Central Asian Journal of Medical and Pharmaceutical Sciences Innovation **2**(2): 37-45 (2022)

REVIEW PAPER

The role of hyperuricemia in the pathophysiology of preeclampsia

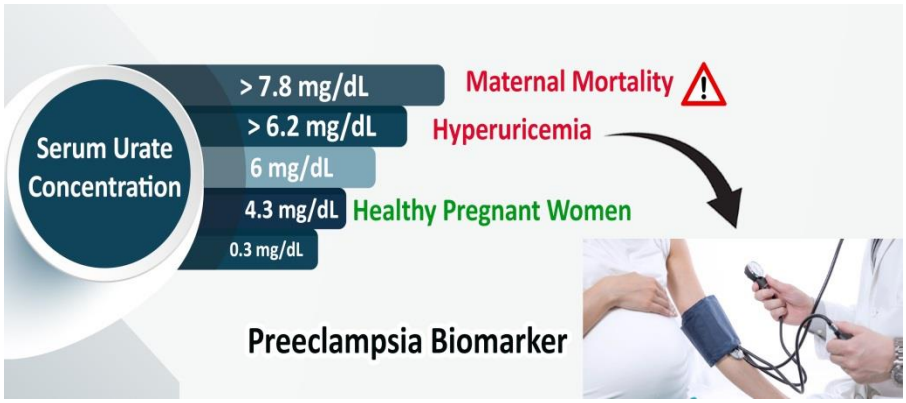
Qassim Hassan Aubais Aljelehawy [1,2,*], Marwa Rahii Abed Almonem Alftlawy [1,2], Hateme Alavi [3]

[1]Department of Medical Laboratory Technique, The Islamic University, Diwaniya, Iraq
[2]Department of Research and Studies, The Islamic University, Najaf, Iraq
[3]Department of Midwifery, Kurdistan University of Medical Sciences, Kurdistan, Iran

Highlights

- Preeclampsia is a disorder characterized by high blood pressure and urinary protein.
- Hyperuricemia is an indicator of preeclamptic pregnancies that could be present from early pregnancy.
- Hyperuricemia can be involved in the pathogenesis of preeclampsia with vascular damage.

Graphical Abstract



Article Info

Receive Date: 31 January 2022
Revise Date: 25 February 2022
Accept Date: 02 March 2022
Available online: 26 March 2022

Keywords:
Preeclampsia
Hyperuricemia
Uric acid
Biomarker

Abstract

Preeclampsia (PE) is a human pregnancy disorder that begins with high blood pressure. This disorder occurs after 20 weeks of pregnancy and is defined by the high pressure of blood and proteinuria symptoms. Also, PE is recognized as a multifactorial disease that causes damage to some systemic organs including the lungs, brain, kidneys and liver. In some cases, high blood pressure might happen without proteinuria but includes complications including acute renal failure, thrombocytopenia, and fetal growth limitations. Hyperuricemia is known as a serum urate concentration of more than 6.8 mg/dL. Uric acid, which is mainly synthesized in the liver, is released into the bloodstream, only a small percentage of which binds to proteins. Thus, most circulating urate is readily available for filtration in the glomerulus and for participation in a number of complex renal mechanisms. Uric acid amounts in non-pregnant women usually range from 0.3 up to 6.0 mg/dL. Surprisingly, the levels of uric acid in pregnant women up to the twentieth week of pregnancy are 20 to 25 percent lower than in non-pregnant women. This reduction in levels of uric acid in the first trimester is due to hemodilution because of increased blood levels due to elevated filtration rate of glomeruli and decreased proximal tubular reabsorption. Uric acid is an identified biomarker for oxidative stress, kidney damage, and placental ischemia. Specifically, these are also the properties of PE. However, uric acid is sometimes referred to as a biomarker of PE. Elevated levels of serum uric acid in PE vs. usual pregnancies have been shown and recommend levels of serum uric acid as a risk indicator for progression of PE. According to the above discussion, the objective of this study was to review the role of hyperuricemia in the pathophysiology of PE. As a conclusion, PE is specified by hyperuricemia and signs of elevated creation of ROS and reduced antioxidants levels. There are GCKR, PDZK1, LRP2, ABCG2, SLC2A9, SLC17A1, LRRC16, SLC22A12, SLC17A3, SLC22A11, and SF1 genes involved in the uric acid transport that may contribute in the hyperuricemia during PE and Alterations in the function of these genes might increase the risk of this disease.

