ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2024, Volume 13, Number 1: 581-591
P-ISSN.2089-1180, E-ISSN: 2302-2914

Preliminary study: the future insight of relationship between nutrigenomic risk and sepsis

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ABSTRACT

Introduction: In field observations, we frequently encountered cases of sepsis at a young age and rarely in older individuals. Most cases are caused by a bacterial infection, which causes pneumonia that progresses to septic shock. There are several possible causes of infection and subsequent septic shock. Among these, certain genetic code abnormalities cause disturbances in nutrient metabolism, which facilitates the emergence of infections. This study aimed to explore the nutrigenomic patterns in patients with septic shock.

Methods: Nutrigenomic examination was performed at the General Academic Hospital in Surabaya, Indonesia, to determine the micronutrient genotype risk in patients with septic shock. We compared cases of septic shock with control groups containing normal subjects to identify a unique pattern in the nutrigenomic results between these two groups. DNA testing was in collaboration with Nutrigenme, using saliva and buccal swabs. The data were analyzed using the chi-square test and all statistical analyses were performed using the R statistics software.

Results: The results of the saliva testing demonstrated that there was an endurance ultra-risk category (PGC1a, rs8192678; genotype GG) in the control group; however, this category was not observed in the case group. In addition, the genomic risk of vitamin C was elevated in the septic shock group (Group A) but was typical in the control group (Group B).

Conclusion: We observed a deletion in GSTT1 rs2266633 in the sepsis group, which may play a role in the development of sepsis. Furthermore, we discovered that the control group exhibited an ultra-type risk for endurance, suggesting that the ability to extract oxygen and frequent exercise may play a role in limiting disease development.

Keywords: Nutrigenomic, septic shock, vitamin C, genotype risk.

Cite This Article: Veterini, A.S., Semedi, B.P., Airlangga, P.S., Rejeki, P.S., Firdaus, K.M., Mutiar, A., Adi, A.C., Sumara, R., Meirawan, R.F. 2024. Preliminary study: the future insight of relationship between nutrigenomic risk and sepsis. *Bali Medical Journal* 13(1): 581-591. DOI: 10.15562/bmj.v13i1.4994

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Received: 2023-10-02
Accepted: 2023-12-30
Published: 2024-01-25

INTRODUCTION

Diet is one of the most fundamental environmental factors that play a role in maintaining health and preventing diseases, with a myriad of nutritional properties that affect energy supply, regulatory functions, and structural roles, and starts from early neonatal life.[1,2] In recent years, omics approaches, including genetic, epigenetic, and gut microbiome analyses, have been incorporated into nutrition research, providing a comprehensive understanding of molecular nutrition studies. Food has been studied not only from a chemical perspective, but also from the perspectives of nutrigenomics, whereby metabolites produced by food oxidation modulate gene expression directly, and nutri-epigenomics, where nutrition plays a role in epigenetic remodelling.[3,4] However, inter-individual differences (i.e., genetic variability) and environmental exposures (e.g., physical activity, drugs, food pesticide residues) contribute to the development of a plethora of multifaceted effects.[5] For these reasons, understanding the molecular effects of food on human health is an ambitious but promising goal, which could strongly impact dietary choices, where not only food composition but also the nutrigenomic and nutri-epigenomic effects are considered.[6,7]

The basic elements of nutritional genomics include the following: (1) Diet is the main predisposing factor for several diseases in some individuals under certain conditions. Similar to saturated fat-containing foods, cardiovascular disease or CVDs should be avoided. (2) Dietary entities and nutrients alter gene structure or gene expression and, subsequently, the human genome. Diet provides several precursors, such

as methionine, folate, choline, betaine, and vitamins B2, B6, and B12, that are essential for the synthesis of S-Adeno-sylmethionine (SAM), which acts as a universal methyl donor during methylation; reduced availability of methyl donors result in low SAM synthesis and global DNA hypomethylation, and vice versa. (3) Genetic variants among individuals can explain the equilibrium between health and disease. Several genotypes/haplotypes that confer more susceptibility to a specific disease have been explored for various diseases. (4) Genes that rely on dietary factors for their regulation may play a role in the initiation, advancement, and progression of chronic diseases. These last elements of nutrigenomics have certain ethical barriers that hinder exploration in human subjects; however, *in vivo* mouse studies have proven that miR-483-3p plays a role in the development of type 2 diabetes and the regulation of metabolic health, and in obese subjects, it is responsible for the deposition of more fat in the adipose tissue.[8,9]

Based on some of the objectives of nutrigenomic examination, as stated above, we aimed to explore the nutrigenomic pattern of patients with septic shock. The types of diagnoses were reviewed based on the nutrigenomic patterns and whether there was a match between the type of disease and the risk level of the micronutrient genotype.

