healthy pregnant controls, using immunohistochemical analysis of skin biopsies. We further compared xanthine oxidase immunoreactivity in skin biopsies from preeclamptic women and patients with several inflammatory conditions. In preeclamptic women, intense xanthine oxidase immunoreactivity was present within the epidermis. By contrast, only very faint xanthine oxidase staining was observed in skin biopsies from healthy pregnant controls. Further, a role for inflammation in the increase of xanthine oxidase was suggested by similar findings of heightened xanthine oxidase immunoreactivity in the skin biopsies from nonpregnant individuals diagnosed with conditions of systemic inflammation. The finding of increased xanthine oxidase in maternal tissue, most likely as the result of heightened maternal inflammation, suggests maternal xanthine oxidase as a source of free radical and uric acid generation in preeclampsia.

KEY WORDS: Xanthine oxidase, preeclampsia, uric acid, reactive oxygen species, epidermis.

INTRODUCTION

Preeclampsia, a multisystemic hypertensive syndrome of pregnancy, is a leading cause of maternal morbidity and mortality and increases perinatal mortality 5-fold. Diagnosed by de novo gestational hypertension and proteinuria, the disorder usually becomes apparent in late pregnancy. Several pathophysiological components of preeclampsia are, however, evident much earlier in pregnancy. Markers of heightened systemic inflammation[1-4] and hyperuricemia[5] are evident weeks to months before clinically evident preeclampsia.

Hyperuricemia is one of the earliest and most consistent observations in preeclamptic pregnancies, first reported at the beginning of the 20th century.[6,7] There is a direct correlation between circulating uric acid concentrations and the severity of preeclampsia, for both maternal and fetal outcomes[8-10]; however, the clinical use of uric acid as a predictive tool for identifying women likely to develop preeclampsia remains contested.[11] Hyperuricemia in preeclampsia is commonly explained as the result of abnormal renal function; reduced glomerular filtration rates, and increased re-absorption leading to decreased excretion of uric acid.[12,13] However, increased circulating concentrations of uric acid are present at less than 15 weeks gestation, prior to evident changes in renal function, and the higher uric acid concentration persists with control for glomerular filtration in women destined to develop preeclampsia.[5] It has therefore been postulated that in addition to alterations in renal handling, increased uric

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Reproductive Sciences Vol. 16 No. 5 May 2009 468-478
DOI. 10.1177/1933719108329817

acid production is also responsible for the hyperuricemia observed in preeclampsia.[7,14,15]

Uric acid is generated by the oxidative hydroxylation of hypoxanthine and xanthine catalyzed by the holoenzyme xanthine oxioreductase (XOR). The enzyme is found primarily in endothelial and epithelial cells of the liver and gut[16] but is also present in skeletal muscle, mammary gland, kidney, and immune cells including monocytes and mast cells.[17] Xanthine oxioreductase has 2 functional forms. Xanthine dehydrogenase (XDH), which couples the production of uric acid to the reduction of nicotinamide-adenine dinucleotide (NAD^+), and xanthine oxidase (XO), which generates the free radical superoxide (O_2^-) in addition to uric acid. Xanthine oxidase is the preferentially active form under conditions of increased substrate availability, metabolic stress, hypoxia, and heightened cytokine production.[17-21]

An increase in XO activity has been proposed as a source for oxidative stress in preeclampsia.[7,14] Xanthine oxidase expression and activity are increased in invasive cytotrophoblasts in preeclamptic pregnancies.[22] Additionally, XO activity is increased in maternal and fetal blood in preeclamptic pregnancies.[23] Increased XO activity would increase both reactive oxygen species and uric acid generation.

Xanthine oxidase activity is increased with heightened inflammation. In animal studies, activation of the inflammatory cascade, through several stimuli including thermal injury,[24] lipopolysaccharide (LPS) treatment,[25] and carcinogen exposure,[26-28] upregulates XOR with preferential XO catalytic activity. A pathogenic role for XO in preeclampsia is suggested by the heightened systemic inflammation, widespread oxidative stress, and hyperuricemia characteristic of preeclampsia, all elements related to the XOR enzyme activity.

Although increased XO activity has been sought and found in the placenta, the potential contributions of maternal tissue XO to the pathophysiology of preeclampsia has received little attention. We sought to determine whether XO protein content was higher in maternal tissues of preeclamptic mothers, compared to healthy pregnant controls, using immunohistochemical analysis of skin biopsies. We further compared XO immunoreactivity in skin biopsies from preeclamptic women and patients with several inflammatory conditions.

