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Lipid-mediated endothelial dysfunction: a common factor to preeclampsia and chronic vascular disease

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Abstract

Preeclampsia is a complex pathophysiological state where regulatory systems of inflammation and endothelial function are stimulated beyond the physiological limits of normal pregnancy. Different lines of evidence indicate that abnormal lipid metabolism is not a mere manifestation but is also involved in the pathogenesis of the disease. Lipid-mediated oxidative stress is likely to contribute to endothelial hyperstimulation leading to dysfunction and damage. Maternal predisposing factors seem to be essential to explain why some pregnant women develop a systemic syndrome such as preeclampsia and why others do not. Preliminary evidence suggests that abnormal lipid metabolism could be one of these factors. In this review the evidence for the contribution of lipid oxidation in the pathogenesis of preeclampsia, the similarities between preeclampsia and lipid-mediated chronic vascular disease will be summarized, and the reasons to believe that constitutional lipid abnormalities could be one of the maternal predisposing factors for developing the disease will be examined and will be discussed.

Keywords: Chronic vascular disease; Lipids; Oxidative stress; Pathogenesis; Preeclampsia

1. Introduction

According to the most recent hypothesis, preeclampsia is a generalised inflammatory state where several plasma factors that regulate endothelial function are altered [1,2]. Such situation initially provokes an endothelial hyperstimulation that eventually leads to severe endothelial dysfunction [3], resulting in disseminated microangiopathic disease with vasospasm and hypercoagulation. Hypertension and proteinuria are the commonest signs among numerous possible clinical manifestations, such as thrombocytopenia, liver dysfunction, hemolysis and cerebral complications.

Accumulating evidence suggests that lipid peroxides and pro-inflammatory cytokines are major causal factors to induce endothelial dysfunction. Other potential contributors are abnormally increased trophoblastic particles and neutrophil activation [1], which are supposed to act through liberation of peroxides and inflammatory cytokines. Most women with preeclampsia show histological or biochemical evidence of poor placentation, ischemia and pro-inflammatory activity [1,2,4]. However, the degree of defective placentation is variable and may not be present in all preeclamptic women, while on the other hand severe placental ischemia does not necessarily lead to preeclampsia [5]. Therefore some other pre-existing maternal factors must be present to result in a preeclamptic syndrome [6]. Those maternal factors are probably alterations associated to the regulation of one or more of the physiological steps altered in preeclampsia and may not always be clinically obvious in the absence of pregnancy [6].

In this review, we will focus on lipid-mediated oxidative stress and lipid metabolism. We will examine how essential they are in the pathogenesis of preeclampsia and how far they could constitute a major predisposing maternal factor for developing the disease.

2. Evidence for the involvement of lipids in the pathogenesis of preeclampsia

Different lines of evidence indicate that abnormal lipid metabolism is not a mere manifestation of preeclampsia, but that it is directly involved in its pathogenesis. It is known for 20 years that preeclampsia is associated with hypertriglyceridemia [7]. In more recent studies it was reported that triglycerides and free fatty acids are already elevated in the first and second trimester in these women [8,9]. In vitro

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experiments have shown an endothelial stimulatory activity of preeclamptic plasma which largely depends on its lipid fraction [10]. Recent studies have demonstrated that lipoproteins in women with preeclampsia show a predominance of the atherogenic small-dense low density lipoprotein (LDL), which is also characteristic of atherosclerosis [11,12].

The link between lipids and endothelial dysfunction in the disease could be oxidative stress. Free radicals can be generated by many different enzymatic processes [13]. They are extremely reactive and interact with polyunsaturated fatty acids to produce lipid peroxides with a much longer half life [14]. Lipid peroxides are normally present in lipoproteins and seem to contribute to vascular tone regulation through stimulation of the arachidonic acid enzymatic pathways [15], responsible for the synthesis of prostacyclin and thromboxane A2. However, beyond a threshold of lipid peroxide concentration prostacyclin synthesis is selectively inhibited while production of thromboxane A2 is further stimulated [16]. Other molecules involved in vasodilation such as nitric oxide are also inhibited by high lipid peroxide concentrations [17]. When oxidative stress reaches a certain level cellular damage occurs, including structural damage in cellular membranes, and mitochondrial and nuclear DNA, and impairment of enzymatic functions at multiple levels [18]. In preeclampsia, the placental concentration and production of lipid peroxides is significantly increased [19–22]. Plasma lipid peroxide levels are also significantly elevated [20,23–26], whereas Vitamin E and other plasma antioxidants are decreased [20,23–28] as a possible indirect sign of consumption. These alterations are specific for women with preeclampsia [20] or with chronic hypertension with superimposed preeclampsia [29], and not for other forms of hypertension during pregnancy, such as non-proteinuric gestational and essential hypertension.

Experimentally raised levels of lipid peroxides can reproduce functional and histologic features of preeclampsia in in vitro culture systems of endothelial [30,31] and trophoblast cells [32], as well as in animal models [33,34]. It is interesting that exposure to plasma from preeclamptic patients reproduces the endothelial stimulation-dysfunction sequence above described for peroxides. In vitro, plasma from preeclamptic women stimulates endothelial prostacyclin production [35,36] and enhances nitric oxide synthase activity [37]. However, this is a temporary effect. Maintained exposure results in inhibition of prostacyclin synthesis [38] as a result of hyperstimulation, which leads to a sublethal state of cellular damage, hypersensitivity to vasoconstrictors, and eventually endothelial cell death [3]. As discussed later, these mechanisms are similar to those operating in atherosclerosis [39].