10.22034/CAJMPSI.2022.02.01 **E-ISSN: 2783-0993**

*Corresponding author: qasemhussan@iunajaf.edu.iq (Q. Hassan Aubais Aljelehawy)

Introduction

A deep understanding of all cellular, molecular, and biomedical aspects of acute and chronic diseases is needed to find effective ways based on novel technology to treat these diseases (1-5). Preeclampsia (PE) is a unique disorder in human pregnancies that begins with hypertension. This disorder happens after 20 weeks of pregnancy and is specified by high pressure of blood and proteinuria. Factors that predispose pregnant women to preeclampsia include a previous preeclampsia history, a chronic hypertension history, kidney disease, cardiovascular disease, gestational hypertension, gestational diabetes, age over 35, and overweight (6).

Preeclampsia is a multifactorial disorder that causes damage to certain organs including the kidneys, lungs, liver, brain, and. In some cases, high blood pressure may occur without proteinuria but includes complications including thrombocytopenia (decreased platelet count), acute renal failure, and fetal growth limitations, as well as long-term complications of cardiovascular disease and diabetes for both mother and baby. PE cause is ambiguous (7, 8). The only currently known treatment is delivery and placental abruption at the same time as the fetus, with accurate monitoring of patient for up to 72 hours after delivery. Moreover, preeclampsia could result in further complications for baby and mother. The mother might later create conditions including stroke, cardiovascular disease, and chronic hypertension, and the baby may suffer from limited growth effects, and later in life coronary heart disease, metabolic disorders including stroke and diabetes. High blood pressure disorders during pregnancy are the leading cause of death for mothers and infants worldwide and affect 2 to 10% of all pregnancies. These disorders are classified into various category and of these categories, preeclampsia is the most prevalent disease with an incidence of 40 to 60% in developing countries. Preeclampsia occurs in about 10% of pregnancies worldwide (9-11).

The pathogenicity of PE is associated with factors that the mother was involved with before pregnancy, including kidney disease, diabetes type 2, autoimmune diseases, chronic hypertension, and thrombophilic syndromes. Some other factors that elevate the PE risk include immune factors, maternal age, metabolic syndrome, insulin resistance, and nutrient deficiencies (calcium, antioxidants, and vitamins). The PE pathogenesis is affected by genetic and environmental factors. Studies show that preeclampsia is a two-stage disease. The first stage is associated with the formation of the defective placenta and failure to remodeling of the spiral artery, which leads to reduced blood flow, and as a result, the growing fetus's need for oxygen and nutrients is not met. Decreased oxygen supply results in placental ischemia and hypoxia, leading to the onset of the second stage. Placental ischemia is a condition that leads to threatens life for the fetus because it can lead to intrauterine growth restriction and death. Some conditions such as oxidative stress also releases inflammatory cytokines including IL-6, IL-1β, and TNF-α (12-14).

The association between levels of uric acid and preeclampsia has been described by several scientists. Uric acid is increased in preeclampsia and might involve in the disease pathogenesis. Preeclampsia is associated with placental hypoperfusion, which leads to ischemia in placenta and the placental factors release into the maternal circulation. These factors cause a systemic inflammation and vascular endothelial impairment. Also, the placental ischemia causes uric acid production. Symptoms of hyperuricemia before hypertension and proteinuria may indicate involvement of uric acid in pathogenesis of PE. In addition, it has been reported that kidney damage from the disease may lead to elevated levels of serum uric acid, which involves in the PE pathogenesis (11, 15). The aim of this study was to review the role of hyperuricemia in the pathophysiology of preeclampsia.

Relationship between preeclampsia and hyperuricemia

Uric acid in the liver is produced from purine-derived nutritional resources including fatty meats, seafood, fruit fructose, excess sugars, and consumption of alcohol due to genetic inhibition of the hepatic uricase enzyme and is oxidized to allantoin soluble in water. The kidneys have a dominant role in the excretion of uric acid and excrete about 70% of the daily urate production. This compound is present as a weak acid at physiological pH and most of it is decomposed in the blood and is filtered freely through the glomerulus, ie it enters the proximal

tube in its anionic form and is excreted. In humans, uric acid is usually completely reabsorbed, eventually leading to the excretion of about 10% of the filtered capacity. In humans, the lack of uricase enzyme and the existence of an actual reabsorption of urate in kidney result in higher levels of blood urate (11, 16). The biological synthesis of urate is caused by the xanthine oxidase (XO) activation. In preeclampsia, cytokines and oxidative stress induced by ischemia in placenta further stimulate the activity of this enzyme. This enzyme changes xanthine to urate by oxidants production, including superoxide anion. Plasma urate concentrations in humans (approximately 300 mM) are much higher than in other mammals. Therefore, impaired renal urate transport is thought to cause hyperuricemia, and decreased urate clearance is thought to lead to hyperuricemia, leading to gout, hypertension, cardiovascular disease, and subsequent preeclampsia (17, 18).