MATERIALS AND METHODS

Study Participants

The study was approved by the institutional review board, and all participants provided informed consent. Skin biopsies from pregnant women were collected at Magee-Womens Hospital (Pittsburgh, PA), at the time of cesarean section. Preeclampsia was diagnosed as new onset gestational hypertension, proteinuria, hyperuricemia, and reversal of hypertension and proteinuria by 12 weeks postpartum. Hypertension was defined as an increase of 30 mm Hg systolic or 15 mm Hg diastolic blood pressure compared to values obtained before 20 weeks gestation and an absolute blood pressure >140/90 mm Hg. Proteinuria was defined as >300 mg/24 h collection or >2+ on voided or 1+ on catheterized random urine sample or a protein creatinine ratio >0.3. Hyperuricemia was defined as >1 SD above normal values for the time of gestation.[29] Women with chronic hypertension or those with additional medical complications were excluded. Pregnant control samples were collected from women at term undergoing elective cesarean section. Women in this group had normal blood pressure and no medical complications.

Skin biopsies from nonpregnant controls and participants with chronic inflammatory conditions were collected at the Veterans Affairs Medical Center (Pittsburgh, PA), for immunopathological examination and diagnosis. The diagnosis of lupus erythematosus was based upon characteristic dermatopathological findings, clinical presentation, and serological profiles such as antinuclear antibody. Dermatitis diagnosis was based upon clinical presentation and nonspecific spongiotic pathologic change. Lichen simplex chronicus was characterized by typical clinical appearance of scaly thickened plaques and epidermis. Diagnosis of mixed connective tissue disease was by the presence of antinuclear antibody on direct skin immunofluorescence and characteristic clinical presentation and presence of high concentrations of circulating autoantibody such as antinuclear antibody and antinuclear ribonucleoprotein (nRNP) antibody. Bullous pemphigoid was diagnosed by the presence of skin blisters on erythematosus skin and presence of immunoreactants along skin basement membrane zone.

Tissue Collection and Processing

Skin samples were collected in nonpregnant individuals using punch biopsies. In the pregnant women, biopsies were obtained from the cesarean section skin incision. In the nonpregnant participants with chronic inflammatory disorders, the biopsies were collected from lesional skin at various sites including abdomen, trunk, thigh, and forearm. In the nonpregnant control population the skin biopsies were collected from benign skin lesions located

on the trunk, back, and forearm. Skin biopsies were immediately collected in optimal cutting temperature (OCT) compound, flash frozen, and stored at –80°C until further processing.

Immunohistochemical Fluorescent Staining

The frozen biopsies were cryosectioned to a thickness of 6 μm, fixed in ice-cold acetone for 10 minutes, and allowed to air dry. Nonspecific binding was blocked with 10% normal goat serum (NGS) in phosphate buffered saline (PBS) for 20 minutes. Endogenous biotin was blocked using the streptavidin-biotin blocking kit (Vector Laboratories; Burlingame, CA). The skin biopsies were incubated with a primary antibody directed against XO (rabbit polyclonal IgG, 1:3000 dilution in 10% NGS, Rockland, Gilbertville, PA) for 60 minutes at room temperature and washed in PBS. Amplification and visualization of antibody-antigen binding was accomplished using the biotin-streptavidin-fluorescein isothiocyanate (FITC) labeling technique in which the sections were incubated with biotinylated goat-anti-rabbit IgG (1:750 dilution in 10% NGS, Vector Laboratories) for 45 minutes, washed extensively with PBS, and subsequently incubated with FITC-conjugated streptavidin (1:500 dilution in PBS, Vector Laboratories) for 15 minutes in the dark at room temperature. Following several PBS rinses, the tissue was counter-stained with 0.5% pontamine sky blue (Sigma) to eliminate auto-fluorescence of connective tissue. The slides were again rinsed with PBS and mounted with Vectasheild mounting media (Vector Laboratories). Negative controls were obtained by omission of primary antibody. Sections were viewed with a Zeiss Axiophot Epiflourescence microscope equipped with filters to selectively view the rhodamine (Pontamine sky blue fluoresces in the rhodamine spectrum) and fluorescein images without cross contamination.

