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Oxidative Stress and Preeclampsia

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Abstract Eclampsia is one of the most common pregnancy complications causing high mortality and morbidity for both mother and foetus. Low birth weight and pre-maturity are very common features. Pre-eclampsia is associated with oxidative stress in the maternal circulation. The etiology and pathogenesis of the pregnancy syndrome preeclampsia remain poorly understood. There is substantial evidence to suggest that the diverse manifestations of preeclampsia, including altered vascular reactivity, vasospasm, and discrete pathology in many organ systems, are derived from pathologic changes within the maternal vascular endothelium. The imbalance between oxidative damage and antioxidant defences in pre-eclampsia leads to endothelial cell dysfunction. Endothelial cell dysfunction appears to be a central feature in the patho-physiology of pre-eclampsia.

Keywords Oxidative stress, Pre-eclampsia, Markers

1. Introduction

Preeclampsia is a complication of pregnancy characterized by hypertension, edema, and proteinuria, and no single test or combination of tests has yet been shown to predict its onset with accuracy[1]. A number of risk factors for preeclampsia have been identified. In clinical practice, preeclampsia is defined by its clinical manifestations, and is often discovered late in its course. An objective screening test to predict the onset of preeclampsia would be clinically valuable in order to identify women who require closer clinical monitoring during pregnancy, and also to aid in evaluating new preventive therapies before the onset of clinical symptoms or signs[2]. Because increased oxidative stress has been implicated in the etiology of preeclampsia[3], a marker of oxidative stress could potentially provide such a screening test. Several studies have employed different markers to estimate oxidative stress, and there is agreement that the level of lipid peroxides in blood is generally higher in pregnant women than in non-pregnant women[4].

2. Free Radicals

A free radical is a very reactive molecule capable of independent existence for only a short time. Free radicals have one or more unpaired electrons (an electron alone in more stable. A molecule with an unpaired electron is prone its orbit). Molecules with all of their electrons paired are to take one from another molecule. When it reacts with molecules making up biologic structures (such as cell membranes), it can damage those structures. Free radicals often contain oxygen atoms. In addition to oxygen radicals there are some non-radical oxygen-containing molecules such as hydrogen peroxide that also cause damage to biologic structures; together these are all called "reactive oxygen species" (ROS).

Reactions involving ROS proceed in a chain reaction. If the original radical takes an electron from a stable non-radical molecule, that molecule becomes a radical and will react with another stable molecule, causing damage all along the way. Lipid peroxidation is a chain reaction in which cell membranes are damaged, causing the cells to function poorly or to collapse.

Some ROS are generated by the human body for a purpose. Phagocytes produce superoxide and use it to kill bacteria they engulf. Others are produced as normal metabolites of many biochemical processes, such as aerobic respiration. They also are formed when there is tissue injury or ischemia followed by reperfusion. They can be acquired (toxins or pollutants such as ozone) or generated in response to something occurring in the environment (such as ionizing radiation, including sunlight). There are many different sources of free radicals within cells and the environment. In aerobic organisms, free radicals are produced during and through normal metabolic processes. Key sources include electron transfer in the plasma membrane and cell respiration in the mitochondrial membrane. Their production can proceed enzymatically (with catalysts) or non-enzymatically.

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Cells make antioxidants to protect themselves from oxidative damage by ROS[5]. Uric acid, superoxide dismutase and bilirubin are examples of antioxidants the body makes for itself. Cell membranes incorporate vitamin E and beta-carotene, antioxidants acquired nutritionally. Vitamin E interrupts lipid peroxidation by giving a radical one of its electrons. It then becomes a tocopherol radical, which is much less reactive and therefore safer, effectively putting an end to the chain reaction. It migrates to the membrane surface where vitamin C recycles the tocopherol radical back into vitamin E, and it goes to work again protecting the cell membrane. Different antioxidants work in different places and in different ways to protect against oxidative stress.

2.1. Antioxidants- Oxidative Stress

In order to counteract intracellular damage by free radicals, cells have developed a so called intracellular antioxidant system. This process transforms free electrons into a nonreactive form by proteins (enzymes). Antioxidants regulate oxidative reactions by inhibiting, delaying or hampering the oxidation of the substances[5]. The intracellular enzymes function as antioxidants are the backbone of this cellular defense system[6, 7]. The key antioxidant enzymes possess certain elements that shield and protect proteins[8,9]. Non-enzymatic antioxidants can also neutralize radicals (e.g. water-soluble substances such as vitamin C, glutathione or fat-soluble substances such as vitamin E or vitamin A/ β- carotene). For example, the enzyme SOD transforms superoxide radicals into hydrogen peroxide, which is then broken down by catalysis into water and oxygen.

Free radicals are not exclusively damaging metabolic products, but also have a series of important functions. For example they serve in immune defense because leucocytes and macrophages utilize their bactericidal effects: they produce free radicals and thus destroy bacteria and other foreign substances. Moreover, free radicals probably play a role in the body's tumor suppression by mediating programmed cell death (apoptosis).

Immune-relevant cells also use the reactive potential of ROS as a cellular defense mechanism against entering pathogens to kill bacteria, viruses and degenerated cells. Radicals also fulfill important physiological function such as regulating the vascular tone and those cell functions controlled by oxygen concentration. They also influence signal transmission mechanisms and trigger oxidative stress responses as well as apoptosis[10].

Oxidative stress is the result of an imbalance between the intracellular production of free radicals and the cellular defense mechanisms. The balance between oxidants and antioxidants can be disrupted by an increase in free radicals or a reduction of anti-oxidative substances. Oxidative stress can trigger a number of potentially damaging biochemical reactions[11]. Production of radicals is directly involved in the oxidative destruction of macromolecules such as lipids, proteins and nucleic acids.