METHODS

This research was conducted after obtaining ethical approval from Dr. Soetomo General Academic Hospital (approval number:0425/KEPK/V/2022). We did a case control study in this research, with 6 subjects for each group. We do not use a large number of samples due to funding limitations provided. The study was conducted at Dr. Soetomo General Academic Hospital, with the inclusion criteria for the case group being as follows: male; aged 17 – 50 years; non-traumatic sepsis; the patient had recently been (within 24 h) admitted to the resuscitation room. The exclusion criteria were as follows: cancer; chronic kidney failure; head tumors; history of diabetes. The cases of septic shock were compared to the control groups (normal subjects) to identify a unique nutrigenomic pattern between the two groups. DNA testing was performed using saliva samples from the control group and buccal swabs from the case group (most of the sepsis patients were unconscious). DNA testing was performed using the Oragene-One ON 600 DNA collection kit (Product by Kalbe Industries manufactured in Canada) at the University of Toronto Nutrigenomic Laboratory in collaboration with Nutrigenme). The results of the nutrigenomic examination were compared in terms of distribution patterns, and the peculiarities of the two groups were examined. Statistical analysis of the relationship, correlation, and odds ratio (OR) was performed using open-source R statistics 4.0.3 version software. The sample size of each group was six.

The basis for selecting the gene along with the rs number in Table 1 is the result of a literature study which proves that certain genes contribute to sepsis.

Table 1 lists the components that were chosen for genotype examination in patients with sepsis, as these components may be related to the patient's response to the therapy administered during treatment in the ICU. For instance, many of these components may be related to the responses to drugs, nutrition, and respiratory muscle rehabilitation.

A risk analysis was conducted for certain genotypes using the above DNA data. The risk category are classifield as 7 category : typical (average population health) is normal or for control, elevated means that it increases towards a negative risk (for example, the emergence of a disease or tissue damage), medium means that the risk is slightly above typical but below elevated, low means it decreases in a negative direction (the opposite is elevated, for example, the ability of an enzyme to physiological activity has decreased), diminished means it decreases in a positive direction (the opposite is enhanced, for example, the amount of energy burned during an important process / resting metabolic rate is lower than the general population), enhanced means it increases towards a positive risk (for example, exercising can significantly increase HDL levels in the blood), ultra means that it increases above enhanced (genetically already has higher muscle endurance than the general population), high means slightly below ultra (requires regular exercise efforts to gain muscle endurance -muscle). Risk analysis was conducted for certain genotypes using the DNA data.

The classification of research subjects to be included in one of the above categories is based on the nutrigenomic examination database owned by the company NutriGEN-ME (supported by Nutrigenomix). The reference to these words is based on the research literature on their respective characteristics and SNPs. This literature study provides data on people with certain SNP variations that cause interference with certain gene traits so that in simplification the vocabulary is made unique (for wild type), high, medium, low, reduced, enhanced, ultra, and high (variants other than Wild-type).[16] In addition, recommendations are based on evidence-based scientific research that has been reviewed by experts in their fields that we have mentioned above (basic explanation of gene selection in Table 1).

Data analysis

The results of the nutrigenomic examination of each sample generated data in the form of gene and risk variants for each participant. The data were analyzed using the Chi-square test, with a particular focus on the pattern of distribution. Chi-square (X^2) analysis was used to examine the distribution pattern. The R statistic was used to conduct the statistical analysis. Statistical analysis was performed using open-source R statistics 4.0.3 version software.

RESULTS

The 12 subjects examined in this study (six per group) are depicted in Figure 1 using a bar plot.

The red bars indicate the individuals in the case group (A) and the blue bars indicate the individuals in the control group (B). Bar plots group show the number of the subjects for the 12 subjects studied (6 cases and 6 controls). The reason why we just chose 3 risk categories in this bar plot is based on the observation of the raw data which was the results of the risk category were typical and elevated dominantly and follow to risk category low to be in deficiency condition.