Immunohistochemical Fluorescent Quantification and Statistical Analysis

Immunohistochemical fluorescent quantification was performed by calculating the mean green fluorescent intensity within the squamous portion of the epithelial layer, including the stratum granulosum and stratum corneum layers of the epidermis. The squamous portion of the epidermis was outlined on blinded digital images for each skin biopsy and mean green fluorescent intensity was measured within the outlined segment using Image J software (National Institute of Health, http://rsbweb.nih.gov/ij/). Because of a relatively small sample size the data were not found to be normally distributed and as such data are presented as median ± interquartile ranges (IQR). Differences in XO immunofluorescent intensity between the healthy nonpregnant, healthy pregnant, and preeclamptic participant groups were examined using a Kruskal-Wallis nonparametric 1-way analysis of variance with Dunn's post hoc analysis. Statistical analysis was set at $P < 0.05$.

RESULTS

Sample Population

Skin biopsies were collected from 5 healthy pregnant controls and 5 preeclamptic women. The demographic data for these 2 groups of women is outlined in Table 1. There were no differences in maternal age, pre-pregnancy body mass index (BMI), and early pregnancy blood pressures between the 2 groups. As expected, both systolic and diastolic pressures were higher in the preeclamptic group at the time of delivery, along with serum uric acid values. Additionally, proteinuria was undetectable in all pregnant control patients. The mean gestational age at delivery was also significantly lower in the preeclamptic group. All women in both groups were nonsmokers.

In the normal nonpregnant population, skin biopsies were collected from 6 nonpregnant controls, 3 men and 3 women. Additionally, biopsies were collected from 5 patients with systemic lupus erythematosus, 3 dermatitis patients, 1 patient with lichen simplex, 1 patient with mixed connective tissue disease, and 5 patients with bullous pemphigoid, of whom 2 had remittent disease. The majority of the patients were women and the ages of patients ranged from 34 to 73 years. The demographic data for these patients is outlined in Table 2.

Increased XO Immunoreactivity in Epidermis of Preeclamptic Women

All 5 skin biopsies collected from preeclamptic patients demonstrated distinct and intense XO immunoreactivity within the stratum granulosum layer of the epidermis (Figure 1B and E and Figure 2). Faint and sporadic XO positive staining was observed in the same layer of the epidermis in all the healthy pregnant control biopsies

Table 1. Clinical Characteristics of Pregnant Patients

Clinical Characteristics	Healthy Pregnant Controls (n = 5)	Preeclampsia (n =5)	Mann-Whitney *P* Value
Maternal age (years)	28.4 ± 4.9	29.6 ± 9.1	0.80
Maternal smoking (%)	0	0	N/A
Maternal race	4 caucasian, 1 black	4 caucasian, 1 asian	N/A
Maternal Pre-pregnancy BMI	26.8 ± 6.8	30.5 ± 5.4[‡]	0.43
Systolic pressure prior to 20 weeks gestation (mm Hg)	114.2 ±13.3	120.0 ± 8.8	0.48
Diastolic pressure prior to 20 weeks gestation (mm Hg)	75.0 ± 7.5	74.5 ± 7.3	0.92
Systolic pressure at term (mm Hg)	115.6 ±14.3	167.8 ± 17.2	<0.01[a]
Diastolic pressure at term (mm Hg)	72.4 ±12.1	94.2 ± 11.1	0.018[a]
Proteinurea	0/5	5/5	N/A
Weeks gestation at delivery	39.0 ± 0.6	32.7 ± 3.8	0.01[a]
Serum uric acid at delivery (mg/dL)	3.98 ± 1.0	5.98 ± 1.3	0.02[a]
Infant birth weight (g)	3470.6 ± 587.3	2399.8 ± 1060.3	0.08
Infant birth weight centile	62.0 ± 37.1	62.7 ± 41.9	0.98
Number of primiparas	5/5	3/5	N/A
Laboring prior to c-section	2/5	1/5	N/A

Abbreviation: N/A, not applicable.
[a] Statistically significant differences between healthy pregnant controls and preeclamptic women.