Hyperuricemia can be defined in many ways. In the physicochemical definition, hyperuricemia is described as a serum urate concentration more than 6.8 mg/dL. Uric acid, which is mainly synthesized in the liver, is released into the bloodstream, with only a small percentage (less than 4%) binding to proteins. Thus, most circulating urate is readily available for filtration in the glomerulus and for participation in a number of complex renal mechanisms. Additional studies have also confirmed that overproduction and decreased renal excretion of uric acid, alone or in combination, is the cause of hyperuricemia. Uric acid levels in non-pregnant women usually range from 0.3 to 6.0 mg/dL. Levels of uric acid in women are lower than in men due to the uricosuric function of estrogen. In pregnancy condition, both the developing fetus and the placenta involve in metabolism of purine. Amazingly, uric acid concentrations in pregnant women up to the twentieth week of pregnancy are 20 to 25 percent lower than in non-pregnant women. This reduction in the level of uric acid in the first trimester is due to hemodilution caused by an elevation in blood levels due to increased glomerular filtration and decreased proximal tubular reabsorption (11, 19).

In the second trimester, levels of uric acid fall as a result of elevated estrogen-related uricosuric activity. Nonetheless, in the third trimester, the levels of uric acid gradually increase and then return to normal due to increased fetal growth and decreased uric acid excretion. Impaired regulation of uric acid metabolism has been recognized as one of the clinical symptoms of PE and has been extensively studied since 1917. Studies have indicated a significant elevation in levels of uric acid in women with preeclampsia vs. usual pregnancies. There are several reasons for the increase in levels of uric acid in preeclampsia. As shown, vasoconstrictors including angiotensin II reduce renal blood flow, reduce urate secretion, and slow glomerular filtration rate, which in turn reduces excretion of uric acid. Second, PE is detected by poor trophoblast invasion, leading to exacerbation of hypoxia, and oxidative stress. Hypoxia induces the production of lactate, which inhibits the secretion of uric acid. As a result, increased uric acid retention increases sympathetic activity. Therefore, it reduces the function of the angiotensin system and increases the blood pressure in PE (11, 20).

In a hyperuricemia condition, nitric oxide is reduced in endothelial cells, leading to weak trophoblast invasion. Nitric oxide is a potent vasodilator that helps relax endothelial cells and migrate trophoblast cells into spiral arteries. The influence of urate on production of nitric oxide not only endangers placental arteries but also could impact arteries of mother. Decreased production of nitric oxide may also impact the endothelial cells function in the mother's arteries and cause vasoconstriction due to nitric oxide deficiency. This mechanism also indicates the role of hyperuricemia in the pathogenesis of PE. In preeclampsia, oxidative stress results in the metabolism of fetal DNA from urate by the xanthine oxidase. Xanthine oxidoreductase has two isoforms, xanthine dehydrogenase (XDH) and xanthine oxidase (XO) (Figure 1). XO isoform is toxic because it is responsible for the reactive oxygen species (ROS) formation. Whereas XDH is considered as the active form. PE intensification is predicted to be correlated with production of uric acid through XO. Whereas healthy pregnant women produce uric acid through XDH. Therefore, increasing uric acid levels are used as a factor in predicting PE (11, 21).

Uric acid also increases repair of endothelial cell by affecting the motility of endothelial precursor cells, which regenerate the endothelial lining of blood vessels. However, this just happens at normal uric acid concentrations. But hyperuricemia in PE might lead to a reduction in progenitor cells of endothelium due to

increased cell damage. The use of hyperuricemia as a diagnostic factor for PE is different in some studies. These studies suggest that PE occurs before hyperuricemia and may not be correlated with the disease pathogenesis. These studies suggest that kidney damage happens in preeclampsia and might result in elevated uric acid concentration. Because kidney damage is specified by endotheliosis of glomeruli, which slows down glomerular filtration and reduces renal blood flow, thereby reducing the excretion of uric acid. As a result, uric acid levels can be associated with glomerular endotheliosis. Uncertainty about whether hyperuricemia is a disease factor or a sign of preeclampsia has been examined. Using a lot of data, they concluded that an elevation in uric acid of serum at the beginning of the twentieth week of pregnancy may be considered as a maternal response and not a disorder-promoting factor. In one study, it was found that serum urate could not be a suitable predictor of early detection of preeclampsia (22, 23).