Based on the results in Figure 1, we observed no differences in the genomic risk of certain components between groups A (case) and B (control). The proportion of both the "elevated" and "typical" categories was more or less the same for all components. However, with regard to the genomic risk of vitamin C, we found that group A (case) tended to be "elevated", while group B (control) tended to be "typical". We visualized the distribution patterns using a Sankey Diagram, as shown in Figure 2.

Figure 2 represents the distribution patterns and categories for each component in groups A (case) and B (control). The patterns between the two groups did not exhibit significant differences. The results indicated that the caffeine component was included in the typical category in both group A (case) and group B (control). This was followed by other components, such as exercise behaviour, saturated eating, sugar preference, and total fat. The most prominent difference between the two groups was that the endurance component was not included in the ULTRA category in the case group, and more components were included in the typical category in the case group than in the control group. Furthermore, the saturated and unsaturated fat components in the control group were the most dominant in the enhanced category compared to those in the case group.

All participants in the control group were in good health and had no comorbidities. The ages of the control group are shown in the below table:

Data Analysis

This study aims to determine the differences in body mass index (BMI), age, and genotype among patients with sepsis and patients without sepsis. The

Table 1. Gene names and rs numbers corresponding to the different nutrition components

Groups	Component	Gene, rs Number	References
Nutrient Metabolism	Vitamin A	BCMO1, rs11645428	10
	Vitamin B_{12}	FUT2, rs601338	11-14
	Vitamin C	GSTT1, rs2266633	15
	Vitamin D	CYP2R1, rs10741657	16-19
		GC, rs2282679	20
	Vitamin E	COMT, rs4680	21-23
	Folate	MTHFR, rs1801133	24–27
	Choline	MTHFD1, rs2236225	28,29
		PEMT, rs12325817	30
	Calcium	GC, rs7041	16,20,31
		GC, rs4588	16,20
Food Intolerances and Sensitivities	Iron Overload	SLC17A1, rs17342717	32
		HFE, rs1800562	33
		HFE, rs1799945	34
		TMPRSS6, rs4820268	32,35
	Low Iron Status	TFR2, rs7385804	32,36
		TF, rs3811647	36
	Lactose	MCM6, rs4988235	37
	Gluten	HLA, rs2395182	38
		HLA, rs7775228	39
		HLA, rs2187668	40
		HLA, rs4639334	41
		HLA, rs7454108	42
		HLA, rs4713586	42
Cardiometabolic Health	Caffeine	ADORA2A, rs5751876	43
	Caffeine	CYP1A2, rs2472300	44,45
	Glycaemic Index	TCF7L2, rs12255372	46–52
	Sodium	ACE, rs4343	29,53,54
	Omega-6 and Omega-3 Fat	FADS1, rs174547	55–57
	Physical Activity	LIPC, rs1800588	58,59
	Physical Activity	FTO, rs9939609	60,61
		ADRB2, rs1042713	62
Weight Management and Body Composition	Energy Balance	UCP1, rs1800592	63
	Protein	FTO, rs9939609	60,61
	Total Fat	TCF7L2, rs7903146	46,47,52
	Saturated Fat	APOA2, rs5082	64
	Saturated and Unsaturated Fat	FTO, rs9939609	60,61
	Monounsaturated Fat	PPARγ2, rs1801282	65

Groups	Component	Gene, rs Number	References
Eating Habits	Fat Taste Perception	CD36, rs1761667	66–68
	Sugar Preference	GLUT2, rs5400	69
	Eating between Meals	MC4R, rs17782313	70
	Motivation to Exercise	BDNF, rs6265	71
	Exercise Behaviour	CYP19A1, rs2470158	72,72
		LEPR, rs12405556	73
Exercise Physiology, Fitness and Injury Risk	Power and Strength	ACTN3, rs1815739	74–77
		NFIA-AS2, rs1572312	78
	Endurance	ADRB3, rs4994	79
		NRF2, rs12594956	80,81
		GSTP1, rs1695	82
		PGC1a, rs8192678	83
	Muscle Damage	ACTN3, rs1815739	74,75,84–86
	Pain	COMT, rs4680	23,87
	Bone Mass	WNT16, rs2707466	88,89
	Achilles Tendon Injury	COL5A1, rs12722	90–92