Table 2. Clinical Characteristics of Nonpregnant Patients

Clinical Characteristics	Healthy Controls (n = 6)	Systemic Lupus Erythematosus (n =5)	Dermatitis (n = 3)	Lichen Simplex (n = 1)	Mixed Connective Tissue Disease (n = 1)	Bullous Pemphigod (n = 5)
Age	34.8 ± 8.7	37.4 ± 14.4	50	42	45	73 ± 6.4
Female: Male ratio	3:3	5:0	2:0	0:1	1:0	0:5
Site of skin biopsy	3 trunk, 2 back, 1 forearm	3 forearm, 1 trunk, 1 chest	2 forearm	1 forearm	1 forearm	2 abdomen, 1 thigh, 2 forearm
Other noted medical conditions	——	——	——	——	——	Hypertension in 2 patients (both on anti-hypertensive medication)

(Figure 1A and F and Figure 2). Omission of primary antibody resulted in no visible staining (Figure 1D).

Increased XO Immunoreactivity in Epidermis of Patients With Inflammatory Conditions

All skin biopsies collected from nonpregnant patients with inflammatory conditions, including lupus, dermatitis, lichen simplex, mixed connective tissue disease, and bullous phemphigod, demonstrated immunoreactivity to XO within the stratum granulosum layer of the epidermis (Figure 3A-E and I). In contrast, skin biopsies collected from healthy nonpregnant individuals, both men and women, demonstrated very little to no XO immunoreactivity (Figure 1C and G and Figure 3G). Similarly in individuals with the inflammatory skin condition bullous pemphigoid that was in remission, XO staining was minimally present when the disease was not active (Figure 3F).

DISCUSSION

Xanthine oxidase generates uric acid and O_2^- and has been postulated to contribute to the pathogenesis of preeclampsia. Increased XOR and XO activity are present in the placentas of preeclamptic pregnancies.[22] Our findings suggest maternal XO as a further source of free radical and uric acid generation. In preeclamptic women, there was intense XO immunoreactivity within the epidermis. By

