INTERNATIONAL ISLAMIC MEDICAL JOURNAL

IIMJ VOLUME 4 | NUMBER 2 | PAGE 1 – 83 | JUNE 2023

PRINT
ISSN 2176-2370
ESSN 2616-2389
ONLINE

Address: Jl. Raya Jemursari No. 67 Surabaya, East Java
e-mail: iimj@unusa.ac.id

International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Intracerebral Hemorrhage-Grading Scale (ICH-GS) Score as a Prognosis Prediction of Spontaneous Intracerebral Hemorrhage at Rumah Sakit Islam Surabaya Jemursari

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DOI : 10.33086/iimj.v4i2.4153

ARTICLE INFO

Keywords:
ICH-GS Score, Intracerebral hemorrhage, prediction of prognosis

Submitted:
April 19th 2023
Reviewed:
April 24th 2023
Accepted:
May 28th 2023

ABSTRACT

Background: Spontaneous intracerebral hemorrhage or hemorrhagic stroke is one of the leading causes of mortality and disability in Indonesia, but until now there is no specific therapy for this disease. The intracerebral hemorrhage (ICH) score is a widely used predictive tool for the prognosis of death 30 days after spontaneous intracerebral hemorrhage, but the intracerebral hemorrhage-grading scale (ICH-GS) score has a more specific interval to assess the prediction of the prognosis after intracerebral hemorrhage. Rumah Sakit Islam (RSI) Jemursari Surabaya has not carried out data collection related to the ICH-GS score with the outcome (death) of patients with spontaneous intracerebral hemorrhage, especially while still receiving hospital treatment.
Objective: To identify the number of ICH-GS scores in patients with spontaneous intracerebral hemorrhage as a predictor of prognosis at RSI Jemursari Surabaya.
Method: The type of this research is retrospective research. The population comprised of all patients with spontaneous intracerebral hemorrhage hospitalized at RSI Jemursari Surabaya in 2017-2019, with affordable population of all patients with spontaneous intracerebral hemorrhage diagnosed by a neurologist.
Results: The data showed that 5.5% (6 people) had an ICH-GS score of 5; 38.2% (42 people) had an ICG-GS score of 6; 21.8% (24 people) had an ICH-GS score of 7; 20 % (22 people) had an ICH-GS score of 8; 5.5% (6 people) had an ICH-GS score of 9; 4.5% (5 people) had an ICH-GS score of 10; 3.6% (4 people) had an ICH-GS score of 11; and 0.9% (1 patient) had an ICH-GS score of 12.
Conclusions: The results of the ICH-GS score can be used to facilitate communication both with fellow health workers and with the patient's family. Trend of the data showed that ICH-GS score is not consistent in showing the prognosis of spontaneous intracerebral hemorrhage (the smaller the ICH-GS score should have better prognosis than the higher score), while the information based only on volume and location can predict the prognosis more consistently`.

Introduction

Stroke is said to be a catastrophic disease because it has a broad impact on the economy and society. The 2018 Basic Health Research (Riskesdas) stated that the prevalence of stroke was 10.9 per mile with the highest prevalence in East Kalimantan Province (14.7 per mile) and the lowest in Papua Province (4.1 per mile). Data from the Healthcare and Social Security Agency

(BPJS) in 2016 showed that stroke cost health care costs of 1.43 trillion rupiahs. Data from the same source in 2017 showed an increase to 2.18 trillion rupiahs and it reached 2.56 trillion rupiahs in 2018 (Ministry of Health, 2019).

Stroke is a disease that affects the arteries leading to and within the brain. A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either blocked by a clot or ruptured blood vessels which result in the brain not being able to get the oxygen and nutrients it needs so that the brain cells die (ASA, 2021).

Data from the Indonesia Stroke Registry in 2012-2013 showed 20.3% of deaths in the first 48 hours after stroke (Anindhita and Wiratman, 2014, pp. 452). Stroke is the number 1 cause of death in Indonesia (Sulistyowati, 2017). In the United States, stroke is the 5th leading cause of death and the most common cause of disability (ASA, 2021).

At least 1 in 5 cases of stroke is related to obesity, 1 in 10 cases is related to smoking, 1 in 4 cases is due to insufficient consumption of fruits and vegetables, and 1 million cases are related to excessive alcohol consumption. There are >50% of stroke cases related to high blood pressure, 1 in 4 cases is related to high LDL levels, and 9% of cases occur due to irregular heart rhythms (Sulistyowati, 2017).

A stroke can be caused by a clot that blocks the blood flow to the brain (ischemic stroke) or by a ruptured blood vessels that block the blood flow to the brain (hemorrhagic stroke) (ASA, 2021). There are 2 types of hemorrhagic stroke, namely intracerebral hemorrhage or subarachnoid hemorrhage (ASA, 2021). Hemorrhagic stroke occurs in 10-15% of stroke cases, with an incidence rate of 24.6 per hundred thousand people each year (Ziawi and Carhuapoma, 2018).

Although the data suggest that stroke has an economic burden and a high mortality rate, intracerebral hemorrhage still has no specific therapy. The financial impact of intracerebral hemorrhage that has been highlighted is that although patients have a long stay in the intensive care unit, intracerebral hemorrhage still has a high mortality after 30 days of bleeding. If the patient survives, severe disability can occur (Ziawi and Carhuapoma, 2018).

Accurate prediction of intracerebral hemorrhage outcome is important in distinguishing patients who require special care or who might receive the benefits from a particular therapeutic strategy. Several scales for predicting mortality due to intracerebral hemorrhage have been developed, suggesting that the intracerebral hemorrhage (ICH) score is the mostreliable scoring system for predicting 30- day mortality in different populations and

clinical settings; yet mortality during hospitalization is also required. Therefore, the intracerebral hemorrhage-grading scale score (ICH-GS score) is calculated for prediction of outcome after intracerebral hemorrhage based on evaluations performed at the time the patient came to the hospital (Sandoval et. al., 2006).

Rumah Sakit Islam (RSI) Jemursari Surabaya is the only type B hospital in Wonocolo District, Surabaya. The researcher has conducted a research on the profile of patients with hemorrhagic stroke before conducting this study, and found that there were no records of ICH score or ICH-GS score in the patient's medical records and there were problems with telephone numbers that could no longer be contacted when the researcher would contact the numbers listed in the medical records. The existence of the 2019 corona virus (COVID-19) pandemic did not allow the researcher to visit the addresses listed in the medical records so that the observation of the ICH-GS score was only based on the data obtained when the patients were hospitalized. The existence of research on the ICH-GS score as a predictor of the prognosis of intracerebral hemorrhage can help health workers to be alert and bridge communication between health workers or between health workers and patients' families in the management of intracerebral hemorrhage.

Objective

To identify the number of ICH-GS scores in patients with spontaneous intracerebral hemorrhage as a predictor of prognosis at RSI Jemursari Surabaya.

For specific objective is to identify the characteristics of patients with spontaneous intracerebral hemorrhage at RSI Jemursari Surabaya based on theGlasgow Coma Scale, age, bleeding volume via head computed tomography (CT), location (infratentorial/supratentorial), and the presence or absence of intraventricular hemorrhage.

Significance of Research

Theorical significance of this research is to identify the characteristics of patients with spontaneous intracerebral hemorrhage at RSI Jemursari Surabaya. Practical significance of this research is to make the results of this study as a communication facilitator usage, both with fellow health workers and with the patient'sfamily.

Methods

The type of this research is retrospective research. The population comprised of all patients with spontaneous intracerebral hemorrhage hospitalized at RSI Jemursari Surabaya in 2017-2019, with affordable population of all patients with vessels to rupture. The blood that comes out will accumulate and form a blood clot (hematoma) in the brain parenchyma. The

spontaneous intracerebral hemorrhage diagnosed by a neurologist. The data that have been collected were entered into the Statistical Package for the Social Sciences (SPSS) version 20.0 data format (SPSS, Inc., Chicago, Illinois).

Theoretical Review

Spontaneous intracerebral hemorrhage

Stroke is a major neurological diseasein adulthood. Stroke describes an event that occurs acutely or suddenly. Based on the pathology, stroke is divided into ischemic stroke and hemorrhagic stroke. Hemorrhagic stroke is also known as spontaneous intracerebral hemorrhage. This type of stroke occurs due to the rupture of an intracerebral blood vessel which causes neurological symptoms that occur suddenly and is often followed by symptoms due to the effects of space compression or increased intracranial pressure. The effect of space compression or increased intracranial pressure causes the mortality rate in spontaneous intracerebral hemorrhage to be higher than in ischemic stroke (Anindhita and Wiratman, 2014, pp. 514).

Stroke is the 5th leading cause of death in the United States and the leading cause of disability. Spontaneous intracerebral hemorrhage accounts for 10% of the 800,000 strokes that occur in the United States each year (ASA, 2021).

This percentage increased in Japan, namely 18% and in Korea 24%. The incidence of spontaneous intracerebral hemorrhage is increasing in low and middle income countries, and Asia. Spontaneous intracerebral hemorrhage is more common in males and increases by age. The fatality of this disease is 25-30% in low and middle income countries (Unnithan et. al., 2020).

The pathophysiology of spontaneous intracerebral hemorrhage is generally preceded by damage to the walls of small blood vessels in the brain due to hypertension. Chronic hypertension causes aneurysms to form in small blood vessels in the brain. The process of turbulence of blood flow results in the formation of fibrinoid necrosis, namely cell/tissue necrosis with the accumulation of fibrin matrix. Herniation of the arteriolar wall and tearing of the tunica intima to form a microaneurysm (Charcot-Bouchard) also happen. This Charcot-Bouchard aneurysm can rupture immediately if the arterial blood pressure increases suddenly. In addition, chronic hypertension can cause a disturbance in the autoregulatory system of cerebral blood vessels due to the hyalinization process in the blood vessels so that the blood vessels lose elasticity. This condition causes the blood vessels of the brain to be unable to adjust to fluctuations in systemic blood pressure; a sudden increase in blood pressure can cause blood

vessels to rupture. The blood that comes outwill accumulate and form a blood clot (hematoma) in the brain parenchyma. The volume of the hematoma will increase, generally within 24-48 hours of onset, causing a space compression effect that compresses the brain parenchyma and causes an increase in intracranial pressure (Anindhita and Wiratman, 2014, pp. 515-516).

Intraventricular hemorrhage may be secondary to spontaneous intracerebral hemorrhage, generally originating from the anterior communicating artery with blood entering the 3rd and 4th ventricles via the lamina terminalis. Bleeding in the 3rd ventricle but not in the lateral ventricles is an indication of basilar artery rupture.

Blood filling in the 4th ventricle and a littlein the 3rd ventricle can be suspected of coming from the posterior inferior cerebellar artery (Anindhita and Wiratman, 2014, pp. 535-536).

Intracerebral Hemorrhage-Grading Scale (ICH-GS) Scores

The ICH-GS score uses 5 points for prognostic evaluation of intracerebral hemorrhage. The components are age, Glasgow Coma Scale score at hospital admission, location of intracerebral hemorrhage, volume of intracerebral hemorrhage, and the presence or absence of expansion of bleeding into the ventricles (Sandoval et. al., 2007).

Table 1. ICH-GS Score

Component	Intracerebral Hemorrhage Point
Age, years old	
<45	1
45-64	2
≥65	3
Glasgow Coma Scale score	
13-15	1
9-12	2
3-8	3
Location of intracerebral hemorrhage	
Supratentorial	1
Infratentorial	2
Volume of intracerebral hemorrhage, mL	
Location of hemorrhage in supratentorial	
<40	1
40-70	2
>70	3
Location of hemorrhage in infratentorial	
<10	1
10-20	2
>20	3
Expansion of bleeding into the ventricles	
No	1
Yes	2
Total ICH-GS score	5-13

Glasgow Coma Scale score was takenon the arrival at the emergency department, volume of intracerebral hemorrhage was counted using the ABC/2 method, and the presence or the absence of intraventricular hemorrhage was assessed at the first head CT.

The use of these 5 points is the same as the points contained in the ICH score, butthere are different intervals. In the ICH score, age is divided into 2 intervals, whereas the ICH-GS score is divided into 3intervals. In addition, what makes it different from the ICH score is that the ICH- GS score, points related to clot volume are also associated with the location of bleeding because of the difference in location space (Sandoval et. al., 2007).

Results and Discussion

The results revealed that there were a total of 110 spontaneous intracerebral hemorrhage patients who had complete data in medical e-records during 2017-2019; 65.5% (72 people) were male and 34.5% (38 people) were female

Table 2. Distribution of Sex

No	Sex	Frequency	Percent
1	Male	72	65,5 %
2	Female	38	34,5%
	Total	100	100%

The data showed that 5.5% (6 people) had an ICH-GS score of 5; 38.2% (42 people) had an ICG-GS score of 6; 21.8% (24 people) had an ICH-GS score of 7; 20% (22 people) had an ICH-GS score of 8; 5.5% (6 people) had an ICH-GS score of 9; 4.5% (5 people) had an ICH-GS score of 10; 3.6% (4 people) had an ICH-GS score of 11; and 0.9% (1 patient) had an ICH-GS score of 12.

Table 3. ICH-GS Score

No	ICH-GS Score	Frequency	Percent
1	Score 5	6	5.5
2	Score 6	42	38.2
3	Score 7	24	21.8
4	Score 8	22	20.0
5	Score 9	6	5.5
6	Score 10	5	4.5
7	Score 11	4	3.6
8	Score 12	1	9
Total		110	100

The data on ICH-GS score and the outcomes of patients showed that among patients who had an ICH-GS score of 5, 5 people were found with survival outcome and 1 person was found with death outcome. Patients with ICH-GS score 6, 40 people were found with survival outcome and 2 people died. Among patients with an ICH-GS score of 7, 24 people were identified with survival outcome and nopatients died. Among patients with an ICH-GS score of 8, 16 people were identified with survival outcome and 6 patients died. Among patients with an ICH-GS score of 9, 3 people were identified with survival outcome and 3 patients died. Of patients with an ICH-GS score of 10, 2 people wereidentified with survival outcome and 3 people died. Among patients with an ICH- GS score of 11, 2 people were identified with survival outcome and 2 people died. Finally, a patient with an ICH-GS score of 12 died.

Table 4. ICH-GS Score and Outcomes

ICH-GS Score and Outcomes	Frequency	Percent (%)	Cumulative Percent (%)
Score 5 with survival outcome	5	4,5	4,5
Score 5 with death outcome	1	0,9	5,5
Score 6 with survival outcome	40	36,4	41,8
Score 6 with death outcome	2	1,8	43,6
Score 7 with survival outcome	24	21,8	65,5
Score 8 with survival outcome	16	14,5	80,0
Score 8 with death outcome	6	5,5	85,5
Score 9 with survival outcome	3	2,7	88,2
Score 9 with death outcome	3	2,7	90,9
Score 10 with survival outcome	2	1,8	92,7
Score 10 with death outcome	3	2,7	95,5
Score 11 with survival outcome	2	1,8	97,3
Score 11 with death outcome	2	1,8	99,1
Score 12 with survival outcome	1	0,9	100
Total	110	100	

Data concerning with age and outcome showed that among patients aged <45 years, 8 people were identified with survival outcome of, whereas among patients aged >45 years, 3 people with death outcome. Patients aged 45-64 years, 79 people were found with survival outcome and 11 people with death outcome. Amongpatients aged 65 years, 7 people were identified with survival outcome and 2 people died.

Table 5. Age and Outcomes

Age and Outcomes	Frequency	Percent (%)	Cumulative Percent (%)
<45 years old with survival outcome	8	7,3	7,3
<45 years old with death outcome	3	2,7	10,0
45-64 years old with survival outcome	79	71,8	81,8
45-64 years old with death outcome	11	10,0	91,8
>=65 years old with survival outcome	7	6,4	98,2
>=65 years old with death outcome	2	1,8	100
Total	110	100	

In the GCS data at the emergency department and the outcome, it was found that among patients with GCS ≥13, 67 people were identified with survival outcome and 3 people died. Patients with GCS 9-12, 14 people were found with survival outcome and 7 people died. Finally, among patients with GCS ≤8, 10 people were identified with survival outcome and 9 people died.

Table 6. GCS and Outcomes

GCS and Outcomes	Frequency	Percent (%)	Cumulative Percent (%)
GCS >=13 with survival outcome	67	60,9	60,9
GCS >=13 with death outcome	3	2,7	63,6
GCS 9-12 with survival outcome	14	12,7	76,4
GCS 9-12 with death outcome	7	6,4	82,7
GCS <=8 with survival outcome	10	9,1	91,8
GCS <=8 with death outcome	9	8,2	100
Total	110	100	

Data regarding the volume of spontaneous intracerebral hemorrhage and the outcome revealed there were 77 patients with survival outcome had a volume <40 mL bleeding in the supratentorial region, whereas 6 patients died. In supratentorial hemorrhage with a volume of 40-70 mL group, 8 people were identified with survival outcome and 1 person died. In supratentorial hemorrhage with volume >70 mL group, 5 people survived and 6 people with death outcome.

In the data regarding infratentorial bleeding with a volume <10 mL, it was found that 1 person had survival outcome and 4 people with a death outcome. In the data regarding infratentorial bleeding volume >20 mL, 1 person had survival outcome and 1 person died.