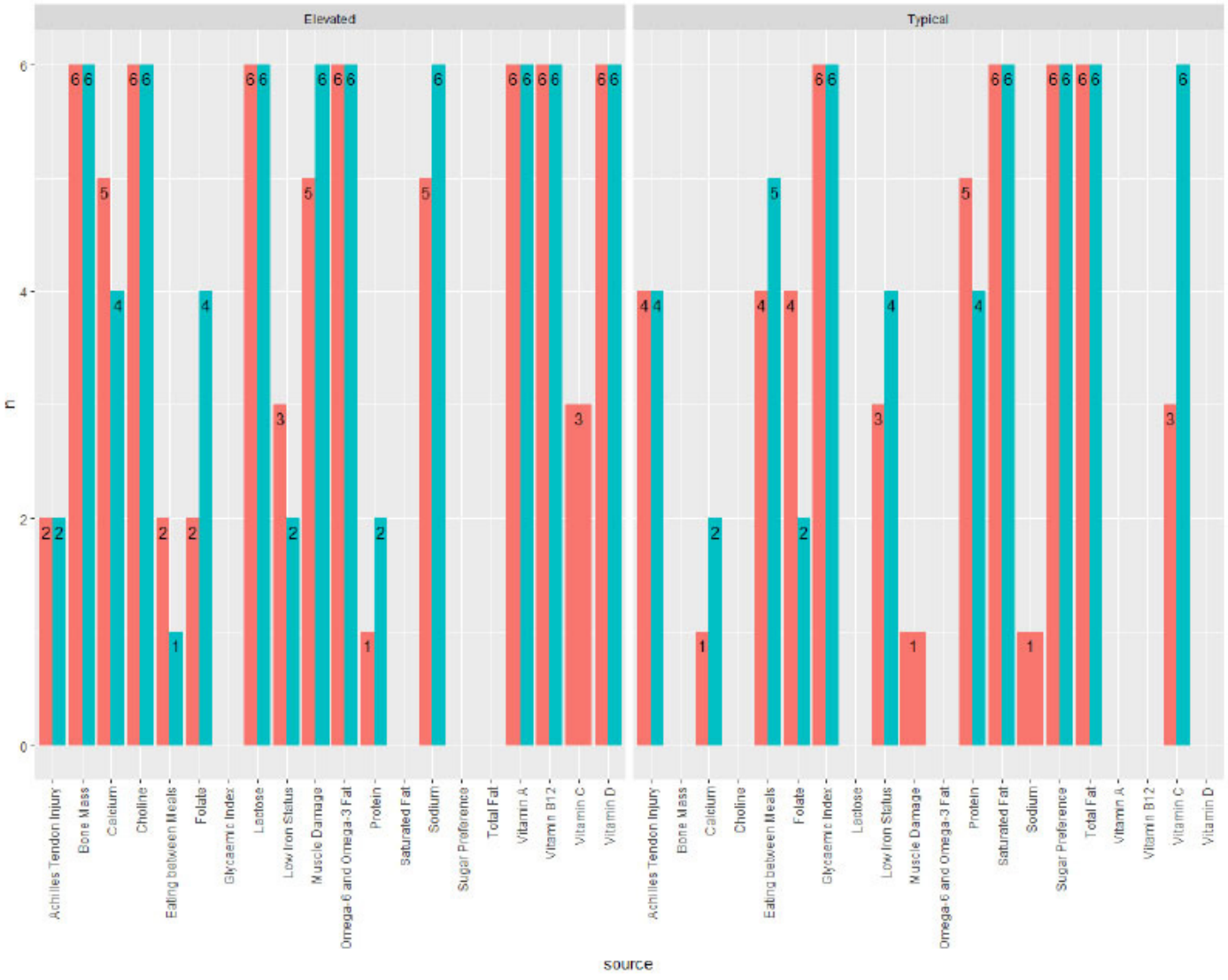

Figure 1. Bar plot for the 12 subjects studied (six cases and six control).