The generation of lipid peroxides in preeclampsia is supposed to be initiated in the placenta. This could result from ischemic and inflammatory phenomena in the feto-maternal interphase. Isolated trophoblastic villi produce increased amounts of lipid peroxides when cultured under hypoxic conditions [40]. The abnormal pro-inflammatory expression pattern of cytokines in the materno-fetal interphase in preeclampsia could play a major role. Cytokines stimulate the synthesis of lipid peroxides, directly [41] and indirectly, through neutrophil activation [42].

3. Common factors in preeclampsia and lipid-mediated chronic vascular disease

Preeclampsia and atherosclerosis share important features. Common epidemiological risk factors are, e.g. diabetes, black race, or hyperhomocysteinemia [6,36]. In classic studies describing vascular lesions in the placental bed of women with preeclampsia, the term ‘acute atherosis’ was introduced because of the presence of lipid-laden macrophages, or foam-cells, as observed in the atherosclerotic plaque [43]. Atherosclerosis and coronary artery disease (CAD) are both associated with a characteristic lipid profile defined by predominance of smaller and denser LDL and by hypertriglyceridemia [44]. This lipoprotein pattern is referred to as pattern B as opposed to pattern A [44], which is characterised by predominance of larger and more buoyant LDL as present in the majority of the population. Expression of this pattern is to a large extent genetically conditioned [45]. As discussed above, lipids in women with preeclampsia present with features of the atherogenic profile, increased small-dense LDL and hypertriglyceridemia [11,12]. Small-dense LDL are less efficiently internalised in the endothelial cell and have a markedly increased potential for endothelial damage compared to larger LDL [46]. Interestingly, small-dense LDL show an abnormally increased susceptibility to in vitro lipid oxidation [47] which may be one of the mechanisms of their deleterious effects on the endothelium [48]. Indeed, oxidative modification of lipoproteins appears to increase substantially their adverse effect on endothelial function [49]. Proposed mechanisms of lipid-mediated cardiovascular pathology in adults are similar to those advanced for preeclampsia: chronic abnormal endothelial hyperstimulation through lipid peroxidation eventually leading to dysfunction and damage [3,39]. Preeclampsia could represent an acute model of endothelial hyperactivation and subsequent dysfunction mediated through massive production of lipid peroxides, in combination with other endothelial and pro-inflammatory stimuli.

4. Potential contribution of genetically determined lipid abnormalities to predisposition to preeclampsia

It is becoming widely accepted that there are several possible pathogenetic pathways leading to the complex systemic unbalance underlying the preeclamptic syndrome [6]. Even severe degrees of placentation failure can develop without the slightest sign of preeclampsia, and therefore maternal factors must also play an essential role. A variable

degree of placental ischemia must be the triggering factor in most cases but in others the pregnant state itself could be sufficient. Over the last years, attention has focused on mutations or polymorphisms affecting the regulation of relevant factors in preeclampsia, such as cytokines, coagulation factors or angiotensinogen [6]. However, so far little interest has focused on lipids.

Abnormalities in lipid metabolism are known for decades to have a genetic basis [50]. Preeclampsia is characterised by profound lipid abnormalities similar to those present in atherosclerosis such as hypertriglyceridemia and predominance of the small-dense LDL, which are likely to play a role in endothelial dysfunction and endothelial damage. The existence of these abnormalities prior to pregnancy could represent one predisposing factor for developing the disease. In the presence of oxidative stress and inflammation, susceptible lipoproteins would become more easily oxidised and help triggering the pathophysiological sequence.

There is preliminary evidence to support that concept. In a recent communication [51], Arngrimsson presented his results on Icelandic post-menopausal women with a well-documented history of preeclampsia. A significantly high proportion of these women expressed the lipoprotein phenotype B, as compared to age matched controls who had normal pregnancies. Recently we have finalised a study on women with severe preeclampsia, two to five years after delivery (unpublished results). About 40% of these women showed significantly increased levels of triglycerides and abnormally reduced in vitro resistance to oxidation of LDL, when compared with controls matched for age, as well as weight and age at the time of delivery. The value of that type of studies is obviously limited by their retrospective nature. Future prospective studies evaluating known gene traits associated with abnormal lipid metabolism [52] could provide valuable information. Pre-existent lipid abnormalities could be only subclinically present, yet stimulated when factors inducing preeclampsia appear. In a proportion of cases of preeclampsia a pro-atherogenic lipid pattern could represent a primary unbalancing event that in combination with an ischemic placenta (or not) could initiate the pathophysiological cascade leading to the maternal syndrome.

5. Conclusions

Preeclampsia is a complex pathophysiologic state where biological systems involved in the regulation of inflammation and endothelial function are stimulated beyond the physiologic limits of normal pregnancy. Direct and indirect evidence suggest that lipid metabolism is one of the altered systems in preeclampsia, leading to lipid-mediated oxidative stress and endothelial damage. The existence of maternal predisposing factors seems to be essential to explain why some pregnant women develop a systemic syndrome such as preeclampsia and why others do not. Preliminary evidence suggests that abnormal lipid metabolism could be one of these factors. The presence of an ischemic placenta in some cases and in others the mere physiological hyperstimulation of pregnancy could interact with abnormal susceptibility to lipid oxidation and trigger the cascade of pathophysiological disorders occurring in preeclampsia.

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