Table 7. Volume and Outcomes

Volume and Outcomes	Frequency	Percent (%)	Cumulative Percent (%)
Supratentorial vol <40mL with survival outcome	77	70,0	70,0
Supratentorial vol <40mL with death outcome	6	5,5	75,5
Supratentorial vol 40-70 with survival outcome	8	7,3	82,7
Supratentorial vol 40-70 with death outcome	1	0,9	83,6
Supratentorial vol >70mL with survival outcome	5	4,5	88,2
Supratentorial vol >70mL with death outcome	6	5,5	93,6
Supratentorial vol <10mL with survival outcome	1	0,9	94,5
Supratentorial vol <10mL with death outcome	4	3,6	98,2
Supratentorial vol >20mL with survival outcome	1	0,9	99,1
Supratentorial vol >20mL with death outcome	1	0,9	100
Total	110	100	

In the data regarding the presence or absence of IVH and outcomes, there were 74 patients who did not experience IVH with survival outcome and 8 people with death outcome. A total of 18 people experienced IVH with survival outcome and 10 people with a death outcome.

Table 8. IVH and Outcomes

IVH and Outcomes	Frequency	Percent (%)	Cumulative Percent (%)
Absence of IVH with survival outcome	74	67,3	67,3
Absence of IVH with death outcome	8	7,3	74,5
Presence of IVH with survival outcome	18	16,4	90,9
Presence of IVH with death outcome	10	9,1	100
Total	110	100	

In the data concerning with the location of bleeding and outcomes, 89 patients with supratentorial hemorrhage were found with survival outcomes and 13 died, while in infratentorial bleeding, 3 patients were alive and 5 people died.

Table 9. Location and Outcomes

Location and Outcomes	Frequency	Percent (%)	Cumulative Percent (%)
Supratentorial with survival outcome	89	80,9	80,9
Supratentorial with death outcome	13	11,8	92,7
Infratentorial with survival outcome	3	2,7	95,5
Infratentorial with death outcome	5	4,5	100
Total	110	100	

Conclusion

The results of the ICH-GS score can be usedto facilitate communication both with fellow health workers and with the patient's family. Trend of the data showed that ICH-GS score is not consistent in showing the prognosis of spontaneous intracerebral hemorrhage (the smaller the ICH-GS score should have better prognosis than the higher score), while the information based only on volume and location can predict the prognosis more consistently.

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International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Profile of Stroke Patients with COVID-19 at Rumah Sakit Islam Surabaya Jemursari, Indonesia

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DOI : 10.33086/iimj.v4i2.4131

ARTICLE INFO

Keywords:
Profile, Stroke, Covid-19

Submitted: April 13th 2023
Reviewed: April 24th 2023
Accepted: May 31th 2023

ABSTRACT

Background: Stroke is the number one cause of death in Indonesia, in America stroke is also the number one cause of disability. In COVID-19, most patients experience mild to moderate respiratory symptoms, and need no specific treatment. However, in some patients with comorbidities such as cardiovascular, diabetes mellitus, chronic respiratory disease, and malignancy, it often gives serious manifestation.
Objective: This study aimed to profile of stroke patients with COVID-19 at Rumah Sakit Islam Surabaya Jemursari, Indonesia.
Method: The type of this research was observational retrospective research. We used all the stroke patient hospitalized at Rumah Sakit Islam Surabaya Jemursari from April to December 2020 that confirmed the diagnosis of COVID-19. We used the general data, data of clinical symptoms, blood pressure, head CT-scan findings, and laboratory findings the data of participants was collected. The data showed as number (frequency) and percentage.
Results: The patient's average age of 57 years, male was common; patients with hypertension were often seen in the comorbidities; ischemic strokes were by far the most prevalent form; subcortical regions were the most frequent location of stroke based on the CT scan. The results of head CT showed that 91.7% of patients had an ischemic stroke and 8.3% of patients had a hemorrhagic stroke.
Conclusions: The stroke patients with COVID-19 and hospitalized at Rumah Sakit Islam Surabaya Jemursari, Indonesia have an average age of 57 year, and most of the patient was male. Comorbid hypertension was commonly observed in this study. Based on the type of stroke, ischemic was the most common manifestation and subcortical regions were the most frequent location.

Introduction

Stroke is an acute neurological emergency that manifests as focal or global neurologic deficits due to central nervous system vascular injury. Stroke can be caused by thrombus or emboli to the brain vessels (ischemic stroke) or by a rupture of blood vessels (hemorrhagic stroke). Stroke become the major cause of mortality and disability in Indonesia.(Singh *et al.*, 2020)- (Sungkar, 2021)

Corona virus disease (COVID-19) is an infectious disease caused by the newly discovered corona virus. Most people with

COVID-19 will experience mild to moderate respiratory illness and need no specific treatment. Elderly patients and patients with other medical problems such as cardiovascular disease, diabetes, chronic respiratory disease, and malignancy often experience serious illness when infected with COVID-19.(Aisyah *et al.*, 2022)- (Pane, Donastin and Al Hajiri, 2022)

According to the World Health Organization (WHO), the risk of an ischemic stroke during COVID-19 is 5%, while hemorrhagic stroke is less common. The median time for ischemic stroke diagnosis in one small, one-center study was 10 days. Patients with COVID-19 who have had a stroke are usually old and have high blood pressure and high D-dimer levels. A study in Wuhan, China, report that among 50 patients with ischemic stroke found any comorbidity, including lower platelet counts, lower leukocyte counts, high D-dimer levels, cardiac troponin I and T, pro-brain natriuretic peptide, and interleukin-6.(David Spence *et al.*, 2020)- (Hidayat *et al.*, 2022)

In a systemic review study, 87.8% of stroke patients in COVID-19 were ischemic stroke, 5.2% of patients had an intracerebral hemorrhage, 1.7% of patients had an intracerebral and subarachnoid hemorrhage, 0.9% of patients had a subarachnoid hemorrhage, 0.9% of patients with a transient ischemic attack (TIA), and 0.9% of patients with subarachnoid hemorrhage and ischemic stroke.(Bhatia *et al.*, 2020)

Rumah Sakit Islam Surabaya Jemursari is the one of secondary referral and academic hospital in Surabaya, East Java, Indonesia. The presence of local study about characteristics of stroke patients with COVID-19 can help alert health workers and provide effective communications between health workers themselves or between health workers and patient's families in the management of stroke and COVID-19. The purpose of this study was to profile the stroke patients with COVID-19 at Rumah Sakit Islam Surabaya Jemursari.

Methods

This is a descriptive study with retrospective design.

Study population

All of stinke patients who hospitalized at Rumah Sakit Islam Surabaya Jemursari from April to December 2020 with confirmed diagnosis of COVID-19 included to this study. We used the secondary data from electronic medical records of the patients.

Study Data

We used the general data, data of clinical symptoms, blood pressure, head CT-scan findings, and laboratory findings The data

of participants was collected. The data showed as number (frequency) and percentage. This study performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 data to collect all of data (SPSS, Inc., Chicago, Illinois).

Results and Discussion

A total of 24 participants was included to this study. All of data study showed in Table 1. The mean age of the patients was 57.67±11.25 years.

Table 1. Profile of Stroke Patients with Covid-19

Profile	Result
Clinical complaints	
Left hemiparesis	5 (20.8%)
Right hemiparesis	5 (20.8%)
Decreased consciousness	6 (25.0%)
Seizure	1 (4.2%)
Dysarthria	3 (12.5%)
Difficult communication	2 (8.3%)
Other	2 (8.3%)
Systolic blood pressure	
<140 mmHg	7 (29.2%)
140-159 mmHg	5 (20.8%)
>159 mmHg	12 (50%)
Diastolic blood pressure	
<90 mmHg	8 (33.3%)
90-99 mmHg	6 (25.0%)
>99 mmHg	10 (41.7%)
Head CT-Scan Findings	
Type of Stroke	
Infarct	22 (91.7%)
Bleeding	2 (8.3%)
Location	
Cortical	5 (20.8%)
Sub-cortical	9 (37.5)
Cortical-subcrotical	5 (20.8%)
Punch	1 (4.2%)
Normal	1 (4.2%)
Others	3 (12.5%)
Side	
Left	7 (29.2%)
Right	6 (25.0%)
Bilateral	6 (25.0%)
Normal	1 (4.2%)
Others	4 (16.7%)

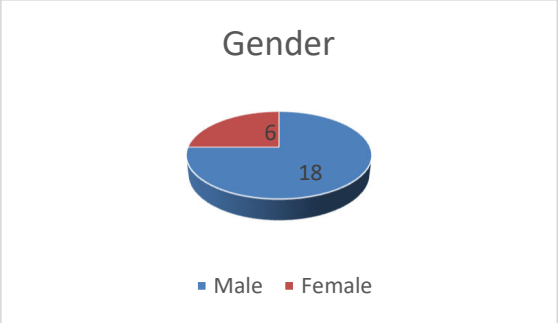

Figure 1. Diagram of gender

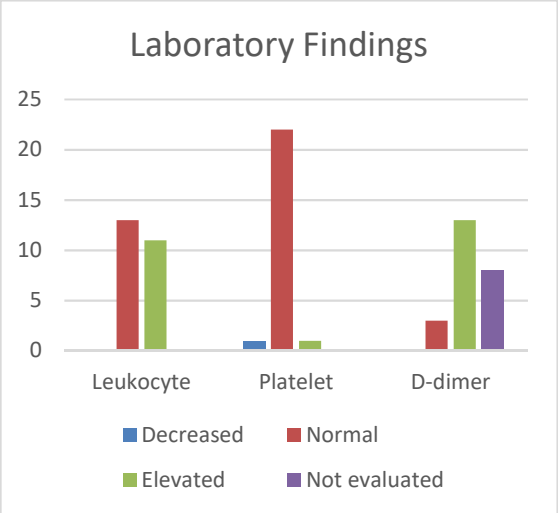

Figure 2. Diagram of laboratory findings

The most common gender of stroke with COVID-19 were 75% male and 25% female. A total of 4 male patients died, and 10 returned home while for women a patient died, and 5 patients returned home. A total of 4 patients had no discharge data. These

results were in line with another study which states that the mortality rate increases in males than females. The major inflammatory storm of COVID-19 is more likely to occur in male patients. In terms of risk factors distribution, stroke subtype, severity, and outcome, women and men were different from one another. While women are more likely to get cardiogenic stroke, males are more likely to experience lacunar infarction. Male patients may also experience more severe new coronary pneumonia, which can worsen inflammation.(Trifan *et al.*, 2020), (Luo *et al.*, 2022)

The results of head CT showed that 91.7% of patients had an ischemic stroke and 8.3% of patients had a hemorrhagic stroke. This is in line with previous study that showed 87.8% patients have an ischemic stroke. A common characteristic of many people with severe COVID-19 infection is the activation of the coagulation cascade with high D-dimer and fibrinogen levels. In young adults without vascular risk factors, stroke from large vessels emboli may be caused by hypercoagulation, which may also cause venous thromboembolism and paradoxical embolism. Plaque rupture or in situ thrombosis may also be less frequent in this situation.(Bhatia *et al.*, 2020), (Trifan *et al.*, 2020), (Nannoni *et al.*, 2021)

Based on head CT results, it was found that 20.8% of patients had a stroke in the cortical region, 37.5% in the subcortical, 20.8% in the cortical-subcortical, 4.2% in the pons, and 12.5% of CT results was not mentioned in the data. From the results of head CT imaging, it was also found that 29.2% of patients had a stroke on the left side of the brain, 25% on the right side of the brain, 25% bilaterally, and 16.7% was not mentioned. According to previous study, these findings were similar. Multifocal subcortical/cortical lesions were seen commonly on head CT imaging.(Nicholson, Alshafai and Krings, 2020)-(Requena *et al.*, 2020)

The results of leukocyte examination showed that 54.2% of patients had normal leukocyte levels and 45.8% of patients had leukocytosis. The elevated white blood cell due to COVID-19 especially depend on the clinical severity. Another study showed a significant correlation between individuals with severe COVID-19 and stroke and higher rates of leukocytosis.(Katz *et al.*, 2021) The hyperinflammatory response to COVID-19 infection and additional bacterial infections is suggested to be the cause of leukocytosis. Leukocytosis generates into inflammatory biomarkers that may be utilized to detect systemic inflammation.(Khorvash *et al.*, 2019), (Gupta *et al.*, 2020)

From the total 24 patients, only 16 patients were tested for D-dimer, the results were 18.8% had normal D-dimer levels while 81.3% had elevated D-dimer levels. A previous case report showed that patients typically had D-dimer values >4 times normal and considerably elevated hypercoagulability indicators. Increased plasma prothrombotic factors such as von Willebrand factor (vWF), factor VIII, D-dimer, fibrinogen, anionic phospholipids, and inflammatory cytokines are indicative of hypercoagulability (cytokine storm). Coagulopathy in COVID-19 infection has been associated with D-dimer, a breakdown product of cross-linked fibrin that shows continuing activation of the coagulation cascade. In patients with COVID-19, an elevated D-dimer level has been found to be a good predictor of death.(Katz *et al.*, 2021), (Iqbal *et al.*, 2021), (Kim *et al.*, 2021)

The results of blood pressure observations showed systolic and diastolic pressures at the first evaluation in the emergency room: 29.2% of patients had normal systolic pressure; 20.8% hypertension grade I JNC VII; and 50% hypertension grade II JNC VII. Data on the patient's diastolic pressure concluded that 33.3% of patients had normal diastolic pressure, 25% of JNC VII grade I hypertension, and 41.7% of patients had JNC VII grade II hypertension. In line with a previous study state that a greater incidence of hypertension was seen in COVID-19 individuals with acute ischemic stroke.(Requena *et al.*, 2020), (Shakil *et al.*, 2022)

Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for the coronavirus. Infection with SARS-CoV-2 is mediated by binding of the viral spine protein to ACE2 which is expressed on type II pneumocytes in the respiratory system. ACE2 commonly coexists with cardiovascular diseases and hypertension. ACE 2 receptors, as well as those in the respiratory tract, are also expressed in the cardiovascular system. Patients with a history of cardiovascular disease will have an increased risk of serious adverse events. Patients with COVID-19 may develop a thrombotic and coagulation abnormality, causing a hypercoagulable state thereby increasing thrombotic and thromboembolic events.(Ortega-Paz *et al.*, 2021), (Shibata *et al.*, 2020)

Conclusion

The profile observed in this study showed that the stroke patients who were confirmed to have COVID-19 and hospitalized at Rumah Sakit Islam Surabaya Jemursari had an average age of 57 year, most of the patients were male. Comorbid

hypertension was commonly observed in this study. Based on the type of stroke, ischemic was the most common manifestation. This supported by laboratory findings which showed increased at D-dimer levels, this was related to systemic hypercoagulable conditions in COVID-19. Location of stroke based on head CT findings showed the most common location was subcortical.

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International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Proximate and Some Micronutrients (Zn, Se, Fe and I) Assessed in Goat Milk, and Cattle Milk in Sokoto, Nigeria

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DOI : 10.33086/iimj.v4i2.4275

ARTICLE INFO

Keywords:
Milk, Protein, Micronutrient, Zinc, Iron

Submitted: May 19th 2023
Reviewed: June 12th 2023
Accepted: June 27th 2023

ABSTRACT

Background: Malnutrition, poverty, and information scarcity are some of the major issues affecting people in West African region. Thus, it is imperative to divulge nutritional information from a cheap and accessible food (the milk) in the region.
Objective: This study aimed at performing a proximate and Zn, Se, Fe and I micronutrients determination in goat and cattle milk in Sokoto, Nigeria.
Method: The concentrations of zinc, selenium, iron, iodine present in goat and cattle in Sokoto, Nigeria were determined using standard methods and materials of analytical grade.
Results: The result reveals (< 0.05) Zn, Se, Fe, and I in goat as follows: 9.10 ± 0.05 ppm, 2.32 ± 0.004 ppm, 10.5 ± 0.05 ppm and 7.8 ± 0.01 ppm. In cattle, the concentrations for Zn, Se, and Fe are: 5.12 ± 1.05 ppm, 1.13 ± 0.005 ppm, 9.5 ± 0.02 ppm, and 5.9 ± 0.02 ppm. The proximate values of moisture content, ash content, protein, and fat in milk collected from goat are as follows respectively: 90.21%, 0.56 %, 3.23%, and 2.44%. The proximate values in cattle milk are: 70.11%, 0.50%, 2.11%, 2.11% and 2.21% for water content, ash content, protein content, and fat content respectively.
Conclusions: Thus, the goat milk contains higher proximate contents (such as fat, water, carbohydrate, and ash), Zn, Fe, and Se than the cow milk. It is imperative for the public to properly utilize milk for its nutritious benefits.

Introduction

Dairy products contribute a lot in the meeting up of recommended dietary requirements because of the proximate and micronutrients in milk (Okpani et al., 2016). Milk is a liquid and whitish nutritious food made by the mammary gland of females in the phenomenon called lactation. It is regarded as a food that contains sufficient nutrients needed by offspring. It provides nutrients for metabolism, development and as well as growth. In milk there are numerous micronutrients, along with macronutrients; thus, milk disgorges nutrients that play key roles in human metabolic activities (Okpani et al., 2016).

Micronutrients are elements needed in small amount by the body, but have to be imported into the body through food materials like milk products. Parable, zinc micronutrient helps in several biochemical processes of the body, and functions in DNA synthesis, alcohol and sugar metabolisms. Fe is essential in hemoglobin and other functions of the human body. In this dispensation, iodine is an essential element due its ability to participate in the making of important thyroid hormones. That is why dietary iodine is very important (Umar et al., 2018). Moreover, carbohydrates, and fats are needed for energy metabolism. Ash provides a portend for the presence of mineral elements. Moisture is needed in nutrition and proteins serve as energy source in rare cases. Additionally, proteins are needed for making and repairing of tissues of the human body among other purposes (Ayuba et al., 2020).

