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Pre-eclampsia and serum antibodies to oxidised low-density lipoprotein
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Abstract

Oxidised low-density lipoprotein (Ox-LDL) has been associated with arterial foam-cell formation, and autoantibodies to Ox-LDL are present in human serum. Lipid peroxidation is enhanced in pre-eclampsia. We assessed whether the titre of IgG autoantibody to an epitope of Ox-LDL, malondialdehyde conjugated low-density lipoprotein (MDA-LDL), was increased in the sera of pre-eclamptic patients. 16 such patients had significantly higher mean titres of autoantibodies to MDA-LDL than healthy pregnant women ($p=0.028$). In a multiple regression model, pre-eclamptic patients still had a significantly higher mean titre ($p=0.048$). Enhanced lipid peroxidation may be involved in the foam-cell formation of decidua and in the pathogenesis of pre-eclampsia.

Oxidatively modified low-density lipoprotein (Ox-LDL) may have an important role in the pathogenesis of atherosclerotic lesions.¹ Ox-LDL is also immunogenic and most people have low titres of serum autoantibodies. An increased titre of autoantibodies to malondialdehydelysine, an epitope of Ox-LDL, was observed in patients with progressive carotid atherosclerosis.² In pre-eclampsia, decidual vessels show fibrinoid necrosis of the vascular wall and focal accumulation of lipid-laden macrophages, similar to the situation in atherosclerosis.³ Pre-eclampsia has also been associated with abnormalities of lipid peroxidation.⁴ Our aim was to study whether the titre of autoantibodies to an epitope of Ox-LDL was also increased in pre-eclamptic patients.

Serum was obtained from 30 women presenting in labour and for delivery. 16 had pre-eclampsia (blood pressures 140/ 90 mm Hg); 11 had highest systolic blood pressures over 160 mm Hg, highest diastolic blood pressure of 110 mm Hg or more, or both. 2 patients had pre-existing chronic hypertension with superimposed pre eclampsia. The control patients were admitted for term labour, repeat caesarean section, or preterm or suspected preterm labour. The controls were healthy and normotensive at presentation. Serum was obtained within 24 h before delivery, and stored at -70°C .

Autoantibodies to native LDL and malondialdehydeconjugated LDL (MDA-LDL) were measured by solid-phase radioimmunoassay.² In preliminary studies we compared the ability of varying dilutions of serum to bind to native LDL with binding to MDA-LDL. The IgG binding to native LDL rapidly diminished with increasing dilutions, so that the ratio of IgG binding to MDA-LDL/LDL rose with increasing serum dilution. At dilutions of about 1:100, absolute binding to native LDL was similar to that of post-coated wells alone (ie, wells without antigen) and therefore serum dilutions of 1:100 were used for this assay. The titre was expressed as the ratio of the IgG binding to MDA-LDL divided by IgG binding to native LDL (MDA-LDL/LDL ratio).² Assay was done in La Jolla without knowledge of patients' diagnoses. Total IgG in each serum sample was measured in a routine clinical laboratory by nephelometry.

We analysed the data with t and U tests as appropriate. After log transformation of the MDA-LDL/LDL ratio, multiple regression was used to examine the association of MDA-LDL/LDL ratio and pre-eclampsia status (yes/no) with adjustment for possible confounders.

No significant differences were found between preeclamptic patients and controls in age, parity, or weight (table). Because of the earlier gestational age at which women with pre-eclampsia presented, there was a difference of 4 weeks in the gestational age at blood sampling. However, all controls and 13 of 16 pre-eclamptic patients were at or beyond 30 weeks' gestation. The patients had a significantly greater mean autoantibody titre than controls. Total serum IgG was the same in controls and patients, excluding the possibility that the higher autoantibody titre in the patients was due to a higher concentration of IgG. The four variables that were statistically different between the groups were considered as confounders in the multiple regression model. Only the lowest platelet count revealed a significant association with the MDA-LDL/LDL ratio ($p = 0.048$), independent of pre-eclampsia. The correlation was positive in controls (Pearson's $r = 0.321$) but was negative in the patients ($r = -0.424$). Our final regression model, including the factors of lowest platelet count and the interaction between pre-eclampsia and the lowest platelet count, showed a positive association between pre-eclampsia and the MDA-LDL/LDL ratio ($p = 0.048$, $r^2 = 0.293$).

We found elevated autoantibodies to an epitope of Ox-LDL in the sera of patients with pre-eclampsia. This finding indirectly supports our hypothesis that the decidual vascular lesions of pre-eclampsia and the arterial lesions of atherosclerosis share components of a common pathophysiological pathway which involves enhanced lipid peroxidation. These findings are consistent with the hypothesis that oxidation of LDL and/or the generation of other lipid peroxidation products contributes to the foam cell formation in the decidua by mechanisms analogous to those involved in atherogenesis.

In normal pregnancies, the distal portions of the decidual arterioles immediately underlying the placenta undergo substantial modification such that the muscular vascular wall is replaced with trophoblastic cells. This "physiological" modification is presumed to render the decidual arterioles unresponsive to vasopressors and other substances that might limit blood flow to the intervillous space. In pre-eclampsia, the number of decidual arterioles that are thus modified is limited. Instead, many vessels are narrowed or occluded by atherosclerotic-like changes, such as intimal thickening and fibrinoid necrosis, as well as by lipid-laden foam cells.

Lipid metabolism is dramatically altered during pregnancy. Normal pregnant women have hyperlipidemia, even more so in women with pre-eclampsia,⁵ suggesting that abnormal lipid metabolism may have a role in the genesis or expression of toxemia. Lipid peroxide products are increased in the serum of pre-eclamptic patients,⁶ and lipid extracts from the plasma of pre-eclamptic women have increased concentrations of diene conjugates, a consequence of lipid peroxidation, which are themselves positively correlated with diastolic blood pressure.⁹ The concentration of vitamin E, an endogenous antioxidant in LDL, is reduced in severe pre-eclampsia.⁸

Increased titres of antibodies to MDA-lysine (eg, MDA LDL) may reflect enhanced lipid peroxidation in general rather than a modification of LDL specifically. It would be of interest to immunostain decidual tissue from preeclamptic pregnancies to assess whether the lipid-laden foam cells also contain the oxidation-specific epitopes found in atherosclerotic lesions.

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	Pre-eclampsia (n=16)	Controls (n=14)	P
Age (yr)	22.6 (1.1)	24.8 (1.3)	0.13
Parity	0.5 (0.2)	1.0 (0.3)	0.12
Gestational age (weeks)	33.2 (1.2)	37.3 (.7)	0.01
Weight (kg)	76 (7)*	77 (3)	0.92
Highest systolic pressure (mm Hg)	169 (4.1)	132 (3.2)	0.0001
Highest diastolic pressure (mm Hg)	102 (2.5)	75 (2.6)	0.0002
Lowest platelet count (x 10 ⁹ /L)	0.162 (0.021)	0.224 (0.013)	0.02
Serum IgG (mg/dL)	770 (64)	856 (69)	0.279
MDA-LDL titre	3.98 (0.32)	3.12 (0.17)	0.028

* n=13

Table: Clinical data (mean, SE)

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