RESEARCH ARTICLE

MCM6 rs4988235 Allele G, *AGT* rs699 Allele C, *ACE* rs4343 Allele A, *FADS1* rs174547 Allele C, *DCHR7* rs12785878 Allele G, and *GC* rs7041 Allele T: Candidate Genes for Preeclampsia Prevention

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Abstract

BACKGROUND: Preeclampsia is the primary cause of maternal and neonatal morbidity and mortality; however, currently there is no definitive method exists to prevent preeclampsia. Recent findings indicate a possible genetic influence on preeclampsia. Therefore, this study was conducted to assess nutrigenomic patterns in preeclampsia as a potential mechanism for identifying appropriate preventive strategies through a nutrigenomic approach.
METHODS: This descriptive study focused on 15 primiparous pregnant women diagnosed with preeclampsia. The nutrigenomic test was performed using DNA microarray method to examine variant genes associated with food response and nutrient metabolites. The genetic tendencies were categorized as "low," "average," and "high." The frequencies of alleles and probabilities were assessed for gene variants expressing "high" and "low" genotypic tendencies.
RESULTS: The identified genetic variations were *MCM6* rs4988235 allele G that indicated lactose intolerance (allele frequency 100%), *AGT* rs699 allele C and *ACE* rs4343 allele A that were associated with sodium metabolism (allele frequency 82% and 90%, respectively), as well as *FADS1* rs174547 allele C that was pertained to omega metabolism (allele frequency 85%). Likewise, *DCHR7* rs12785878 allele G and *GC* rs7041 allele T were relevant for vitamin D (allele frequencies 82% and 77%, respectively). However, *MCM6* rs4988235 allele G, *FADS1* rs174547 allele C, *DCHR7* rs12785878 allele G, and *GC* rs7041 allele T had not been explicitly linked to preeclampsia.
CONCLUSION: *MCM6* rs4988235 allele G, *AGT* rs699 allele C, *ACE* rs4343 allele A, *FADS1* rs174547 allele C, *DCHR7* rs12785878 allele G, and *GC* rs7041 allele T are the dominant variant genes observed. The associations between preeclampsia and *AGT* rs699 allele C and *ACE* rs4343 allele A are consistent with other study.
KEYWORDS: preeclampsia, nutrigenomics, nutrition metabolism

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Introduction

Preeclampsia, a hypertensive disorder of pregnancy, is a complicated disease that can have devastating implications for both mother and fetus. One of the main causes of maternal and perinatal illness and mortality, it affects 2% to 8% of pregnancies.(1) Preventive strategies for preeclampsia have been extensively investigated over the past three decades. (2) Labor is the current management of preeclampsia; it is thought that terminating the pregnancy resolves most signs and symptoms; however, preeclampsia may persist after delivery and, in some cases, may develop in the postpartum period.(3) Notwithstanding the potential of aspirin and other emerging medicines for preeclampsia prevention, preeclampsia continues to be a significant contributor to

morbidity and mortality in both developed and developing nations.(1) Pharmacologic therapy for preeclampsia is limited due to contraindications for placenta and fetal development. This makes the possibility of manipulation and dietary interventions a promising method for preventing and treating preeclampsia.(4)

There is evidence to suggest that diet is a potentially significant factor in the development of preeclampsia. Recent studies have investigated the relationship between dietary patterns and preeclampsia risk; however, the findings of these studies may not be universally applicable. Consequently, comprehensive nutritional recommendations for the prevention of preeclampsia remain limited.(4)

A consistent, nutritious, balanced diet based on healthy eating standards is recommended for pregnant women to ensure adequate energy, nutrients, vitamins, and minerals. Guidelines underscore that a balanced diet should take precedence, with the possibility of administering supplements if necessary. Excess or lack of micronutrients can adversely affect health; thus, it is essential to ascertain the proper dosage for the individual context.(5)

The Human Genome Project is revealing how nutrition interacts with human's genes. Studies have shown that dietary components can influence specific genes, and these genetic variations may positively impact our health.(6) Individual differences in the response of dietary components to nutrient metabolism are determined by gene variation. Nutrigenetics and nutrigenomics are the basis of personalized nutrition, which is the main concept of personalized medicine. The emergence of nutrigenomics and nutrigenetics has rendered a universally applicable healthy diet obsolete. Human's genetic makeup dictates the dietary choices necessary for optimal health and longevity.(7,8) Investigations into nutritional therapy have been beneficial for cardiovascular disease, and it seems likely that dietary interventions may be helpful for preeclampsia both to the mother and to the fetus.(9)