However, the milk is produced popularly for human consumption in Sokoto through the cow and goat animals that make the predominant animals in the area. The several factors associated with animals (goat and cow) such as feeding methods, genetics, season, parity, health status, environment, and localities provide an insight that determines the levels of nutrients in milk (Okpani et al., 2016). On the other hand, there is evident fact that, information about exact nature and levels of nutrients in goat and cow milk in Nigeria and Sokoto is very scarce. Many people pay less attention to the goat milk or other dietary products despite its ability to provide much nutrients even better than other animals like cow (Mazroea et al., 2018). In the same vein, the awareness about the nutritional facts of milk will guide the public and influence their actions in taking milk to circumvent nutrition issues of the populace (Okpani et al., 2016). Thus, the objective of this study was to determine the proximate values and concentrations of Zn, Fe, Se, and I in goat milk and cow milk in Sokoto, Nigeria.

Methods

Study area

Nigeria is a country located in the West Coast of Africa; lying 5º North Equator and between 3º and 4ºEast of the Greenwich Meridian. It has 36 states and the Abuja Capital. One of the zones where Sokoto lies is the Northwest zone. Sokoto state is a state that lies in the northwestern part of the country bordering Kebbi, Zamfara, states, and Niger Republic. The research was conducted in Sokoto, Sokoto state, government Areas or Council (LGAs).

Micronutrients Zn, Fe, I, and Se determination

Through random sampling method approach, fresh milk was collected from the two different animals (goat and cattle) within Sokoto state, Nigeria. Each sample was collected trice, and each element was determined thrice and mean was computed. The micronutrients Zn, Fe, and Se were determined in milks of goat and cow collected from Sokoto town using atomic absorption spectroscopy (AAS).

Proximate content study

Proximate content of milks collected in Sokoto, Nigeria was determined using methods and procedures related in Nweze & Nwagwe (2019). The moisture, ash, crude fats, proteins and carbohydrates of all the samples were carried out using standard AOAC method (1990). The moisture and ash were determined using weight difference method. Crude fat was extracted by means of the Soxhlet apparatus with petroleum ether (40 to 60°C) for 6 hours. The nitrogen value, which is the precursor for protein of a substance, were determined by micro Kjeldahl method, involving digestions, distillation and finally titration of the sample. The nitrogen value was converted to protein by multiplying a factor of 6.25. Carbohydrate was determined by difference method. The carbohydrate was calculated by difference method and as the nitrogen free extract (NFE), calculated as % NFE = 100 - % (a + b + c + d + e) where a = protein, b = fat, c = fibre, d = ash, e = moisture. All the proximate values were reported in %. The proximate analyses were done in triplicates as in Nweze & Nwagwe (2019).

Statistical analysis

The descriptive statistics and one-way analysis of variance (ANOVA) were carried out at ($p<0.05$) significance level using Microsoft excel version 7.

Results and Discussion

The results for determination of some micronutrients and proximate content of goat milk and cow milk in Sokoto were shown in Tables 1 and 2.

Table 1. Some elemental contents of goat and cattle milk collected from Gwadabawa, Sokoto, Nigeria

Elements	Goat (ppm)	Cattle (ppm)
Zinc	9.10 ± 0.05	5.12 ± 1.05
Selenium	2.32 ± 0.004	1.13 ± 0.005
Iron	10.5 ± 0.05	9.5 ± 0.02
Iodine	7.8 ± 0.01	5.9 ± 0.02

Key: Values are expressed as mean ± standard deviation

Table 1 shows the concentrations of zinc, selenium, and iron present in goat and cattle in Sokoto, Nigeria. In goat Zn, Se, Fe and I are: 9.10 ± 0.05 ppm, 2.32 ± 0.004 ppm, 10.5 ± 0.05 ppm, 7.8 ± 0.01 ppm. In cattle, the values for Zn, Se, Fe, and I are: 5.12 ± 1.05 ppm, 1.13 ± 0.005 ppm, 9.5 ± 0.02 ppm, 5.9 ± 0.02 ppm. And The result indicates that the goat contains more Zn, Fe,

and Se than the cattle. This is in tandem with the previous studies that show more nutrients in goat milk than in cow milk. In another similar study, a similar trend (to the concentrations in Table 1) was shown with selenium, and zinc concentrations in goat milk higher than in cattle milk; therewith, only cow milk iron was higher than that of goat (Almazroea et al., 2018). In a dissimilar case, a study from Abakaliki, Southern Nigeria displayed more Fe and Zn in cow milk than in goat milk observed (Okpani et al., 2016). Moreover, another Southern Nigeria study unveiled that zinc and iron present in cow milk is more elevated than that of cow Nweze & Nwagwe (2019).

Certainly, there are varied concentrations of Zn, Fe, and Se in goat milk and cow milk collected in Sokoto, Nigeria (Table 1). The milk from these two animals is very paramount in the state as it is being sold and served along with grains (such as corn and millet) preparations in a popular food called *Fura* and the milk is served raw as a result of its cheapness, sweetness, energy-yielding and other uses by most of the population in the state. However, the Sokoto state is being faced by malnutrition, hunger, and other nutrition issues in rampant cases especially in rural dwellings (Sarkingobir et al., 2023). Thus, the milk would be a better source of nutrients at affordable rate to the teeming population in the state. Indeed, the determination of micronutrients will inform the public on some useful contents of the popularly consumed milk in the state. And in turn instigate more consumption. Therein, the presence of zinc, iron, and selenium provides many benefits to consumers. Parable, selenium (2.32 ± 0.004 and 1.13 ± 0.005 ppm as in Table 1) is a trace/micronutrient that acts in selenoproteins (such as Thioredoxin reductase, deiodinases, gluthathione peroxidase) playing significant functions in many instances such as antioxidant defense, DNA synthesis, fertility, synthesis of thyroid hormones, reproduction, and cancer prevention (Soetan et al., 2010; Mehdi et al., 2013; Sen et al., 2019). The level of determined selenium will invariably contribute to the Recommended selenium intake of 40 ug daily (Sen et al., 2019).

In a similar vein, significant amount of iron (10.5 ± 0.05 and 9.5 ± 0.02 ppm) was determined in goat milk and cow milk respectively as shown in Table 1. Iron possesses several functions in the human body, such as serving as oxygen carrier in the blood, participating in many enzymes, acting in ferritin, myoglobin, etc. (Abbaspour et al., 2014; Gupta, 2014; Iqbal et al., 2014 Umar et al., 2022). Likewise, the concentrations (9.10 ± 0.05 and 5.12 ± 1.05 ppm) of determined zinc in goat milk and cow milk are important because they make the milk to serve as zinc source to

consumers. The recommended dietary zinc intake daily is around 8-11 mg/day depending on the age of the consumer (Devi et al., 2014). Zinc is a micronutrient participating in growth, immune function, and cell differentiation events (Ebisintei, 2018). More than 200 metalloproteins utilized zinc, it is also involved in blood glucose regulation, regulation of thyroid function, regulation of gonads, requires in acid base balance, and plays role in adrenal and prolactin synthesis. Structural roles of zinc include: component of membrane, component of cell receptors, required by taste buds, and act as antioxidant for stabilization of membranes. In cell growth, replication, and maturation, zinc plays vital functions by influencing enzymes such as DNA polymerase, thymidine kinase, RNA synthetase. Therefore, zinc is versatile in normal growth and development and has to be imported through foods such as the common and cheap milk from goat or cow (Soetan et al., 2010; Narwal et al., 2017; Maywald & Rink, 2022). Likewise, iodine was determined in the observed milk as shown in Table 1. Iodine acts to regulate basal metabolic rate through thyroid hormones biosynthesis. Therefore, 100-200 ug/day amount of iodine is needed in this regard. Insufficient amount of iodine in the body called iodine deficiency triggers disorders such as goiter, central nervous system disorders (for instance cretinism, mental retardation, and relations). Indeed, iodine is essential in the synthesis of thyroid hormones in thyroid glands by iodination (formation of oxidized iodine species), iodization of iodine derivatives. Therein, the hormones T_3 and T_4 formed a conformation of twist-skewed fashion. The iodine is the most effective lipophilic substituent required to fix the twist-skewed confirmation of T_3 and T_4 hormones (Umar et al., 2023).

Table 2. Proximate contents of goat and cattle milk collected from Gwadabawa, Sokoto, Nigeria

Proximate	Goat (%)	Cattle (%)
Water	90.21	70.11
Ash	0.56	0.50
Protein	3.23	2.11
Fat	2.44	2.21
Carbohydrate	6.23	5.67

Table 2 shows the proximate content of milk collected from goat and cattle in Sokoto, Nigeria. The proximate values of moisture content, ash content, protein, and fat in milk collected from goat are as follows respectively: 90.21%, 0.56 %, 3.23%, and 2.44%. The proximate values in cattle milk are: 70.11%, 0.50%, 2.11%, 2.11% and 2.21% for water content, ash content, protein content, and fat content respectively. Therein, the goat milk contains more proximate parameters than the cattle milk. This is in consonant with the study that reveals more water, protein, and fat in goat milk than the cow and buffalo

milks (Yuherman et al., 2018). In a contrast case, a study from Southern part of Nigeria shows that proximate values in cow are more elevated than in goat milk Nweze & Nwagwe (2019).

Additionally, proximate contents (as revealed in Table 2) are essential in nutrition. The proteins give out aminoacids essential for making of new tissues and repairing of wounded tissues. Proteins are utilized in formation of enzymes, hormones, and other factors such as blood clotting factors and immunoglobulins. Carbohydrates are needed for energy provision for the routine activities of the body system. Fats too is a source of energy twice the carbohydrates and are needed to form important components of the body such as hormones, membranes, and relations. Therefore, presence of these proximate values indicates that the milk is nutritious and a cheap source for the dwellers of the state for curbing nutrition issues (Muhammad et al., 2015; Hassan et al., 2018). Therefore, people are enjoined to appropriately utilized milk for provision of Zn, Fe, Se, I and proximate parameters as well.

Conclusion

Milk is versatile in nutrition of many populations including that of Sokoto, Nigeria. However, few studies have been conducted in the country to reveal nutrients in milk fold. Therefore, this work assesses the proximate and Zn, Fe, and Se nutrients in goat and cow milk in Sokoto, Nigeria. Thus, the goat milk contains higher proximate contents (such as fat, water, carbohydrate, and ash), Zn, Fe, Se, and I than the cow milk. It is imperative for the public to properly utilize milk for its nutritious benefits.

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International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

The Effect of Honey Administration on The Histopathology of The Duodenum of Wistar Rats as a Inhibition of The Toxic Effects of Borax (Sodium tetraborate)

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DOI : 10.33086/iimj.v4i2.4445

ARTICLE INFO

Keywords: Borax, Free Radicals, Oxidative Stress, Honey, Duodenum

Submitted: June 8th 2023
Reviewed: June 23th 2023
Accepted: July 11th 2023

ABSTRACT

Background: Borax can result in oxidative stress and cause the onset of gastrointestinal ulcerations that will dampen the duodenal villi to become shorter and can even disappear. Cell damage due to oxidative stress can be prevented by administering antioxidants. Antioxidants will inhibit the onset of chain reactions in the formation of free radicals by complementing the existing electron deficiency. Honey is one of the natural ingredients that is rich in antioxidants and part of thibbun Nabawi as one of the inhibitors of the toxic effects of borax.
Objective : The purpose of this study is to to analyze the effect of honey administration on the histopathological description of submucosa and epithelial mucosa of duodenal wistar rats as an inhibitor of the toxic effects of borax (Sodium tetraborate).
Methods: This study used the true experimental method with Post Test Only Control Group Design using 25 mice which will be divided into five groups, namely K (negative control), P (positive control), M1 (borax and honey dose 1), M2 (borax and honey dose 2), M3 (borax and honey dose 3). This study was conducted for 22 days then. Took the duodenal organ on all samples and then made histological preparations with HE staining. Observations were made with an Olympus microscope to see submucosal edema and damage to the epithelium of the duodenal mucosa.
Results: The results of the study found that borax 26 mg / head / day had an influence on the histopathological picture of duodenal borax. In addition, the administration of honey dose 75 mg / Kg BB provides a toxic inhibitory effect of borax in the duodenum best among other treatment groups. However, statistically there was no effect of honey administration on the histopathological picture of the duodenum of wistar rats as an inhibitor of the toxic effect of borax (Sodium Tetraborate) with $p>0.05$.
Conclusion: Statistically it can be concluded that there is no effect of the administration of honey on the histopathology picture of the duodenum of wistar rats as an inhibitor of the toxic effects of borax (Sodium tetraborate).

Introduction

In modern times, manufacturers continue to develop food processing techniques in order to meet public demand. One effort have widely applied is the addition of additives to food products. Adding these

additives generally aims to extend the durability of food so that food can be stored for a more extended period. (Amalia et al., 2017).

BPOM (Indonesian Food and Drug Administration Monitoring) intensifies Food Control in all regencies/cities throughout Indonesia. Sampling was carried out on iftar/takjil snacks for later testing. The test result found that food samples contained hazardous ingredients, namely 0.73% rhodamine-B, 0.59% borax, and 0.45% formalin (BPOM RI, 2021). Following the Regulation of the Minister of Health No.033/MenKes/Per/XI/2012 concerning Food Additives, stipulating that borax is prohibited from being used as a food additive because borax is a hazardous and toxic substance. However, substance abuse is still common (Permenkes, 2012).

Borax is a source of radicals that can cause oxidative stress, which can cause cell damage. Antioxidants can prevent cell damage due to oxidative stress (Puspadewi, 2012). Antioxidants will inhibit the emergence of a chain reaction in the formation of free radicals by completing the existing electron deficiency so that these free radicals can be stable and prevent oxidative stress (Amalia et al., 2017)

The use of honey as medicine has been carried out since ancient times and has even existed since the time of the Prophet Muhammad. This method of treatment is known as Thibbun Nabawi. Thibbun Nabawi is a method of treatment that refers to all the sayings, teachings, and actions of the Prophet Muhammad related to the health sector, both in terms of prevention and treatment cure of a disease (Fatahilah, 2016). Honey has many ingredients that are very beneficial, such as minerals, antioxidants, vitamins, and oligosaccharides. (Cahyani, 2015). A study conducted by Anggraeni (2018) stated that giving honey to the treatment group at doses of 25 mg/Kg BW, 50 mg/Kg BW, and 75 mg/Kg BW could improve the histopathology of the duodenum of Wistar rats due to free radicals generated by lead acetate.

Duodenum is the first part of the small intestine, located under the stomach, shaped like a horseshoe (C shape). The duodenum absorbs all chemicals that enter the body and undergoes a process of absorption, distribution, metabolism, and excretion pharmacokinetically (Cahyani, 2015). Boric acid in borax will enter the digestive system and be absorbed by the intestinal villi. If the intestinal villi continuously absorb borax, it can result in increasingly aggravating oxidative stress and cause gastrointestinal ulceration, which will impact the villi of the duodenum, jejunum, and ileum to become shorter and may even disappear (Purnama et al., 2013).

Based on the background above, the authors are interested in conducting research on the effect of giving honey on histopathological features of the duodenum of wistar rats as an inhibitor of the toxic effects of borax (Sodium tetraborate).

Objective

The purpose of this study is to analyze the effect of honey administration on the histopathological description of submucosa and epithelial mucosa of duodenal wistar rats as an inhibitor of the toxic effects of borax (Sodium tetraborate).

Significance of Research

This study are expected to be used as an inhibitor of the toxic effects of borax (sodium tetraborate). Then as the development of knowledge in forensic toxicology medicine and honey treatment according to the Prophet's method (Thibbun Nabawi) and to support existing theories.

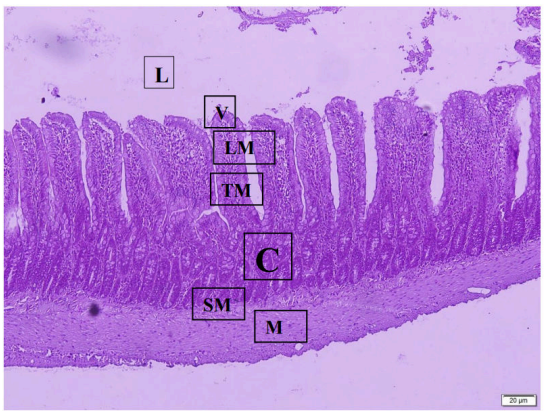
Methods

This study used the true experimental method with Post Test Only Control Group Design using 25 mice which will be divided into five groups, namely K (negative control), P (positive control), M1 (borax and honey dose 1), M2 (borax and honey dose 2), M3 (borax and honey dose 3). This study was conducted for the next 22 days. Took the duodenal organ on all samples and then made histological preparations with HE staining. Observations were made with an Olympus microscope to see submucosal edema and damage to the epithelium of the duodenal mucosa.

Result

The negative control group of rats (Grup K) was only given eat and drink as usual; Group P as the positive rat control group, was given oral exposure to borax 26 mg/head/day; Group M1 as the first treatment group was given oral exposure to borax 26 mg/head/day and honey at a dose of 25 mg/Kg BW orally/day; Group M2 as the second treatment group was given oral exposure to borax 26 mg/head/day and honey at a dose of 50 mg/Kg BW per orally/day; Group M3 as the third treatment group was given oral exposure to borax 26 mg/head/day and honey at a dose of 75 mg/Kg BW orally/day.

Furthermore, after 14 days of treatment, all samples were taken from the duodenal organs. Histological preparations were made and observed under a microscope through 100x magnification to see duodenal submucosal edema and 400x magnification to see damage to the duodenal mucosal epithelium. Then do the scoring on the level of cell damage. After all the data is obtained, the data is tabulated and then analyzed.