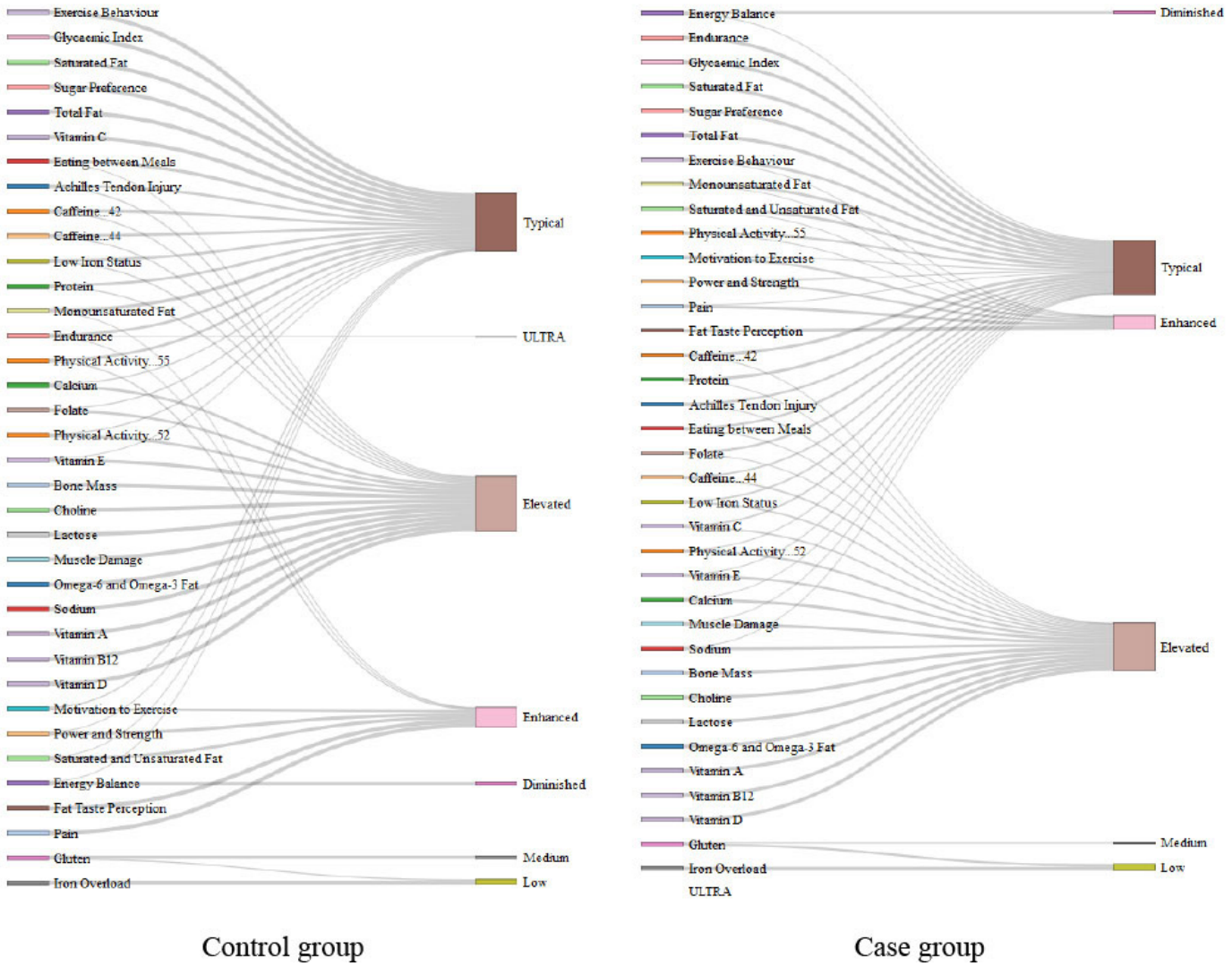

Figure 2. Distribution pattern depicted using a Sankey Diagram. The line thickness of the Sankey diagram depicts the distribution strength.

Table 2. The diagnoses of the subjects in the case group

Number	Diagnosis	BMI	Age
1	Meningoencephalitis bacterial differential diagnosis of viral	22.2	37 y.o
2	Liver abscess pro laparotomy exploration	17.3	22 y.o
3	Cellulitis surface hand Dextra	22.6	61 y.o
4	Pneumonia post-cardiac arrest	24.1	32 y.o
5	Abscess submandibular post needle aspiration + pneumonia	24.2	36 y.o
6	Meningoencephalitis Tuberculosis post External Ventricular Drainage Kocher Dextra	20.7	28 y.o

analysis used to conclude the differences is a statistical test. Descriptive statistical tests are used to determine the mean value in parametric data. That is data on age and BMI variables. In genotype variables, there are several categories of genes. Namely typical, elevated, medium, enhanced, low, and ultra. Descriptive statistical tests were performed to determine the proportion of each genotype category in each variable, both in the group of patients who had sepsis and without sepsis.