The precise influence of genetic-environmental interactions on the risk and occurrence of preeclampsia is not fully understood; nevertheless, accumulating evidence indicates that a genetic component may contribute to the tendency for preeclampsia.(2) The severity of the risk associated with preeclampsia and the absence of a patented prevention method prompt the authors' interest in assessing nutrigenomic patterns in patients with preeclampsia as a potential mechanism for identifying suitable preventive strategies through a nutrigenomic approach. This study might serve as a preliminary investigation for subsequent research.

Methods

Study Design

This study was a descriptive study involving 15 cases of preeclampsia. Sampling was done by total sampling during July 2023 and April 2024. The inclusion criteria of the study were all primipara pregnant women who were diagnosed with preeclampsia and treated at Wahidin Sudirohusodo Hospital, Makassar, Indonesia. The diagnosis of preeclampsia was confirmed by the presence of particular hypertension, defined as systolic blood pressure of 140 mmHg or higher and diastolic blood pressure of 90 mmHg or higher, resulting from pregnancy, along with dysfunction of other organ systems or proteinuria (proteinuria >+1), acute kidney failure sign by creatinine >1.1 gr/dL; alanine transaminase (ALT) and or aspartate transaminase (AST) >40 Iu/ dL; or thrombocytes <100,000 cell/mm^3), occurring at a gestational age above 20 weeks.(10,11) Subjects with a history of systemic diseases such as Diabetes Mellitus, including Gestational Diabetes, cardiovascular disease, autoimmune disease, obstructive pulmonary disease, and smoking history were excluded from the study. Informed consents were obtained from all participating subjects, and the results of the nutrigenomic examination would be given to the research subject after the examination. The study was conducted following the Declaration of Helsinki and the protocol was approved by the Hasanuddin University Research Ethics Commission (Approval No. 7621UN4.6.4.5.31/PP36/2023).

Laboratory Data Collection

Laboratory examination results, including hemoglobin, leukocytes, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine were obtained from the subjects' medical record.

Nutrigenomic Test

The nutrigenomic test by Prodia Nutrigenomics (PNG) was performed using DNA microarray method to examine variant genes associated with food response and nutrient metabolites. The genomic assessment determined the taste perception, food response, nutrient metabolism, weight management, body composition, and exercise preferences and benefits based on over 75 single nucleotide polymorphisms (SNPs), offering actionable insights tailored to individual genotypes. The interpretation of the genetic tendencies were classified as "low," "average," and "high." "Low" and "high" represented genetic variants that might

affect the body's response to specific foods or nutrients, dependent upon the function of the enzymes regulated by the gene under exploration; while "average" represented the absence of genetic variation. Allele frequencies and probabilities were assessed for gene variants expressing "high" and "low" genotypic tendencies.

Genotype Analysis

DNA was extracted from 6 cc of whole blood in the cubital vein and stored in EDTA tubes at 2–8°C for 72 hours. The buffy coats were isolated which was achieved by centrifuging blood at 3000 rpm for 15 minutes at ambient temperature. Two-hundreds µL of buffy coat were transferred to a 1.5 mL microcentrifuge and continue with the DNA extraction protocol. DNA extracts were preserved at -70°C. DNA extract concentration was measured using the Qubit Fluorometer 3.0, following the Qubit dsDNA HS Assay Kit (Cat. No. Q32851; Invitrogen, Waltham, MA, USA) protocol. The DNA was amplified using the hybridization oven (Illumina, San Diego, CA, USA) and was set to a temperature of 37°C. The Hybex Microsample incubator (SciGene, Sunnyvale, CA, USA) was used to prepare DNA fragments and precipitate DNA. The pellets were dried for one hour at ambient temperature, followed by DNA resuspension utilizing the Illumina hybridization oven. The subsequent phase involved hybridization to BeadChip. The BeadChip imaging utilizes iScan Control Software (Illumina). The examination procedure was conducted within a biosafety cabinet classified as level 2.