Abbreviation:

L	Lumen
TM	Tunika Mukosa
V	Vili
LM	Lamina Propis
S	Submukosa
M	Muskularis
C	Crypt

Figure 1. Histopathology of the rat duodenum with HE staining at 100x magnification was normal, the submucosa was normal, and the mucosal epithelium was not damaged. Both pathological changes did not occur.

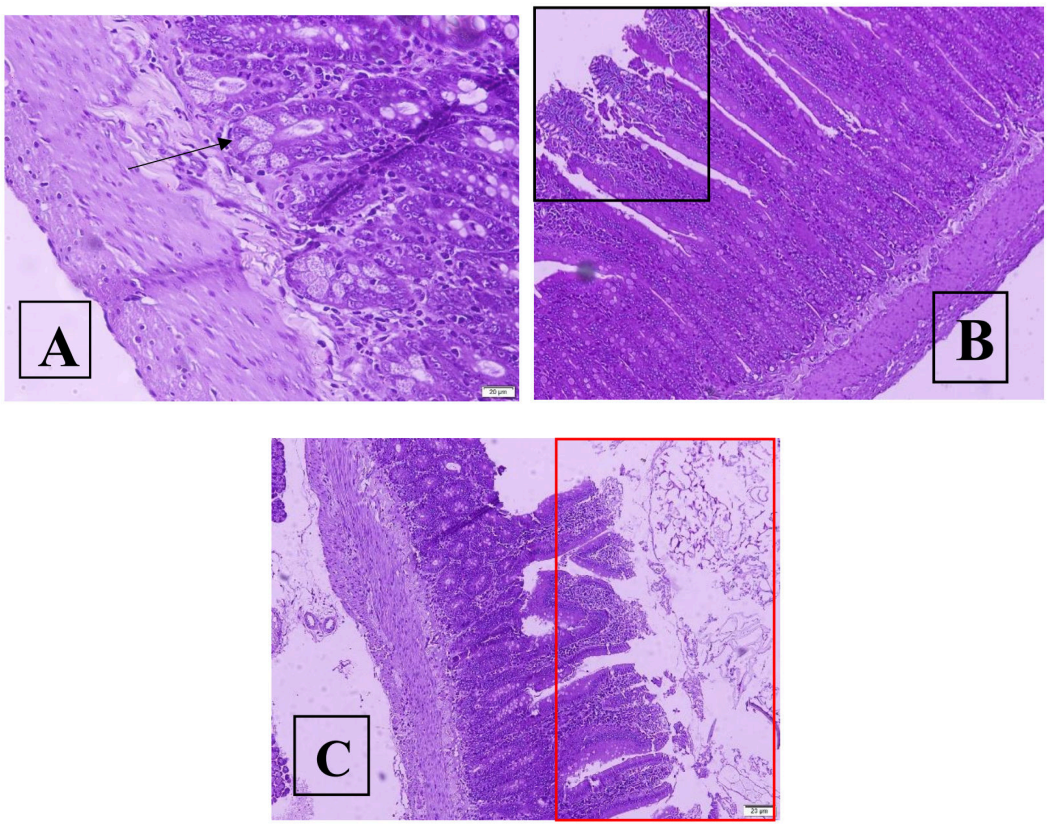


Figure 2. Duodenum histopathology with HE staining. The submucosa is edematous (A), and the mucosal epithelium is damaged (B and C)

Description:

Black arrow:	Submucosal edema
Black square:	Epithelial desquamation
Red square:	Epithelial erosion

Table 1. Results And Mean Scores of Submucosal Edema And Mucosal Damage White Rat Duodenum

Submucosal Edema			
Sample	Mean	N	Standard Deviation
Negative Control	0,8	5	0,447213595
Positive Control	0,4	5	0,547722558
Treatment 1	0,4	5	0,547722558
Treatment 2	0,4	5	0,547722558
Treatment 3	0	5	0
Mucosal Epithelial Damage			
Sampel	Mean	N	Standard Deviation
Negative Control	0,8	5	1,095445115
Positive Control	0,4	5	0,894427191
Treatment 1	0,4	5	0,547722558
Treatment 2	0,8	5	0,447213595
Treatment 3	0	5	0

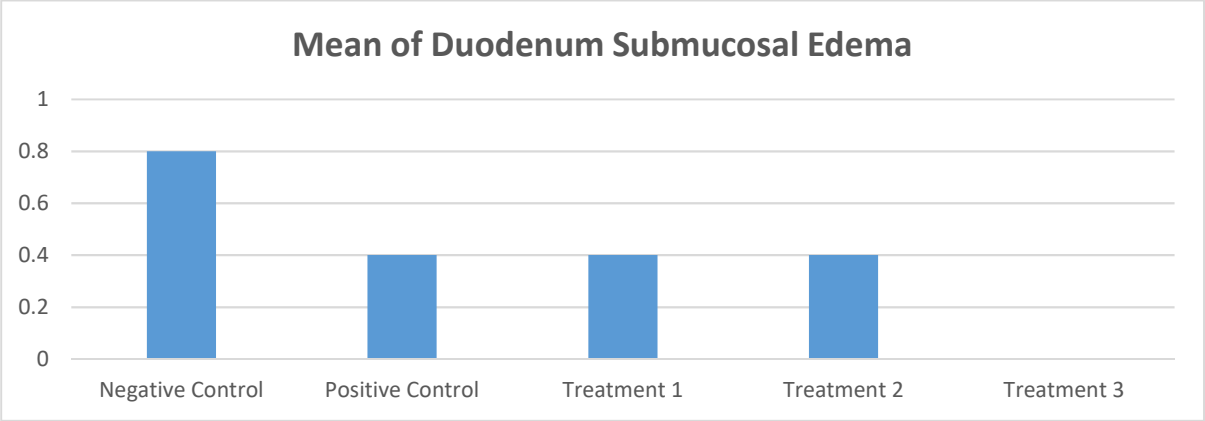


Figure 3. Average Duodenal Submucosal Edema of White Rats

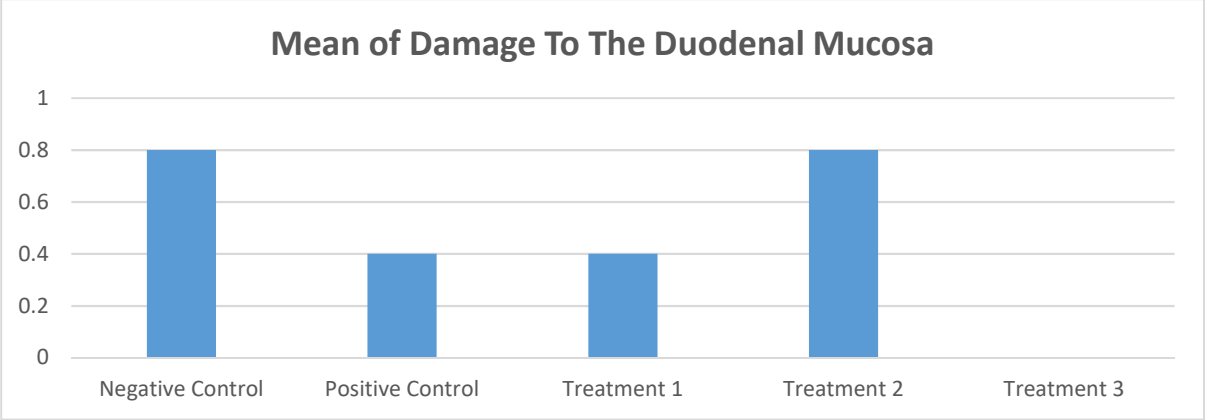


Figure 4. Average Damage to The Duodenal Mucosa of White Rats

Figure 3 shows that the negative control has the highest mean value of submucosal edema among the other groups, which is equal to 0.8. Treatment One and Treatment 2 were in the second position for the positive control group with the same value of 0.4. In the treatment group, Group 3 is the lowest average submucosal edema among the other treatment groups, which is equal to 0.

In Figure 4, it can be seen that the negative control and treatment 2 have the highest average value of mucosal damage among the other groups, which is equal to 0.8. The positive control group and treatment 1 are in the second position with the same value of 0.4. In the treatment group, 3 has the lowest average value of mucosal damage among the other treatment groups, equal to 0.

The results of the study found that borax 26 mg/head/day had an influence on the histopathological picture of duodenal borax. In addition, the administration of honey dose 75 mg / Kg BB provides a toxic inhibitory effect of borax in the duodenum best among other treatment groups. However, statistically there was no effect of honey administration on the histopathological picture of the duodenum of wistar rats as an inhibitor of the toxic effect of borax (Sodium Tetraborate) with $p>0.05$.

Discussion

Histological Picture of Wistar Rat Duodenum with Borax Administration

The research results show that administering borax as much as 26 mg/rat/day orally in Wistar rats shows the presence of submucosal edema and necrosis of the duodenal mucosa in the rats studied. This result follows a study conducted by Elziyad (2013), which stated that a dose of borax of 37 mg/head/day had a more severe effect on duodenal submucosal edema, 57%, and duodenal mucosal necrosis, 45% more severe than a dose of 26 mg/rat/day. It can be concluded that borax has an effect on edema and necrosis in the cells of the rat duodenum.

The result also follows the theory that using borax-containing borax acid as an active ingredient can go through the digestive system and then be absorbed by the intestinal villi. If the intestinal villi continuously absorb borax, it can cause oxidative stress, which will have an impact on the villi of the duodenum, jejunum, and ileum to become shorter and may even disappear (Purnama et al., 2013). The use of borax can interfere with mitochondrial function by causing the failure of energy synthesis so that ATP also fails to form.

The failure of energy synthesis is caused by the formation of bonds between NAD+ coenzymes (H+ ions) and boric acid, resulting in an obstacle to the sodium-

potassium pump, which maintains intracellular stability (Elziyad, 2013). Manifestation of inhibition carried out by boric acid will cause the failure of energy synthesis and impact cell damage. The process of glycolysis produces 2 moles of ATP needed for the smooth running of sodium (Na+) and potassium (K+). The inhibited glycolysis process cannot produce sufficient ATP, so Na+ will attract water, as a result of which there will be an accumulation of water in cells followed by hydrophilic degeneration (Amalia et al., 2017).

This study also found that the negative control group of rats that were not given any treatment experienced submucosal edema and damage to the duodenal mucosal epithelium. This result can be caused by many factors, namely, excessive physical activity in rats or stress due to environmental influences. The findings follow the research of Pujaswarini et al. (2019), which states that all physical activity, both light and strenuous physical activity, can increase levels of ROS (Reactive oxygen species), which in turn will have an impact on increasing free radicals in the body. The negative control group was not given honey, so the endogenous antioxidants in the mice's bodies had to work alone against these free radicals. The imbalance between the amount of antioxidants and the high number of free radicals in the body will lead to oxidative stress.

Duodenum Histology with Borax and Honey Administration

Based on this research, giving borax and honey to 'Treatment 1' rats at a dose of 25 mg/Kg BW showed a decrease in duodenal mucosal epithelial necrosis compared to positive control rats. Whereas in 'Treatment 2' with a dose of 50 mg/Kg BW turned out to have a more significant effect on mucosal epithelial necrosis when compared to all other treatments. The same thing could cause this as in the negative control rat group, where the activity of the rats could not be controlled by the researchers or due to enzymes forming endogenous free radicals in the body, which could cause levels of free radicals in the body of the 'Treatment 2' rats to be higher when compared to the treatment group. So the other dose of honey as an antioxidant becomes inadequate and still causes submucosal edema and necrosis of the duodenal mucosal epithelium (Sirait, 2016).

The results of the research show that the administration of honey at a dose of 75 mg/Kg BW per oral/day could inhibit the toxicity of borax at a dose of 26 mg/head/day so that no submucosal edema or duodenal mucosal necrosis was seen in Wistar rats better than other doses of honey. This shows that the best dose of honey at a

75 mg/Kg BW dose protects the duodenum from borax toxicity. These findings support research by Anggraeni (2018), which states that giving honey can reduce MDA levels in rats. MDA levels are lipid peroxidation products that can be used as a marker to measure free radical levels. Honey contains flavonoids that have benefits as endogenous antioxidants; these substances will inhibit lipid peroxidation reactions due to free radicals and neutralize free radicals in the body (Anggraeni, 2018).

The mechanism of flavonoids' action in inhibiting lipid peroxidation reactions is by donating one of their hydrogen atoms. Flavonoids can give an H+ (Hydrogen) atom from the OH- (Hydroxyl) group to free radicals and produce flavonoid phenoxyl radicals. This flavonoid phenoxyl radical will bind again with free radicals and then form a second phenoxyl radical. This second flavonoid phenoxyl radical is a compound with conjugated double bonds. It can balance the structure of its compounds by delocalizing electrons and providing benefits by eliminating the effects of free radicals in the body (Pratama, 2016). The effect of lost free radicals will also eliminate oxidative stress due to Borax administration so that submucosal edema and mucosal necrosis do not occur in the duodenum.

The duodenal submucosal edema test obtained a significance value of 0.171 from the Kruskal-Wallis test. In the Kruskal-Wallis test, damage to the duodenal mucosal epithelium had a significance value of 0.234. The value of these two significances is greater than α (0.05).

Conclusion

Statistically, it can be concluded that honey administration does not affect the histopathological appearance of the Wistar rat duodenum as an inhibitor of the toxic effects of borax (Sodium tetraborate).

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Epidemiological Review: Mapping Cases and Prevalence of Helminthiasis in Indonesia on 2020-2022

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ARTICLE INFO

Keywords: Epidemiology, Prevalence, Helminthiasis, Tropical disease, Parasitology

Submitted: May 1st 2023
Reviewed: May 6th 2023
Accepted: June 15th 2023

ABSTRACT

Background: Helminthiasis cannot be separated from society in Indonesia. In 2020, the World Health Organization (WHO) classified helminth infections as neglected tropical diseases (NTD) that require large-scale control, because morethan 23% of the world's population is infected with helminthiasis. In Indonesia, there are still few articles that comprehensively review the epidemiological mapping of the latest helminthiasis cases. The purpose of writing this article is to map the prevalence of helminthiasis in Indonesia in 2020-2022. This article is a systematic studyconducted from January-April 2023. The literature search was carried out through an electronic database.

Result: The findings of this study indicate that in the last three years, helminthiasis has not been eliminated in Indonesia. The results of helminth species found to infest communities in several provinces in Indonesia include *Ascaris lumbricoides, Trichuris trichiura, Hookworm, Hymenolepis nana, Taenia saginata, Taenia solium, Oxyuris vermicularis, Schistosoma japonicum, Strongiloides stercoralis,* and *Wuchereria bancrofti.* The diagnosis of helminth infestation and infection is confirmed through microscopic examination by finding eggs, larvae, proglottids, and even adult worms that come out spontaneously through defecation. In addition, helminth transmission can occur through food contaminated with worm eggs. The government has tried to control helminthiasis through Permenkes number 15 of 2017 concerning Helminthiasis Management. However, the indicators of achieving the target of reducing the prevalence of intestinal worms to below 10% in eachRegency/City as stated in Pasal 3 ayat 2 of the Permenkes have not been fully met.

Conclusion: It can be seen in this study that there are still many provinces that have not reached the helminth control target. This condition is especially experienced by high-risk groups, such as children, mining workers, plantation workers, farmers, livestock workers, staff at slaughterhouses, and waste collectors.

Introduction

Helminthiasis are still a widespread health problem in tropical and subtropical regions. According to WHO, more than 1.7 billion people worldwide suffer from helminthiasis, making this disease classified as a neglected tropical disease. (WHO, 2020) This is due to the chronic and asymptomatic nature of helminth infections, especially in the early stages. (Idris et al, 2019) When the infection becomes more severe, it will be associated with anemia, nutritional malabsorption, general malaise, gastrointestinal symptoms,

also resulting in impaired physical development and cognitive performance. (Makata, 2020) The morbidity associated with these tropical diseases creates a substantial disease burden, which promotes the formation and defense of endless cycles of infection, decreased productivity, poverty and inadequate socioeconomic status. (WHO, 2020)

More than 266 million preschool-aged children and more than 567 million school-age children infected with helminthiasis live in areas where this parasite is intensively transmitted. (Sofiana et al, 2022) In Indonesia, helminthiasis is widespread in rural and urban areas. The survey results of helminth infections in primary schools in several provinces show a prevalence of around 61% - 79%, while for all ages it is around 41% - 59%. Surveys in Indonesia also show that the high prevalence of *Ascaris lumbricoides* is often followed by a high incidence of *Trichuris trichiura* as well. A high prevalence of Ascariasis was found in several villages in Sumatra (77%), Sulawesi (87%), West Java (89%), Kalimantan (78%), and West Nusa Tenggara (91%). Trichuriasis prevalence is also high in Kalimantan (82%), Sumatra (82%), West Nusa Tenggara (83%), West Java (90%) and Sulawesi (82%). On the other hand, hookworm prevalence ranges from 31% - 49% in various regions in Indonesia. (Nainggolan, 2022)

Approximately 69% of infections from the Soil Transmitted Helminth (STH) nematode group occur in Southeast Asia and more than 25% of the study population in Asia is infected with at least one species of helminth. (Silver et al, 2018) The prevalence of helminthiasis in Indonesia is close to 30% with the incidence in elementary school students around 61-79%. (Suharmiati et al, 2018) The prevalence of helminthiasis in Central Java is almost 27% and dominated by *Ascaris lumbricoides* 7.3%, Hookworm 4.9%, *Trichuris trichiura* 5.9%, *Necator americanus* 2.9%, *Strongyloides strercoralis* 4.9 %. (Subagiono, 2019)

Helminthiasis cases in Banten Province were 60.6% with the highest number being Lebak Regency at 63.3%. (Dinkes Lebak, 2019) These cases were dominated by elementary school children who were the group most at risk for helminth infections. Factors that will lead to a high rate of worm infection in children are factors of children, parents and the environment:

a. Child factors: not washing hands before eating and after defecation, cleanliness of nails, eating snacks in any place, open defecation behavior that causes soil and environmental pollution by worm eggs contained in feces, consumption of deworming medicine every 6 months.

b. Parental factors: low personal hygiene behavior, not being able to keep

children clean, not washing vegetables and fruit that will be consumed by children, level of education and knowledge of parents.

c. Environmental factors: latrine ownership, dirty house floors, availability of clean water and socio- economic conditions, as well as environmental sanitation. (Sadjimin, 2022)

In Indonesia, there are still few articles that comprehensively review the epidemiological mapping of the latest helminthiasis cases. Based on the explanation above, the purpose of writing this article is to map the prevalence of helminthiasis in Indonesia in 2020-2022. This article is a systematic study conducted from January-April 2023. The literature search was carried out through an electronic database. The publications selected in the selection of titles and abstracts were extracted using a standard format table and processed using a Microsoft Excel spreadsheet. The extracted data are the author, year of publication, journal, and conclusion. The results are then presented qualitatively.

