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Uric Acid & Preeclampsia

(Dr Mador)

The association of hyperuricemia with Preeclampsia has been known since 1917 (Slemons and Bogert, 1917) while the relationship of the degree of hyperuricemia and the severity of disease has been known since 1934 (Stander and Cadden, 1934). What is not clear is the role that uric acid plays in the pathophysiology of preeclampsia – whether it is a marker of disease or whether it actively takes part in the pathogenesis of disease. Although hyperuricemia does not predict the development of preeclampsia, the severity of hyperuricemia has been observed to correlate with maternal and fetal morbidity and severity of renal lesion, and to be inversely proportional to birth weight. Most often, increase of the uric acid level precedes the onset of proteinuria and hypertension, suggesting a possible causal role of uric acid. In human blood plasma, the reference range of uric acid is between 139 μmol/l – 393 μmol/l in women. Serum uric acid can be elevated due to reduced excretion by the kidneys, fasting or rapid weight loss.

Each organism has a strictly defined genetic makeup. This is inherited from its predecessors and used by the organism itself to direct its cellular functions. It then passes on its own genetic information to its progeny. Each cell of a particular organism contains the same genetic information. This genetic information is stored in the chromosomes of the cell as nucleic acids. The nucleic acids are subdivided into two types: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The two types are both polymers built from the same type of subunit called nucleotides. Each nucleic acid is a polymer usually many thousands of nucleotides long, but each polymer is composed of a variable sequence of only four different nucleotide structures. Each nucleotide consists of:

1. a base composed of a carbon and nitrogen ring structure,
2. a pentose (5 carbon) sugar which is either deoxyribose or ribose, and
3. one, two or three phosphates attached to the sugar.

There are four different bases in each class of nucleic acid. Three are common to both and one is unique to each. The bases are described as either a purine type or a pyrimidine type. The five bases are:

1. adenine (A) – purine type.
2. guanine (G) – purine type.
3. cytosine (C) – pyrimidine type.
4. thymine (T) – pyrimidine type.
5. uracil (U) – pyrimidine type.

There are subtle but important differences between the subunits used in the synthesis of DNA and those which are incorporated into RNA. In addition, there are differences in the structure of the two nucleic acids.

DNA	RNA
Contains A, G, C and T	Contains A, G, C and U
Contains deoxyribose	Contains ribose
Is double stranded	Is single stranded
Stores genetic information	Is used in the EXPRESSION of genetic information

Uric acid is generated in mammalian systems as an end product of purine metabolism. Metabolism is an inclusive term for the chemical reactions by which the cells of an organism transform energy, maintain their identity, and reproduce. All life forms are dependent on many hundreds of simultaneous and precisely regulated metabolic reactions to support them from conception through growth and maturity to the final stages of death. Each of these reactions is triggered, controlled, and terminated by specific cell enzymes or catalysts, and each reaction is coordinated with the numerous other reactions throughout the organism. Two metabolic processes are recognized. These are anabolism and catabolism. Anabolism, or constructive metabolism, is the process of synthesis required for the

growth of new cells and the maintenance of all tissues. Catabolism or destructive metabolism on the other hand, is a continuous process concerned with the production of the energy required for all external and internal physical activity. Catabolism also involves the maintenance of body temperature and the degradation of complex chemical units into simpler substances that can be removed as waste products from the body through the kidneys, intestines, lungs, and skin.

Anabolic and catabolic reactions follow what are called pathways that are linked to produce specific, life-essential end products. Scientists have been able to determine how some of these pathways weave together, but many of the finer intricacies are still only partly explored. Basically, anabolic pathways begin with relatively simple and diffuse chemical components, called intermediates. Taking their energy from enzyme-catalyzed reactions, the pathways then build toward specific end products, especially macromolecules in the forms of carbohydrates, proteins, fats and nucleic acids. Using different enzyme sequences and taking the opposite direction, catabolic pathways break down complex macromolecules into smaller chemical compounds for use as relatively simple building blocks. When anabolism exceeds catabolism, growth or weight gain occurs. When catabolism exceeds anabolism, such as during periods of starvation or disease, weight loss occurs. When the two metabolic processes are balanced, the organism is said to be in state of dynamic equilibrium.