Results

Clinical Characteristics

Among 15 subjects included in this study, the subjects were mainly in the age range between 20 and 35 years old, with a high school education level and above (diploma and bachelor's degree), and their body mass index (BMI) was primarily abnormal. The subjects mainly suffered from severe preeclampsia with systole blood pressure of more than 160 mmHg and diastole of more than 110 mmHg (Table 1). Laboratory parameters such as hemoglobin, leukocytes, platelets, liver, and kidney function were mostly normal. Fourteen subjects (93.3%) showed normal hemoglobin, ALT, urea, and creatinine levels. As much as 66.7% of subjects showed normal leucocytes, 86.7% of subjects showed normal platelets, and 53.3% of subjects showed normal AST levels (Table 2). Three subjects experienced an increase in AST and ALT accompanied by a decrease in platelet levels, which were the criteria for hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.

The Distribution of Genotypic Tendencies of Genes Related to Food Response and Nutrient Metabolism

This study evaluated genetic variants associated with alcohol, caffeine, gluten, lactose, sodium, whole grains, calcium, choline, iron overload, low iron status, omega profile, vitamin A, vitamin B12, vitamin B6, vitamin C, vitamin D, vitamin E, folate, antioxidants, liver detoxification, monounsaturated fat, saturated fat, and protein. Figure 1 demonstrated the distribution of nutritional pictures concerning genetic expression. A dominant genotypic polymorphism that impacts food response and the nutritional metabolism of lactose, salt, iron, omega fatty acids, vitamin D, folate, antioxidants, and oxidative stress was found in this study.

Gene Variant and Allele Frequencies

Table 3 illustrated the genetic variants in nutrients exhibiting pronounced genotypic tendencies, either high, average, or low. The allele frequencies and the probability of genetic variation in this investigation were presented in Table 4.

Lactose Intolerance

The *MCM6* rs4988235 allele G variant was linked to lactose metabolism and was associated with lactose intolerance. All subjects in this study had a high genetic predisposition for lactose intolerance and an increased risk of lactose

Table 1. Sample characteristics.

Variable	n (%)
Age	
<20	2 (13.3)
20–35	11 (73.3)
>35	2 (13.3)
BMI	
Underweight	4 (26.7)
Normal	1 (6.7)
Overweight	6 (40.0)
Obesity	4 (26.7)
Sistole	
140–160 mmHg	6 (40.0)
160–180 mmHg	7 (46.7)
>180 mmHg	2 (13.3)
Diastole	
90–110 mmHg	6 (40.0)
110–120 mmHg	9 (60.0)
>120 mmHg	0 (0.0)

Table 2. Laboratory parameters.

Variable	n (%)
Hemoglobin	
Normal	14 (93.3)
Anemia	1 (6.7)
Leukocytes	
Normal	10 (66.7)
Leukocytosis	5 (33.3)
Platelets	
Normal	13 (86.7)
Thrombocytopenia	2 (13.3)
AST	
Normal	8 (53.3)
Increased	7 (46.7)
ALT	
Normal	11 (73.3)
Increased	4 (26.7)
Urea	
Normal	14 (93.3)
Increased	1 (6.7)
Creatinine	
Normal	14 (93.3)
Increased	1 (6.7)

maldigestion. According to Hardy-Weinberg equilibrium (HWE), allele frequency was established at 100%, signifying a likelihood of occurrence in the population of 100%.

Sodium

All subjects demonstrated a significant genetic predisposition to heightened hypertension risk associated with elevated sodium intake. As per HWE, allele frequency for *AGT* rs699 allele C and *ACE* rs4343 allele A was 82% and 90%. Sixty-seven percent of those with the homozygous recessive form of the *AGT* rs699 allele C and 80% of those with the *ACE* rs4343 allele A were susceptible to hypertension.

Lower Serum Iron

This study's HWE calculations revealed that the frequency of homozygous recessive alleles for *TF* rs3811647 allele A was 13%, no subject showed *TFR2* rs7385804 allele C, and *TMPRSS* rs4820268 allele G was 40%. These genetic variations were related to iron metabolism. Individuals with genetic variations in this gene are predisposed to diminished blood iron levels. Thirteen subjects have shown a tendency for reduced iron levels in the bloodstream. Each gene exhibits a low allele frequency. The genotype tendency occurs when each gene exhibits the variant concurrently. In this study, only 1 subject suffered from anemia out of 14 people. In Indonesia, most pregnant received iron and folate supplement tablets routinely, so even though 13 subjects tended to experience low iron levels in this study; most did not suffer from anemia.