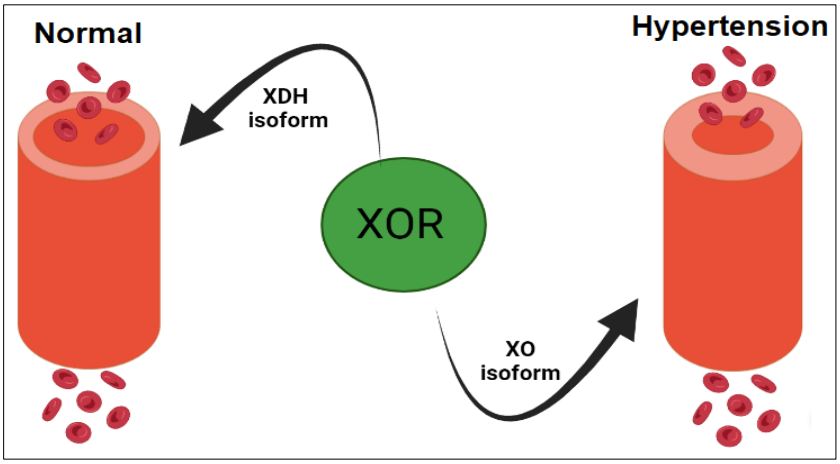


Figure 1. Two isoforms of XOR enzyme. The XO isoform results in ROS production and hypertension while the XDH isoform is the active form of XOR enzyme (24).

Uric acid as a preeclampsia biomarker

Uric acid is an identified biomarker for the ischemia of placenta, oxidative stress and kidney impairment (25, 26). Particularly, these are also properties of preeclampsia, which stimulate xanthine oxidase, which in turn triggers the production of uric acid. As a result, it leads to hyperuricemia (27). Uric acid is sometimes used as a biomarker, indicates an elevation in the levels of serum uric acid in preeclampsia vs. usual pregnancies, and suggests the levels of serum uric acid as a risk indicator for PE progression (11).

In addition, in a similar experiment, levels of serum uric acid were recorded in women with PE and women with usual pressure of blood (6.2±1.4 mg/dl in PE and 4.3±0.8 mg/dl in healthy pregnant women). The results of this experiment also suggest the application of uric acid as a PE predictor. Nevertheless, the uric acid application as a predictor of PE progression appears to have conflicting outcomes. Some studies have not shown significant differences in levels of serum uric acid in preeclampsia vs. usual pregnancies. In fact, although a substantial increase in levels of serum uric acid was reported in severe preeclampsia vs. usual pregnancies, no truly difference was observed between patients with mild preeclampsia compared to normal. Also, they reported that pre-eclamptic women with levels of uric acid above 6.0 mg/dL were at a higher risk for preterm delivery than pre-eclamptic women with uric acid levels below 6.0 mg/dL. Levels of uric acid above 5.5 mg/dL are diagnosed in women with preeclampsia and syndrome of HELLP and postpartum hemorrhage. Levels of uric acid above 7.8 mg/dL are powerfully associated with maternal mortality (11, 28).

Hyperuricemia is considered as a diagnostic and predictive factor of fetal condition in PE. Uric acid with a low molecular weight could pass from the placenta to the fetus, and has been shown to inhibit the growth of nephrons in the fetus. Studies have shown that women with hyperuricemia have babies before the 35th week of pregnancy with unfavorable fetal conditions. Approximately 56% of hyperuricemic women with had intrauterine death, intrauterine growth restriction, or both. It has also been reported that hyperuricemia has a

negative effect on fetal weight at birth. 72% of babies born to mothers with hyperuricemia are underweight at birth. Only 20% of these babies are at a healthy weight, whereas 62% of babies with usual levels of uric acid are normal at birth (11). In short, hyperuricemia occurs in early PE. As levels of uric acid increase at 10 weeks of gestation, glomerular endotheliosis may reduce uric acid secretion. It is noteworthy that the elevation in uric acid causes abnormal invasion of trophoblasts in preeclampsia. Uric acid is not the main source of the disorder. Nevertheless, hyperuricemia is associated with the severity of PE. In addition to being involved in the disease progression, hyperuricemia is also a valuable predictor of maternal and fetal status (29).

Protein factors involved in hyperuricemia

The interaction between genetic variations and environmental factors could clarify the progression of hyperuricemia and its involvement in gout and PE. One of the largest genomic studies in more than 110,000 Europeans and other races has identified 28 genetic loci associated with urate. These sites contain genes encoding uric acid transporter proteins in the kidneys and gastrointestinal tract that affect the reabsorption or excretion of uric acid. Some of these genes are SLC2A9, SLC22A6, SLC22A8, SLC22A11, SLC22A12, SLC16A9, SLC17A1, GCKR, LRR16A, ABCG2, and PDZK1. For example, the ATP binding cassette transporter, encoded by the ABCG2 gene, is a major transmitter of urate excretion and is positioned in the apical membrane in the proximal tube of the kidney. This gene encodes a transporter for urate in cells of the proximal tubule of the kidney and gastrointestinal tract and encodes a transporter of ATP, thus the existence of variations might have clinical consequences, increasing or decreasing the risk of hyperuricemia and gout. The ABCG2 gene has a high affinity and capacity for excretion of uric acid and is expressed in various tissues such as the intestines, kidneys, and liver. So, the polymorphism of this gene can result in reduced urate excretion and insufficient response to urate-lowering drugs, such as allopurinol (30-32).