2.2. Pre-eclampsia

Pre-eclampsia or eclampsia is a pregnancy specific disorder, which complicates 7-10% of all gestations[12]. The disorder was first recognized almost 2000 years ago. Celsus described pregnant women with seizures that abated with delivery. This disorder was termed eclampsia and for 2000 years was considered a pregnancy-specific seizure disorder. In the late 1800s the association of, initially, proteinuria and later increased blood pressure with eclampsia was recognized. It was also noted that increased blood pressure and urinary protein antedated the seizures. From this came the term preeclampsia[13]. Even in the absence of seizures, maternal and infant risk was increased. Interestingly, despite the recognition by care providers that blood pressure was not usually the major problem for mother or baby but was rather a marker of a multi systemic syndrome, blood pressure was the focus of preeclampsia research for nearly 100 years.

Pre-eclampsia is a triad of oedema, hypertension and proteinuria occurring primarily after the 20th gestational week and most frequently near term[14]. Pre-eclampsia when complicated with convulsion and or coma is called eclampsia[15]. Intrauterine growth retardation (IUGR), pre-term delivery, low birth weight, foetal death and neonatal death due to complications of pre-term delivery are common perinatal outcomes associated with pre-eclampsia[16]. Etiology of pre-eclampsia and eclampsia is still obscured. Endothelial cell dysfunction appears to be a central feature in the patho-physiology of pre-eclampsia[17].

Increase in oxidative stress markers has been implicated to damage the maternal vascular endothelium leading to the elevation in diastolic pressure which further aggravates the condition of pre-eclamptic patients[18, 19]. The imbalance between oxidative damage and antioxidant defences in pre-eclampsia leads to endothelial cell dysfunction[20]. The free radicals produce cellular injury by lipid peroxidation, enzyme inactivation, DNA damage and degradation of structural proteins.

2.3. Oxidative Stress in Preeclampsia

Compared with healthy pregnant women, pre-eclamptic women have low levels of several dietary antioxidants in their blood, including vitamin C, vitamin E, lycopene and beta carotene. They also have higher levels of ROS and frequently have increased levels of uric acid, probably resulting from the body's attempt to cope with oxidative stress. The placentas of pre-eclamptic women also have lower than normal antioxidant levels and higher than normal levels of ROS.

In overtly preeclamptic women it is impossible to decipher cause from effect. Nonetheless, current concepts of the genesis of preeclampsia that include endothelial dysfunction, inflammatory activation, oxidative stress and predisposing

maternal factors provide targets for nutritional aspects.

2.4. Nutrition and Preeclampsia

For many years diet has been suggested to play a role in preeclampsia. Increased and reduced dietary sodium, protein, fats or carbohydrates were proposed as possible etiological factors. Current concepts of preeclampsia suggest nutrient or micronutrient deficiencies might be the cause or effect[13].

Preeclampsia appears to arise after a multistage process. Whether or not dietary factors influence healthy trophoblast migration into the myometrium has not been investigated. Diet does influence blood volume expansion, and this is necessary to optimally perfuse the placenta. Oxidative stress is the likely culprit in the endothelial dysfunction that predates clinically apparent preeclampsia and explains its signs and consequences. A woman's antioxidant status influences her susceptibility to oxidative stress. Many antioxidants are manufactured within the body, but a good intake of dietary antioxidants may help.

2.5. Clinical Aspects of Preeclampsia

Oxidative stress has been implicated in the pathophysiology of pre-eclampsia because it damages the maternal vascular endothelium, and there is indisputable evidence that normal role of this cell layer is severely compromised in pre-eclampsia. Cumulative evidence in recent years points towards biochemical imbalance in pre-eclampsia with an increase of oxidative stress and, at the same time, a deficient antioxidant protection. Significant elevation of malondiadehyde (MDA) levels in cord blood of pair matched pre-eclamptic mothers have been reported[21,22] whereas others have reported decline in its level[23] or no significant change[24,25] but Karabulut et al[26] inferred elevation of MDA levels in cord and mother during pre-eclamptic development compared to normal pregnancy. Similar contradictions exist about the level of antioxidant enzymes in the cord blood of pre-eclamptic mothers.

DNA is among the main targets of free radical induced oxidation. There are some reports on the oxidative DNA damage in pre-eclamptic pregnancies. According to one such studies, the concentration of 8-OHdG was significantly higher in the placental DNA from pre-eclampsia complicated pregnancies[27]. Elevated free radicals and a decrease in antioxidant capacity create an imbalanced state in the diseased state. Lipid peroxidation represents lipidic damage, 8-OHdG represents oxidative DNA damage and total antioxidant status represents antioxidant capacity or defensive state. Alterations in the levels of markers of oxidative stress as a result of biochemical imbalance clearly indicate the role of oxidative stress in the pathophysiology of pre-eclampsia or eclampsia.

3. Conclusions

The imbalance between oxidative damage and antioxidant defences in pre-eclampsia leads to endothelial cell dysfunction. A recurrent theme is that free radical reactions, promoted by “cross-talk” between the diseased placenta and maternal dyslipidemia, promote a vicious cycle of events that make cause and effect difficult to distinguish but may contribute to the progression of preeclampsia. Oxidative stress play a significant role in the pathophysiology of pre-eclampsia and that supplemental dietary antioxidants may have a beneficial role in the prevention of the disease and improvement in maternal and child health.

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