Omega

FADS1 encodes an enzyme that participates in the metabolism of omega-3 and omega-6 fatty acids. The *FADS1* rs174547 allele C elevated the risk of deficits in arachidonic acid (AA) and eicosapentaenoic acid (EPA), especially omega-3 and omega-6 fatty acids. All subjects

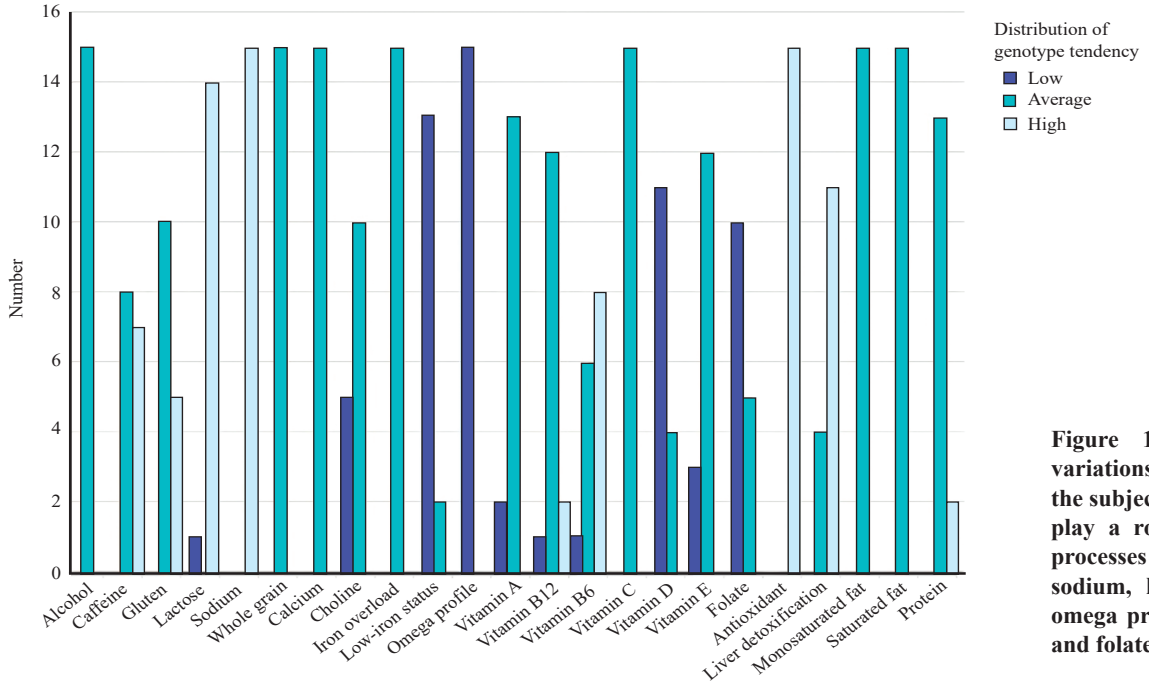

Figure 1. The genetic variations mainly found in the subjects are genes that play a role in metabolic processes for lactose, sodium, low iron status, omega profile, vitamin D, and folate.

Table 3. Genotype tendency.

Gen	Polymorphisms (SNPs)	Alleles	Nutrient and Food Response	Risk	Genotype Tendency Frequency [n (%)]		
					Low	Average	High
MCM6	rs4988235	G	Lactose	Lactose intolerance	0 (0.0)		15 (93.3)
AGT	rs699	C	Sodium	High blood pressure			15 (100.0)
ACE	rs4343	A					
TF	rs3811647	A	Iron	Lower serum iron	13 (86.7)	2 (13.3)	
TFR2	rs7385804	C					
TMPRSS6	rs4820268	G					
FADS1	rs174547	C	Omega profile	Lower blood levels of AA and EPA	15 (100.0)		
DHCR7	rs12785878	G	Vitamin D	Lower vitamin D levels in the blood	11 (73.3)	4 (26.7)	
CYP2R1	rs10741657	G					
GC	rs7041	T					
	rs4588	A					
MTHFR	rs1801131	C	Folate	Lower folate level in blood	10 (66.7)	5 (33.3)	
	rs1801133	T					
MnSOD	rs4880	C	Antioxidant	Reduced oxidative stress			15 (100)
GPX1	rs1050450	T					
CYP1B1	rs1056836	G	Oxidative stress	Good liver detoxification		4 (26.7)	11 (73.3)
COMT	rs4680	A					
GSTP1	rs1695	A					

had a genotype associated with low activity, demonstrating a genetic predisposition that heightens the risk of diminished AA and EPA levels in the bloodstream. The allele frequency of the *FADS1* rs174547 allele C was 73%, with a probability of recessive allele frequency of 85%.