Inferential statistical tests were used to determine the differences in age, BMI, and genotype between the two groups of patients. An Independent T statistical test was used to determine the difference in age and BMI in both groups of patients. Because the age and BMI variables are variables with parametric data scales. Chi Square statistical test is used to determine the presence of genotypes among patients who have sepsis and do not have sepsis.

In this study, the level of accuracy used was 95%. So, the α value is 0.05. Differences in age, BMI, and genotype between the two groups, based on statistical p values below 0.05 ($p < \alpha$). The results of tabulations and statistical tests of all variables are presented in Table 1.

The results of the analysis showed no difference in age and BMI between the group of patients who had sepsis and the group of patients who did not have sepsis. The results of statistical analysis for all genotype variables also showed no significant differences between the two groups of patients.

Table 3. The diagnoses of the subjects in the control group

Number	History of illness	BMI	Age
1	No co-morbidities	21.7	36 y.o
2	No co-morbidities	22.9	37 y.o
3	History of arrhythmia	23.7	45 y.o
4	No co-morbidities	22.4	24 y.o
5	History of renal stone	24.1	47 y.o
6	No-comorbidities	23.7	39 y.o

Table 4. Analysis result

Variable	Group of Patients		p
	Sepsis	Without Sepsis	
BMI (mean)	21.85	23.03	0.30
Age (mean)	36	38	0.76
Vitamin C			
Typical	3	6	0.18
Elevated	3	0	
Vitamin E			
Typical	2	1	1.00
Elevated	4	5	
Folate			
Typical	4	2	0.56
Elevated	2	4	
Calcium			
Typical	1	2	1.00
Elevated	5	4	
Low			
Low Iron Status			
Typical	3	4	1.00
Elevated	3	3	
Gluten			
Medium	4	2	0.56
Low	2	4	
Caffeine			
Typical	5	4	1.00
Elevated	1	2	
Sodium			
Typical	1	0	1.00
Elevated	5	6	
Physical Activity			
Typical	2	2	1.00
Elevated	4	4	
Energy Balance			
Typical	2	1	1.00
Diminished	4	5	
Protein			
Typical	5	4	1.00
Elevated	1	2	
Saturated & Unsaturated Fat			
Typical	5	1	0.08
Enhanced	1	5	
Monosaturated Fat			
Typical	5	5	
Enhanced	1	1	1.00

However, it should be noted the genotype of vitamin C, saturated and unsaturated fat, and endurance. In the vitamin C genotype, it is known that there are differences in the proportion of genotype categories between the two groups of patients. It is known that all patients in the group that did not have sepsis or the control group, had genotypes in the typical category. In the group of patients who had sepsis, 50% (3) of patients had genotypes in the elevated category. This suggests that there is a hypothesis that vitamin C genotypes in the elevated category are associated with sepsis incidence.

In the analysis of saturated and unsaturated fat genotypes, it is known that there are differences in the proportion of typical and enhanced genotype categories. It is known that 84% (5) of patients with sepsis have saturated and unsaturated fat genotypes in the typical category. In contrast, 84% (5) of patients with no sepsis had saturated and unsaturated fat genotypes in the enhanced category. This finding assumes that unsaturated and unsaturated fat genotypes in the enhanced category are associated with the prevention of sepsis.

In endurance genotype analysis, there are differences in the proportion of enhanced and ultra-category genotypes. In the group that did not have sepsis, there was one patient with the enhanced genotype category and one patient in the ultra category. This shows that the factors associated with the prevention of sepsis are endurance genotypes in the enhanced and ultra categories.

In the study, the total number of observations was 12 patients. This number is very limited, to be able to reveal a meaningful relationship between age, BMI, and genotype with sepsis incidence. More in-depth studies with a greater number of observations are needed to strengthen the findings and hypothesis that genotype factors associated with sepsis incidence are vitamin C, saturated and unsaturated fat, and endurance.

Variable	Group of Patients		p
	Sepsis	Without Sepsis	
Eating Between Meals			
Typical	4	5	1.00
Elevated	2	1	
Motivation to Exercise			
Typical	2	2	1.00
Enhanced	4	4	
Exercise Behaviour			
Typical	5	6	
Enhanced	1	0	1.00
Power & Strength			
Typical	2	1	1.00
Enhanced	4	5	
Endurance			
Typical	6	4	0.30
Enhanced	0	1	
Ultra	0	1	
Muscle Damage			
Typical	1	0	1.00
Elevated	5	6	
Pain			
Typical	1	0	1.00
Enhanced	5	6	
Achilles Tendon Injury			
Typical	4	4	1.00
Elevated	2	2	

DISCUSSION

Nutrigenomics is an upcoming area of science with the potential to provide new insights into health and disease management. Until recently, a generalized approach towards health and disease management has been employed in the health sector, in which human genetics and its respective environment are considered; nevertheless, in this contemporary approach, nutrition and its interaction with the human genome hold a focal position.