Result

Helminthiasis Prevalence Mapping in Indonesia

From several literatures reviewed, the authors mapped cases of helminthiasis that spread in various provinces in Indonesia. (Figure 1)

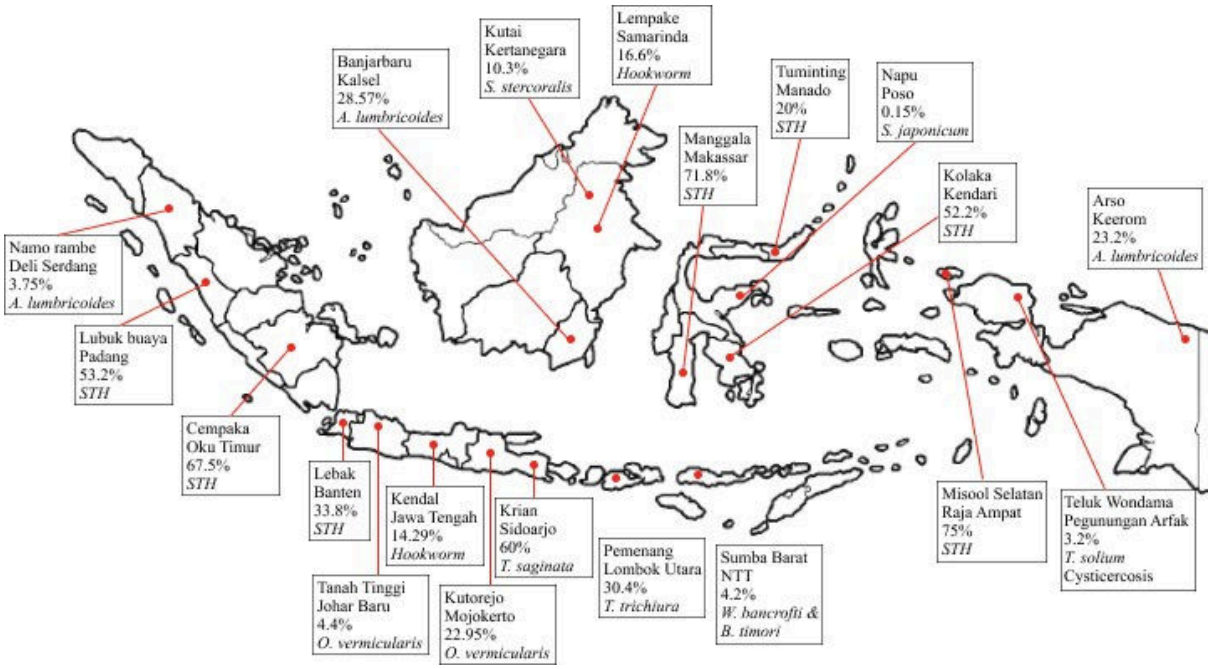

Figure 1. Helminthiasis Prevalence Mapping in Indonesia

Systematic Overview of Helminthiasis in Indonesia

From several publications reviewed, the authors systematically reviewed the incidence of helminthiasis studied in various cities/districts in Indonesia. (Table 1)

Table 1. Helminthiasis Prevalence in Indonesia

Province	City/Regency	District	Subject	Prevalence	Specimen	Finding
Jawa Tengah	Banyumas	Kembaran	Children	3,1%	Faeces	*Hymenolepis nana*
	Semarang	Bandarharjo	Children	2,9%	Faeces	STH
	Kendal		Plantation workers	14,29%	Faeces	Hookworm
Banten	Lebak	Cihara	Children	33,8%	Faeces	STH
Jawa Timur	Jember		Plantation workers	92,6%	Faeces	Hookworm
	Blitar	Plosokerep	Children	66%	Faeces	*Ascaris lumbricoides*
	Sidoarjo	Krian	Slaughter-house workers	60%	Nail	*Taenia saginata*
	Mojokerto	Kutorejo	Children & Adulthood	22,95%	Anal swab	*Oxyuris vermicularis*
Sumatera Barat	Padang	Lubuk buaya	Children	53,2%	Faeces	STH
Sumatera Utara	Deli Serdang	Namo Rambe	Children	3,75%	Faeces	*Ascaris lumbricoides*
	Karo	Naman Teran	Farmers	6,6%	Nail	STH
Sumatera Selatan	Oku Timur	Cempaka	Children	67,5%	Faeces	STH
Kalimantan Selatan	Banjarbaru		Miners	28,57% 9,52%	Faeces	Ascariasis Hookworm
Kalimantan Timur	Samarinda	Lempake	Farm workers	16,6%	Faeces	Hookworm
		Bukit pinang	Cleaning workers	3,3%	Nail	*Ascaris lumbricoides*
	Kutai kertanegara		Children	31,8% 10,3%	Faeces	Hookworm *Strongiloides stercoralis*
Sulawesi Selatan	Makassar	Manggala	Garbage collector	71,8%	Faeces	STH
Sulawesi Utara	Manado	Tuminting	Children	20%	Faeces	STH
Sulawesi Tenggara	Kendari	Kolaka	Children	52,2%		STH
Sulawesi Tengah	Poso	Napu	Children	0,15%	Faeces	*Schistosoma japonicum*
Jakarta Pusat	Johar Baru	Tanah Tinggi	Children	4,4%	Anal swabs	*Oxyuris vermicularis*
Nusa Tenggara Barat	Lombok Utara	Pemenang	Children	30,4%	Faeces	*Trichuris trichiura*

Finding Helminth Eggs Contamination in Food

In its life cycle, STH worms can enter the human body through contamination of worm eggs from the soil to food and drinks consumed by humans. Several studies related to the identification of parasitic contamination in food are summarized in Table 2.

Table 2. Proportion of Helminth Eggs Contamination in Food

Province	City/Regency	District	Proportion	Sample	Finding
Sumatera Utara	Medan		17,5%	Cabbage & Lettuce	STH
Jawa Barat	Bekasi	Rawalumbu	100%	Basil	Hookworm
Jawa Tengah	Klaten	Pedan	14,3%	Basil & Cabbage	*Ascaris lumbricoides*
Riau	Pekanbaru		13,3%	Cabbage	*Ascaris lumbricoides*

Discussion

Helminthiasis in Children

Based on table 1, it is shown that the largest population with worms is children. Several studies have shown that there is a relationship between school age children and the incidence of worms, where the age group of toddlers and children has a high infection rate. (Mukti et al, 2022) The high incidence of worms in children is related to self-care habits. The world of children who often play barefoot makes them more susceptible to infection. Contact with the soil will cause larvae or worm eggs that stick to the skin to enter the body and infect them. (Kamila et al, 2018) Low personal levels such as lack of awareness of washing hands before eating, awareness of maintaining nail hygiene and transmission from school/play friends are contributing factors to the number infection. (Dinkes Lebak, 2019)

In addition to causing an acute impact on health, in the long term this infection can cause disturbances in the growth and development of children, iron deficiency anemia, short stature (stunting), malnutrition, and cause impaired intelligence in children, thus affecting the achievement and performance of the sufferer. If chronic and untreated, some of these infections can also lead to death due to the complications caused by the presence of parasites in a child's body. (Munawaroh et al, 2022)

However, there has been a shift in children's hygiene behavior as a result of the worldwide pandemic. This condition

makes some parents forbid their children to play outside. Children then spend more time playing at home. The type of play that is done at home makes children less and less direct contact with the ground. (Mukti et al, 2022) In addition, the production of kinetic sand toys is allegedly able to replace soil as a means of developing children's fine motor skills.

Although rarely cause mortality, helminthiasis infection causes many complications such as malabsorption syndrome, chronic dysentery, gastrointestinal obstruction, rectal prolapse, airway complications, and growth faltering. The results of the analysis test in a study between helminthiasis and BMI/Age measurements showed that there was a significant relationship between worm status and BMI/Age. Degarege et al found that children infected with worms had a lower BMI/Age mean than with healthy children. (Ramarantika et al, 2022)

Symptoms of helminthiasis are generally almost the same, namely the child looks thin, easily tired, nausea and vomiting, flatulence, abdominal pain, and feces mixed with blood. Worms can interfere with children's growth and development, interfere with learning concentration, cause anemia, fatigue, weight loss, and diarrhea. This condition can be prevented by maintaining personal hygiene and environmental cleanliness. Clean and healthy living behavior can be done by washing hands with soap, using the latrine when defecating. Environmental sanitation can be done by using clean water and disposing of pet waste in a special disposal area. Food and beverage sanitation can be done by washing food ingredients with clean water, and cooking food until cooked. The behavior of washing hands before and after preparing food, wearing slippers outside the house and cutting nails regularly are also ways to prevent helminth infections. (Panjaitan, 2022)

STH class worms are widely distributed, both in tropical and subtropical regions. The determinants of transmission include humidity and hot temperatures that support optimal growth of worms. Transmission is supported by poor socio-economic conditions, insufficient clean water supply, lack of sanitation facilities, low education, poor personal hygiene, and non-standard housing. Other environmental factors in the public sphere include the state of drainage and the contribution of waste to individual exposure. These conditions have an impact on the condition of health, nutrition, and intelligence. Adult worms that live in the intestine will absorb nutrients, so that it becomes one of the causes of nutritional deficiencies in the food consumed by children. This will affect the potential and quality of human resources as the nation's next generation (Konoralma et al, 2022).

WHO targets to reduce the incidence of helminthiasis in children in endemic areas by 75% by implementing regular treatment. One of the drugs recommended to control STH infection in the community is Albendazole 400 mg single dose for adults and 200 mg for children aged 12-24 months. Albendazole belongs to the methyl carbamate group, which is a benzimidazole derivative with high anthelminthic activity with low doses and few side effects. The spectrum of activity is very broad, including nematodes, cestodes, and echinococcal infections in humans. The Indonesian Ministry of Health uses Albendazole 400 mg as a worm control program because it is relatively safe, single dose, cheap, and easy to obtain. (Munawaroh et al, 2022)

Children are very important human resources for the development of the Indonesian nation in the future. However, a report from the World Bank states that helminthiasis hampers development in the world because it is 12% of the total burden of illness in children aged 5-14 years. Although eradication has been carried out since the last 50 years by the government and various parties, the prevalence of this disease remains high. This is because some of the population is still living unhealthy and related to the economic status and cleanliness of the living environment. (Suriani et al, 2019)

Helminthiasis in Adult Workers

In the plantation area of a company in Kendal Regency, most of the soil is loose and slightly sandy, so it can be an appropriate medium for hookworm breeding. The condition of the village, which is inhabited by approximately 50 residents and there are only 20 dwellings with soil floors, has the potential to become a medium for hookworm larvae to live. The habit of Ungaran mountain climbers who cross the Kendal hiking trail often defecate along the tea plantations can also be a cause of contamination of hookworm eggs in plantation soil. Indeed, clean and healthy living behavior is not the only factor related to the transmission of hookworm infection because the main factor in hookworm transmission is the presence of worms in the infective stage that penetrate the legs. The incidence of hookworm infection among tea pickers in Kendal is very likely related to the entry of hookworm larvae attached to long fingernails and rarely cut. (Yuntrio et al, 2022)

Supporting factors that cause STH infection include the work of someone who is closely related to the soil, such as farmers, diamond miners and sand miners. One of the livelihoods of residents in Sungai Tiung Village, Banjarbaru City is sand mining. The sand mining workers do not use full PPE. The workers have a bad habit of washing their hands before eating,

which can lead to STH infection. Likewise, the sand miners in the Pemataan Village, Landasan Ulin Subdistrict, Banjarbaru, who mostly carry out their activities around the work environment that support the transmission of hookworm infection. This condition results in a decrease in Hb levels in workers to below normal due to high and chronic infection intensity. (Husniar et al, 2022)

Cattle breeders in Indonesia still pay less attention to the problem of parasitic diseases. Some cattle breeders still let the cows find their own food (shepherd system) and are not penned at all (traditional system). Cattle rearing with these two systems increases the chances for trematode, nematode and cestode parasites to continue their life cycle. Most of the population in North Samarinda sub-district work as farmers (78%) and ranchers (22%). As cattle breeders, their daily job is to take care of the cattle, such as cleaning the cage, bathing, separating the mother cow from her calf, and feeding the cows which encourages farmers to cut grass in the fields, roadside or in the field as cow food. The work is always in contact with the soil and usually they do not use PPE in their work, such as footwear and gloves, even though soil is an excellent medium for the growth of worm eggs. They also do not wash their hands with soap after doing these activities and live close to the cowshed. (Salsabila et al, 2021)

Based on observations made of cleaning staff in Samarinda when collecting waste without using PPE, it is known that they are susceptible to helminthiasis due to contamination from the waste. From the results of the nail clippings of the cleaning staff taken as a sample in Samarinda, one of the samples was found to have detected Ascaris lumbricoides worm eggs.24 A similar thing happened in Manggala Antang District, Makassar City, where there were findings of 71.8% of STH eggs in the feces samples of waste transport workers. Due to poor personal hygiene and environmental sanitation. (Amalia et al, 2022)

Naman Teran Village is a village where 90% of the residents work as farmers. Soil conditions that are fertile, loose and mixed with pests in Karo Regency have the potential for the life cycle of STH worm eggs to become infective. In doing their job, farmers in Naman Teran Village still don't care about personal hygiene. This can be seen from not washing hands with soap and running water after finishing work, before eating or chewing betel, not washing feet, and not wearing footwear and gloves when working. Based on this, it is very likely that farmers will be infected with STH because of their daily contact with the ground intensely. The use of footwear is considered

to limit their activities because the land used for farming is loose and waterlogged. (Napitupulu, 2022)

Slaughterhouse is an area that is vulnerable and at risk of endemic worm infection. Cattle imported from various regions in East Java have a risk of being infected with worms. Previous research found the prevalence of Taenia saginata was 62.3%. This prompted a study on slaughterhouse staff in Krian, Sidoarjo, by taking samples of their nails. Nails can be a place of attachment for various feces that contain parasites, one of which is worm eggs that get stuck in the nails and are swallowed when eating. The high contamination of dirty nails by intestinal cestode eggs is due to the presence of a thick hyaline layer and an albuminoid layer that serves to protect the egg contents, so that the eggs can last a long time on dirty nails. Then, fertile eggs will become infective after a few weeks depending on humidity, climate, and soil conditions. (Charisma et al, 2022)

Parasite Contamination Findings in Food

Vegetable traders in traditional markets in Medan City often do not pay attention to the hygiene of the vegetables they sell. Some vegetables are placed carelessly in dirty, muddy and earthy conditions. Some types of vegetables that are often consumed raw are watercress, cabbage, cabbage and basil. These types of vegetables are less delicious when cooked first. The habit of eating fresh vegetables in Indonesia must be more careful if the washing is not clean enough, thus providing an opportunity for contamination of worm eggs in raw vegetables. The wavy surface of the cabbage leaves makes it difficult to clean, thus allowing the worm eggs to still stick to the leaves, especially if the washing process is not carried out under running water. (Husaini et al, 2022)

In vegetable cultivation, contamination of worm eggs from soil to vegetables can occur in vegetables that spread or are close to the ground. In addition, the farmers' habit of using organic fertilizers in the form of humus or livestock manure also contributes to the attachment of STH eggs from fertilizers to vegetables. If someone eats these vegetables without being peeled, washed, and cooked first, of course there will be the potential for worm transmission. For this reason, a study conducted on food vendors along Dasa Darma Street, Rawalumbu District, Bekasi City found 100% of basil samples contaminated with Hookworm eggs. (Anindita et al, 2022) The same thing happened to the finding of 14.3% of STH eggs from fresh cabbage and basil in 14 lesehan food stalls in District of Pedan Klaten. (Pramana et al, 2022) A total of 13.3% of cabbage samples at the Pekanbaru City market were also positive

for Ascaris lumbricoides worm eggs. (Yulianti et al, 2022)

Conclusion

Helminthiasis are included in 11 of the 20 neglected tropical diseases in Indonesia. The government has tried to control helminthiasis through Permenkes number 15 of 2017 concerning Worm Management. However, the indicators of achieving the target of reducing the prevalence of intestinal worms to below 10% in each Regency/City as stated in Pasal 3 ayat 2 of the Permenkes have not been met. It can be seen in the explanation above that there are still many provinces that have not reached the worm control target. This condition is especially experienced by high-risk groups, such as children, mining workers, plantation workers, farmers, livestock workers, staff at slaughterhouses, and waste collectors. The findings of this study indicate that the worm species found to infest communities in several provinces in Indonesia include *Ascaris lumbricoides, Trichuris trichiura, Hookworm, Hymenolepis nana, Taenia saginata, Taenia solium, Oxyuris vermicularis, Schistosoma japonicum, Strongiloides stercoralis, and Wuchereria bancrofti.*

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International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Treatment Problems in Triple Negative Breast Cancer

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DOI: 10.33086/iimj.v4i2.3951

ARTICLE INFO

Keywords: Chemotherapy, Treatment response, Pembrolizumab, Capecitabine, Olaparib

Submitted: February 25th 2023
Reviewed: April 24th 2023
Accepted: June 15th 2023

ABSTRACT

Background: Breast cancer ranks second on the list of common diseases worldwide. It causes many deaths in the United States and Europe, second only to lung cancer. Triple-negative breast cancer (TNBC) does not express Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epithelial Receptor (HER2). It represents 24% of new cases of all breast cancer, and its incidence increases yearly. TNBC is a hormone-resistant breast cancer, so no current standard therapy exists. This article aims to explore regimen-resistant and troubleshooting treatment responses in TNBC cases. The method of writing this article is a literature review of studies using the keywords triple-negative breast cancer treatment and regimen, which are limited to only the most recent articles, 2012-2022, using search engines from PubMed, Science Direct, and Google Scholar.
Results: There is no definitive therapy for the triple-negative breast cancer subtype, in which the TNBC type has no target receptor. Chemotherapy is the SOC of TNBC for early stage treatment. For late-stage and relapsed TNBC, however, chemotherapy is no longer the first choice. Currently there is no standard chemotherapy regimen that can be given to patients who experience relapse after chemotherapy because they will have a short response and lead to metastases. Some studies have shown that chemotherapy gives a better response, but the prognosis of TNBC remains poor. TNBC has different responses to therapy. TNBC showed a good response to combination chemotherapy along with pembrolizumab, capecitabine, olaparib, and radiotherapy, compared to chemotherapy by itself. Surgical therapy, such as Breast-Conserving Surgery (BCS), does not improve better prognosis in TNBC patients.
Conclusions: Combining pembrolizumab, olaparib, capecitabine, and radiotherapy with chemotherapy increased survival rates compared to chemotherapy only.