Vitamin D

Eleven subjects exhibited a genetic predisposition to vitamin D insufficiency. Probability of *DHCR7* rs12785878 allele G, *CYP2R1* rs10741657 allele G, *GC* rs7041allele T and was 67%, 7%, 60%, consecutively, and no found for *GC* rs4588 allele A. The allele frequency of *DHCR7* rs12785878 allele G was 82%, *CYP2R1* rs10741657 allele G was 26%, *GC* rs7041allele T was 77%, and no for *GC* rs4588 allele A.

Folate

Ten of the subjects exhibited a genotypic propensity to decrease folate levels. The probability of homozygote recessive for *MTHFR* rs1801131 allele C and *MTHFR* rs1801133 allele T was 7% with a frequency of 26%, respectively. Individuals with variations in both alleles showed a genotype tendency to experience folic acid deficiency and, therefore, require more folic acid intake than individuals who did not show these two elements.

Antioxidant

The *MnSOD* rs4880 allele C and *GPX1* rs1050450 allele T were linked to reduced enzyme activity, increasing oxidative stress. All subjects in this study had a propensity for increased enzyme activity, diminishing the risk of oxidative stress. No variant gene was identified in both the *MnSOD* rs4880 C allele and the *GPX1* rs1050450 T allele.

Liver Detoxification

The detoxification process was disrupted by the G allele of *CYP1B1* rs1056836, the A allele of *COMT* rs4680, and the G allele of *GSTP1* rs1695 due to oxidative stress reactions. Eleven subjects demonstrated increased activity in this study, suggesting efficient liver detoxification. No frequency of homozygote recessive for *CYP1B1* rs1056836 allele G and *COMT* rs46489 allele A in this study, while the *GSTP1* rs1695 allele G was 26%, and probability for homozygote recessive for *GSTP1* rs1695 allele G was 7%.

Discussion

Nutrigenomics relies on two aspects of the paradigm, characterized as an applied science within nutritional

Table 4. Allele frequency and probability.

Variable	Allele Frequency		p		
	Dominant (%)	Recessive (%)	Dominant	Carrier	Recessive
Lactose intolerance					
MCM6 rs4988235 allele G	0	100	0	0	1
Sodium					
AGT rs699 allele C	18	82	0.03	0.3	0.67
ACE rs4343 allele A	10	90	0.01	0.19	0.80
Low iron status					
TF rs3811647 allele A	64	36	0.41	0.46	0.13
TFR2 rs7385804 allele C	100	0	1	0	0
TMPRSS rs4820268 allele G	37	63	0.14	0.46	0.40
Omega profile					
FADS1 rs174547 allele C	15	85	0.02	0.25	0.73
Vitamin D					
DHCR7 rs12785878 allele G	18	82	0.03	0.30	0.67
CYP2R1 rs10741657 allele G	74	26	0.55	0.38	0.07
GC rs7041allele T	23	77	0.05	0.35	0.60
GC rs4588 allele A	100	0	1	0	0
Folate					
MTHFR rs1801131 allele C	74	26	0.55	0.38	0.07
MTHFR rs1801133 allele T	74	26	0.55	0.38	0.07
Antioxidant					
MnSOD rs4880 allele C	1	0	1	0	0
GPX rs1050450 allele T	1	0	1	0	0
Liver detoxification					
CYP1B1 rs1056836 allele G	1	0	1	0	0
COMT rs4680 allele A	1	0	1	0	0
GSTP1 rs1695 allele G	74	26	0.55	0.38	0.07

Hardy-Weinberg Equilibrium (HWE) = p2+2(pq)+q2=1. p: probability.