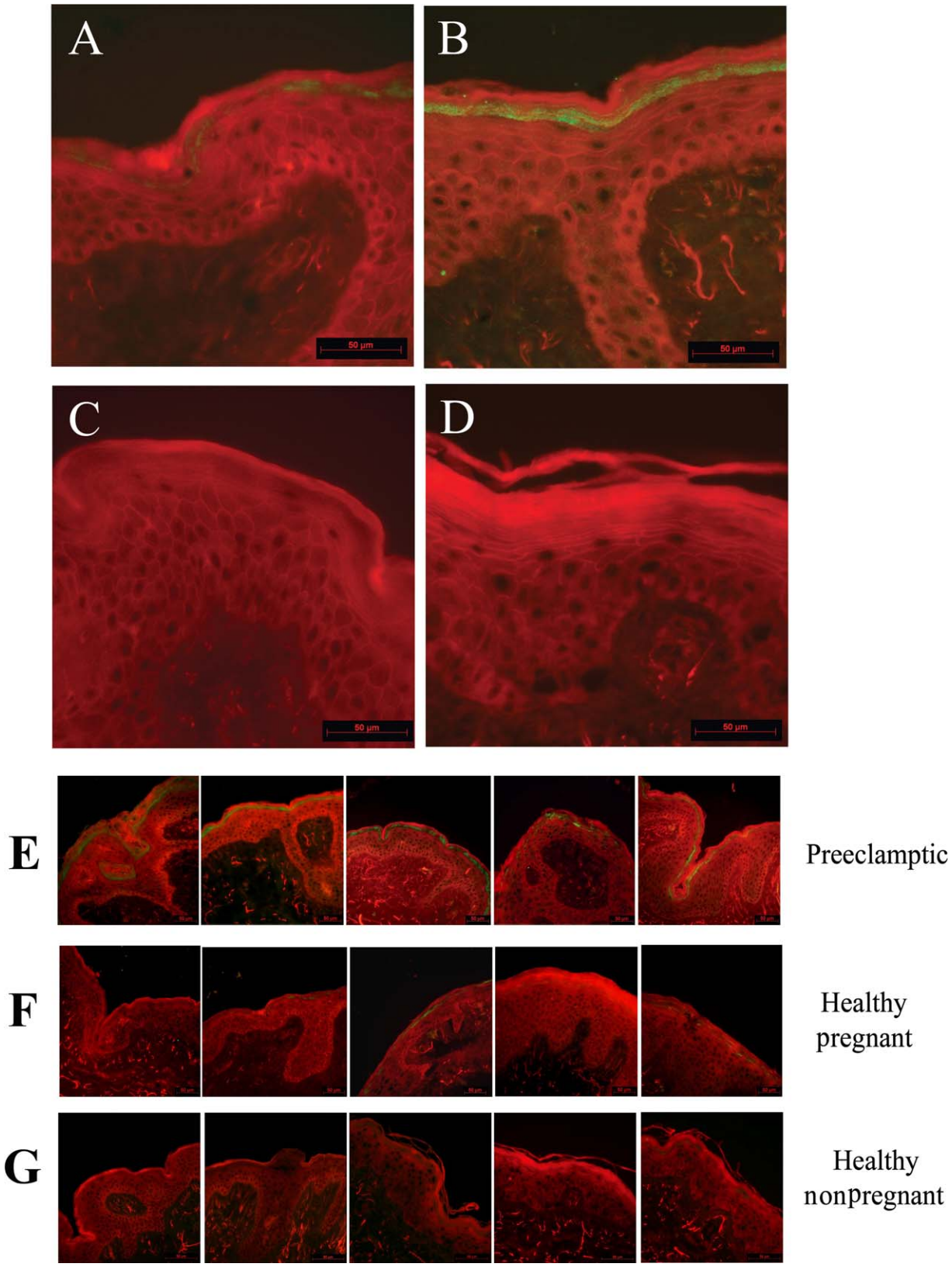

Figure 1. Xanthine oxidase (XO) immunoreactivty (green staining) is present in stratum granulosum layer of epidermis in preeclamptic women (panel B) compared to faint XO immunoreactivity in the same epidermal layer of healthy pregnant controls (panel A). Healthy nonpregnant controls demonstrate minimal epidermal XO immunoreactivity (panel C). These patterns of immunohistochemical staining were observed in all 5 preeclamptic skin biopsies (panel E), all 5 healthy pregnant controls (panel F), and all 5 healthy nonpregnant controls (panel G). Omission of the primary antibody directed against XO results in no observable immunoreactivity (panel D). Scalebar = 50 µm.

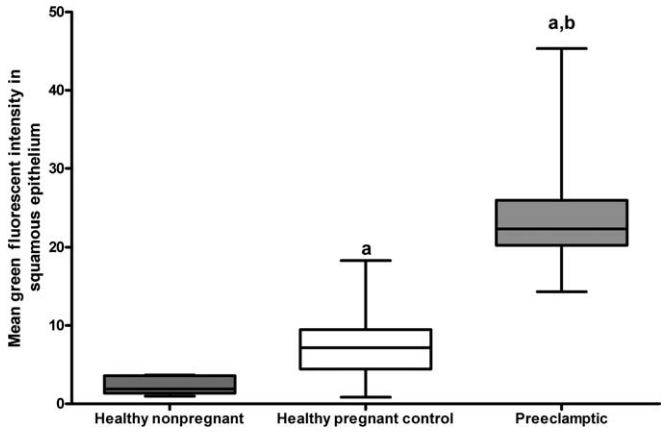

Figure 2. Quantitative analysis of xanthine oxidase (XO) immunohistochemical fluorescent intensity within the squamous epithelial layers of skin biopsies collected from healthy nonpregnant (n = 5), healthy pregnant (n = 5), and preeclamptic (n = 5) study participants. Data is presented as median ± IQR. $P < 0.05$, Kruskal-Wallis 1-way analysis of variance; (a) $P < 0.05$, Dunn's post hoc analysis compared to healthy nonpregnant participants; (b) $P < 0.05$, Dunn's post hoc analysis compared to healthy pregnant participants.

contrast, only very faint XO staining was observed in skin biopsies from healthy pregnant controls. Furthermore, a role for inflammation in the increase of XO was suggested by similar findings in nonpregnant individuals diagnosed with conditions of systemic inflammation.

Xanthine Oxidase in Skin

The epidermis is composed of keratinized stratified squamous epithelium arranged in 4 distinct layers: the stratum basalis, stratum spinosum, stratum granulosum, and stratum corneum. In both the preeclamptic and inflammatory conditions, XO staining was localized within the stratum granulosum layer of the epidermis. This highly keratinized layer consists of flattened cells containing keratohyalin granules and is thought to play an important barrier role toward the external environment. Xanthine oxidase activity has previously been reported in human hair roots and several catabolites of nucleic acids, including hypoxanthine, xanthine and uric acid have been described in keratinized structures[30,31]; however, we could find no further studies directly demonstrating either the presence or activity of the enzyme within healthy human epidermis. The presence of enzymatically active XO has, however, been documented within this barrier layer of the epidermis in rats, mice, and guinea pigs.[32] It is speculated that the spatial localization of XO within the stratum granulosum may be linked to terminal differentiation of keratinocytes.[33] It is proposed that the activity may be a component of the innate immunity of the integumentary system, protecting the skin against microbial attacks.[32,34]