Introduction

Breast cancer ranks second on the list of common diseases worldwide based on World Health Organization (WHO). In the United States and Europe breast cancer is a second rank cause of death, after lung cancer (Almansour, 2022). In 2012, globally, around 1.67 million cases of breast cancer were reported, while in 2020, it increased to 2.2 million cases with 684,996 deaths (International, 2020) (Momenimovahed, 2019).

TNBC is a subtype of breast cancer that does not have Estrogen Receptor (ER),

Progesterone Receptor (PR), and Human Epithelial Receptor (HER2) (Kumar, 2016). It is reported that 24% of new cases of TNBC are diagnosed each year, and the incidence is increasing (Tsai, 2016). In addition, TNBC often affects women of reproductive age under 40 years old (Yin, 2020).

TNBC is classified as an invasive, heterogeneous breast cancer and has a poor prognosis and wide metastatic capabilities (Sukumar, 2021). From the perspective of current therapy, the survival rate for TNBC is around 10.2 months, with and 5-year survival rate of 65% in regional cancer and 11% if cancer has spread to other organs (Kohler, 2015).

TNBC is a hormone-resistant breast cancer, so no current standard therapy exists. TNBC is sensitive chemotherapy, so chemotherapy is one of the therapies of choice, but its effectiveness as a standard therapy is still lacking. This is because residual metastatic lesions of cancer cells can recur after therapy (Kumar, 2016). Chemotherapy has become the Standard Of Care (SOC) for TNBC patients, but it still has weaknesses, such as the possibility of cancer relapses and treatment resistance during treatment (Won, 2020).

The limitations of TNBC therapy cause the death rate from breast cancer to be more significant. The condition is also supported by the characteristics of TNBC, which have a fast growth rate, a very high degree of invasiveness, wide metastatic potential, and poor prognosis.

Methods

The writing of this article uses the method of a literature review or article review, which comes from the results of the analysis and synthesis of various journals. The number at this writing is 27 articles. This article is written using the keywords triple-negative breast cancer, therapy, and resistance. Article search is limited to the latest articles in the last ten years (2012-2022). The selection of journals in this article is full-text related to the topic and published. Journal searches came from PubMed, Science Direct, and Google Scholar.

Results and Discussion

Breast Cancer Emergency

Breast cancer is a malignancy originating from the epithelial cell of the mammary glands, and it causes high rates of hospitalization, mortality, and morbidity. According to the WHO report, breast cancer causes 19.6 million Disability-Adjusted Life Years (DALYs) each year, so the world burden due to this malignant neoplasm is enormous (Lukasiewicz, 2021).

In 2020, breast cancer was the most frequently diagnosed worldwide, with 2.26 million cases. In addition, breast cancer is

also the most frequent cause of death for women worldwide, with 684,996 cases (Ferlay, 2020). The trend of breast cancer over the last three decades has increased, i.e., doubling from 1990 to 2016 (Sharma, 2019).

Triple Negative Breast Cancer Case Emergency

TNBC is a subtype that does not have ER, PR, and HER2+ expression on immunohistochemical staining (Kumar, 2016). This cancer develops from basal-like breast cancer cells and is characterized by the loss of some expression of BRCA1 receptors or random (Alluri, 2014). TNBC is a malignant breast neoplasm that represents 12%-20% of breast cancer. TNBC has a higher mortality rate than other breast cancer subtypes due to its aggressive and heterogeneous nature (Brewster, 2014). TNBC has an 8% to 16% lower survival rate than luminal subtype breast cancer and often affects women of African ethnicity (Howard, 2021).

Estimation of around 1 million breast cancer cases worldwide, of which approximately 170,000 cases (12-20%) are TNBC cases (Wahba, 2015). According to the current therapeutic perspective, the survival rate for TNBC patients is about 10.2 months, with five years of survival for people with regional cancer is 65% and 11% if cancer has metastasized to other organs (Kohler, 2015).

Problem of Treatments

Definitive therapy for triple-negative breast cancer subtypes is unavailable, where the TNBC type has no target receptors (Kumar, 2016). So far, surgical therapy also showed unfavorable results.

Several chemotherapeutic drugs have been shown to respond to therapy in TNBC including anthracyclines, alkylation agents (e.g., cyclophosphamide), an anti-microtubule agents taxane, and the anti-metabolite fluorouracil (5-FU). The median Progression-Free Survival (PFS) with chemotherapy ranges from 1.7 to 3.7 months and the median Overall Survival (OS) from the onset of metastasis is 10 to 13 months. (Won, 2020).

Although some studies show that chemotherapy gives a better response, the prognosis for TNBC remains poor. No standard chemotherapy regimen can be given to patients who experience recurrence after chemotherapy because it will have a short response, then recur and be followed by metastases (Won, 2020).

Several things make TNBC more resistant and difficult to treat because TNBC has Tumor Infiltrating Lymphocytes (TILs) in the microenvironment. TNBC is known to be more immunogenic than other breast cancer subtypes. In addition,

chromosomal instability that underlies the pathogenesis of TNBC causes cancer cells' ability to adapt easily and the immune system to become quickly resistant to chemotherapeutic agents (Wein, 2017).

Chemotherapy is the TNBC SOC for early-stage treatment. However, for advanced TNBC and relapse, chemotherapy is no longer the first choice.

Therapy and Regimen in Triple Negative Breast Cancer

Despite its aggressiveness, heterogeneity, and metastatic ability, TNBC is unique in immunogenicity and DNA damage structure. TNBC has a different response toward the therapy as shown in Table 1.

Table 1. Study of Types and Response to Therapy in TNBC Patients

References (Author)	Treatment	Response
Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer (Cortes *et al.,* 2022)	Pembrolizumab was given 200 mg every three weeks plus a chemotherapy regimen	TNBC showed an excellent response to chemotherapy combined with pembrolizumab, capetabine, olaparib, and radiotherapy, compared to just chemotherapy alone. Combination chemotherapy increases survival rates, DFS, and BCSS of TNBC compared to chemotherapy alone. On the other hand, BCS does not show a better prognosis.
Chemoresistance Evolution in Triple-Negative Breast Cancer Delineated by Single Cell Sequencing (Kim *et al.,* 2018)	Administration of anthracycline chemotherapy (epirubicin) and taxane (docetaxel) for 2 cycles then 4 cycles of the same chemotherapy plus an angiogenesis inhibitor (bevacizumab).	Chemotherapy provides optimal effects in TNBC patients with clonal extinction. In contrast, clonal persistence patients still retain large numbers of tumor cells with altered genotypes and phenotypes.
Pathologic Complete Response (pCR) to Neoadjuvant Treatment with or without Atezolizumab in Triple-Negative, Early High-Risk and Locally Advanced Breast Cancer: Neotrip Michelangelo Randomized Study (Gianni *et al.,* 2022)	Intravenous administration of carboplatin and nab-paclitaxel without or with atezolizumab 1200 mg i.v were given 3 weeks for eight cycles.	The analysis revealed that the pCR level after treatment with atezolizumab (48.6%) compared to without atezolizumab (44.4%) was not statistically significant.

References (Author)	Treatment	Response
Neoadjuvant Atezolizumab in Combination with Sequential Nab-Paclitaxel and Anthracycline-Based Chemotherapy versus Placebo and Chemotherapy in Patients with Early-Stage Triple-Negative Breast Cancer (Impassion031): A Randomised, Double-Blind, Phase 3 Trial (Mittendorf *et al.,* 2020)	Chemotherapy plus atezolizumab or placebo every two weeks. Chemotherapy consisted of nab-paclitaxel followed by doxorubicin and cyclophosphamide followed by surgery.	In patients with early-stage TNBC, atezolizumab treatment combined with nab-paclitaxel-based chemotherapy and anthracycline significantly increased the pathological complete response rate with an acceptable safety profile.
Outcomes after Breast-Conserving Surgery or Mastectomy in Patients with Triple-Negative Breast Cancer: Meta-Analysis (Fancellu *et al.,* 2021)	Meta-analytic research evaluating survival rate in TNBC undergoing Breast Conservation Surgery (BCS) versus mastectomy	TNBC patients with Breast Conserving Surgery (BCS) still have a poor prognosis compared to mastectomy.
Effect of Postmastectomy Radiotherapy on T1-2N1M0 Triple-Negative Breast Cancer (Xia *et al.,* 2022)	TNBC patients undergoing Postmastectomy Radiotherapy (PMRT) and non-postmastectomy radiotherapy.	5-year Breast Cancer-Specific Survival (BCSS) for the PMRT and non-PMRT groups were 79.1% and 74.7%, respectively. The analysis showed that radiotherapy after PMRT in TNBC patients significantly increased BCSS.
A Phase 2 Clinical Trial Assessing the Efficacy and Safety of Pembrolizumab and Radiotherapy in Patients with Metastatic Triple-Negative Breast Cancer (Ho *et al.,* 2020)	TNBC patients were given radiotherapy doses of 3000 cGy in 5 daily fractions followed by administration of pembrolizumab intravenously.	The addition of pembrolizumab and radiotherapy is safe and shows a poor prognosis and metastases.
Combination of Olaparib with Radiotherapy for Triple-Negative Breast Cancers: One-Year Toxicity Report of the RADIOPARP Phase I Trial (Loap *et al.,* 2021)	Olaparib was administered orally starting 7 days before radiotherapy until the end of radiotherapy.	The results of olaparib administration related to breast radiotherapy in TNBC patients showed a very good late tolerance profile. This combination is slightly toxic to the skin and there are no side effects.
Adjuvant Capecitabine with Docetaxel and Cyclophosphamide Plus Epirubicin for Triple-Negative Breast Cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial (Li *et al.,* 2020)	Patients treated with capecitabine (3 cycles of capecitabine with docetaxel and capecitabine, epirubicin, and cyclophosphamide) and patients treated with controls without capecitabine	Capecitabine when added to docetaxel followed by a combination of 3 anthracycline drugs significantly increased Disease Free Survival (DFS) in TNBC without problems.

References (Author)	Treatment	Response
Suboptimal Therapy Following Breast Conserving Surgery in Triple-Negative and HER2-Positive Breast Cancer Patients (Johnson *et al.,* 2021)	Women ≥ 40 years with TNBC treated with primary and axillary surgery.	7,843 of 11,785 women received optimal therapy. Therapy becomes less and less optimal with age, comorbidities, and characteristics of the cancer.

Conclusion

TNBC showed a good response to combination chemotherapy along with pembrolizumab, capecitabine, olaparib, and radiotherapy, compared to just chemotherapy alone. Combination chemotherapy increases survival rates, DFS, and BCSS of TNBC compare to chemotherapy alone. On the other hand, breast-conserving surgery (BCS) does not show a better prognosis.

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International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Literature Review: Vitamin D Levels and Perinatal Depression Association

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DOI: 10.33086/iimj.v4i2.4366

ARTICLE INFO

Keywords:
Vitamin D level, perinatal, antepartum, postpartum, depression

Submitted: June 2nd 2023
Reviewed: June 12th 2023
Accepted: July 5th 2023

ABSTRACT

Background: Vitamin D levels have been linked to psychological symptoms such as anxiety, depression, and impaired cognitive performance. It is found that lower vitamin D levels in early pregnancy are associated with depressive symptoms in perinatal.This study examines the association between vitamin D levels and perinatal depression. This article based on literature source from Pubmed/MEDLINE and Science Direct with keywords: vitamin D levels including 25(OH)D levels or vitamin D deficiency, prenatal, antenatal, and postpartum depression. The discussion of this study will assist readers and health professionals analyze how vitamin D levels in the body affect the incidence of antepartum depression.
Results: these are five filtered literature, the journal discusses the relationship between vitamin D levels and antepartum depression. This literature review shows that pregnant women with less than 20 ng/mL vitamin D levels are 3.3 times more at risk than pregnant women with more than 20 ng/mL. Vitamin D plays a role in the process of increasing serotonin synthesis and increasing anti-inflammatory so that it can suppress the increase in pro-inflammatory cytokines that play a role in the incidence of depression.
Conclusion: There is a correlation between vitamin D levels and the occurrence of depression during the perinatal period. It can be suggested that pregnant women check their vitamin D levels regularly.

Introduction

Depression, or major depressive disorder (MDD), is currently one of the most common illnesses in psychiatry, affecting around 121 million people worldwide (WHO, 2018). Depression comes in many forms, such as loss of interest, constant sadness, worthlessness, hopelessness, and, worst of all, a feeling that there is no value in life anymore (NIMH, 2018).

Mood disturbances often occur during pregnancy and the postpartum period, which can lead to depression. Researchers have focused a great deal of attention on this issue in recent decades and found that childbirth-related mental disorders can cause significant difficulties for the mother, fetus, baby, and family. This situation can potentially negatively impact the infant's growth and lead to long-lasting challenges in their behavior, cognition, social

interactions, and even emotional well-being (Vaziri et al., 2016).

A study conducted by Wijaya (2016) on pregnant women with high risk in Bandung, West Java, showed a higher prevalence of depressive symptoms as much as 34,7% (Wijaya, 2016). In 2018, Riset Kesehatan Dasar or Riskesdas reported that the Special Region of Yogyakarta (DIY) had the second highest prevalence of severe mental disorders in Indonesia (Perwitasari & Wulandari, 2022). Other study that was made from 196 pregnant women as its samples in East Jakarta and Central Jakarta also showed that 59.7% of them were found to be showing signs of depression. Antenatal depression was shown to be significantly more likely to occur in pregnant women with a history of depression (95% CI, Pv = 0.001) (Misrawati & Afiyanti, 2020).

It is common for women to experience depression throughout pregnancy and up to a year after giving birth in low- and middle-income countries, and this situation urgently calls for action to enhance maternal and newborn health outcomes (Roddy Mitchell et al., 2023).

The answer may rely on vitamin D, where previous studies have shown that vitamin D levels influence depression in the body. In vitro, vitamin D functions in maintaining extracellular serotonin concentrations in the brain, which acts as a neurotransmitter center that is responsible for cases of depression (Sabir et al., 2018) ((Dregan et al., 2019) (Raison & Miller, 2011). The vitamin D receptor (VDR) mediates the biological activity of vitamin D. The binding complex between VDR and VDRE on the promoter of a gene will initiate a transcription process associated with the production of brain serotonin, namely TPH2. When the enzyme TPH2 is activated, it promotes tryptophan metabolism, leading to the synthesis of serotonin. However, an imbalance in vitamin D levels can disrupt serotonin levels and their functioning in the brain. This disruption can subsequently affect behavior and the executive functions of the brain (Patrick and Ames, 2015; Pratiwi and Sukmawati, 2020). The primary components of executive function encompass various cognitive abilities. These include inhibition, which involves self-control and the ability to resist impulses; interference control, which relates to selective attention and cognitive inhibition; working memory, which involves holding and manipulating information in mind; and cognitive flexibility, which encompasses creative thinking, adopting new perspectives, and adapting effectively to changing circumstances. Together, these components form the core of executive function (Diamond, 2013).