pharmacology, considering genetic polymorphism and clinical experience, utilizing microarray technology, and integrated into an informatics platform from the perspective of molecular biology. A healthy phenotype may develop chronic illnesses due to gene expression alterations, leading to protein and enzyme activity modifications. Chemicals consumed through food directly or indirectly influence gene expression, indicating that nutrition can transform healthy phenotypes into pathological ones, from commencement to severe stages.(12)

The interesting result of this study was the high frequencies for *MCM6* rs4988235 allele G gene related to lactose intolerance. Literature clarified that undigested lactose in the small intestine undergoes fermentation, resulting in an eightfold increase in short-chain fatty acid (SCFA) production in the large intestine. SCFAs are the primary metabolites of the gut microbiota. Research on the correlation between human genetic variation and the microbiota has repeatedly identified a link between the LCT-13'910:C/T SNP (rs4988235) and the presence of *Bifidobacterium*. Such interactions may be beneficial as SCFAs generated from the microbial fermentation of lactose have a role in immunological control and glucose and lipid balance. SCFAs typically suppress immunological and inflammatory pathways, such as blocking nuclear factor kappaB (NF-kB).(13) SCFA is a reliable biomarker for the early detection of preeclampsia. SCFA levels are elevated in preeclampsia compared to non-preeclampsia.(14) Another

study reported that the prevalent genetic feature of the European C/T = 13,910 polymorphism correlated with elevated BMI, but it did not correlate with hypertension. They pointed out differences in results between observational studies and the use of Mendelian randomization.(15) Further research is needed to evaluate the association between lactose intolerance and preeclampsia risk.

A systematic study reported that no evidence was found that advice to reduce sodium intake during pregnancy has a beneficial effect in preventing or treating preeclampsia or any other outcome. Sodium consumption during pregnancy should remain a personal choice.(16) The Indonesian Society of Obstetrics & Gynecology recommendations state that restriction of salt consumption has no benefit in preventing preeclampsia and its complications.(10) The angiotensinogen enzyme (AGT) encoded by the *AGT* gene comprises the Renin-Angiotensin-Aldosterone system (RAAS), which effectively controls blood pressure and is related to cardiovascular function. A Meta-analysis study reported that *AGT* rs699 polymorphism was significantly associated with hypertension. Angiotensin-converting enzyme (ACE) is a crucial enzyme in the RAAS system and is required for electrolyte balance and blood pressure regulation. This gene indicates that individuals will be sensitive to sodium through the RAAS system. Individuals with AG or AA variants of the *ACE* gene will have a significant risk of experiencing increased blood pressure when consumed excessively.(17,18) The research based on data from the UK Biobank that the rs5051 C > T and rs699 A > G polymorphisms exhibit a robust association with systolic blood pressure in black participants, showing an impact size four times greater than that seen in white people.(19) Research in the Iranian population showed that the *ACE* rs4343 G allele polymorphism frequency was significantly higher in the preeclampsia group compared to normal pregnancies.(20) In this study, all subjects showed a high genotype tendency to have a risk for elevated blood pressure and high frequency for the *ACE* rs4343 allele A. Therefore, the recommended sodium restriction in pregnant women at risk should not be applied in general and must be re-evaluated.

Previous observational studies showed inconsistent findings regarding the association between iron levels and preeclampsia/eclampsia. Research suggests a correlation between increased iron levels and an elevated risk of preeclampsia/eclampsia, likely due to oxidative stress associated with excess iron. Conversely, additional studies indicate that iron deficiency could contribute to endothelial dysfunction and oxidative stress linked to preeclampsia. Studies using SNPs from Genome-wide Association Studies GWAS datasets reported no genetic association between iron status and preeclampsia. However, it is stated that the results obtained do not rule out the existence of a relationship between the two at other mechanistic levels.(21) Research into African ethnicity correlating the *TMPRSS* rs4820268 polymorphism with preeclampsia yielded inconclusive results; still, the heterozygous allele was more prevalent in preeclampsia patients. This study evaluated a distinct allele variant compared to our study.(22) In this study, it was found that most of the subjects showed a genotype tendency to have low iron status. The highest allele frequency in this study was the *TMPRSS* rs4820268 allele G.