Another sample is the SLC2A9, which encodes the GLUT9 vector with a high affinity for urate and is said to be strongly involved in the regulation of urate in the human body. This gene is chiefly expressed in the liver and kidneys, but can also be expressed in articular cartilage of human, and it has been reported that about 3.5% of changes in levels of serum uric acid are related to a variety of changes in this gene. The transfer of uric acid by GLUT9 is electrogenic and associated to the potential of membrane. GLUT9, along with ABCG2, OAT4, URAT1, and OAT10, is believed to be the most important carriers of uric acid. GLUT9 is an exception to the glucose transporter family, meaning that although it was originally used to transport fructose and glucose, its chief substrate is uric acid. Monosaccharides and other small carbon compounds are transported through cell membranes by glucose transporter proteins encoded by the SLC2 gene family. Membrane transporter GLUT9 (SLC2A9) differs from other members of the GLUT glucose transporter family (SLC2) due to its different substrate and sequence. A structural feature common to all members of the glucose transporters (SLC2 family) is the existence of 12 membrane helixes with cytoplasmic N- and C-terminal and an N-linked glycosylation region. GLUT9b and GLUT9a are two variants of the SLC2A9 gene that differ only in the 29 primary amino acid residues at the N-terminal. Excess glucose or fructose does not prevent uric acid transfer. In the proximal tube of the kidney, GLUT9 could transport urate through the basolateral membrane to the blood as part of the reabsorption procedure (16, 33).

Though other urate transporters in the renal system involve in homeostasis of urate, GLUT9 is functionally the most chief transporter of uric acid, so loss of function leads to renal hyperuricemia. Renal hyperuricemia is a common inherited disease specified by damaged reabsorption of renal urate, followed by low levels of serum urate, and is usually correlated with severe problems including acute renal failure. A mutation in the gene encoding URAT1, called SLC22A12, has been reported to cause renal hyperuricemia. However, in some renal hyperuricemic patients, no mutation in URAT1 is observed. This indicates the presence of another key urate transporter called GLUT9 in the human kidney. It has shown important genetic associations between the most important single nucleotide polymorphisms (SNPs) in the GLUT9 gene and urate concentrations. In addition, the presence of certain polymorphisms in this gene may increase the risk of hyperuricemia and increase serum

uric acid levels. For example, the rs734553 polymorphism (G> T) in this gene is correlated with an alteration in the affinity of GLUT9 transporter for urate transport. This type of polymorphism powerfully influences uric acid levels, especially in women. Another protein factor involved in uric acid transport is URAT1, which is encoded by the SLC22A12 gene and is existed on the apical side of the kidney. This carrier is responsible for most of the urea reabsorption from the kidneys and is the primary target of urate reduction treatments. Loss of activity in URAT1 causes hyperuricemia, indicating that URAT1 has a main role in regulating renal urate reabsorption. Cases with this disease show very low levels of serum urate, generally below 2.0 mg/dL (34-36).

GCKR is a gene that encodes a glucokinase-regulating protein. This protein factor is involved in the development of metabolic syndrome as well as in the regulation of triglyceride and glucose metabolism. Several studies have shown a correlation between the levels of uric acid and metabolic syndromes, including hypertension and insulin resistance, via the inflammatory pathway and oxidative stress. The presence of some polymorphisms in this gene is significantly correlated with increased levels of uric acid. Because this protein is involved in modulating metabolic activity, genetic changes in its genes may lead to metabolic heart disorders, including hyperuricemia and gout, as well as the symptoms of gestational diabetes and hypertension in pregnant women (37, 38).

Investigation of genetic polymorphism of uric acid transporter proteins

Hyperuricemia is affected by genetic factors as well as heredity. Genome association studies have recognized genes that control the serum concentration of urate. According to research, polymorphism of genes involved in uric acid metabolic pathways such as SLC and ABCG2 is associated with chronic kidney damage. In addition, this type of genetic variation affects the regulation of the levels of serum uric acid in humans. In a study, the association between 11 single-nucleotide polymorphisms of uric acid (LRP2, PDZK1, GCKR, ABCG2, SLC2A9, LRRC16, SLC17A3, SLC17A1, SLC22A12, SLC22A11, and SF1) and urate levels in the serum of the Chinese population was investigated. The schematic of these genes is summarized in Figure 2. According to the results of this study, 3 SNPs including SLC2A9 (rs11722228), GCKR (rs780094), and SF1 (rs606458) were associated with uric acid levels in men, while SLC2A9 (rs3775948) and SF1 (rs606458) are correlated with uric acid levels regardless of sex. Polymorphism in SLC22A12 is correlated with uric acid level in women. However, more studies are needed to clarify this effect. Researchers later identified a number of single nucleotide polymorphisms that affect uric acid levels, including SLC2A9, ABCG2, SLC17A1, and SLC22A11. They have a wonderful effect on the level of uric acid (39, 40).