Low vitamin D levels in early pregnancy have a higher risk of experiencing perinatal depression. Vitamin D can be active in the body with the help of sunlight in the form of absorption of UVB by 7-dehydrocholesterol in the skin and then converted into vitamin D3 (the most natural form of vitamin D), which can be isomerized into Vitamin D3, which will later form biological products that play a role in in the brain (Vaziri et al., 2016; Wacker & Holick, 2013). There are few literature studies on perinatal depression related to vitamin D deficiency. Therefore, further analysis is needed to determine whether there is a relationship between vitamin D levels and perinatal depression.

Method

The data collection and analysis in this systematic review adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. These guidelines were employed as a standardized and transparent framework to collect and report information consistently throughout the entire review process. Studies were obtained from two databases: Pubmed/MEDLINE and Science Direct, with keywords: vitamin D levels including 25(OH)D levels or vitamin D deficiency, prenatal, antenatal, and postpartum depression, published between 2000 and 2022. This review included randomized controlled trials, case series, controls case, cross-sectional, crossover, cohort, prospective, and retrospective studies. After obtaining eligible studies, the articles were evaluated using the Joanna Briggs Institute scoring tool to assess the study's methodology and determine how well it was subject to bias, conduct, and analysis.

Results

The results of the search in PUBMED are a total number of 83 studies, with the keyword being “Vitamin D Level” and “Perinatal”, or “Postnatal” or “Antenatal” or “Prenatal” or “Postpartum” and “Depression”. The year of the study are chosen from 2000-2023 which leave 78 studies. There are 10 studies out of 78 remaining after selecting the studies with only clinical trials and RCTs methods that are available for free access. Then we delete the duplicates with Mendeley Reference Manager resulting 3 studies left.

The results of the search in ScienceDirect are a total number of 20,763 studies, with the keyword being “Vitamin D Level” and “Perinatal”, or “Postnatal” or “Antenatal” or “Prenatal” or “Postpartum” and “Depression”. The year of the study are chosen from 2000-2023 which leave 14,826 studies. There are 852 studies remaining after selecting the design of the studies with only research and case report that have free access. Due to plenty unsuitable titles, the

studies are filtered down resulting in final result of 3 studies.

The total of 6 studies from both search engines are then assessed for its quality through Joanna Briggs' Institute Critical Appraisal. Based on the results of the review, the following results were obtained:

Table 1. Data from a review of 6 articles on the relationship between vitamin D levels and antepartum, antenatal, and postpartum depression

Author (year)	Title	Study design type	Assessment	Patient's vitamin d level	Outcome	Confounding factors (bias risk)	Conclusion
Williams J., Romero V., Clinton C. Et all. (2016)	Vitamin D levels and perinatal depressive symptoms in women at risk: a secondary analysis of the mothers, omega-3, and mental health study	Secondary analysis of a randomized trial	Beck Depression Inventory (BDI) and MINI International Neuropsychiatric Interview.	Selected a vitamin D level≥20 ng/ml (N= 98) for our reference group and <20 ng/ml (N=19) for our "low vitamin D" group for sub-analysis.	This study provides evidence indicating a significant association between low vitamin D levels during early pregnancy (between 12-20 weeks) and elevated depression symptom scores in early and late pregnancy among women at risk for depression.	It is still possible that the inter-vention, or even the participation in a clinical trial itself, led to inappropriate conclusions	In women at risk for depression, early pregnancy low vitamin D levels are associated with higher depressive symptom scores in early and late pregnancy.
Abedi P., Bovayri M., Fakhri A., et all (2018)	The Relationship Between Vitamin D and Postpartum Depression in Reproductive-Aged Iranian Women	Case-control study	Beck Depression Scale	25(OH)D<10ng/ml and 10–20ng/ml were considered as severe deficiency and moderate insufficiency respectively, 20–30ng/ml as mild insufficiency and >30ng/ml was considered normal	Women of experiencing postpartum depression was 3.30 times higher among women with vitamin D levels below 20 ng/ml compared to those with vitamin D levels above 20 ng/ml.	Taking supplements and sunlight exposure may be affected by recall bias. Data collection and vitamin D measurements have been done in the two seasons (winter and spring) which may affect the	Women with postpartum depression had a lower mean of 25-OH-D. Also, the number of women with moderate insufficiency and severe deficiency was significantly higher in the postpartum depression

						level of vitamin D	group compared to normal women
Accort E., Schetter C., Peters R., et all. (2016)	Lower Prenatal Vitamin D Status and Postpartum Depressive Symptomatology in African American Women: Preliminary Evidence for Moderation by Inflammatory Cytokines	Cohort study	The Edinburgh Postnatal Depression Scale (EPDS)	The sample's average level of 25(OH)D (a form of vitamin D) from January to March was 13.2 ng/ml. This value falls below the standard cutoff criteria for vitamin D inadequacy, indicating that the participants had insufficient vitamin D levels during that period.	Among women with higher levels of inflammatory markers, lower prenatal log 25(OH)D was associated with significantly higher PPD symptoms ($p < 0.05$).	Maternal age, marital status, prenatal depressive symptoms (CES-D), and season of vitamin D measurement.	These preliminary results are intriguing because if replicable, simple translational opportunities, such as increasing vitamin D status in pregnant women with elevated pro-inflammatory cytokines, may reduce PPD symptoms
Accort E., Arora C., Miroha J., et all. (2021)	Low Prenatal Vitamin D Metabolite Ratio and Subsequent Postpartum Depression Risk	Analytical Cross-Sectional Studies	BDI (Beck's Depression Inventory) and 21-item CES-D (Center for Epidemiologic Studies Depression) Scale		A total of 89 women had complete depression, biomarker and demographic data and 34% were at risk for PPD (CES-D‡16). Stepwise multiple logistic regression models for PPD risk were carried out with eight predictors.	BMI, maternal age, smoking, and BDI (risk for prenatal depression)	Vitamin D insufficiency as measured by the VMR is associated with higher risk for PPD.

Ogiji J., Rich W. (2022)	An exploratory study of vitamin D levels during pregnancy and its association with postpartum depression, Australia	Retrospective observational study, used 161 sample	Blood samples were collected from women during their first trimester of pregnancy and were analyzed at the local pathology lab for 25(OH)-vitamin D serum concentration and Edinburgh Postnatal Depression Scale (EPDS) was used to screen for PND	Vitamin D level 25-50 nmol/L (N:22), 51-74 nmol/L (N: 39), 75-99 nmol/L (N: 29) and ≥100 nmol/L (N:2). low vitamin d levels if ≤50 nmol/L	Women with PPD had significantly lower levels of vitamin-D antenatally ($p<0.01$) compared to women without PPD. PPD was significantly negatively correlated with antenatal vitamin D levels ($p<0.01$)	Previous psychiatric history, smoking and unplanned pregnancies were also positively correlated with PPD which suggests that overall healthcare and nutritional status are likely to have an impact on developing PPD and may therefore confound results.	Low vitamin-D levels during pregnancy are associated with developing PPD.
Wang Y., et al. (2023)	Perinatal depression and serum vitamin D status: A cross-sectional study in urban China	cross-sectional study, used 1773 sample	Edinburgh Postnatal Depression Scale (EPDS) was used to screen for PND and Serum 25-hydroxyvitamin D concentrations were assessed with high-performance liquid chromatography	Vitamin D level <20 ng/mL (N:349), 20-30 ng/mL (N:228) and >30 ng/mL (N:289), low vitamin d levels if <30 ng/Ml	There is a relationship between vitamin D deficiency with a higher prevalence of PPD (OR = 1.71, 95%CI: 1.01–2.88, p = 0.044).	confounding factors that have not been considered, such as a family history of depression and nutrition.	In conclusion, this study suggested a significant association between vitamin D status and PPD

From the studies obtained, all patients first need to be assessed with BDI (Beck depression inventory) and EPDS (Edinburgh post-natal depression scale) assessment to determine symptoms of perinatal depression. The assessment is done during gestational weeks. After assessment, blood samples were then taken to measure each of the patient's vitamin D levels.

In the assessment of perinatal depression, BDI and EPDS were used in all of the studies obtained. The EPDS is the most used instrument for detecting depression associated with childbirth. This instrument contains ten items that provide ranks from 0 to 3 that reflect the patient's experience over the past week. This instrument has received considerable validation for usage both throughout pregnancy and after delivery.

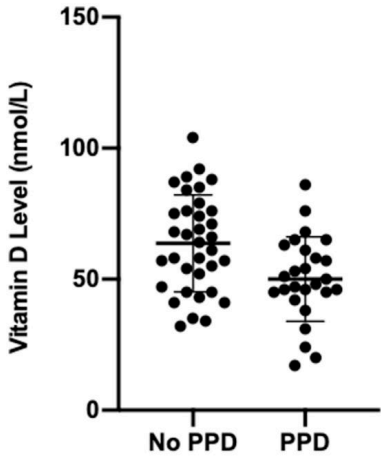

Figure 1. Scatter plot comparing vitamin D levels in women with postpartum depression (PPD) vs the control group (No PPD)

Source : Ogiji J., & Rich W. (2022)

An acceptable cut-point for identifying women at risk for severe depression in clinical settings is an EPDS score of ≥13. The Research Diagnostic interview detected a major or minor depression in 86% of postpartum women with an EPDS score ≥13 (specificity=78%, positive predictive=73%). According to a screening of a community sample of women 4–6 weeks postpartum (n=400), 6% of screened patients had PPD verified by the SCID. The optimal time to screen for EPDS is 4–6 weeks after delivery. (Sit, D. K., & Wisner, K. L., 2009).

A study identified more instruments with good psychometric qualities to measure perinatal symptoms in a thorough study. These instruments include the General

Health Questionnaire (GHQ), the Beck Depression Inventory (BDI I or II), and the Inventory of Depressive Symptomatology. These tests all had enough evidence to show their reliability among women who spoke various languages. High scores on either instrument may indicate a risk for anxiety disorders. The EPDS and BDI have a strong correlation with anxiety measures. (Sit, D. K., & Wisner, K. L., 2009).

From the result, all studies show associations between vitamin D and perinatal depression, especially in circumstances where there is a presentation of perinatal depression in individuals with lower vitamin D levels. A study done by (Accort E. et al., 2016) found that low prenatal 25(OH)D and high prenatal inflammation might predict future postpartum depressive symptomatology in African-American women and potentially in other subgroups of the population as well. It is also stated that pro- and anti-inflammatory cytokines (e.g., IL-6 and IL-10, respectively) would moderate the association between prenatal 25(OH)D and PPD symptomatology. Lower prenatal vitamin D levels are also associated with higher PPD symptoms.

In another study by (Accort E. et al., 2021), Vitamin D insufficiency measured by VMR is proven to be associated with a higher risk of PPD. It also states that women with darker skin generally have a lower total of 25(OH)D suggesting that the total serum 25(OH)D may be misleading by falsifying vitamin D status in various ethnic groups without evidence of vitamin D insufficiency.

A study from (Abedi P. et al. l.) also showed evidence that women with Vitamin D <20ng/ml have a higher risk of having postpartum depression, as much as 3.30 times that of those with Vitamin D >20ng/ml. It suggests a significant relationship between age, economic situation, and the desire for pregnancy connected with postpartum depression. Their results showed that undesired pregnancy, age, and poor economic situations could be included as risk factors for postpartum depression.

According to (Ogiji J., & Rich W., 2022), it is stated that lower antenatal vitamin D levels were greatly associated with postpartum depression in women with PPD (Postpartum Depression). This study also demonstrated favorable correlations between PPD and prior psychiatric history, smoking, and unplanned deliveries. This shows that overall health care and nutritional status are likely to have an impact on the development of PPD. The research suggests the most effective way to prevent PPD during pregnancy is to make sure vitamin D levels are at adequate levels.

A study from (Wang Y., et al., 2023) reported results that breastfeeding woman

with vitamin D insufficiency had a greater risk of PDD compared to those who had sufficient vitamin D. Pregnant women, however, did not show a similar correlation between vitamin D levels and antenatal depression. Additionally, it was discovered that there was no significant correlation between serum 25(OH)D and PSQI (Pittsburgh Sleep Quality Index) scores, although there was a significant correlation between serum 25(OH)D and PPD. Therefore, sleep was not an influential variable in the 25(OH)D and PPD mediation study.

It is stated in a secondary analysis of a randomized trial study done by (Williams J., Romero V., Clinton C., et al., 2016) that depressive symptoms were prevented by prenatal omega-3 fatty acid supplementation. Despite the fact that vitamin D levels had no relation to diagnoses of major depressive disorder or generalized anxiety disorder, low vitamin D levels in early pregnancy are associated with greater depressive symptom scores in both the early and late stages of pregnancy in women at risk for depression.

Discussion

Vitamin D has been demonstrated to promote the Th2 or humoral immunity pathway while down-regulating the Th1 or cellular immunity route (McCann and Ames, 2007). By presumably enhancing anti-bacterial and anti-inflammatory responses in both the maternal and fetal components of the placenta, vitamin D also regulates placental development and function and encourages fetal tolerance (Arora and Hobel 2010). The production of pro-inflammatory cytokines is decreased, while the production of anti-inflammatory cytokines is increased, which helps to achieve these regulatory changes (McCann and Ames, 2007). The circumventricular organs, specific regions of the brain outside the blood-brain barrier (BBB), or vagal afferents are additional pathways that allow cytokine signals from the periphery to be transmitted to the brain. These pathways may alter maternal neurotransmission and later depression symptomatology (Webb A., Kazantzidis A., Kift R., et al., 2018).

A few studies stated that each race and the variety of colors have varied needs for vitamin D levels. According to a 2013 study by O'Connor et al., Africans living in tropical areas should create a lot of vitamin D3 internally due to their considerable UVB exposure (O'Connor et al., 2013). However, 7-dehydrocholesterol and epidermal melanin compete for UVB absorption. Therefore, longer sun exposure is required to generate vitamin D3. Stated from (Harris, 2006), most young and healthy African Americans (blacks) in North America never achieve the recommended 25-

hydroxyvitamin D [25(OH)D] 48 concentrations. This is because African Americans (blacks) are more likely than other Americans to be vitamin D deficient.

A number of studies carried out in South and Southeast Asian countries have demonstrated that vitamin D deficiency and insufficiency are extremely prevalent. Epidemiologic research from several regions of India revealed that vitamin D deficiency [25(OH)D 50nmol/L] was more frequent than 70% of the time in all age groups, including infants, children, pregnant women, their newborns, and adult males, even where there is enough sunlight all year long. In Singapore, local residents are found to be in the same situation. Singapore has a significantly higher risk of vitamin D deficiency than Thailand even though it is closer to the equator. This is in part due to Singapore's higher level of industrialization (Nimitphong & Holick, 2013).

Specific type of clothing is an additional factor that could affect vitamin D levels. According to (Mohamed et al., 2021), the issues of vitamin D insufficiency may be increased by the style of clothing worn, particularly fully covering garments like the headscarf or hijab. It was found that women who wear concealing apparel have a 2.28 times higher risk of having vitamin D deficiency than those who do not.

The hypothalamus-pituitary-adrenaline or HPA axis is linked to serotonin and oxytocin as two primary contributors. It is also likely that the HPA axis play a role in the development of depression. Based on certain studies, oxytocin may play a number of roles in the regulation of mood, behavior, social interaction, and brain development. Numerous mental disorders, including depression have been linked to its absence. The necessity of steroid hormones, including vitamin D for the synthesis and release of the nano-peptide oxytocin is becoming acknowledged progressively. The same study, however, revealed that vitamin D supplementation was unable to significantly alter the levels of platelet serotonin and serum oxytocin in the intervention group. Therefore, it is still unproven that the antidepressive effects of vitamin D treatment was produced by the changes in the measured neurotransmitters (Kaviani et al., 2020).

This study's limitation lies on the fact that some populations or races (such South East Asians) were left out of the research that were conducted. The conclusion that there is a link between vitamin D levels and prenatal depression cannot, therefore, be generalized to all communities or races. Additionally, it was not able to determine how the levels of vitamin D were associated to some of the risk factors in this study,

including socioeconomic status and pregnancy uncertainty.

Conclusion

This study suggests that there is strong association between Vitamin D levels with perinatal depression. The association is an indirect relationship through reducing serotonin synthesis and increasing interleukin levels, which initially have gone up due to the natural inflammation process of pregnant women.

From the results of this systematic review, it can be suggested that pregnant women check their vitamin D levels regularly. In patients with a vitamin D deficiency, supplements can be given to reduce the risk factors for perinatal depression.

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International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Consanguinity via Breastfeeding in view of Islam and Science of Epigenetics

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DOI : 10.33086/iimj.v4i2.4823

ARTICLE INFO

Keywords: consaguinity, breastfeeding, epigenetics, Islam

Submitted: July 28th 2023
Reviewed: Aug 2nd 2023
Accepted: Aug 20th 2023

ABSTRACT

Background : One of the unique features of the Qur´an and Sunna is that never contradict the Science. Qur´an is not considered as a scientific book, however, includes many extraordinary signs and true scientific facts that have not been known at the time of the Qur´an revelation. Over the past few decades, several of them have been revealed, but many are still waiting to be uncovered.
Result : Breastfeeding is the most natural and safest way to provide nutrition, protection and unique bonding experience for newborn babies. The term "milk-kinship" is a kind of relationship via breastfeeding that was established hundreds of years ago via the Qur´an and Sunna. Recent study revealed that the life expectancy of the F2 offspring obtained from milk-sublings mating was much shorter than the offspring from control group. Which mean that there is period in which offspring are susceptible to breast milk induced epigenetic changes, especially in the first 2 years of life.
Conclusion : Latest research suggests that consanguinity via breastfeeding can be explained by heritable mechanism of epigenetic modifications.