Certain types of fatty acids, particularly omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), may play a role in the development of preeclampsia. Omega-3 PUFAs have anti-inflammatory and antioxidant properties that could potentially reduce the risk of preeclampsia. A diet high in docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) was associated with a lower risk of preeclampsia. However, no similar link was found between the overall intake of fatty acids, saturated fatty acids (SFAs), and monounsaturated fatty acids (MUFAs) and the risk of preeclampsia.(23) The contents of alpha-linolenic acid (ALA), EPA, DHA, omega-3, gamma linoleic acid (GLA), AA, dihomo gamma-linolenic acid (DGLA), omega-6, and oleic acid in erythrocyte measures were considerably diminished in preeclampsia relative to the control group.(24) *FADS1*, a constituent of the fatty acid desaturase (FA) gene family, encodes the delta-5 desaturase (D5D) enzyme, which facilitates the conversion of linoleic acid (LA) and ALA into AA and EPA. All subjects in this study showed the presence of variant C at SNP rs174547, indicating that they are at risk of low blood levels of AA and EPA. Thus, consideration of omega-3 and omega-6 supplementation for pregnant women's health deserves attention. There was no research linking *FADS1* rs174547 allele C with preeclampsia or hypertension in pregnancy.

Recent studies have thoroughly examined the association between vitamin D insufficiency and adverse pregnancy outcomes. A notion suggests that vitamin D deficiency may elevate the risk of preeclampsia, gestational diabetes mellitus, cesarean delivery, and bacterial vaginosis during pregnancy. Diminished vitamin D levels in pregnant women diagnosed with preeclampsia or those at risk for the condition. Nevertheless, specific investigations have demonstrated no disparity in vitamin D levels

between preeclamptic individuals and those with normal pregnancies.(5) One study performed candidate marker analysis to identify the genetic effects of common SNPs in the vitamin D metabolic system on circulating 25(OH) D in a multi-ethnic sample. The four markers selected for this analysis were rs12785878 (*DHCR7)*, rs4588 (*GC*), rs10741657 (*CYP2R1*), and rs2228570 (*VDR*). The results obtained showed different distributions of alleles between ethnic groups. Maori ethnicity, European ethnic groups/ other ethnic groups showed similar variations for SNPs rs4588, rs12785878, and rs10741657. However, there were consistent differences in 25(OH)D across the four ethnic groups, with South Asians having the lowest 25(OH)D. Based on the four markers, the lowest are rs12785878 and rs4588. These results follow those reported by studies in Kuwait, India, and Bangladesh.(25) A study on a European ethnicity revealed no consistent evidence of relationships between the three genetic risk scores and gestational hypertension or preeclampsia in the two cohorts. This study utilized single nucleotide polymorphisms in genes related to vitamin D production (rs10741657 and rs12785878) and metabolism (rs6013897 and rs2282679) as instrumental variables. There was weak evidence of a connection between an increased copy number of the 25-hydroxyvitamin D risk allele in rs2282679 and preeclampsia.(26) In this current study, eleven subjects showed a genotype tendency to have a risk for impaired vitamin D metabolism and a tendency to have low vitamin D blood levels, and the most allele frequencies were *DHCR7* rs12785878 allele G and *GC* rs7041allele T.

The Folic Acid Clinical Trial (FACT) found that taking high doses of folic acid after the first trimester did not prevent preeclampsia or other related problems for mothers and babies. This suggests that there is no benefit to taking high doses of folic acid after the first trimester for women at risk of preeclampsia. Therefore, the recommendation to take high doses of folic acid after the first trimester should be stopped. The search for effective treatments and strategies to prevent preeclampsia should continue.(27) The potential of folic acid supplementation to mitigate the risk of preeclampsia has been assessed, with results contingent upon dosage, length of administration, and the patient's ethnic origin. Consequently, additional case-control studies must be undertaken to elucidate the significance of folic acid supplementation in preventing preeclampsia.(28) The current study's results show that more subjects have genetic variations that play a role in folic acid metabolism, thus requiring additional folic acid intake. The results are consistent with the study in the Bai population of Yunnan, that *MTHFR* C677T (rs1801133) and *MTHFR* A1298C (rs1801131) polymorphisms are essential determinants of hypertension susceptibility. Thus, it is concluded that folate supplementation is vital to prevent and treat hypertension in the region.(29) The tendency genotype in this study showed a risk of low folate in the blood of 10 subjects. However, allele frequencies were low for *MTHFR* rs1801131 allele C and *MTHFR* rs1801133 allele T. This results might need additional investigation.