Xanthine Oxidase and Inflammation

Our data demonstrate increased XO protein content in skin with increased systemic inflammation. Small amounts of XO were observed in the skin of healthy nonpregnant women, more with the heightened inflammation characteristic of pregnancy[35] and much more in women with preeclampsia in which the inflammatory response of normal pregnancy is further increased. Increased XO immunoreactivity was also present in participants with several inflammatory skin diseases or with the systemic inflammation of lupus erythematosus but not in patients with the inflammatory condition bullous pemphigoid when the disease was not active. The correlation we have demonstrated between XO enzyme in skin and inflammation in humans is complemented by prior studies demonstrating a dramatic increase in circulating XO activity in patients with autoimmune conditions that was reduced by glucocorticoid treatment.[36] Specific to skin, XO activity is increased in dermal tissue homogenates from psoriatic plaques,[37] thought in part to explain the hyperuricemia often observed in individuals with psoriasis.[38] In vitro stimulation of inflammatory cascades in human keratinocytes through ultra violet (UV) irradiation also stimulates an upregulation of XO expression with subsequent increases in O_2^- production by these cells.[39]

The role of inflammation to increase skin XO content is supported by animal experiments. Thermal skin injury in rats results in amplified catalytic activity of XO with increased circulating uric acid and reactive oxygen species.[24] Direct stimulation of proinflammatory cascades by subdermal injections of lipopolysaccharide increases O_2^- and peroxynitrite formation within the epidermis of mice, subsequently abolished by the XO inhibitor allopurinol.[25] Additionally, skin tumor promotion in mice activates the immune system with a parallel increase in epidermal XO protein content and activity.[26–28] Notable in many of these studies is the demonstration of XO enzymatic activity in the skin, which we did not determine in our study.

The association between inflammation and increased tissue XO content is consistent with proinflammatory response elements in the 5′ flanking region of the human