Working towards illness prevention to lower the cost of disease management and drug development is urgently needed due to the ever-growing global population. Therefore, a diet tailored to an individual's needs based on DNA analysis could be useful, as opposed to a generalized plan that only addresses a small number of health issues. Nutrigenomics and nutrigenetics are intended to achieve the long-standing goals of health and disease management with the help of diet rather than external means so that humans can have an overall improved quality of life.[93,94] Appropriate scientific research in this area is crucial to achieve this goal.

In the present study, we focused on identifying the patterns of certain genes that are affected by nutrients and daily activities before an individual falls into a state of sepsis. The results of our study indicated a specific pattern in the control and case groups. Interestingly, we identified muscle endurance as a key component in the control group; however, this was not observed in the case group. This raises the question of whether regular exercise will reduce the risk of sepsis if someone has an infection. The hypothesis that we put forward is that a person with ultra features on muscle endurance will have a higher cell hypoxia threshold compared to an untrained person. In addition, supporting immune cells will work in balance.

This result suggests that someone with high muscle endurance is less likely to develop sepsis. An explanation for this would be the higher oxygen extraction, longer blood transit time, and increase in homogeneous perfusion in endurance-trained subjects when compared to untrained subjects at the same workload. These changes may be associated with improved exercise efficiency in endurance-trained individuals.[95] In the control group, the majority of subjects had normal BMI's and were more diligent in exercising. Furthermore, when someone experiences conditions that require a lot of oxygen, people with an ultra-model may be more resistant to hypoxic conditions and infections. Unfortunately, our research is still preliminary, in this study only 1 subject was found with features of ultra muscle endurance, so we cannot conclude very strongly that ultra features are a genetic factor that can trigger sepsis or not. The good thing about this study is that 5 out of 6 control group people don't have the ultra category, but they have very good and regular exercise habits. Oxygen consumption (VO_2 max) is an important indicator of cardiorespiratory health.

Some statements that support our hypothesis in the previous paragraph are as follows: The VO_2 level refers to the amount of oxygen consumed by the body to perform physical activities or organ functions over a certain period. A higher VO_2 is usually associated with better health.[96] Oxygen extraction is the process by which oxygen is absorbed from the blood by the body's tissues and is facilitated by the difference in the partial pressure of oxygen between the blood and body tissues. A higher oxygen extraction rate indicates that the body tissues are more effective at absorbing oxygen from the blood. Immunity is the body's ability to fight infections and diseases. Several types of immune cells work together to combat pathogens. There is significant evidence suggesting that high levels of VO_2 and oxygen extraction can increase the effectiveness of the immune system in fighting infections.[97] Several studies have shown that regular physical exercise can increase the VO_2 max and oxygen extraction, which in turn, increases the effectiveness of the immune system in fighting infections.[98]

Our results also demonstrated that the genomic risk of vitamin C was elevated in the case group but tended to be typical in the control group. Given that Vitamin C cannot be produced by the human body, and thus must be acquired through

food, then there is a risk of disruption of vitamin levels in a person's body in the condition of one of the genetic code variations that support the utilization of vitamins. Vitamin C, also known as l-ascorbic acid, is a water-soluble vitamin and a potent non-enzymatic antioxidant.[99] In healthy adults, the generally accepted serum ascorbic acid level is approximately 0.4 mg/dL.[100] Additionally, it has been demonstrated that ascorbic acid levels are decreased in critically ill patients, which may be related to the progression of organ failure and mortality.[101,102]

Further research needs to be done after this study, to prove the effect of genetic code variations on serum vitamin C levels and the body's ability to utilize vitamin C. Ascorbic acid is concentrated intracellularly via the active transport of sodium-dependent vitamin C transporter 2, particularly in leukocytes and neurons. Due to the elevated levels of oxidative stress during inflammation, transporters are activated, lowering the serum ascorbic acid levels. Vitamin C levels have been reported to be frequently low in acute illnesses including myocardial infarction, acute pancreatitis, and sepsis.[103-106] Our results suggest that a risk of vitamin C deficiency may occur due to the inability of cells to optimize vitamin C consumption owing to the predominance of the deletion type of the GSTT1 genetic code rs2266633. We discovered that three of the six cases in the sepsis group were included in the deletion category, while all of the patients in the control group were included in the insertion category.