Oxidative stress produces reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl radicals. These molecules can damage the structure and function of DNA, RNA, and proteins. High levels of free radical molecules are thought to contribute to the pathogenesis of preeclampsia.(9) In hypertensive situations, excessive oxidative stress enhances vascular stiffness and promotes vascular smooth muscle cell adhesion, expediting endothelial deterioration. *MnSOD*, in particular brain areas, has been demonstrated to have antihypertensive effects by scavenging mitochondrial superoxide anions. Research on animals revealed that reduced levels of *MnSOD* in the brain's subfornical organ (SFO) compared to peripheral tissues dramatically elevated systemic mean arterial pressure and heightened the suppressive response, exacerbating angiotensin II (AngII)-induced hypertension.(30) *GSTP1* rs1695 and *GPX1* rs1050450 SNPs did not influence the risk of preeclampsia in the Han Chinese population.(31) Compared to controls, the increased frequency of the TC/ CC genotype of *MnSOD* rs4880 and the CT genotype of rs1050450 polymorphism in Iranian preeclampsia patients suggests these variants' involvement in preeclampsia susceptibility.(32) This syudy findings indicated no variants for *MnSOD* rs4880 and *GPX1* s1050450, suggesting elevated antioxidant enzyme activity in all patients, indicating a reduced necessity for supplementary antioxidants compared to the general population. Elevated antioxidant enzyme activity in the body suggests a reduced requirement for supplementary antioxidant consumption compared to the general population. Antioxidant enzyme supplements, tailored to individual requirements and administered routinely, necessitate additional assessment in cases of preeclampsia.

In preeclampsia patients, localized placental damage arises from an imbalance between angiogenic and anti-angiogenic factors. This leads to systemic inflammation, endothelial activation, systemic oxidative stress, and alterations in developing endothelial nitric oxide radical sites. The activation and malfunction of the vascular endothelium in the liver, kidneys, brain, and placenta

exacerbate the clinical manifestations of preeclampsia. (33) Liver failure and rupture may arise as complications of preeclampsia due to microcirculatory impairment and hepatic necrosis.(1) A Norwegian cohort study observed no association between the two studied *COMT* SNPs and non-recurrent preeclampsia. However, a significant overrepresentation of the wild-type allele (Val (G)), not the low activity allele (Met (A)), of the Val108/158Met polymorphism (rs4680) was observed in the group of women with recurrent preeclampsia. (34) In this study, no G allele of *CYP1B1* rs1056836 or A allele of rs4680 *COMT* and G allele of *GSTP1* rs1695 were identified, thus indicating a predisposition to impaired detoxification in the liver is low due to their capacity to reduce the consequences of severe oxidative stress. No research has linked *CYP1B1* rs1056836 to the occurrence of preeclampsia.

This study had small sample size and had no of a control group to compare it with normal pregnancy. This study also did not evaluate the dietary patterns of the patients. So, the results obtained in this current still need to be explored further, especially concerning ethnic tribes in our region.

The genes *AGT* rs699 allele C and *ACE* rs4343 allele A, which play a role in sodium metabolism, were found to be dominant in this study. Further exploration needs to be undertaken, especially to evaluate the guidance that salt restriction is unnecessary to prevent preeclampsia. The *MCM6* rs4988235 G allele gene that plays a role in lactose intolerance is an interesting thing that we found in this study. These results are new and still need further exploration. Based on our results, personalized nutrition should be the focus of research to reduce the risk of preeclampsia by conducting a study with a larger sample and comparing it with pregnant women who do not have preeclampsia.

Conclusion

The dominant variant genes discovered were the *MCM6* rs4988235 allele G, *AGT* rs699 allele C, *ACE* rs4343 allele A, *TMPRSS* rs4820268 allele G, *FADS1* rs174547 allele C, *DCHR7* rs12785878 allele G, and *GC* rs7041 allele T. No research has explicitly evaluated the connection of the *MCM6* rs4988235 allele G with preeclampsia, nor with the *FADS1* rs174547 allele C, *DCHR7* rs12785878 allele G, and *GC* rs7041 allele T. But the correlations between preeclampsia and *AGT* rs699 allele C and *ACE* rs4343 allele A are consistent with findings from other countries.

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Authors Contribution

DSR prepared the research proposal, collected samples, processed data, and prepared the manuscript. IS and EL participated in sample collection and assisted in manuscript preparation.

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