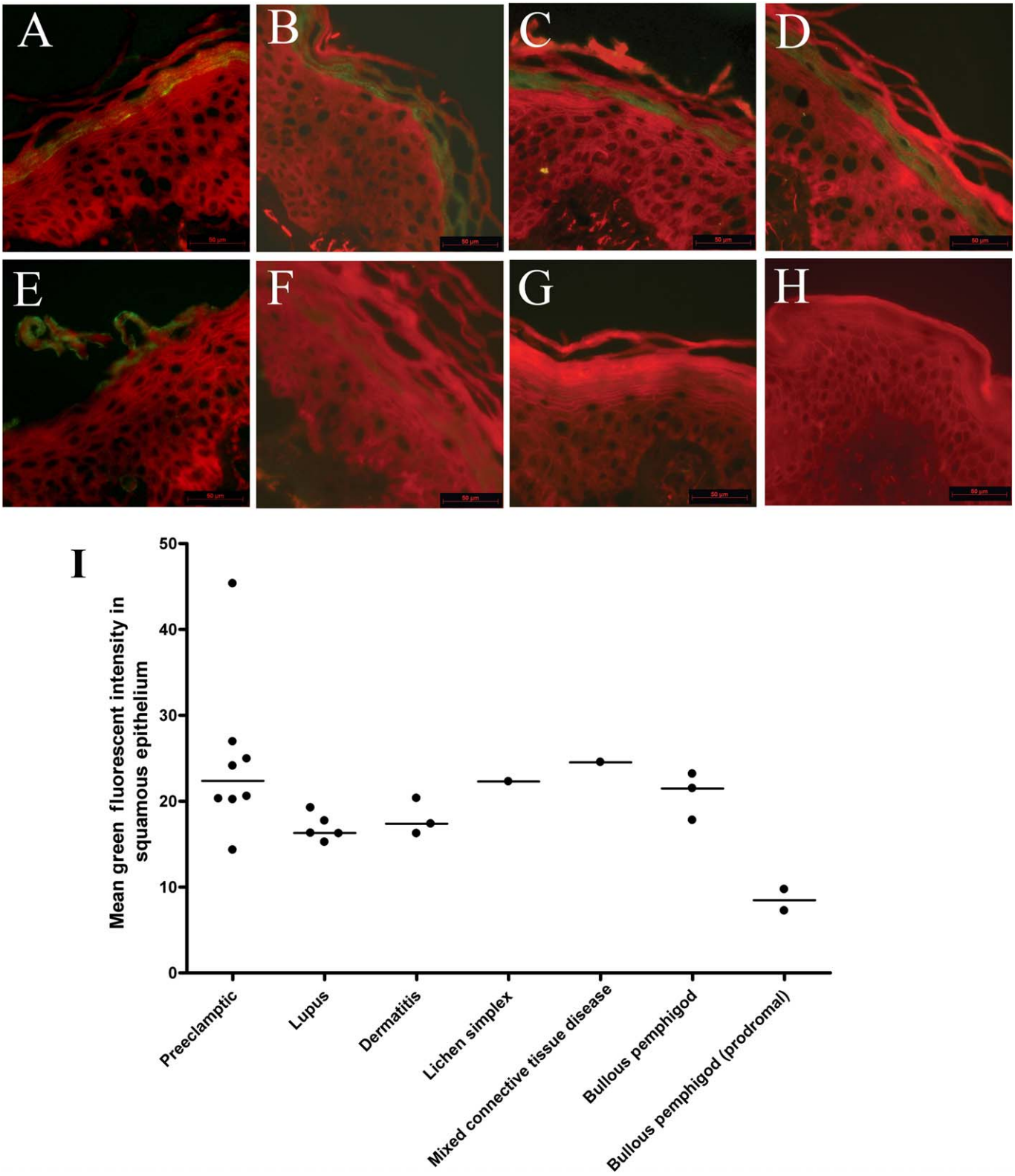

Figure 3. Xanthine oxidase (XO) immunoreactivity (green staining) is present in the stratum granulosum layer of the epidermis from patients with conditions of chronic inflammation including systemic lupus erythematosus (panel A), dermatitis (panel B), lichen simplex (panel C), mixed connective tissue disease (panel D), and bullous phemphigod (panel E). Patients with bullous phemphigod in which the disease is in remission demonstrate little epidermal XO immunoreactivity (panel F). Similarly, minimal XO immunoreactivity is observed in epidermis of healthy nonpregnant controls (panel G). Omission of the primary antibody directed against XO results in no observable immunoreactivity (panel H). Representative images are shown, along with qualitative analysis of XO immunofluorescent intensity within the squamous epithelial layers (panel I). Scalebar = 50 μm.

XDH/XO gene.[40] Further, activated leukocytes preferentially convert XDH into XO in endothelial cells.[41–43] Importantly, cytokine-induced increases in XO protein content translates into measurable increases in catalytic activity, resulting in increased generation of uric acid and O_2^-. In human mammary epithelial cell tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and interferon γ, respectively, elicited a 2-, 2.5-, and 8-fold increase in enzymatic activity.[19]

Limitations of the Study

There are limitations of this study to consider when interpreting this data. First is the limited number of skin biopsies available for examination from the study groups. Although the results of this study warrant further collection of samples and examination of the XO enzyme system within maternal epidermis, we feel that the observation of heightened immunoreactivity in *all five* skin biopsies collected from preeclamptic women with limited imunoreactivity in *all five* skin biopsies collected from our healthy pregnant controls (Figure 1E and F) is a finding worth expedited dissemination.

Second, all skin biopsies collected from pregnant women were collected from one anatomical site on the lower abdomen, at the site of cesarean section incision. Therefore, we cannot conclusively determine whether this heightened XO immunoreactivity would be observed in the epidermis from other locations on the body. Because the skin samples were taken at the conclusion of the cesarean section procedure, it is possible that this may have resulted in localized inflammation within the skin at the incision site. However, because this same insult would be present in both the healthy pregnant controls as well as the preeclamptic women, it is most likely not a contributing factor to the differential XO expression observed in the skin biopsies from this area. Furthermore, biopsy sites from nonpregnant patients with inflammatory condition were located at numerous locations on the body, including abdomen, trunk, thigh, and forearm, and no differences in XO immunoreactivity was observed based on biopsy site alone.