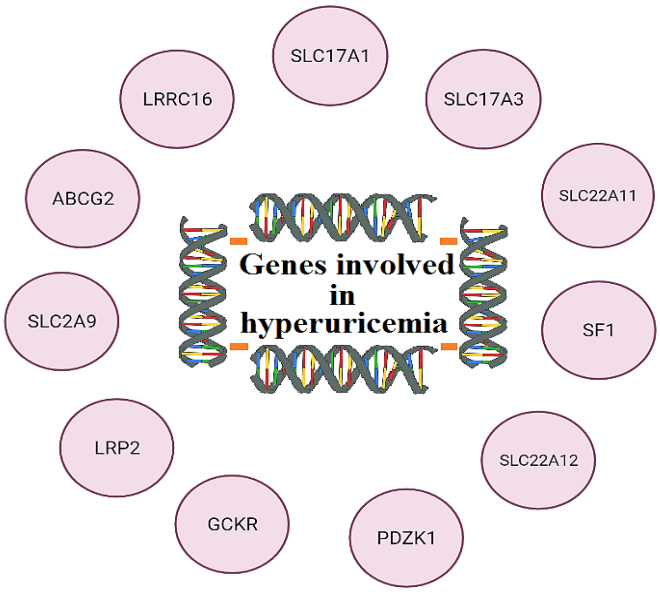


Figure 2. Genes involved in hyperuricemia. There are many genes involved in hyperuricemia including GCKR, PDZK1, LRP2, ABCG2, SLC2A9, SLC17A1, LRRC16, SLC22A12, SLC17A3, SLC22A11, and SF1 (41).

Also, in recent studies, a significant relationship in terms of rs1014290 polymorphism has been observed between the control group and the early onset preeclampsia (EOPE) group. These studies indicate that this variant is correlated with the EOPE pathogenesis. Early-onset of preeclampsia accounts for 20% of all PE patients and is possibly the leading cause of fetal and maternal mortality. Early-onset of preeclampsia has been reported to be more harmful to the fetus than the mother because it causes the weak placenta to form, leading to intrauterine growth restriction and subsequent infant death (41).

Conclusion

Hyperuricemia is correlated with the preeclampsia severity and outcome of fetal. Usually the high concentrations of uric acid in this disorder have been attributed only to the impaired kidney function. Preeclampsia is similarly specified by elevated ROS and increased oxidative stress. Xanthine dehydrogenase/oxidase is involved in the production of uric acid. This enzyme has two different isoforms in vivo. Production of uric acid is coupled with the ROS formation when the mentioned enzyme is in the form of oxidase. Some factors could elevate the activity of holoenzyme and the conversion of the enzyme to the form of oxidase. Preeclampsia is specified by hyperuricemia and signs of elevated creation of ROS and reduced antioxidants levels. There are some genes involved in the uric acid transport that may contribute in the hyperuricemia during PE. Alterations in the function of these genes might increase the risk of this disease.