Introduction

The Czech monk Gregor Mendel is considered as a father of genetics, one of the modern sciences that focuses on the heredity and variation. According to Mendel´s simple model with a pea, each gene consists of two alleles, one dominant and one recessive. Human genome consists of approximately 22000 genes (Jackson et al., 2018). In autosomal inheritance, homozygous recessive genotype means that organism carries two identical copies of the recessive allele that are expressed in the phenotype. Phenotypes involve any observable traits, including different abnormalities, and clinical features encountered in human disease. In dominant phenotype, one dominant allele is sufficient for the expression, (heterozygote dominant genotype). It means for example in a case of

genetic disorder, dominant allele hides recessive allele in one generation, however may "reappear" in a subsequent generation in a homozygote recessive genotype form. In fact, the reality of most human traits is more complicated, and the phenotype is usually determined by the interplay between genes and environment.

The concept of "reappearing" from Islamic point of view have been explained by using the hadith of the prophet Mohammed, peace be upon him (PBUH), who described this phenomenon several hundred years before Genetics was introduced (Ghareb, 2011).

„There came a person to the Prophet, PBUH, from Banu Fazara and said: My wife has given birth to a child who is black, whereupon Allah's Apostle, PBUH, said: Have you any camels? He said: Yes. He again said: What is their colour? He said: They are red. He said: Is there a dusky one among them? He said: Yes, there are dusky ones among them. He said: How has it come about? He said: It is perhaps the strain to which it has reverted, whereupon he (the Holy Prophet) said: It is perhaps the strain to which he (the child) has reverted." (Sahih Muslim, 1500a).

Understanding genetic possibilities may prevent any false accusation of paternity or predict the probability of developing some inherited diseases caused by changes in the DNA sequence known as mutation. Links between the Qur´an, hadith and ethical and genetic understanding of diseases have been already discussed (Ghareeb, 2010). In the present paper we focus on the implications of the recent epigenetic research which are in concordance with the signs from Qur´an and Sunna. Epigenetics that can be translated as being above or upon genetics explores heritable and stable alterations in the gene expression without direct change in the DNA sequence. It refers to the chemical modifications to the DNA or histones around which the DNA is packaged forming nucleosomes. Nucleosomes condense to make chromatin and remodelling the chromatin structure enables to understand how environmental factors including nutrition, stress, toxins and pollution, smoking, etc. may at any time of life span contribute to the development of many diseases including cancer. There are three main epigenetic mechanisms; DNA methylation, histone modification (acetylation, methylation, phosphorylation, deimination, ubiquitylation, sumoylation, and ADP ribosylation) and micro RNAs. Micro RNA (also miRNA or miR) are short non-coding functional RNA molecules that mediate gene silencing. They are transcribed but not translated into proteins. It can be microRNA (miRNA), short (less than 30 nucleotides) interfering RNAs (siRNA) and

long (200 or more nucleotides) non-codig RNA (lncRNA).

Result and Discussion

Breastfeeding and Islam

The Qur'an appointed breastfeeding as a fundamental right for every newborn child and infant. It highly recommends completing a breastfeeding cycle of 2 years (Qur'an, 2: 233), and highlights the urgent need for mother milk's nutrition of the child.

"Mothers may breastfeed their children two complete years for whoever wishes to complete the nursing [period]. Upon the father is the mothers' provision and their clothing according to what is acceptable. No person is charged with more than his capacity. No mother should be harmed through her child, and no father through his child. And upon the [father's] heir is [a duty] like that [of the father]. And if they both desire weaning through mutual consent from both of them and consultation, there is no blame upon either of them. And if you wish to have your children nursed by a substitute, there is no blame upon you as long as you give payment according to what is acceptable. And fear Allah and know that Allah is Seeing of what you do."
(Sahih International translation of Holy Qur´an, chapter 2 (The Cow, Al-Baqara): 233)

The „complete" cycle according to the Qur´an is a duration of two years which Ibn Kathir, highlighted as recommendation not obligation, depending on the personal choice of mothers, their circumstancies and health conditions (Ibn Kathir, 1999). This explanation is in congruence with the World Health Organization's guidance that children should be breastfed for 2 years (WHO, 2021).

Another phenomenon known from the Qur´an and Sunna is relationship via breastfeeding another`s child. According to the Islamic law (sharia) kinship is based on blood, marriage, or breastfeeding (Arabic: al-rida`a). The kinship, known as "milk-children" or "milk-siblings", according to the Qur´an and Sunna does not allow a marriage between two people who were nursed from the same woman ("wet nurse").

„Prohibited to you [for marriage] are your mothers, your daughters, your sisters, your father's sisters, your mother's sisters, your brother's daughters, your sister's daughters, your [milk] mothers who nursed you, your sisters through nursing, your wives' mothers, and your step-daughters under your guardianship [born] of your wives unto whom you have gone in. But if you have not gone in unto them, there is no sin upon you. And [also prohibited are] the wives of your sons who are from your [own] loins, and that you take [in marriage] two

sisters simultaneously, except for what has already occurred. Indeed, Allah is ever Forgiving and Merciful.“
(Sahih International translation of Holy Qur´an, chapter 4 (The women, An-Nisa: 23)

From the authentic narrations, Prophet´s wife, Aisha, may Allah be pleased with her, reported that Salim was the freed slave of Abu Hudhayfa and lived with him and his family in their house. The wife of Abu Hudhayfa came to the Prophet, PBUH, and she said, “Salim has reached puberty as men do, he knows what they know. He enters our house freely, and I sense that this disturbs the heart of Abu Hudhayfa.” The Messenger of Allah, PBUH, said:

„Let him be fed with breast milk and he will be unlawful for you to marry, then the disturbance in Abu Hudhayfa’s heart will disappear.“ (Hadith Ṣaḥīḥ, Muslim 1453b)

Ibn Hajar comments on this tradition, saying: Al-Qadi ‘Iyad answers the question with the interpretation that the milk was put into a cup and he did not drink it from her breast. According to the Al-Nawawi this interpretation is the best. (Fatḥ al-Bārī 4814, In: Abu Amina Elias, 2013)

It was also narrated that Aisha, may Allah be pleased with her, said: “One of things that Allah revealed in the Qur`an and then abrogated was that nothing makes marriage prohibited except ten breastfeedings or five well-known“ (breastfeedings) (Sunan Ibn Majah 1942, authenticated by Al-Albaani). According to this hadith, the Qur’an initially stated that ten times of confirmed breastfeeding make the breastfed person unmarriageable (Arabic: Mahram) to those who shared breastfeeding from the same woman and their Mahram relatives. Yet, both the ruling and wording of this verse were abrogated and replaced with another verse stipulating five times of confirmed breastfeeding. Later, only the wording of the latter verse was abrogated while its ruling remained in force. As for Aisha´s statement that the Prophet, PBUH, died while this verse was still being recited as part of the Qur'an, means that the abrogation came so late that news of it did not reach some people and, thus, they continued reciting the abrogated verse as part of the Qur’an due to their ignorance of its abrogation.

Abdullah ibn Abbas, may Allah be pleased with him, reported that the Messenger of Allah, PBUH, said about

Hamzah bin Abdul-Muttalib´s daughter: "She is the daughter of my brother through breastfeeding, and breastfeeding makes unlawful (for marriage) the same things that blood ties make unlawful” (Sunan Ibn Majah 1938).

This hadith is known also through another narrator, Ali ibn Abi Talib, may

Allah be pleased with him, desired that the Prophet, PBUH, would marry the daughter of their uncle Hamzah, but the Prophet informed him that she is not lawful for him to marry because she is the daughter of his brother by breastfeeding (Musnad Ahmed 931).

The Prophet, PBUH and Hamzah, may Allah be pleased with him, were both breastfed by Thuwaybah, the maid servant of Abu Lahab. Therefore, Hamzah became his brother by breastfeeding and the Prophet is the paternal uncle of Hamzah's daughter and cannot marry her. In Islam, marriage that is permanently unlawful because of blood relationship is also permanently unlawful due to breastfeeding.

Composition of the human milk

Human milk is the most unique nutritional food for optimal infant growth, protection and development. This complex fluid is considered as a natural version of personalized nutrition and its composition vary depending on the infant age, gender, health status, etc. (Golan and Assaraf, 2020). Concentration of many macronutrients and micronutrients present in breast milk declines with the duration of breastfeeding, adapting to meet the child's needs. Interestingly, production of nutrient deficient breast milk, or genetic variations that reduce breast milk quantity and quality in terms of nutrients are relatively rare and is against the evolutionary selection (Dror and Allen, 2018). Breastfeeding has been negatively associated with gastrointestinal tract infections or developing the type-2 diabetes (Horta et al., 2015). Protective effect of breastfeeding with some possible residual confounding has been shown in relation to the risk of obesity, high level of arterial blood pressure, high total level and LDL-blood cholesterol in adulthood (Horta et al., 2015). Protective effects of breastfeeding have been indicated also in autoimmune disorders including coeliac, diabetes type-1 or bowel inflammatory diseases. The n-3 long chain polyunsaturated fatty acids, the main components of breast milk, have been indicated to be involved in neurodevelopment and cognitive abilities of the child. Next to well-studied nutritional components of human milk such as mentioned fatty acids, immunological factors, growth factors, maternal cells, there are also abundant amounts of bioactive elements such as stem cells and miRNAs.

Stem cells in human milk and their therapeutic potential

Experiments in animal mouse models have shown that breast milk stem cells are able to migrate to the various organs of the infant, such as heart, brain, thymus and pancreas (Kakulas, 2015) and potentially be

able to differentiate into the tissues in which they will end up in the newborn child´s body. In addition, stem cells found in human breast milk offer an attractive, relatively readily accessible alternative to the problematic embryonic stem cell research as they include cells exhibiting both multipotent and pluripotent capabilities. The moral implications of using an embryonic stem cell in research have sparked a discussion amongst the scientists, religious communities, and the wide public. Noteworthy, breast milk stem cells provide immense potential for developing new promising therapies that can treat, cure, or manage diseases such as hematopoietic, neurological, cardiovascular, and bone disorders (Peterson, 2016).

MicroRNA

Another valuable bioactive material present in human milk are microRNAs (miRNAs). These molecules play pivotal role in epigenetic expression and differentiation in phenotype between species and within human populations despite similarity in encoded proteins. The epigenetic consequences of miRNAs, transmission through maternal milk on future generations, are not yet understood.

Small non-coding RNA molecule have been demonstrated in all three fractions of breast milk and the levels of miRNAs and their expression are similar in colostrum and mature milk (Tingö et al., 2021). The richest in miRNAs are cells (leukocytes, lactocytes, myoepithelial cells, a hierarchy of progenitor and stem cells, and bacteria), in comparison to the fraction of lipids and skim milk. They are carried to the infant via the exosomal and cellular components of breast milk. Due to less acidic stomach environment of a child, miRNAs from human milk can survive, absorb and integrate in infant exerting gene regulatory function at the cellular level (Alsweed et al. 2016). miRNAs are resistant and stable when pasteurized by the Holder method (high pressure processing) of human donor milk at 62.5°C for 30 minutes (Smyczynska et al., 2020). An epigenome wide association study has shown association between breastfeeding duration and methylation level at 4276 CpG sites, corresponding to the 2635 genes (Naumova et al., 2019). Besides their job in cell-cell communication and regulation the immune system, miRNAs are likely involved in the epigenetic regulation of stem cells fate and function. In human milk have been abundantly discovered the following microRNA: miR-148a, miR-30a, miR146b, miR-200a, miR-21, let-7f, let-7i, miR-146b (Tingö et al., 2021) regulating mainly DNA methylation by targeting DNA methyltransferases (Bodo and Melnik, 2017). MiR -148a is the most abundant

microRNA in human milk extracellular vesicules and is involved in many cellular processes, such as suppressing tumour growth, metastasis, mitigating NF-kB mediated intestinal inflammation, exerting neuroprotective effect (Alzheimer´s disease, epilepsy), or modulating angiogenesis (see cit. in Chutipongtanate et al., 2022). Dysregulation of miR-21 was suggested to be linked with the increased risk of hepatocellular carcinoma by changing mTORC1 signaling, such as PTEN expression (Meng et al., 2007). PTEN is also a direct target of miRNA-148a that was down-regulated following incubation with milk derived exosomes suggesting that miRNAs from human milk may protect children from cancer from birth to adulthood (Reif et al., 2019). Thus, understanding more about the communication between mother and infant may have key clinical impact and applications as a predictive marker and therapeutic agent.

Epigenetic mechanism of "Milk-kinship"

Milk-kinship according to the religion of Islam defines the consanguinity caused by breastfeeding genetically not related individuals by the same woman. To understand how milk-kinship marriage maybe associated with risk of certain disorders in future generations, Ozkan and his research group set up an experimental animal model using a/a and Avy/a mice on C57Bl6J background (Ozkan et al., 2012; 2021). Since the genetic structures and environmental conditions of the crosssibling and control groups were the same in their model, breast milk was supposed to be the only responsible factor for existing epigenetic changes. Because of the similarity of the genetic backgrounds and environmental exposures of the two groups, posttranscriptional epigenetic mechanisms, especially through miRNAs, were investigated instead of DNA methylation patterns or histone modifications. Thus, randomly selected animals in the both F2 groups (milk-siblings vs control) were sacrificed for miRNA expression analysis and the remaining were screened for phenotypic features (coat colour, obesity, hyperglycemia, liver pathology, lifespan). Their study revealed that the life expectancy of the F2 offspring obtained from milksublings mating was much shorter than the offspring from control group (387 vs 590 days, $p = 0.011$). Offspring of milk-siblings were more obese during the aging period and histopathological examination of liver tissues displayed abnormal findings that have not been observed in the offspring from control matings, e.g., lymphoproliferative nodules, abnormal iron accumulation, and fibrosis (Ozkan et al., 2021). The microRNA profiling identified particularly mTOR

signalling, P13-Akt, ErbB, MAPK and insulin signalling pathways that were targeted by miRNAs differentially expressed in milk-siblings. These signalling pathways are associated with the development of the metabolic syndrome and its complications, fatty liver disease, respiratory disease, diabetes, cardiovascular disease, and cancer development (Templeman and Murphy, 2018). Moreover, miR-186-5p was downregulated and GSK3b upregulated in milk-siblings compared to control groups. Downregulation of miR-186-5p and upregulation of GSK3B have been reported in ovarian carcinoma (Hilliard et al., 2011; Templeman and Murphy, 2018). Overexpression of GSK3B has been implicated in insulin resistance, polycystic ovary syndrome, platinum-resistance in ovarian cancer (Hilliard et al., 2011).

Their finding have shown that there is period in which offspring are susceptible to breast milk induced epigenetic changes. The period that begins with conception and covers the first 2 years of life is suggested as the most active period in terms of epigenetic regulation, especially in terms of DNA imprinting. Therefore, this period is referred to as "1000 day period" (Linner and Almgren, 2020). And this period is in agreement with the verse from the Quran:

„We have commanded people to honour their parents. Their mothers bore them in hardship and delivered them in hardship. Their ˹period of˺ bearing and weaning is thirty months. In time, when the child reaches their prime at the age of forty, they pray, "My Lord! Inspire me to ˹always˺ be thankful for Your favours which You blessed me and my parents with, and to do good deeds that please You. And instil righteousness in my offspring. I truly repent to You, and I truly submit ˹to Your Will˺."
(Sahih International translation of Holy Qur'an, chapter 46 (The Wind-Sandhills (Al-Ahqaf):15)

The Qur'an highlights a physiologic bond between a mother and child lasting 30 months. This has been interpreted as a period that starts during gestation and continues until weaning when the child is 2 years old (Subudhi et al., 2021).

Nevertheless, these remarkable findings open important bioethical problems and put new barrier in potential necessity of using human donor milk from the human milk bank where all donors are usually anonymous. It created uncertainty and serious concerns of Muslim communities because no single donor is identifiable or recorded. It should be standard norm to provide all necessary documentation about donor woman and even all recipients of her milk to avoid marriage between individuals of these families. Ghaly (2018) recommended that newborn baby can

receive milk from three to five donors with known identity and four feeding from one donor only. Another solution is suggestion of Daud et al. (2020) to introduce Sharia Compliant Human Milk with the option to establish milk kinship when the requirements are met (wan Yusoff and Abidin, 2022). For example, Human Milk bank in Spain has established mixing milk from only a single donor, allowing batches to be classified as female or male depending on the gender of the donor´s child, "gender-specific donor milk". This solution was based on the interviewing different Muslim families, and developing a specific informed consent for Muslim families who preferred that their child could receive donor milk in case the gender of donor´s child and theirs is the same. Furthermore, the donor milk has been pasteurized by high-temperature short-time that is thermal process in which milk is forced between plated or pipes and heated on the outside by hot water at the temperature 72 °C for 5-15s (Moro et al., 2019).

Conclusion

Recent research supports the idea of consanguinity via breastfeeding. It has been indicated that factors modifying epigenetic mechanisms might be transmitted via breast milk to offspring and suggested the heritable unfavourable epigenetic effects of cross-fostering on future generations. However, further research in human model is required to verify and confirm these preliminary and undeniably impressive results which enlighten the superior wisdom of the Qur´an.

Acknowledgement

I am deeply grateful to Almighty for His guidance and help. I would like to thank Dr. Abdulwahab al-Sbenaty, associate professor Norbert Lukan and my daughter Aisha for the critical reading of the manuscript as well as sheikh Salem alAmry and sheikh Dr. Sajid Umar for their advice.

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