The fact that cells and tissues retain their dynamic equilibrium throughout the life of an organism clearly shows that metabolic processes are under fine control. Cells and entire tissues are constantly dying, yet all the chemical ingredients that replenish and form new cells and their products are supplied by metabolism, striking a nearly perfect balance. Although much remains to be revealed about metabolic processes, scientists now agree that regulatory, or rate-limiting, enzymes figure largely in the reactions involved. Affecting metabolic pathways

at the earliest steps, each enzyme molecule has a specific, or active, site that matches, or "fits," its particular substrate-the compound with which the enzyme forms a product. The precision with which rate-limiting enzymes and substrates join to set off a particular reaction inhibits reactions from occurring indiscriminately in cells, where so many diverse chemical compounds are in flux. Tiny amounts of a rate-limiting enzyme can cause profound changes in the metabolism of a cell. Another way in which metabolic pathways are controlled is through negative feedback. Thus, once a cell synthesizes the correct balance of a product, such as ATP, the accumulation of that product will inhibit the enzymes that trigger its production. Metabolism, especially in higher animals, is also regulated by the nervous system and by the pancreas, the pituitary and adrenal glands of the endocrine system. Hormones, secreted into the bloodstream, reach target tissues, often altering the permeability of cell membranes and thereby altering the amounts of substances that get into and out of cells. Liver is the major organ involved in degradation of purine nucleotides. Lysosomal enzymes convert nucleic acids to nucleotides. Majority of purine nucleotides so produced are AMP and GMP. AMP is converted to IMP by adenylate deaminase present in most of the tissues. Next, nucleotidases convert IMP, AMP and GMP to corresponding nucleosides namely inosine, adenosine and guanosine. By the action of adenosine deaminase adenosine is converted to inosine. Now purine nucleoside phosphorylase converts guanosine to guanine and inosine to hypoxanthine by transferring ribose. Deamination of guanine by guanase produces xanthine. Finally hypoxanthine and xanthine are converted to uric acid by xanthine oxidase. Uric acid produced in different tissues diffuses into circulation and carried to kidneys for elimination. Uric acid daily production is about 500-600mg. However, most of it is removed by kidney. Daily output is about 0.3-0.5 g/day on normal diet. The normal blood uric acid level is below 6 mg/100ml. So, one can expect that impaired renal function may lead to accumulation of uric acid in blood. Gout is common disease associated with excessive purine catabolism. It is

characterized by hyperuricemia and excessive excretion of uric acid in urine. It is more common in men (95%). Incidence rate is 3 in 1000. Since uric acid is less soluble in the body fluid aqueous environment excessive uric acid leads to formation and deposition of urate crystals in joints, cartilage of fingers, big toe and other soft tissues. Deposition of urate in joints leads to gouty arthritic attacks.

Humans and great apes have higher uric acid levels than most vertebrates because they lack the enzyme Uricase in the liver which breaks down uric acid into allantoin. In normal pregnancy, serum uric acid level slowly decreases until 16 weeks of gestation, secondary to plasma volume expansion, increased renal clearance, and the uricosuric effect of oestrogen. For most of the 2nd trimester, the uric acid level remains stable and then increases during the 3rd trimester because of increase catabolism/production. The placenta in normal pregnancy is an abundant source of purines because of its high cell turn over, resulting in higher production of uric acid. Serum uric acid is also higher in normal multifetal pregnancies compared with normal pregnancies, which could be explained by the fetus as an additional source of xanthine oxidase. Alternatively, increased serum uric acid levels in multifetal pregnancies could be secondary to the increased number of placentas. In a report of patient with xanthuria (Simmonds *et al*., 1984), an autosomal recessive disorder that results in XO deficiency, serum uric acid levels were found to be increased at 32 weeks of gestation, but returned to baseline low levels by 6 weeks postpartum, suggesting a definitive role for fetal and/or placental uric acid production.

Fetuses exposed to hypoxia (e.g. because of decreased placental perfusion) have been shown to have increased serum levels of purine metabolites (Saugstad, 1975). Of note, since 1944, there have been 6 reported cases of gout attacks in women during or around the time of pregnancy, 4 of whom were felt to have primary or idiopathic gout (Lee and Loeffler, 1962; Irgens *et al*., 2001). Two of

the 6 patients have a history of preeclampsia documented. The relationship of uric acid with nitric oxide has been explored in a number of studies. A circadian reciprocal pattern of nitric oxide and uric acid levels has been observed (Kanabrock *et al*., 2000). Infusion of allopurinol into hyperuricemia patients with congestive heart failure has been shown to improve endothelium-dependent (i.e. acetylcholine co-infusion) but not endothelium-independent (e.g. nitroprusside, nitroglycerin) forearm vasodilatation (Doehner *et al*., 2002; Farquharsan *et al*., 2002). These patients also had improved peak blood flow distally after treatment with allopurinol (Doehner *et al*., 2002).

To date, only one study has looked at allopurinol use in clinical preeclampsia (Gulmezoglu *et al*., 1997). Women with severe preeclampsia between 24 and 32 weeks of gestation of gestation were given allopurinol 200mg, vitamin E 800i.u, and vitamin C 1000mg/dl for up to 14 days. The median uric acid level was 5.3, range 3.1 – 13.4mg/dl (0.32; range 0.19 – 0.81 mmol/l) in antioxidant group; and 7.1, range 4.6 – 9.1mg/dl (0.43; range 0.28 – 0.55mmol/l) in the control group. Although there was a trend towards prolonging pregnancy in the treatment group, this was not significant. Fetal outcome was not different in both groups, and there was no significant change in level of lipid peroxides between the two groups.