It is also important to note that all preeclamptic skin biopsies were collected from women demonstrating overt signs and symptoms of the disorder. Therefore, it cannot be determined whether these women entered pregnancy with a heightened immune response and constitutive elevations in tissue XO expression, or whether this increase developed during pregnancy prior to clinically evident disease, and/or whether this observed increase in XO protein was the result of the disease process. Thus, we cannot state that this increase in tissue XO in preeclamptic women contributes to the initiation of this syndrome. We would, however, argue that this potentially very large increase of XO observed in the third trimester skin, in association with an increased source of substrate from the enhanced placental aponecrosis characteristic of preeclampsia,[4] could help drive forward the pathological processes of preeclampsia. These observations suggest an interesting link between the maternal epidermis and the pathological process of preeclampsia. It is intriguing to consider that the elevations in circulating uric acid observed in our preeclamptic patients may possibly be in part the result of increased production in the skin in a fashion similar to that observed in patients with psoriasis in whom increased XO expression in the epidermal psoratic plaques is paralleled with an increase in circulating uric acid.[38] However, it should be stressed that the epidermal tissue bed is most likely only one of many potential sources of both uric acid and O_2^-. It is likely that numerous maternal, and possibly fetal, tissue beds demonstrate a parallel increase in XO.

This study demonstrated an increase in XO protein content in the epidermis of preeclamptic women. Increased XO mass may not necessarily reflect increased XO enzyme activity. Although this does limit our conclusions regarding increased maternal tissue XO activity, animal studies of epidermal XO generated in response to inflammatory activators demonstrate significant increases in XO in a similar epidermal location identified in our study.[26–28,32] Furthermore, in these studies, increased epidermal XO expression and protein concentrations were paralleled by an increase in enzyme activity, as measured by increases in circulating uric acid and reactive oxygen species generation.[24–26,28]

Finally, it is worth considering that maternal BMI may play a role in altered XO expression in preeclamptic women. Xanthine oxidase has been characterized as a novel regulator of adipogenesis. In vitro knockdown of XOR expression results in inhibition of adipocyte generation.[44] In vivo, XOR knockout mice demonstrate a 50% reduction in adipose mass while conversely a mouse strain with a spontaneously obese phenotype (ob/ob) exhibit increased concentrations of XOR mRNA and urate in adipose tissue.[44] Although there were significant differences in maternal BMI between our control and preeclamptic group (Table 1), there was significant overlap between the BMI values in the 2 groups and we found no obvious increases in XO immunoreactivity with increasing maternal BMI in our preeclamptic

group. However, the role of maternal obesity in the pathophysiology of preeclampsia is a research priority within our group and we hope to further investigate the impact of maternal BMI on XO expression and activity in future investigations.

CONCLUSION

The relevance of these findings to the understanding of the pathophysiology of preeclampsia, is 2-fold. First they emphasize the importance of increased inflammation within the syndrome, demonstrating the far-reaching effects of an activated maternal immune system. Second, skin is an enormous organ and if what we have demonstrated in abdominal skin is representative of the entire surface area of skin of a preeclamptic woman, this could potentially be an enormous contributor to the high concentrations of uric acid and increased reactive oxygen species in preeclamptic women.

The increased production of O_2^- would contribute significantly to the widespread oxidative stress observed in preeclamptic mothers, directly and indirectly impacting the health and functioning of vascular endothelium. Although the implications of increased XO activity rest largely with the increased generation of O_2^-, it is possible that uric acid may also contribute to the pathophysiology of preeclampsia. Although moderate amounts of uric acid have a protective antioxidant effect, elevated concentrations of uric acid, particularly with compromised antioxidant availability, manifest free radical activity.[45,46] There is clinical and experimental evidence that uric acid can directly contribute to the pathological processes leading to hypertension, cardiovascular, and renal disease.[47–49] Similar studies in preeclampsia are warranted as well as further examination of the effects of uric acid on other components of the pathogenesis of preeclampsia such as anti-angiogenic factors. These findings, highlighting the pathogenic potential of uric acid, have led to speculation by our group,[15] and others,[14,50] that hyperuricemia observed in preeclamptic women may be more than simply a marker of disease severity and may in fact directly contribute to the pathology of the disorder.

The finding of increased XO in maternal tissue, most likely as the result of heightened maternal inflammation, provides another potential factor contributing to the pathological processes involved in the progression of preeclampsia. The safety during pregnancy of directly inhibiting XO with allopurinal remains to be determined before tests of therapy would be appropriate. However, if uric acid itself is a pathogen, there is likely enough experience with the use of the uricosuric probenecid in pregnancy to allow clinical trials.

ACKNOWLEDGMENTS

This work was supported in part by National Institute of Health (NIH) grant P01 HD303967 and the Magee-Womens Research Institute Postdoctoral Fellowship.

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