References

1. Abbas-Al-Khafaji ZK, Aubais-aljelehawy QH. Evaluation of antibiotic resistance and prevalence of multi-antibiotic resistant genes among Acinetobacter baumannii strains isolated from patients admitted to al-yarmouk hospital. Cell Mol Biomed Rep 2021; 1(2): 60-68.
2. Almasian-Tehrani N, Alebouyeh M, Armin S, Soleimani N, Azimi L, Shaker-Darabad R. Overview of typing techniques as molecular epidemiology tools for bacterial characterization. Cell Mol Biomed Rep 2021; 1(2): 69-77.
3. Fathi A, Barak M, Damandan M, Amani F, Moradpour R, Khalilova I, Valizadeh M. Neonatal Screening for Glucose-6-phosphate dehydrogenase Deficiency in Ardabil Province, Iran, 2018-2019. Cell Mol Biomed Rep 2021; 1(1): 1-6.
4. Tourang M, Fang L, Zhong Y, Suthar RC. Association between Human Endogenous Retrovirus K gene expression and breast cancer. Cell Mol Biomed Rep 2021; 1(1): 7-13.
5. Azeez SH, Jafar SN, Aziziaram Z, Fang L, Mawlood AH, Ercisli MF. Insulin-producing cells from bone marrow stem cells versus injectable insulin for the treatment of rats with type I diabetes. Cell Mol Biomed Rep 2021; 1(1): 42-51.
6. Malik A, Jee B, Gupta SK. Preeclampsia: Disease biology and burden, its management strategies with reference to India. Pregnancy Hypertens 2019; 15: 23-31. https://doi.org/10.1016/j.preghy.2018.10.011
7. Armaly Z, Jadaon JE, Jabbour A, Abassi ZA. Preeclampsia: novel mechanisms and potential therapeutic approaches. Front Physiol 2018; 9: 973. https://doi.org/10.3389/fphys.2018.00973
8. Moser M. Working group report on high blood pressure in pregnancy. J Clin Hypertens 2001; 3(2): 75-88. https://doi.org/10.1111/j.1524-6175.2001.00458.x
9. Tikkanen M. Placental abruption: epidemiology, risk factors and consequences. Acta Obstet Gynecol Scand 2011; 90(2): 140-149. https://doi.org/10.1111/j.1600-0412.2010.01030.x
10. Cunningham Jr MW, LaMarca B. Risk of cardiovascular disease, end-stage renal disease, and stroke in postpartum women and their fetuses after a hypertensive pregnancy. Am J Physiol Regul Integr Comp Physiol 2018; 315(3): R521-R528. https://doi.org/10.1152/ajpregu.00218.2017
11. Khaliq OP, Konoshita T, Moodley J, Naicker T. The role of uric acid in preeclampsia: is uric acid a causative factor or a sign of preeclampsia?. Curr Hypertens Rep 2018; 20(9): 1-9.

12. Mol BW, Roberts CT, Thangaratinam S, Magee LA, De Groot CJ, Hofmeyr GJ. Pre-eclampsia. Lancet 2016; 387(10022): 999-1011. https://doi.org/10.1016/S0140-6736(15)00070-7
13. Staff AC, Fjeldstad HE, Fosheim IK, Moe K, Turowski G, Johnsen GM, Alnaes-Katjavivi P, Sugulle M. Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. Am J Obstet Gynecol 2020. https://doi.org/10.1016/j.ajog.2020.09.026
14. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. Annu Rev Pathol Mech Dis 2010; 5: 173-192. https://doi.org/10.1146/annurev-pathol-121808-102149
15. Al-Jameil N, Khan FA, Khan MF, Tabassum H. A brief overview of preeclampsia. Journal of clinical medicine research. 2014; 6(1): 1-7. http://dx.doi.org/10.4021/jocmr1682w
16. Witkowska K, Smith KM, Yao SY, Ng AM, O'Neill D, Karpinski E, Young JD, Cheeseman CI. Human SLC2A9a and SLC2A9b isoforms mediate electrogenic transport of urate with different characteristics in the presence of hexoses. Am J Physiol Renal Physiol 2012; 303(4): F527-F539. https://doi.org/10.1152/ajprenal.00134.2012
17. Many A, Hubel CA, Roberts JM. Hyperuricemia and xanthine oxidase in preeclampsia, revisited. Am J Obstet Gynecol 1996; 174(1): 288-291. https://doi.org/10.1016/S0002-9378(96)70410-6
18. Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in preeclampsia. Placenta 2008; 29: 67-72. https://doi.org/10.1016/j.placenta.2007.11.001
19. Punthumapol C, Kittichotpanich B. Serum calcium, magnesium and uric acid in preeclampsia and normal pregnancy. J Med Assoc Thai 2008; 91(7): 968-973.
20. Nair A, Savitha C. Estimation of serum uric acid as an indicator of severity of preeclampsia and perinatal outcome. J Obstet Gynaecol India 2017; 67(2): 109-118. https://doi.org/10.1007/s13224-016-0933-8
21. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol 2016; 213: 8-14. https://doi.org/10.1016/j.ijcard.2015.08.109
22. Jeyabalan A, Conrad KP. Renal function during normal pregnancy and preeclampsia. Front Biosci 2007; 12(1): 2425-2437. https://doi.org/10.2741/2244
23. Moran P, Lindheimer MD, Davison JM. The renal response to preeclampsia. Semin Nephrol 2004; 24(6): 588-595. https://doi.org/10.1016/j.semnephrol.2004.07.008
24. Bortolotti M, Polito L, Battelli MG, Bolognesi A. Xanthine oxidoreductase: One enzyme for multiple physiological tasks. Redox Biol 2021; 41: 101882. https://doi.org/10.1016/j.redox.2021.101882
25. Aziziaram Z, Bilal I, Zhong Y, Mahmod AK, Roshandel MR. Protective effects of curcumin against naproxen-induced mitochondrial dysfunction in rat kidney tissue. Cell Mol Biomed Rep 2021; 1(1): 23-32.
26. Hu J, Xu W, Yang H, Mu L. Uric acid participating in female reproductive disorders: a review. Reprod Biol Endocrinol 2021; 19(1): 1-1. https://doi.org/10.1186/s12958-021-00748-7
27. Lim KH, Friedman SA, Ecker JL, Kao L, Kilpatrick SJ. The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. Am J Obstet Gynecol 1998; 178(5): 1067-1071. https://doi.org/10.1016/S0002-9378(98)70549-6
28. Dekker GA, Sibai BM. Etiology and pathogenesis of preeclampsia: current concepts. Am J Obstet Gynecol 1998; 179(5): 1359-1375. https://doi.org/10.1016/S0002-9378(98)70160-7
29. Feig DI, Nakagawa T, Karumanchi SA, Oliver WJ, Kang DH, Finch J, Johnson RJ. Hypothesis: uric acid, nephron number, and the pathogenesis of essential hypertension. Kidney Int 2004; 66(1): 281-287. https://doi.org/10.1111/j.1523-1755.2004.00729.x
30. Karumanchi SA, Maynard SE, Stillman IE, Epstein FH, Sukhatme VP. Preeclampsia: a renal perspective. Kidney Int 2005; 67(6): 2101-2113. https://doi.org/10.1111/j.1523-1755.2005.00316.x
31. Lüscher B, Surbek D, Clemençon B, Huang X, Albrecht C, Marini C, Hediger M, Baumann M. Different Pharmacological Properties of GLUT9a and GLUT9b: Potential Implications in Preeclampsia. Cell Physiol Biochem 2019; 53(3): 508-517. https://doi.org/10.33594/000000154