Genetic variation of Vitamin C insertion involves the addition or insertion of DNA sequences that impact the synthesis of vitamin C in the human body. Individuals with this genetic insertion lack the ability to produce vitamin C naturally, leading to impaired synthesis of ascorbic acid. Consequently, those with this insertion may need to supplement their vitamin C intake through food or supplements. Vitamin C gene insertion can occur naturally through mutations or via genetic manipulation. On the other hand, the Vitamin C deletion gene refers to the removal of specific DNA sequences necessary for vitamin C synthesis. Similar to individuals with the gene insertion, those with this gene deletion are unable to produce vitamin C naturally. The absence of these DNA sequences hampers the body's ability to synthesize ascorbic acid. Therefore, individuals with gene deletion may also require additional vitamin C intake to meet their daily needs. Vitamin C gene deletion can occur through genetic mutations or genetic manipulation, resulting in the partial or complete loss of the vitamin C gene from the human genome. This loss impairs the body's capacity to produce or convert the necessary chemicals for vitamin C synthesis.[107-110]

Based on the explanation above, deletion and insertion of the vitamin C genome in humans seem to have the same effect on the body's ability to produce vitamin C. But will the existence of these two genetic types provide a different therapeutic response in administering vitamin C supplements from outside the body? It is necessary to carry out clinical trials on both groups of genetic variations of vitamin C in humans. However, we believe two types of genetic variation in vitamin C will affect vitamin C utilization in different pathways, possibly affecting human physiological or pathological response pathways. When this veil is opened, it may be possible to determine how many grams of vitamin C dose are appropriate for these various genetic conditions.

In response to the varying results associated with high-dose IV vitamin C, we attempted to investigate it from a nutrigenomic perspective. The GSTT1 gene encodes proteins for the glutathione S-transferase family of enzymes. These enzymes play a fundamental role in the utilization of vitamin C. Our study found that six subjects in the control group had one type of insertion genomic variant in the GSTT1 gene. At the same time, the case group had three deletions and three insertion genomic variant characteristics for GSTT1. Each enzyme generally has one of two existing GSTT1 variants. Variants of this gene affect vitamin C use in the body. The effect is still an unresolved subject, as previously explained.

In this preliminary investigation, we observed a unique pattern in nutrigenomic descriptions between the control group and the case group to determine the micronutrient genotype risk in patients with septic shock. This study had certain limitations. First, due to the small sample size, we were unable to analyze the effect of the GSTT1 deletion variant on the risk of sepsis and the outcomes. However, this type of deletion may contribute to an unfavourable clinical response. Second, a larger sample size was required to determine the ultra-pattern of endurance. We hope that further research with a larger sample size will be conducted in this area to determine the ultra-pattern of endurance and believe that this research may help clinicians in providing more personalized medicine.

CONCLUSION

Our nutrigenomic examinations of patients with sepsis provided useful information for the management of patients in the ICU. We observed a deletion in GSTT1 rs2266633 in the sepsis group, which may play a role in the development of sepsis. Furthermore, we discovered that the control group exhibited an ultra-type risk for endurance, suggesting that the ability to extract oxygen and frequent exercise may play a role in limiting disease development.

CONFLICTS OF INTEREST

The authors declare that have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ETHICAL CONSIDERATIONS

This experimental study received ethical approval from the ethics committee of Dr. Soetomo General Academic Hospital (ethics No.: 0425/KEPK/V/2022). Informed consent was obtained for this experimentation with human subjects. The privacy rights of human subjects must always be observed.

FUNDING

The source of funding for this research came from Dr Soetomo General Academic Hospital. The role of the funding agency in this research was to provide financial support for research implementation such

as purchasing materials/reagents, lab tests, and interpretation.

AUTHORS' CONTRIBUTION

ANN responsible for concept and design of the study, manuscript preparation. BPS responsible for definition of intellectual content and data acquisition. PSA responsible for literature search. PSR responsible for manuscript preparation. KID responsible for clinical studies and experimental studies. AIR responsible for data acquisition and manuscript editing. ACA responsible for data acquisition and manuscript review. RSU and RIZ responsible for data analysis and statistical analysis.

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