32. Mueckler M, Thorens B. The SLC2 (GLUT) family of membrane transporters. Mol Asp Med 2013; 34(2-3): 121-138. https://doi.org/10.1016/j.mam.2012.07.001
33. So A, Thorens B. Uric acid transport and disease. J Clin Investig 2010; 120(6): 1791-1799. https://doi.org/10.1172/JCI42344
34. Xu L, Shi Y, Zhuang S, Liu N. Recent advances on uric acid transporters. Oncotarget 2017; 8(59): 100852-100862. https://doi.org/10.18632/oncotarget.20135
35. Xuan-Long YI, Jiang LI, Dong-Mei ME, Yan-Jun LI, Yan-Hong LI, Hong-Min MA, Ying YU, Shi-Chao XI. An intron variant of SLC2A9 increases the risk for type 2 diabetes mellitus complicated with hyperuricemia in Chinese male population. Iran J Public Health 2018; 47(6): 844-851.
36. Fernández-Torres J, Martínez-Nava GA, Oliviero F, López-Reyes AG, Martínez-Flores K, Garrido-Rodríguez D, Francisco-Balderas A, Zamudio-Cuevas Y. Common gene variants interactions related to uric acid transport are associated with knee osteoarthritis susceptibility. Connect. Tissue Res 2019; 60(3): 219-229. https://doi.org/10.1080/03008207.2018.1483359
37. Sanchez-Lozada LG, Rodriguez-Iturbe B, Kelley EE, Nakagawa T, Madero M, Feig DI, Borghi C, Piani F, Cara-Fuentes G, Bjornstad P, Lanaspa MA. Uric acid and hypertension: an update with recommendations. Am J Hypertens 2020; 33(7): 583-594. https://doi.org/10.1093/ajh/hpaa044
38. Li L, Zhang Y, Zeng C. Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. Am J Trans Res 2020; 12(7): 3167-3181.
39. Sun X, Zhang R, Jiang F, Tang S, Chen M, Peng D, Yan J, Wang T, Wang S, Bao Y, Hu C. Common variants related to serum uric acid concentrations are associated with glucose metabolism and insulin secretion in a Chinese population. PLoS One 2015; 10(1): e0116714. https://doi.org/10.1371/journal.pone.0116714
40. Tu HP, Chung CM, Min-Shan Ko A, Lee SS, Lai HM, Lee CH, Huang CM, Liu CS, Ko YC. Additive composite ABCG2, SLC2A9 and SLC22A12 scores of high-risk alleles with alcohol use modulate gout risk. J Hum Genet 2016; 61(9): 803-810. https://doi.org/10.1038/jhg.2016.57
41. Khaliq OP, Konoshita T, Moodely J, Ramsuran V, Naicker T. Gene polymorphisms of uric acid are associated with pre-eclampsia in South Africans of African ancestry. Hypertens Pregnancy 2020; 39(2): 103-116. https://doi.org/10.1080/10641955.2020.1741608

How to cite this paper:
Hassan Aubais Aljelehawy Q, Rahii Abed Almonem Alftlawy M, Alavi H. The role of hyperuricemia in the pathophysiology of preeclampsia. Cent Asian J Med Pharm Sci Innov 2022; 2(2): 37-45.